3RD Edition

VOLUME 2. Use, Health, and Environment

Handbook of SOLVENTS

George Wypych, Editor

ChemTec Publishing

Handbook of
Solvents, 3rd Edition
Volume 2. Use, Health, and Environment

George Wypych, Editor

ChemTec Publishing

Toronto 2019

Published by ChemTec Publishing
38 Earswick Drive, Toronto, Ontario M1E 1C6, Canada

© ChemTec Publishing, 2000, 2014, 2019
ISBN number: 978-1-927885-41-3 (hard copy); 978-1-927885-42-0 (epub)

Cover: Anita Wypych

All rights reserved. No part of this publication may be reproduced, stored or transmitted in any form or by any means without written permission of copyright owner. No responsibility is assumed by the Author and the Publisher for any injury or/and damage to persons or properties as a matter of products liability, negligence, use, or operation of any methods, product ideas, or instructions published or suggested in this book.

Library and Archives Canada Cataloguing in Publication

Handbook of solvents / George Wypych, editor. -- 3rd edition.

First edition issued in one volume.
Includes bibliographical references and index.
Contents: Volume 2. Use, health, and environment.
Issued in print and electronic formats.
ISBN 978-1-927885-41-3 (v. 2).--ISBN 978-1-927885-42-0 (v. 2)

1. Solvents--Handbooks, manuals, etc. I. Wypych, George, editor

TP247.5.H35 2019 661'.807 C2018-904011-4
C2018-904012-2

Printed by Lightning Sources in Australia, UK, and USA

13

Solvents Use in Various Industries

Attempts to reduce the solvent used in the production of various materials require background information on the current inventory, the reasons for selecting certain solvents, the effect of various solvents on the properties of final products, future trends, and the candidates for solvent replacement.

The starting materials for this chapter were in many sections based on a thorough evaluation provided by large groups of scientists and engineers assembled by US Environmental Protection Agency. This has produced Compliance Sector Notebooks which contain information on solvent use in close to 30 sectors of industry relevant for this book (not all groups of materials included in this chapter were covered by Notebooks). Full documents can be found on the EPA website at http://www.epa.gov/compliance/resources/publications/assistance/sectors/notebooks/. No further improvements or updates to these Notebooks are known to be published by the EPA. This useful initial information is updated here based on new findings published in the open and patent literature available worldwide.

13.1 ADHESIVES AND SEALANTS

George Wypych
ChemTec Laboratories, Toronto, Canada

Adhesives and sealants are manufactured from a variety of polymers. Their selection and their combinations impact solvent selection. Most solvent systems are designed to optimize the solubility of the primary polymer. Adhesives can be divided into ones which bond by chemical reaction and ones which bond due to physical processes.[1] Chemically reactive adhesives are further divided into three more categories to those that bond through polymerization, polyaddition, or polycondensation. Physically bonding adhesives include pressure sensitive and contact adhesives, melt, or solution adhesives, and plastisols. Polymerization adhesives are composed of cyanoacrylates (no solvents), anaerobic adhesives (do not contain solvents but require primers for plastics and some metals which are solutions of copper naphthenate),[2] UV-curable adhesives (solvent-free compositions of polyurethanes and epoxy), rubber-modified adhesives (variety solvents discussed below).

Polyaddition adhesives include epoxy and polyurethane polymers which can either be 100% solids, water-based, reactive or non-reactive hot melts or contain solvents mostly

to regulate viscosity. Typical solvents include methyl ethyl ketone, acetone, mineral spirits, toluene, and xylene.[3] Polycondensation adhesives include phenol-formaldehyde resin, polyamides, polyesters, silicones, and polyimides. With the exception of polyesters (which require ethanol and N-methylpyrrolidone as solvents) and polyimides (which require methyl amyl ketone, butyl acetate, methyl ethyl ketone, 2-ethoxyhexyl acetate as solvents), these adhesives can be made without solvents.

Pressure-sensitive and contact adhesives are made from a variety of polymers including acrylic acid esters, polyisobutylene, polyesters, polychloroprene, polyurethane, silicone, styrene-butadiene copolymer, and natural rubber. With the exception of acrylic acid ester adhesives which can be processed as solutions, emulsions, UV curable, 100% solids, and silicones (which may contain only traces of solvents), all remaining rubbers are primarily formulated with substantial amounts of solvents such as hydrocarbon solvents (mainly heptane, hexane, naphtha), ketones (mainly acetone and methyl ethyl ketone), esters (propyl acetate), and aromatic solvents (mainly toluene and xylene).

Melt adhesives and plastisols do not contain solvents. The solution adhesives group includes products made from the following polymer-solvent systems: nitrocellulose (typical solvents include solvent combinations usually of a ketone or an ester, an alcohol and a hydrocarbon selected from isopropanol, 2-butylhexanol, amyl acetate, acetone, methyl ethyl ketone), nitrile rubber (main solvent – methyl ethyl ketone), polychloroprene (which is usually dissolved in a mixture of solvents including a ketone or an ester, an aromatic and aliphatic hydrocarbon selected from naphtha, hexane, acetone, methyl ethyl ketone, benzene, toluene), and polyvinyl acetate (water).

In addition to the solvents used in adhesives, solvents are needed for surface preparation[4] and primers. Their composition may vary and is usually designed for a particular substrate, often using fast evaporating solvents and environmentally unfriendly materials with significant adverse health effects.

Detailed data on the total amount of solvents used by adhesive industry could not be found. The adhesive manufacturing industry continues to grow at a very fast pace. Total adhesive production, according to Frost & Sullivan, was $18.25 billion in 1996 and this was expected to grow to $26.2 billion in 2003.[5] According to ChemQuest Group, Inc., the global adhesive and sealant market was $36 billion in 2006. In 2010, according to BCC Research, world consumption of adhesives and sealants was $41 billion (12 million tons) and it was expected to grow to $52 billion in 2015. Solvent-based materials in 1995 constituted 13% of total production in North America, 14% in Europe, 15% in Japan, and 25% in the Far East.[6] Many industries which use solvent-based adhesives have moved to South America and Asia where regulations restricting emissions are less strict.[5] The shoe industry is now concentrated in South America. There are many initiatives to decrease solvent emissions. For example, World Bank's assistance program for developing countries focuses on this issue.[5] But, in spite of the fact that solvent-based adhesives lost some of their markets (3.3% during the period of 1994-1996),[5] they still hold 14-15% of the European market.[6] It is estimated that the use of solvents contributes 24% of all VOC emissions. According to one source, adhesives were responsible for a 6% share in these

emissions in 1993.[7] Another source[8] blames adhesives for 7% of total VOC emissions in Germany in 1995.

Sealants are divided into groups according to the generic names of polymer base. The main groups include polyurethanes, silicones, acrylics, polysulfide, and others (PVC, polybutylene, styrene-butadiene-styrene copolymers, polychloroprene, and several others). The amount of solvent used in sealants is controlled by the standards which previously divided sealants into two groups: these below 10% VOC and those above. A provision was made to include water-based acrylics and the limit of VOC for class A sealant was increased to 20%. Polyurethane sealants and structural adhesives can be made without solvent (the first solvent-free polyurethane sealant was made in 1994).[9] Solvents are added to reduce sealant viscosity and to aid in the manufacture of the polymer. Typical solvents used are mineral spirits, toluene, and xylene. A small amount of solvent is emitted from curatives which contain methyl ethyl ketone. Most formulations of silicone sealants do not contain solvents. In some sealants, traces of benzene and toluene can be found.

Acrylic sealants are water-based but they may also contain ethylene and propylene glycols, mineral spirits, and mineral oil. There are also solvent-based acrylic sealants which contain substantial amounts of solvents such as mineral spirits, toluene, and xylene. Polysulfide sealants usually contain toluene but methyl ethyl ketone is also used. The group of class B sealants contains substantially more solvents (up to 40% by volume) but there are some exceptions. PVC sealants are based on plastisols and they can be made without solvents. Butyl rubber-based sealants usually contain hydrocarbons (C_6-C_{12}). Styrene-butadiene-styrene-based sealants usually have a large number of solvents selected from a group including toluene, heptane, hexane, methyl ethyl ketone, isobutyl isobutyrate, n-amyl acetate, n-amyl ketone. They are usually processed in solvent mixtures. Polychloroprene is usually dissolved in a mixture of solvents including ketones or esters, and aromatic and aliphatic hydrocarbons. The list includes naphtha, hexane, acetone, methyl ethyl ketone, benzene, and toluene.

The world market for sealants was estimated in 1996 at $2 billion and was expected to grow in 2003 to $2.75 billion with an annual growth rate of 4.5% which is slightly lower than that expected for adhesives (5.3%).[5] In 2010, the global sealant market was $5.7 billion and it was expected to grow to $7.6 billion, which gave a growth rate of 4.8% per year.

The changing trends are clearly visible when developments in technology are studied but many barriers to reductions in solvent use exist such as the high investment required, longer processing time, frequently higher material cost of adhesives, and the psychological barrier of changing established adhesive practices. In many instances, adhesive performance is predicted by its superficial characteristics such as strong smell which might suggest that the material has superior properties, its initial green strength which for many indicates good bonding properties, and high viscosity often related to good processing characteristic.[10] Since the alternative materials may not have much odor, or require of longer time to reach strength and have a low viscosity, users are suspicious that their potential performance may be inferior. The following information reviews some recent findings which may contribute to future changes.

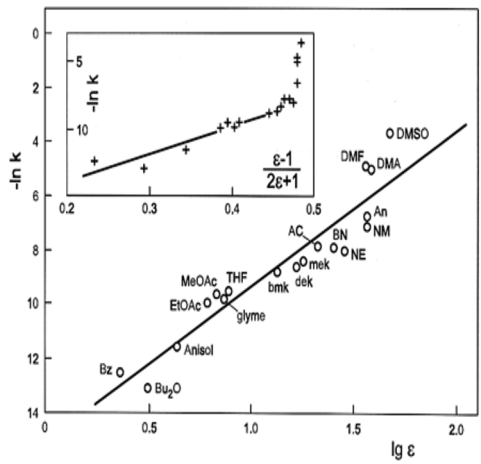


Figure 13.1.1. Green strength and adhesion of several adhesives. Symbols are explained in the text. [Data from B Archer, *Internt. J. Adhesion & Adhesives*, **18**, No.1, 15-8 (1998).]

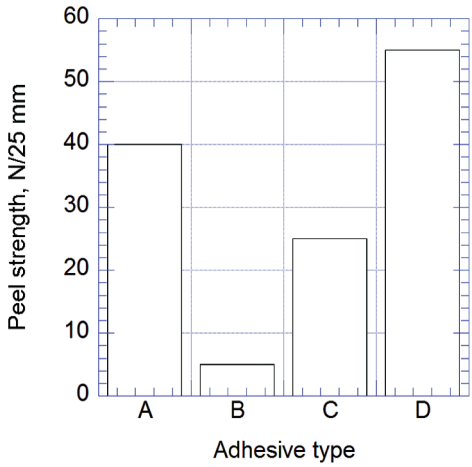


Figure 13.1.2. Contactability of various adhesives. Symbols are explained in the text. [Data from B Archer, *Internt. J. Adhesion & Adhesives*, **18**, No.1, 15-8 (1998).]

In the shoe industry, a major breakthrough occurred in 1928 when polychloroprene was first introduced.[1,10] The first, simple formulation is still manufactured and is used worldwide because the glue can be easily prepared by simply making a solution of the polymer. This gives a product with good adhesion to various substrates. Many new products are available today as potential replacements. Hot melt adhesives can be used in some applications but they still require solvents for cleaning, degreasing, and swelling. Also, their bond strength is frequently inadequate. Reactive systems are not yet used in the shoe industry but reactive hot melts are finding applications. Their broader use is hampered by their sensitivity to moisture which requires special equipment and special care.[10] Water-based adhesives are the most likely replacement product. They also need special equipment for processing because of the high heat of evaporation of water (although water-based adhesives contain 50% polymer compared with 15-20% in solvent-based adhesives).[10] Two sport shoe manufacturers, Nike and Reebok, already use this technology.

Traditional polychloroprene adhesives can be modified in several ways to be useful in water-based systems. Figure 13.1.1 shows peel strength of several adhesives. The solvent based adhesive (A) has excellent properties both in terms of green strength and bond strength. A simple emulsion of polychloroprene (B) has relatively good ultimate strength but lacks green strength and, therefore, does not meet the performance requirements of shoe manufacturers and other industries.[11] Adhesive (C) is a blend of polychloroprene with polyurethane in a water-based system. This modification gives both green strength and peel strength but Figure 13.1.2 shows that peel strength of a freshly applied adhesive is lower than that of solvent-based polychloroprene which may cause problems in holding both adhering surfaces together. The adhesive (D) was developed in an interesting new process which involves the emulsification of a solvent-based adhesive obtained from sty-

rene-isoprene-styrene rubber.[11] After emulsification, the solvent is stripped under vacuum to produce a solvent-free adhesive. The reason for emulsification of the complete adhesive, as opposed to emulsification of the rubber alone, is to produce a homogeneous adhesive system which would otherwise suffer from the separation of polymer particles surrounded by a layer of emulsifying agents. Figures 13.1.1 and 13.1.2 show that this system is superior to solvent-based adhesives. Adhesives can be further improved by polymer blending and by adhesive foaming. A foamed adhesive layer requires less material (approximately 4 times less than a conventional adhesive), it requires less drying time (less water and faster evaporation) and provides an improved bond strength. A foamed adhesive has a larger surface area which increases the surface area of contact with the substrate. The compressed rubber foam has a higher tear strength than unfoamed film of the same thickness.[11]

Also, regulations are helping to reduce the solvent content of adhesives.[12,13] The use of chlorinated solvents, frequently included in primers and cleaning solutions, has been discontinued based on the Montreal Protocol. From June 1998, the production of a pair of shoes in Europe did not involve the use of more than 20 g of solvent. This is an only partially successful solution since shoe production is expected to move out of developed countries to less restrictive jurisdictions. Solvent Emission Directive will continue to restrict solvent use in Europe.

Many changes have occurred and more are expected in adhesives based on thermoplastic polyurethanes (TPU).[3,14,15] In the last 40 years, TPU based adhesives were manufactured with solvents for shoes, food packaging, and textile and plastic film lamination. Current technologies use TPU in the form of a hot melt, as a reactive PUR and as a thermoplastic laminating film.[3] Reactive hot-melts were first introduced in the early 1980s and since then have grown very rapidly. After application, the adhesive is cured by moisture.[14] These adhesives are already in use by the automotive industry (bonding carpet to door panels, tray assembly, lenses of headlamp housing, and lamination of foam to fabric) and in furniture and building products (moldings, picture frames, decorative foil, edge-banding), in bookbinding, and in the footwear industry. Polyurethane water dispersions are expected to grow 8-10%/year from the current 5,000-6,000 tonnes/year market in Europe.[14] Applications are similar to those of hot melts.

UV-curable pressure-sensitive adhesives are the more recent application of the advancing radiation curing technology.[16] Low viscosity formulations allow the use of standard application techniques with several advantages such as improved production rate, energy efficiency, improved properties of the final products, and new potential applications for pressure-sensitive adhesives in thicker films with mechanical performance. It is expected that radiation-cured materials will expand at a rate of 10%/year.[17] Adhesives constitute 16% by value and 13% by volume of radiation-cured products (two major applications for radiation-cured materials are coatings and inks). Henkel introduced a series of water-based laminating adhesives.[18] Hot melt systems, high-solids solvent systems with 3 times higher solids content, and water-based adhesives have been introduced to textile lamination to replace traditional low-solids solvent-based adhesives.[19]

UV-crosslinkable acrylic hotmelt pressure-sensitive adhesives combine the economic advantages of the hotmelt coating technology with the high-performance characteristics of the acrylic chemistry, including an excellent aging resistance, optical transparency, and heat resistance.[20] They also have good tack, good adhesion, excellent cohesion and very high shrinkage resistance.[20] Good performance was achieved by use of H-abstractor 4-acryloyloxy benzophenone as a photoinitiator.[20] Pressure sensitive adhesives were crosslinked with different level of diphenylmethane-4.4'-di-isocyanate.[21] The increased amount of crosslinker caused an increase of adhesive's glass transition temperature and its zero shear viscosity. Creep recovery and peel strength were increased.[21]

Odor elimination is the additional benefit which has helped to drive the replacement of solvent-based systems.[22] In packaging materials, most odors are related to the solvents used in inks, coatings, and adhesives. Also, coalescing solvents from water-based systems caused odors. Elimination of solvent is a priority but solvent replacement may also change the response to the odor because solvents such as toluene and xylene smell like lubricating oils or turpentine whereas isopropanol smells more like a disinfectant. Odors stem not only from solvents but also from products of the thermal and UV degradation of other components and solvents.[22] More information on the effect of solvents and other components of adhesive and sealant formulations can be found in the specialized monograph.[23]

In view of the above efforts, it was surprising that many patents on adhesives published before the first edition of this book were still for solvent-based systems.[24-29] Some of these inventions included a universal primer,[24] an adhesive composition in which solvents have been selected based on Snyder's polarity (only solvents which belong to group III are useful in adhesive for automotive applications to avoid a deleterious effect on paint),[25] a low VOC adhesive for pipes and fittings,[26] a solvent-containing heat-resistant adhesive based on siloxane polyimide,[27] a water-based polyimide adhesive,[28] and two-component solvent-free polyurethane adhesive system for use in automotive door paneling.[29]

Inventions show improvements in solvent utilization, as follows. PVC-based adhesive for PVC pipes, typically containing a solution of PVC in tetrahydrofuran, was replaced by a solution of chlorinated PVC in 1,3-dioxolane and/or its derivatives which are far less toxic than THF.[30] Ethanol was used in polyimide adhesive[31] and dental adhesive.[32] Monomer solvent mixture was used in crosslinkable acrylate adhesive, which permits formulation of VOC-free composition.[33] Polyurethane hot-melt adhesive produced from polyacrylates and polyesters did not need solvents for its production and cure which occurs under the effect of moisture.[34] Similar observations can be made for sealants. For example, the sealing agent for semiconductor light emitting elements has been made from acrylic monomers without application of a solvent.[35] Material for production of printed wiring board was produced and cured without solvent from polymethacrylate.[36] It is clear from these examples that new processes are consciously directed towards less toxic solutions.

Contact adhesives frequently contain hazardous air pollutants and volatile organic compounds.[37] Commercial formulations containing polychloroprene, SIS, and other rubbers and resins impose requirements that balance solubility, viscosity, evaporation, color,

odor, and cost.[37] The solvent compositions that contain safer alternatives to toluene and hexane but maintain properties of contact adhesives were predicted using Hansen solubility parameters.[37] A database of solvents was used to select solvents based on health and environmental data and Hansen solubility parameters from the Hansen Solubility Parameters in Practice.[38] Solvent database is a suitable database which contains both solubility data and health and safety information.[39]

REFERENCES

1 R Vabrik, G Lepenye, I Tury, I Rusznak, A Vig, *Internt. Polym. Sci. Technol*., **25**, No.3, T/1-9 (1998).
2 D Raftery, M R Smyth, R G Leonard, *Internt. J. Adhesion Adhesives*, **17**, No.4, 349-52 (1997).
3 J B Samms, L Johnson, J. Adhesive Sealant Coun., Spring 1998. Conference proceedings, Adhesive & Sealant Council, Orlando, Fl., 22nd-25th March 1998, p. 87.
4 A Stevenson, D Del Vechio, N Heiburg, Simpson R, *Eur. Rubber J*., **181**, 1, 2829, (1999).
5 K Menzefricke, *Adhesive Technol*., **15**, No.1, 6-7 (1998). Sealing Technology Jan 2012.
6 L White, *Eur. Rubber J*., **179**, No.4, 24-5 (1997).
7 J Baker, *Eur. Chem. News*, **69**, No.1830, 20-2 (1998).
8 P Enenkel, H Bankowsky, M Lokai, K Menzel, W Reich, *Pitture e Vernici*, **75**, No.2, 23-31 (1999).
9 J. van Heumen, H Khalil, W Majewski, G. Nickel, G Wypych, **US Patent 5,288,797**, *Tremco, Ltd*., 1994.
10 S Albus, *Adhesive Technol*., **16**, No.1, 30-1 (1999).
11 B Archer, *Internt. J. Adhesion & Adhesives*, **18**, No.1, 15-8 (1998).
12 J C Cardinal, *Pitture e Vernici*, **74**, No.6, 38-9 (1998).
13 *Pitture e Vernici*, **73**, No.20, 39-40 (1997).
14 M Moss, *Pigment Resin Technol*., **26**, No.5, 296-9 (1997).
15 Hughes F, TAPPI 1997 Hot Melt Symposium. Conference Proceedings. TAPPI. Hilton Head, SC, 15th-18th June 1997, p.15-21.
16 D Skinner, *Adhesive Technol*., **15**, No.3, 22-4 (1998).
17 B Gain, *Chem. Week*, **160**, No.14, 28-30 (1998).
18 G Henke, *Eur. Adhesives & Sealants*, **14**, No.1, 18-9 (1997).
19 G Bolte, *J. Coated Fabrics*, **27**, 282-8 (1998).
20 Z Czech, A Kowalczyk, J Kabatc, J Swiderska, *Eur. Polym. J*., **48**, 1446-54 (2012).
21 X Zhang, Y Ding, G Zhang, L Li, Y Yan, *Internt. J. Adhesion Adhesives*, **31**, 760-66 (2011).
22 R M Podhajny, *Paper, Film & Foil Converter*, **72**, No.12, 24 (1998).
23 G Wypych, **Handbook of Odors in Plastic Materials**, 2nd Edition, *ChemTec Publishing*, Toronto, 2017.
24 M Levy, **US Patent 5,284,510**, *Paris Laque Service*, 1994.
25 I R Owen, **US Patent 5,464,888**, *3M*, 1995.
26 C D Congelio, A M Olah, **US Patent 5,859,103**, *BFGoodrich*, 1999.
27 D Zhao, H Sakuyama, T Tomoko, L-C Chang, J-T Lin, **US Patent 5,859,181**, *Nippon Mektron Ltd*., 1999.
28 H Ariga, N Futaesaku, H Baba, **US Patent 5,663,265**, *Maruzen Petrochemical Co. Ltd*., 1997.
29 E Konig, U F Gronemeier, D Wegener, **US Patent 5,672,229**, *Bayer AG*, 1997.
30 J P M Bierens, J P M Klerks, **WO2013122458**, **Bison International BV**, 22 Aug 2013.
31 **CN103242797**, 14 Aug 2013.
32 B I Suh, L Chen, **CA2805569**, *Bisco, Inc*., 16 Aug 2013.
33 M A Kavanagh, **US8524836**, *3M*, 3 Sep 2013.
34 M Krebs, U Franken, **US20130210989**, *Henkel*, 15 Aug 2013.
35 N Koito, **WO2013146607**, *Fujifilm Corporation*, 3 Oct. 2013.
36 S Choi, **WO2013146705**, *Taiyo Chlodings Co. Ltd.*, 3 Oct. 2013.
37 C. P. Barry, G. J. Morose, K. Begin, M. Atwater, C. J. Hansen, *Int. J. Adh. Adh*., **78**, 174-81, 2017.
38 https://www.hansen-solubility.com/HSPiP/
39 A. & G. Wypych, **Solvent Database**, v. 4.0, *ChemTec Publishing*, Toronto, 2014.

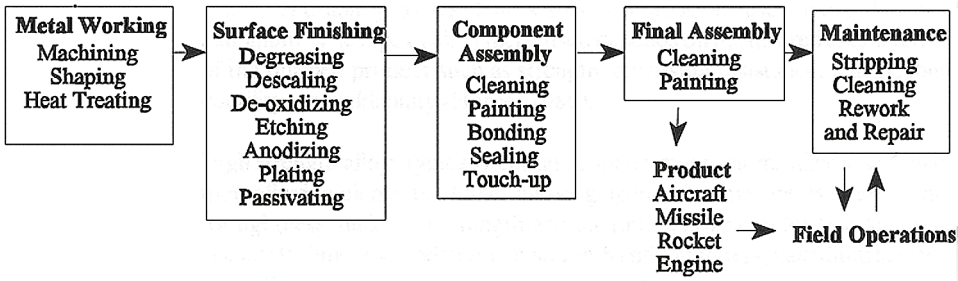


Figure 13.2.1. Schematic diagram of aerospace manufacturing process. [Reproduced from Profile of the Aerospace Industry. EPA Office of Compliance Sector Notebook Project. US Environmental Protection Agency. November 1998.]

13.2 AEROSPACE

GEORGE WYPYCH
ChemTec Laboratories, Toronto, Canada

Figure 13.2.1 shows a schematic diagram of the aerospace manufacturing process.[1] Metal finishing is the process in which most solvents and solvent-containing materials are used. The main function of the metal finishing process is corrosion protection which requires proper cleaning, surface preparation, and the selection of suitable coatings.

The functions of coatings used in aircraft are different from those used in ordinary coating applications, therefore, an extrapolation of the progress made with solvent replacement in other coating types is not justified. The typical flight conditions of operating altitude (about 10,000 m above the earth), speed (most frequently 900 km/h), temperature (very low in space at about -60°C and substantially higher after landing up to 80°C), humidity (low in space and high at earth level are combined with condensation due to the temperature difference), UV radiation (substantially higher during flight), mechanical abrasion due to the high speed of travel, exposure to salt in the atmosphere, exposure to higher level of acids and sulfur dioxide, and exposure to de-icing fluids during winter.[2,3] These unusual conditions should be considered in conjunction with the mechanical movement of the coating caused by rapid changes in temperature and the flexing of aircraft elements because of changes in pressure and severe load variations on wings.[2] In addition, because of their size, aircraft must often be painted at low temperatures which requires a coating that will cure at these temperatures without leaving entrapped volatiles. These could evaporate in the low-pressure conditions at high altitude and cause the formation of voids where corrosion could start. These factors make the design of an effective coating system a severe technological challenge.

Table 13.2.1. Total releases of solvents by the aerospace industry. [Data from ref. 1]

Solvent	Amount, kg/year	Solvent	Amount, kg/year
benzene	62,000	methyl ethyl ketone	995,000
bromotrifluoromethane	750	methyl isobutyl ketone	47,000
n-butyl alcohol	7,000	methyl tetr-butyl ether	550
sec-butyl alcohol	10,000	tetrachloroethylene	285,000
cyclohexane	400	1,1,1-trichloroethane	781,000
1,2-dichlorobenzene	600	trichloroethylene	429,000
1,1-dichloro-1-fluoroethane	10,000	trichlorofluoromethane	1,800
dichloromethane	314,000	toluene	414,000
isopropyl alcohol	1,000	xylene	103,000
methanol	21,000		

Coatings are used by the aerospace industry both for OEM and maintenance purposes. In each case, surface cleaning and preparation are required. A paint stripping operation is added to the task of maintenance repainting. Coatings are applied by spraying, brushing, rolling, flow coating, and dipping. Depending on the method of application, the rheological properties of coatings must be adjusted with solvents and, in some cases, with water. An alternative method of viscosity adjustment involves heating the coatings to lower its viscosity by increasing its temperature. This reduces solvent usage. Solvents are also used for equipment cleaning.

In addition to paints, sealants are also used. Sealants are mostly based on polysulfides, containing solvents as discussed in the previous section. Also, non-structural adhesives containing solvents are used as gaskets around windows and for carpeting.

Paint removal is accomplished by either chemical or blast depainting. Dichloromethane is the most common solvent used for this application. Aerospace industry estimates that 15,000 to 30,000 different materials are used for manufacturing some of which are potentially toxic, volatile, flammable, and contain chlorofluorocarbons. Some of these substances may result in air emissions, waste-waters, and solid waste.

Table 13.2.2. Total transfers of solvents by the aerospace industry. [Data from ref. 1]

Solvent	Amount, kg/year	Solvent	Amount, kg/year
n-butyl alcohol	2,600	methyl ethyl ketone	500,000
cyclohexane	18,000	methyl isobutyl ketone	17,000
1,2-dichlorobenzene	4,000	tetrachloroethylene	110,000
1,1-dichloro-1-fluoroethane	230	1,1,1-trichloroethane	133,000
dichloromethane	68,000	trichloroethylene	98,000

Table 13.2.2. Total transfers of solvents by the aerospace industry. [Data from ref. 1]

Solvent	Amount, kg/year	Solvent	Amount, kg/year
N,N-dimethylformamide	500	trichlorofluoromethane	3,800
ethylene glycol	14,000	toluene	87,000
methanol	12,000	xylene	12,000

Air emissions result from sealing, painting, depainting, bonding, as well as from leakage in storage, mixing, drying, and cleaning. The most common solvents involved in coatings are trichloroethylene, 1,1,1-trichloroethane, toluene, xylene, methyl ethyl ketone, and methyl isobutyl ketone. Wastewater is generated through contamination by paints and solvents used for cleaning operations. Solid waste containing solvents comes from paint overspray intercepted by emission control devices, depainting, cleanup, and disposal of unused paint. Solvents used for cleaning are usually a mixture of dimethyl-benzene, acetone, 4-methyl-2-pentanone, butyl ester of acetic acid, naphtha, ethyl benzene, 2-butanone, toluene, and 1-butanol. Some solvents used for painting and cleaning are either recycled are burned to recover energy.

In 1996, 199 aerospace facilities (out of 1885 analyzed in the report) released and transferred off-site or discharged to sewers about 12,000 kg of 65 toxic chemicals (solvents in these releases are reported in Table 13.2.1 and transfers in Table 13.2.2).

Methyl ethyl ketone, 1,1,1-trichloroethane, trichloroethylene, and toluene accounted for 66% of all releases. 70% of all transfers were for recycling purposes. The aerospace industry released 10,804 tons of VOC in 1997 which constituted 0.61% of the total releases from 29 industries which were analyzed. Thirteen other industries release more VOC than the aerospace industry.

Recycling and disposal of solvents in the aerospace industry equal the purchase cost of the solvents. Therefore, reduction of solvent use is very cost effective. Some chemical stripping operations are being replaced by cryogenic stripping with liquid nitrogen. Also, supercritical carbon dioxide has been used in Hughes Aircraft Company in some cleaning applications. Solvent emissions can be reduced through control of evaporation (lids, chillers), by dedicating process equipment (reduces cleaning frequency), production scheduling, immediate cleaning of equipment, better operating procedures, reuse of solvent waste, and use of optimized equipment for paint application. There were plans to evaluate powder coatings and water-based paints.[1,2] There were trials to use water as the paint thinner and to lower the viscosity of paints by application of resins which have lower viscosity.[2] Work was under the way to replace dichloromethane/phenol stripper with benzyl alcohol.[2] The introduction of an intermediate layer between the primer and the topcoat had been proposed. This will aid the stripping action of the proposed stripping solvent, benzyl alcohol. VOC have already been reduced in several components: bonding primer (from 1030 to 850 g/l), undercoats (from 670 to 350), topcoats (from 700-900 to 250-800), clear coats (from 700-800 to 250-520), surface cleaners (from 850 to 250) as well as other materials.[3]

Layton Technologies developed ultrasonic cleaning system for the aerospace company facing stringent environmental regulations.[4] The system meets California regulations, saves 60% solvent, and has full carbon adsorption.[4]

Composite materials are joined in aerospace, similar to other industries, by adhesive bonding to form structural components.[5] Adhesive bonding provides uniform stress distribution over the entire bond line.[5] Polybenzimidazole has a high thermal resistance which is required in this application.[5] It is used as an adhesive in form of 26% solution in dimethylacetamide.[5] Curing temperature is an essential parameter of joint strength and performance (125°C gives required performance).[5]

Analysis of current patents shows that solvents are still important components of technology in aerospace applications. Solvent-based primer modifies the surface of the rigid substrate and then contributes to chemical bonding.[6] Many applications of materials require that they are solvent resistant when solvents are used for cleaning, jointing, or other purposes.[7,8] Environmentally safe solvent compositions[9] are also actively pursued and solvent-free compositions are developed.[10]

In 2004, there were hundreds of aerospace companies in the USA.[11] After elimination of trichloroethane and CFC-113, the alternatives that were adopted included VOC solvents, such as MEK, toluene, xylene, MIBK and isopropyl alcohol. Some of these solvents are also considered to be toxic.[11]

Several less toxic solvents are used by aerospace industry, including EnSov 5408, Next 3000, ALK-774, CH207, SolvSat, and MPK. EnSolv®-5408 Aerospace Solvent is a Boeing-approved, stabilized n-propyl bromide-based solvent for the replacement of trichloroethylene, perchloroethylene and 1,1,1-trichloroethane in aerospace vapor degreasing. Next 3000 is non-flammable, high-trans fluorinated solvent which is ozone-friendly and has very low global warming potential. Next 3000 also boasts exceptionally low human toxicity compared to the vast majority of aerospace solvents on the market. Next 3000 is formulated for precision aerospace cleaning, such as vapor degreasing in existing equipment, cold wiping applications, oxygen cleaning and many other functions. It can be used as a carrier fluid for deposition of materials such as silicone and other lubricants. PPG developed ALK-774 is biodegradable, water-dilutable, environmentally safe cleaning compound, primarily used for light to heavy-duty removal of oil, grease, hydraulic fluid, and exhaust tract film from aircraft exteriors. It may be used for general purpose cleaning of cabin and baggage areas of aircraft interiors, as well, as gas trucks, ground service units, and freight-handling equipment. ALK-774 is also intended to be used to clean surfaces prior to recoating with adhesives, primers, sealants, and paint topcoats. ALK-774 is based on C9-11 ethoxylated alcohols such as (2-methoxymethylethoxy)propanol. Callington's CH207 is a non-flammable, acid activated, phenolic paint stripper for the removal of epoxy, polyurethane and other chemically resistant coatings, including primers and base coats. Texwipe's SolvSat™ wipers are designed for industrial and precision cleaning applications. They are saturated with acetone, IPA, toluene or MPK. Eastman™ MPKa and Eastman™ MPK (methyl propyl ketone), UHP (ultra high purity) solvents are being used as solvent alternatives to MEK and toluene for cleaning military and commer-

cial aircraft. Eastman™ MPK solvent satisfies the aerospace surface cleaning performance requirements and is also suitable for the cleaning of paint gun equipment.

The above-listed solvents are just a small number of commercial products which are suggested (and approved) for the aerospace industry. Continues improvement is certainly taking place in an industry which relied on many unfriendly solvents for both humans and environment.

Poly(vinyl fluoride) films are extensively used as protective, easy-clean materials in the photovoltaic and aerospace industries.[12] Vinyl fluoride has high solubility in fluorinated ionic liquids and concentrated aqueous ionic salt solutions at low pressures (<1000 psi).[12] Polymerization of vinyl fluoride in the presence of ionic liquids or ionic salt solutions was pursued as a means of reducing the pressure (>5000 psi) needed to achieve high monomer conversion and molecular weight.[12] Polymerization of vinyl fluoride in the presence of lithium salts of the ionic liquid anions (trifluoromethylsulfonyl imide, triflate, and trifluoroacetate) resulted in high vinyl fluoride conversion and production of high molecular weight polymer at low vinyl fluoride pressures.[12]

REFERENCES

1 Profile of the Aerospace Industry. EPA Office of Compliance Sector Notebook Project. US Environmental Protection Agency. November 1998.
2 R W Blackford, *Surf. Coat. Int*., **80**, No.12, 564-7 (1997).
3 R Blackford, *Polym. Paint Colour J.*, **186**, No.4377, 22-4 (1996).
4 Anon. Case study in solvent degreasing for precision aerospace parts, *Metal Finishing*, **110**, 6, 50-51 (2012)
5 H M S Iqbal, S Bhowmik, R Benedictus, Interntl. J. Adhesion Adhesives, **48**, 188-93 (2014).
6 R Boghossian, **US20130296489**, 7 Nov. 2013.
7 Y-S Wang, **EP2627710**, *Hexcel Corporation*, 21 Aug. 2013.
8 B R Decaire, R Hulse, D Mercier, K D Cook, **WO2013096742**, *Honeywell International Inc*., 27 Jun. 2013.
9 E D Lally, R J Menke, **EP1179041**, *The Boeing Company*, 20 Feb. 2008.
10 F Tran, **WO2012015604**, *Huntsman Advanced Materials Americas Llc*, 2 Feb. 2012.
11 M. Morris, K. Wolf, **Development of safer cleaning alternatives in the aerospace, printing, and coating industries**. *EPA*, 2004.
12 B. D. Mather, N. M. Reinartz, M. B. Shiflett, *Polymer*, **82**, 295-304, 2016.

13.3 ASPHALT COMPOUNDING

George Wypych
ChemTec Laboratories, Toronto, Canada

Numerous construction products are formulated from asphalt and coal tar for such applications as driveway sealers, cutback asphalts, flashing cement, concrete primers, concrete cold mixes, roof cement, expansion joint fillers, patch liquids, waterproofing liquid-applied membranes, and pipeline coatings. All these products are likely to contain solvents.

The simplest formulations are mixtures of asphalt and (usually) mineral spirits used for sealing, priming, and coating of concrete. These are usually very low-performance products which are used in large quantities because of their low price. They release about 40% of their weight to the atmosphere during and after application. Since they do not perform well they have to be re-applied at frequent intervals. Driveway sealer is an example of a product which is used every spring, in spite of the fact that, in addition to the pollution it causes, it also produces a gradual degradation and cracking of the driveway. The only solution for elimination of this unnecessary pollution seems to be banning the product by regulation. Some of these products can be replaced by asphalt emulsions which contain water in place of organic solvents.

Several products are used for patching and joint filling purposes. These materials (flashing cement, roof cement, patch liquid, and expansion joint filler) also use solvents to regulate viscosity. The solvents are usually mineral spirits, fuel oil, or polycyclic aromatic hydrocarbons. In addition to the base components, inexpensive fillers such as calcium carbonate or limestone but also still asbestos (**!** Russia, China, Brazil, Kazakhstan, India; China used 570,000 tons in 2013; at the 2015 Rotterdam Convention aiming to ban asbestos, held in Geneva, Switzerland, seven nations voted against adding chrysotile to the list: Cuba, India, Kazakhstan, Kyrgyzstan, Pakistan, Russia and Zimbabwe; in 2017 Russia and China were leading in production of asbestos) are added. These products harden on evaporation of the solvent and fill the joints, adhere to surfaces, and provide some waterproofing. These are again, low technology materials, traditionally used because of their very low cost. Most of these products can be replaced by modern sealants which will result in higher initial cost but longer service life.

The most technologically advanced products are used for waterproofing and pipeline coatings. These products are also based on the dispersion of asphalt in the above-mentioned solvents but reinforced by the addition of polymer. The addition of polymer modifies the plastic behavior of asphalt and renders it elastomeric. Additional solvents are usually added to improve the solubility of polymeric components. Reactive polyurethanes are the most frequently used modifiers for waterproofing liquid membranes. Toluene and xylene are the most frequently used additional solvents. These materials partially solidify because of evaporation of the solvent. Their elastomeric properties are derived from chain extension and crosslinking reactions which form an internal polymeric network which reinforces asphalt.

There is no data available on the solvent emissions from these materials but their scale of production suggests that their emissions are probably comparable with the entire rubber industry. This is one industry which should be closely watched not only because of the emission of the above-listed solvents but because of some of the low-grade solvents used which contain large quantities of benzene and hexane. It is also cause for concern that asphalt and tar have carcinogenic components.

Inventions[1-5] are driven by product improvement needs and environmental aspects of the application of these products. Janoski's patent[1] describes a product which is an anhydrous blend of polymer and asphalt and is substantially solvent-free. This technology shows that it is possible for an ingenious designer to produce low viscosity materials without using solvents but by selecting the appropriate type and concentration of bituminous materials, polyurethane components, and plasticizers.

In another invention,[2] a modifier is introduced to increase the adhesion of asphalt/water emulsions to aggregates. Emulsified asphalt is not so deleterious to the environment but its performance suffers from aggregate delamination. In yet another invention,[3] terpene solvent, which is a naturally occurring (but never at this high concentration), biodegradable material, was used to replace the mineral spirits, xylene, trichloroethane, toluene, or methyl ethyl ketone normally used in cutback formulations (cutback asphalt is a dispersion of asphalt in a suitable solvent to reduce viscosity and allow for cold application). The two other patents[4,5] discuss an improvement of high and low-temperature properties of asphalt with no special impact on the reduction of solvents used.

Solvent composition was developed to remove asphalt attached to rubber belt.[6] It contains water, toluene, ink cleaning agent, and lubricant.[6]

The hydrothermal water was utilized to recover asphalt from asphalt concrete in a batch-type reactor.[7] The recovery of asphalt from asphalt concrete permitted production of recycled fine aggregate having asphalt content smaller than 0.5%.[7]

In the roadwork sector, extraction is a crucial step of separation of the bituminous binder from the mineral matter in asphalt mixture or reclaimed asphalt using a chlorinated solvent.[8] The nature of solvent has a significant impact on the final properties of the recovered binder. The effect of extraction and binder recovery depends on the solubility of the binder in the solvent.[8] According to Hansen solubility parameters, the lowest relative energy difference parameters are for perchloroethylene, 1,1,1-trichloroethane, and xylene. This means that these solvents are the most compatible with bitumen.[8] There are no alternative products that are as effective as chlorinated solvents which represents a challenge to find a substitute for chlorinated products that meet the sustainability and economy criteria.[8]

Asphalt-based compositions that contain little or no VOCs (useful in roofing applications, including as plastic roofing cement, flashing cement, roof coatings, and primers) include asphalt, a VOC-free solvent, a surfactant, and clay. Suitable solvents include bio-oils (oils derived from soy, palm, rapeseed, canola, algae, or man-made oils). Preferred solvents include bio-oils such as soybean and blends of bio-oils. The asphalt and the solvent are blended together in a ratio of about 65:35 to about 70:30 parts asphalt to parts solvent.

REFERENCES

1 R J Janoski, **US Patent 5,319,008**, *Tremco, Inc*., 1994.
2 P Schilling, E Crews, **US Patent 5,772,749**, *Westaco Corporation*, 1998.
3 R W Paradise, **US Patent 5,362,316**, *Imperbel America Corporation*, 1994.
4 M P Doyle, J L Stevens, **US Patent 5,496,400**, *Vinzoyl Petroleum Co.*, 1996.
5 M P Doyle, **US Patent 5,749,953**, V*inzoyl Technical Services, LLC*, 1998.
6 **CN103131560**. 5 Jun. 2013.
7 R. I. H. D. T. Amoussou, H. Tanoue, M. Sasaki, M. Shigeishi, *Constr. Build. Mater.*, **125**, 1196-1204, 2016.
8 L. Ziyani, L. Boulangé, A. Nicolaï, V. Mouillet, *J. Cleaner Prod*., **161**, 53-68, 2017.
9 C. J. Luccarelli, D. Amicucci, **US20140373754**, Dec. 25, 2014.

13.4 BIOTECHNOLOGY

13.4.1 ORGANIC SOLVENTS IN MICROBIAL PRODUCTION PROCESSES

Michiaki Matsumoto, Sonja Isken, Jan A. M. de Bont
Division of Industrial Microbiology Department of Food Technology and Nutritional Sciences, Wageningen University, Wageningen, The Netherlands

13.4.1.1 Introduction

Solvents are not dominating compounds in the biosphere of our planet. Under natural conditions, their presence in appreciable amounts is restricted to the specific areas. Only a very limited number of solvents is of biological origin and some may reach higher concentrations in nature. The best-known example is ethanol. However, also butanol and acetone can be formed readily by microbes and locally high concentrations may occur. In fact, at the beginning of the 20th century, very large production facilities were in operation for the microbial production of butanol and acetone. Furthermore, terpenes are natural solvents that are produced mainly by plants and locally they can reach high concentrations. For instance, limonene is present in tiny droplets in the peel of oranges. All these solvents are toxic to microbial cells. Some others as higher hydrocarbons, that are present, for instance, in olive oil, are not toxic to microbes as will be discussed later.

With the advent of the chemical industry, this picture has changed dramatically. In polluted locations, microorganisms may be confronted with a large number of solvents at high concentrations. With a few exceptions only, it has turned out that microbes can be found that are able to degrade these compounds if their concentration is low. This degradative potential is not unexpected in view of trace amounts that may be present locally in the natural biosphere. But the exposure of cells to unnaturally high concentrations of these solvents usually leads to irreversible inactivation and finally to their death.

The chemical industry is largely based on solvent-based processes. But in biotechnological processes, the microbes usually are exploited in a water-based system. This approach is quite understandable in view of the preference of microbes for water and the problems solvents pose to whole cells. Solvents often are used to extract products from the aqueous phase but only after the production process has been completed. At this stage, damage to whole cells is obviously no longer relevant. In both, chemical industry and biotechnology, organic solvents have many advantages over water because of the nature of either product or substrate. Consequently, during the last decades, many possibilities have been investigated to use solvents in biocatalytic processes.[1,2] The more simple the biocatalytic system, the less complex it is to use solvents.

Free or immobilized enzymes have been exploited already in a number of systems. Here, biocatalysis may take place in reversed micelles or in an aqueous phase in contact with an organic solvent.[3] In a powdered state, some enzymes are able to function in pure organic solvents.[4] Furthermore, modified enzymes such as polymer bound enzymes[5] or surfactant-coated enzymes[6] have been developed so that they can solubilize in organic sol-

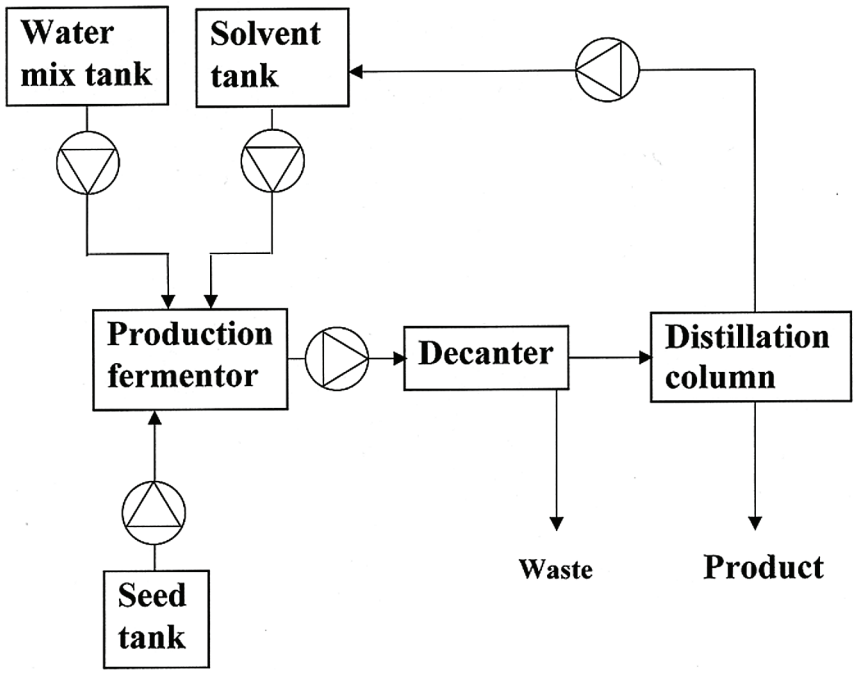


Fig.13.4.1.1. Schematic diagram of a two-phase bioreactor system for continuous 1-octanol production. 1-Octanol is produced from n-octane in hexadecene by *Pseudomonas oleovorans* or recombinant strains containing the alkane oxidation genes. [Adapted, by permission, from R.G. Mathys, A. Schmid, and B. Witholt, *Biotechnol. Bioeng*., **64**, 459 (1999).]

vents to overcome diffusion limitation. The advantages of enzymatic reactions using organic solvents can be briefly summarized as follows:[1,3,4]

1. hydrophobic substances can be used
2. synthetic reactions can take place
3. substrate or production inhibition can be diminished and
4. bioproducts and biocatalysts can easily be recovered from the systems containing organic solvents.

Although organic solvents have often been used in enzymatic reactions, the application of organic solvents for biotransformation with whole-cell systems is still limited. Cells might be continuously in direct contact with the organic phase in a two-phase water-solvent system during the whole production cycle (Figure 13.4.1.1).[7] Alternatively, cells may remain separated from the bulk organic phase by using membrane bioreactors (Figure 13.4.1.2).[8] In these instances, cells encounter phase toxicity[9] or molecular toxicity, respectively.

Because whole bacterial cells are more complex than enzymes, they pose far greater problems in operating bioproduction processes when organic solvents are present. The most critical problem is the inherent toxicity of solvents to living organisms.[1,2,10,11] As

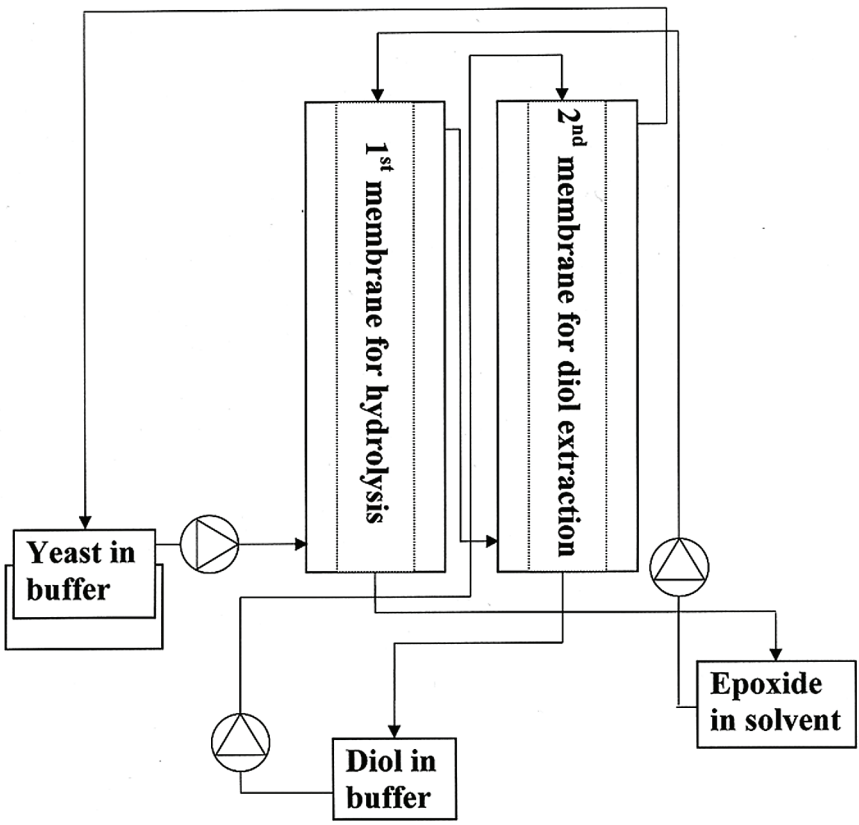


Fig.13.4.1.2. Schematic diagram of a two-phase hollow-fiber membrane bioreactor system for hydrolytic epoxide resolution.The yeast cells contain an epoxide hydrolase that enantioselectively hydrolyzes racemic epoxide resulting in enantiopure epoxide that partitions to the organic phase. Diol produced partitions to the water phase. [Adapted, by permission, from W.Y. Choi, C.Y. Choi, J.A.M. de Bont, and C.A.G.M. Weijers, *Appl. Microbiol. Biotechnol.*, **53**, 7 (1999).]

some solutions have been already found in this area, further progress is expected in the near future. A key problem is the selection of useful solvents in combination with a suitable microbe. Many solvents may be considered with their specific process properties, and many microorganisms may be considered also with their specific advantages or disadvantages. Only on the basis of a detailed understanding of the functioning of a microbial cell in the presence of solvents will it be possible to make a rational selection for a good combination solvent/organism. In the following section, we will discuss these key questions. We will also describe recently found solvent-tolerant bacteria and will provide some examples of biotransformation using solvent-tolerant bacteria.

13.4.1.2 Toxicity of organic solvents

The toxicity of an organic solvent is closely related to its hydrophobicity, as expressed by the $\log P_{O/W}$ values,[12-16] the logarithm of the partition coefficient of the solvent between 1-

octanol and water (Table 13.4.1). In general, the Gram-negative bacteria show relatively higher solvent tolerances than the Gram-positive bacteria.[12,14] This may be caused by the difference in the composition of the cell envelope. Solvents with a high $logP_{O/W}$ resulted in the highest activities, but the range of $logP_{O/W}$ tolerated by an organism is dependent on the type of microorganism. In the following section, we will describe what happens in the cell in the presence of solvents.

Table 13.4.1. Relationship between the growth of a cell exposed to an organic solvent and the value of log PO/W of the solvent. [After reference 14**]**

Solvent	$logP_{O/W}$	1	2	3	4	5	6	7	8	9
dodecane	7.0	+	+	+	+	+	+	+	+	+
decane	6.0	+	+	+	+	+	+	+	+	–
nonane	5.5	+	+	+	+	+	+	+	+	–
n-hexyl ether	5.1	+	+	+	+	+	+	+	+	–
octane	4.9	+	+	+	+	+	+	+	+	–
isooctane	4.8	+	+	+	+	+	+	+	–	–
cyclooctane	4.5	+	+	+	+	+	+	–	–	–
diphenyl ether	4.2	+	+	+	+	+	–	–	–	–
n-hexane	3.9	+	+	+	+	+	–	–	–	–
propylbenzene	3.7	+	+	+	+	–	–	–	–	–
o-dichlorobenzene	3.5	+	+	+	–	–	–	–	–	–
cyclohexane	3.4	+	+	+	–	–	–	–	–	–
ethylbenzene	3.2	+	+	–	–	–	–	–	–	–
p-xylene	3.1	+	+	–	–	–	–	–	–	–
styrene	2.9	+	–	–	–	–	–	–	–	–
toluene	2.6	+	–	–	–	–	–	–	–	–
benzene	2.1	–	–	–	–	–	–	–	–	–

+, growth; –, no growth

1 – *Pseudomonas putida* IH-2000, 2 – *Pseudomonas putida* IFO3738, 3 – *Pseudomonas fluorescens* IFO3507, 4 – *Escherichia coli* IFO3806, 5 – *Achromobacter delicatulus* LAM1433, 6 – *Alcaligenes faecalis* JCM1474, 7 – *Agrobacterium, tumefaciens* IFO3058, 8 – *Bacillus subtilis* AHU1219, 9 – *Saccharomyces uvarum* ATCC26602.

Bar[9] suggested that the toxicity in two-phase systems was caused by both the presence of a second phase (phase toxicity) and solvent molecules which dissolved in the aqueous phase (molecular toxicity). Basically, both mechanisms are governed by the same principle in that the solvent accumulates in the microbial membrane. In the case of the direct contact between cells and pure solvent, the rate of entry of solvents in a membrane will be very high. If the solvent has to diffuse *via* water phase, then the accumulation in the membrane will be slower. This latter mechanism on the molecular toxicity has been

investigated in more detail.[17] In experiments with liposomes from *E. coli* and ten representative organic solvents labeled by ^{14}C under aqueous-saturating levels, it was found that solvents are accumulated preferentially in the cell membrane. The partition coefficients ($logP_{M/B}$) of the solvents between the model liposome membrane and buffer correlate with those ($logP_{O/W}$) in a standard 1-octanol-water system:[17]

$$logP_{M/B} = 0.97 \times logP_{O/W} - 0.64 \qquad [13.4.1.1]$$

The accumulation of an organic solvent in the membrane causes changes in the membrane structure. Organic solvents residing in the hydrophobic part of the membrane disturb the interactions between the acyl chains of the phospholipids. This leads to modification of membrane fluidity which eventually results in swelling of the bilayer.[10] In addition to this, the conformation of the membrane-embedded protein may be altered.[10] These changes in the integrity of the membrane also affect the membrane function.

The principal functions of the cytoplasmic membrane involve:

1. barrier function
2. energy transduction
3. formation of a matrix of proteins.

The disruption of lipid-lipid and lipid-protein interactions by the accumulation of organic solvents has a strong effect on the membrane's function as a selective barrier for ions and hydrophilic molecules. Permeability is of particular importance for protons because the leakage of protons directly affects the primary energy transducing properties of the membrane. The initial rates of proton influx in the absence and presence of different amounts of hydrocarbon were measured.[17] The permeability of protons increases with increasing amounts of hydrocarbon. Hence, leakage of protons occurs in the presence of organic solvents.[17] Not only the impairment of the barrier function is caused by the alterations that occur in the membrane structure when it interacts with organic solvents. It is well-known that the activities of the proteins embedded in the membrane are regulated by the membrane thickness, head group hydration, fluidity and fatty acid composition.[18,19] All these parameters are also known to be affected by the accumulation of organic solvents. The effects of solvents on these parameters were reviewed by Sikkema *et al.*[10]

13.4.1.3 Solvent-tolerant bacteria

As described in the previous section, the organic solvents with $1 < logP_{O/W} < 4$ are considered toxic to microorganisms. In 1989, Inoue and Horikoshi[21] found a toluene-tolerant *Pseudomonas putida* strain that grew in a two-phase toluene-water system ($logP_{O/W} = 2.5$ for toluene). This finding was surprising and went against the dominant paradigm at that time. Solvent tolerance was confirmed by other strains of *P. putida*[22-26] and by other representatives of the genus *Pseudomonas*.[27-30] Furthermore, solvent tolerance has been found in the strains of Gram-positive bacteria *Bacillus*,[31,32] *Rhodococcus*,[33] *Staphylococcus*,[53] and *Arthrobacter*.[53] The key question now is: How do solvent-tolerant bacteria overcome the toxic effects of organic solvents? Some of the possible mechanisms involved in solvent tolerance according to various researchers are shown in Fig.13.4.1.3.[32]

Current research on changes in the structure of the cytoplasmic membrane shows the involvement of:

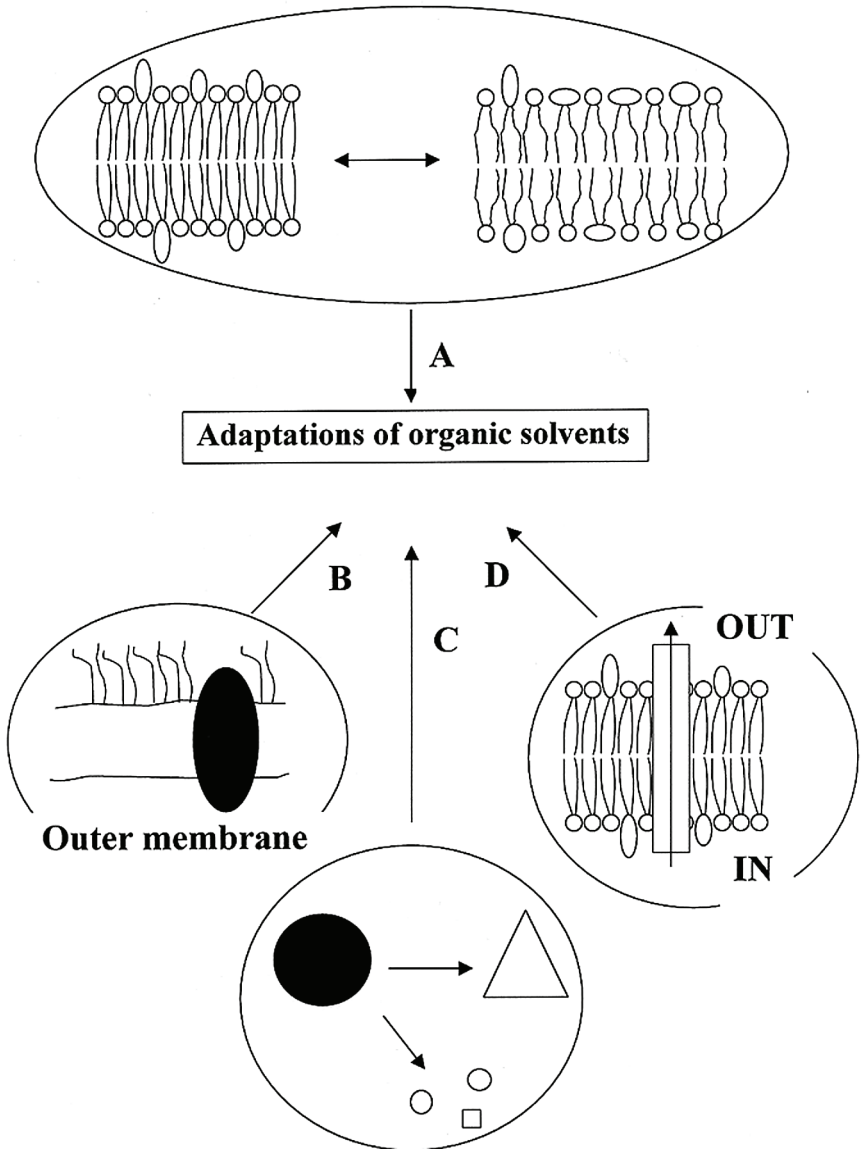


Figure 13.4.1.3 Schematic presentation of possible mechanisms of solvent tolerance. **A** Changes in the structure of cytoplasmic membrane. **B** Changes in the structure of outer membrane. **C** Transformation of the solvent. D Active export of the solvents. [Adapted, by permission, from S. Isken and J.A.M. de Bont, *Extremophiles*, **2**, 229 (1998).]

1. the composition of the fatty acids of the phospholipids like the *cis/trans* isomerization of unsaturated fatty acids
2. the composition of phospholipid headgroups

3. the rate of turnover of membrane components.

Organic solvents cause a shift in the ratio of saturated to unsaturated fatty acids.[34,35] In a solvent-tolerant strain, an increase in the saturation degree has been observed during adaptation to the presence of toluene. Solvent-tolerant strains also have the ability to synthesize *trans*-unsaturated fatty acids from the *cis*-form in response to the presence of organic solvents.[34,36-38] Increases in the saturation degree and the ratio of *trans*-form change the fluidity of the membrane and the swelling effects caused by solvents are depressed.

Alterations in the headgroups of lipids during the adaptation to solvents have also been observed in some solvent-tolerant strains.[37,39] The changes in the composition of the headgroups cause changes in the affinity of the lipids with the organic solvents and in the stability of membrane due to an alteration of bilayer surface charge density. These changes compensate the effect caused by solvents. In one strain, the rate of phospholipid synthesis increases after exposure to a solvent.[40] This strain has a repairing system which is faster than the rate of damage caused by the organic solvent.

Unlike Gram-positive bacteria, Gram-negative bacteria such as *Pseudomonas* have an outer membrane. The outer membrane has been shown to play a role in the protection of cell from solvent toxicity. Ions such as Mg^{2+} or Ca^{2+} stabilize the organization of the outer membrane and contribute to solvent tolerance.[38] Low cell surface hydrophobicity caused by changes in the lipopolysaccharide content has been reported to serve as a defensive mechanism.[41,42] It has also been reported that the porins which are embedded in the outer membrane are relevant to solvent tolerance.[37,42-44]

The metabolism of organic solvents in solvent-tolerant strains contributes to solvent tolerance by degradation of the toxic compounds. This contribution, however, is considered to be limited[33,45] because many solvent-tolerant strains show non-specific tolerance against various organic compounds.

Non-specific tolerance to toxic compounds is well known in the field of antibiotic resistance. A wide range of structurally dissimilar antibiotics can be exported out of the cell by multidrug-efflux pumps. Could the export of organic solvents contribute to solvent tolerance?

Isken and de Bont[46] conducted experiments to determine whether the solvent tolerant *Pseudomonas putida* S12 was able to export toluene by monitoring the accumulation of ^{14}C labeled toluene in the cells. Toluene-adapted cells were able to export toluene from their membranes whereas the non-adapted cells were not. Furthermore, it was observed that in the presence of energy coupling inhibitors, toluene accumulation was the same as in the non-adapted cells. The amount of toluene in the cell was concluded to be kept at a low level by an active efflux system. The presence of a toluene-efflux system is supported by genetic research.[47,48] The pump has a striking resemblance to multidrug-efflux systems. Active efflux pumps for solvents have also been detected in other *Pseudomonas* strains.[25,26,30,37]

It is obvious that solvent tolerance is caused by a combination of the mechanisms described above. Figure 13.4.1.4 shows a schematic picture of toluene penetration and efflux in the solvent tolerant strain *P. putida* S12.[20] Toluene enters the cell through the outer membrane. At present, it is unclear whether toluene passes through porins or

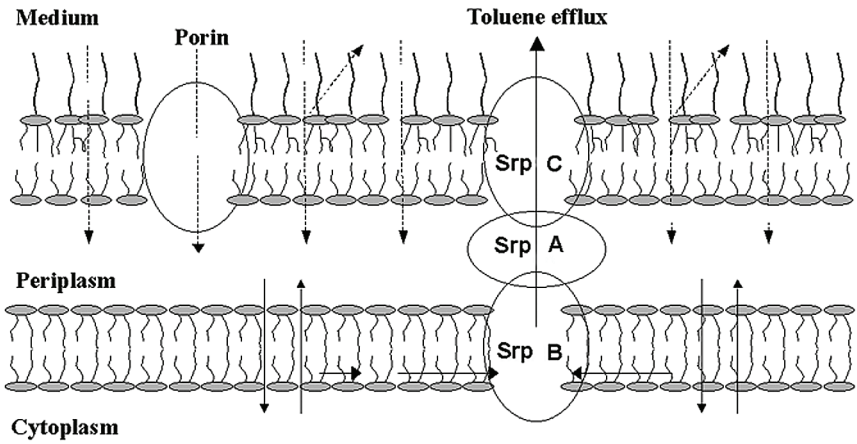


Figure 13.4.1.4. Schematic picture of toluene penetration and efflux in the solvent-tolerant *Pseudomonas putida* S12. [Adapted, by permission, from J.A.M. de Bont, *Trends Biotechnol.*, **16**, 493 (1998).]

through the phospholipid part of the cell. The efflux pump recognizes and interacts with toluene in the cytoplasmic membrane. Toluene is then pumped into the extracellular medium.

13.4.1.4 Biotransformation using solvent-tolerant microorganisms

Many important fine chemicals, including catechols, phenols, aldehydes and ketones, low molecular epoxides and diepoxides, medium-chain alcohols, and terpenoids fall within the range of $1 < \log P_{O/W} < 4$. The discovery of solvent-tolerant bacteria leads to the new possibility of biocatalytic reaction systems containing organic solvents. By using solvent-tolerant bacteria, a variety of fine chemicals can be formed in microbial production processes.

The organic solvents used so far in published research had to be very hydrophobic ($\log P_{O/W} > 5$) in order to prevent microbial inactivation.[1] Consequently, many fine chemicals cannot be beneficially produced in the presence of such solvents because they simply remain in the water phase and cannot partition to the organic phase. The use of solvent-tolerant microorganisms enables the use of less hydrophobic solvents ($2.5 < \log P_{O/W} < 4$) and in such a system, chemicals with a $1 < \log P_{O/W} < 4$ preferentially will go into the organic phase. Up to now, however, only a few applications using solvent-tolerant microorganisms have been reported.

Aono *et al.*[49] reported the oxidative bioconversion of cholesterol as a model biocatalytic reaction using a solvent-tolerant Pseudomonas species. Cholesterol and its products are insoluble in an aqueous solution but dissolve in some organic solvents. The attempt was successful. The conversion of cholesterol was more than 98% and the yield of oxidative products was 80%.

Speelmans *et al.*[50] reported on the bioconversion of limonene to perillic acid by a solvent-tolerant *Pseudomonas putida*. The microbial toxicity of limonene is known to be very high. It is a major component of citrus essential oil and is a cheap and readily avail-

able base material. By using a solvent-tolerant strain perillic acid was obtained at a high concentration. This finding brings commercial production nearer.

The applications of solvent-tolerant strains in microbial production processes are at present limited, but two strategic options are currently available to use such bacteria.[20] Relevant genes can be introduced into solvent-tolerant organisms in order to produce the required product. This approach has been followed successfully by J. Wery in our laboratory who employed an 1-octanol-aqueous system. Methylcatechol was produced from toluene by solvent tolerant *P. putida* S12. Alternatively, the efflux pump can be expressed in a suitable solvent-sensitive host which would then be more tolerant of a particular solvent.

Other benefits may arrive from solvent-resistant bacteria. Ogino *et al*.[26] isolated *Pseudomonas aeruginosa* LST-03 which can grow in organic solvents with $\log P_{O/W} > 2.4$ and secrets organic solvent-stable lipolytic enzymes. They were able to purify an organic solvent-stable protease which was more stable than the commercially available proteases.[51] Hence, solvent-tolerant strains have become a source for new enzymes.[52]

In the near future, the use of solvent-tolerant strains will make the application of organic solvents in biotransformations by whole cells a more realistic option.

REFERENCES

1 R.A Sheldon, *Green Chem.*, **7**, 267 (2005).
2 A. Illanes, A. Cauerhff, L. Wilson, and G.R. Castro, *Bioresource Technol.*, **115**, 48 (2012).
3 N, Doukyu and H. Ogino, *Biochem. Eng. J.*, **48**, 270 (2010).
4 A.M. Klibanov, *Trends Biotechnol*., **15**, 97 (1997).
5 Y. Inada, A. Matsushima, M. Hiroto, H. Nishimura, and Y. Kodera, *Methods Enzymol*., **242**, 65 (1994).
6 Y. Okahata, Y. Fujimoto, and K. Iijiro, *J. Org. Chem*., **60**, 2244 (1995).
7 R.G. Mathys, A. Schmid, and B. Witholt, *Biotechnol. Bioeng*., **64**, 459 (1999).
8 W.Y. Choi, C.Y. Choi, J.A.M. de Bont, and C.A.G.M. Weijers, *Appl. Microbiol. Biotechnol.*, **53**, 7 (1999).
9 R. Bar, *J. Chem. Technol. Biotechnol.*, **43**, 49 (1988).
10 J. Sikkema, J.A.M. de Bont, and B. Poolman, *Microbiol. Rev*., **59**, 201 (1995).
11 M.D. Lilly and J.M. Woodley, in *Biocatalysis in organic synthesis*, J. Tramper, H.C. van der Plas, and P. Linko, Ed., *Elsevier*, Amsterdam, 1985, pp.179-192.
12 M. Vermuë, J. Sikkema, A. Verheul, and J. Tramper, *Biotechnol. Bioeng*., **42**, 747 (1993).
13 S.D. Doig, A.T. Boam, D.J. Leak, A.G. Livingston, and D.C. Stuckey, *Biocatal. Biotransform*., **16**, 27 (1998).
14 A. Inoue and K. Horikoshi, *J. Ferment. Bioeng*., **71**, 194 (1991).
15 A.J. Harrop, M.D. Hocknull, and M.D. Lilly, *Biotechnol. Lett.*, **11**, 807 (1989).
16 A.N. Rajagopal, *Enz. Microb. Technol.*, **19**, 606 (1996).
17 J. Sikkema, J.A.M. de Bont, and B. Poolman, *J. Biol. Chem*., **269**, 8022 (1994).
18 H. Sandermann, Jr., *Biochim. Biophys. Acta*, **515**, 209 (1978).
19 P.L. Yeagle, *FASEB J*., **3**, 1833 (1989).
20 J.A.M. de Bont, *Trends Biotechnol.*, **16**, 493 (1998).
21 A. Inoue and K. Horikoshi, *Nature*, **338**, 264 (1989).
22 D.L. Cruden, J.H. Wolfram, R.D. Rogers, and D.T. Gibson, *Appl. Environ. Microbiol*., 58, 2723 (1992).
23 F.J. Weber, L.P. Ooykaas, R.M.W. Schemen, S. Hartmans, and J.A.M. de Bont, *Appl. Environ. Microbiol*., **59**, 3502 (1993).
24 J.L. Ramos, E. Deque, M.J. Huertas, and A. Haïdour, *J. Bacteriol*., **177**, 3911 (1995).
25 K. Kim, S.J. Lee, K.H. Lee, and D.B. Lim, *J. Bacteriol.*, **180**, 3692 (1998).
26 F. Fukumori, H. Hirayama, H. Takami, A. Inoue, and K. Horikoshi, *Extremophiles*, **2**, 395 (1998).
27 H. Nakajima, H. Kobayashi, R. Aono, and K. Horikoshi, *Biosci. Biotechnol. Biochem*., **56**, 1872 (1992).
28 H. Ogino, K. Miyamoto, and H. Ishikawa, *Appl. Environ. Microbiol.*, **60**, 3884 (1994).
29 Y. Yoshida, Y. Ikura, and T. Kudo, *Biosci. Biotechnol. Biochem*., **61**, 46 (1997).
30 X.Z. Li, L. Zhang, and K. Poole, *J. Bacteriol.*, **180**, 2987 (1998).
31 K. Moriya and K. Horikoshi, *J. Ferment. Bioeng*., **76**, 397 (1993).
32 S. Isken and J.A.M. de Bont, *Extremophiles*, **2**, 229 (1998).

33 M.L. Paje, B.A. Neilan, and I. Couperwhite, *Microbiology*, **143**, 2975 (1997).
34 F.J. Weber, S. Isken, and J.A.M. de Bont, *Microbiology*, **140**, 2013 (1994).
35 H.C. Pinkart, J.W. Wolfram, R. Rogers, and D.C. White, *Appl. Environ. Microbiol.*, **62**, 1129 (1996).
36 H.J. Heipieper, G. Meulenbeld, Q. van Oirschot, and J.A.M. de Bont, *Chemosphere*, **30**, 1041 (1995).
37 J.L. Ramos, E. Duque, J.J. Rodriguez-Herva, P. Godoy, A. Haidour, F. Reyes, and A. Fernandez-Barrero, *J. Biol. Chem*., **272**, 3887 (1997).
38 F.J. Weber and J.A.M. de Bont, *Biochim. Biophys. Acta*, **1286**, 225 (1996).
39 V. Pedrotta and B. Witholt, *J. Bacteriol*., **181**, 3256 (1999).
40 H.C. Pinkart and D.C. White, *J. Bacteriol.*, **179**, 4219 (1997).
41 R. Aono and H. Kobayashi, *Appl. Environ. Microbiol.*, **63**, 3637 (1997).
42 H. Kobayashi, H. Takami, H. Hirayama, K. Kobata, R. Usami, and K. Horikoshi, *J. Bacteriol*., **181**, 4493 (1999).
43 L. Li, T. Komatsu, A. Inoue, and K. Horikoshi, *Biosci. Biotechnol. Biochem*., **59**, 2358 (1995).
44 H. Asano, K. Kobayashi, and R. Aono, *Appl. Environ. Microbiol.*, **65**, 294 (1999).
45 G. Mosqueda, M.-S. Ramos-González, and J.L. Ramos, *Gene*, **232**, 69 (1999).
46 S. Isken and J.A.M. de Bont, *J. Bacteriol.*, **178**, 6056 (1996).
47 J. Kieboom, J.J. Dennis, G.J. Zylstra, and J.A.M. de Bont, *J. Biol. Chem.*, **273**, 85 (1998).
48 J. Kieboom, J.J. Dennis, G.J. Zylstra, and J.A.M. de Bont, *J. Bacteriol.*, **180**, 6769 (1998).
49 R. Aono, N. Doukyu, H. Kobayashi, H. Nakajima, and K. Horikoshi, *Appl. Environ. Microbiol*., **60**, 2518 (1994).
50 G. Speelmans, A. Bijlsma, and G. Eggink, *Appl. Microbiol. Biotechnol*., **50**, 538 (1998).
51 H. Ogino, F. Watanabe, M. Yamada, S. Nakagawa, T. Hirose, A. Noguchi, M. Yasuda, and H. Ishikawa, *J. Biosci. Bioeng*., **87**, 61 (1999).
52 N. Doukyu and R. Aono, *Appl. Environ. Microbiol*., **64**, 1929 (1998).
53 S. Torres, A. Pandey, and G.R. Castro, *Biotechnol. Adv*., **29**, 442 (2011).

13.4.2 SOLVENT-RESISTANT MICROORGANISMS

Tilman Hahn, Konrad Botzenhart
Institut für Allgemeine Hygiene und Umwelthygiene, Universität Tübingen, Tübingen, Germany

13.4.2.1 Introduction

Several main properties of microorganisms in relation to solvents can be considered:

- Toxic or antimicrobial effects of solvents
- Solvent resistance or adaptation of microorganisms
- Metabolic activities of microorganisms

Antimicrobial effects or solvent-resistant microorganisms are the main topics of this section.

13.4.2.2 Toxicity of solvents for microorganisms

13.4.2.2.1 Spectrum of microorganisms and solvents

The growth-inhibiting effects of several solvents on microorganisms are described.[1,2] Organic solvents have a toxic effect on microorganisms. Table 13.4.2.1 summarizes the relevant organic solvents and their toxicity concerning selected microorganisms.

Table 13.4.2.1. Toxicity of organic solvents – examples

Solvent	Microorganism	References
Toluene, benzene, ethylbenzene, propylbenzene, xylene, hexane, cyclohexane	*Pseudomonas putida*	Isken *et al*. (1999)[3] Gibson *et al.* (1970)[4]
Terpenes, e.g., α-pinene, limonene, β-pinene, terpinolene	*Bacillus sp., Saccharomyces cerevisiae,* isolated mitochondria	Andrews *et al*. (1980)[5] Uribe *et al.* (1985)[6]
Styrene	soil microorganisms	Hartmans *et al.* (1990)[7]
Cyclohexane	yeast cells, isolated mitochondria	Uribe *et al*. (1990)[8]
Aromatic hydrocarbons	isolated bacterial and liposomal membranes	Sikkema *et al*. (1992)[9] Sikkema *et al.* (1994)[1]
Ethanol	yeasts	Cartwright *et al*. (1986)[10] Leao and van Uden (1984)[11]

13.4.2.2.2 Mechanisms of solvent toxicity for microorganisms

The toxicity of organic solvents or hydrophobic substances for microorganisms depends mainly on their effects on biological membranes[1,9,12-14] – similar to membrane effects of several anesthetics. This concerns especially effects on cytoplasmatic membranes. The following main changes of membrane structures and functions have been observed:

- Accumulation of hydrophobic substances such as organic solvents in cytoplasmatic membranes. This accumulation causes structural and functional changes in the cytoplasmatic membranes and microbial cells.
- Structural changes in cytoplasmatic membranes, e.g., swelling of membrane bilayers, an increase of surface and thickness of the membranes, changes in the

composition of the membrane (e.g., changes in the fatty acid composition), modification of the microviscosity, damage of membrane structures (see below).

- Loss of membrane integrity, especially disruption of cytoplasmatic membranes, less damage to outer membranes. Because of these damages often complex cellular structures (e.g., vesicula) or cell functions (decrease of respiratory activities of mitochondria) are destroyed or inhibited.
- Interactions of the accumulated lipophilic substances with the cytoplasmatic membranes and especially hydrophobic parts of the cell or cell membranes. Lipid-lipid interactions and interactions between proteins and lipids of the membrane structure (lipid bilayers, membrane-embedded proteins) are discussed.
- Effects on passive and active membrane transport systems, e.g., increase of passive efflux and flux of ions such as protons, cations Mg^{++} and Ca^{++} or small molecules, stimulation of the leakage of protons and potassium, changes in the uptake of compounds (e.g., solvents) and excretion (e.g., metabolic products), inhibition of active transport systems (e.g., ATP depletion).
- Damage of cellular homeostasis and cell physiology, e.g., reduction of transmembrane electrical potentials and proton chemical potentials or proton motive forces as a result of membrane changes (efflux of ions), changes of pH gradients.
- Changes in enzyme activities, e.g., inhibition of oxidases and depletion of ATP. Of special relevance are various interactions with enzymes (proteins) in the membrane, e.g., lipid-protein interactions.
- Loss of particular cellular functions, e.g., respiratory system of mitochondria or active transport systems (see above).
- Loss of complex cell functions, e.g., reduced growth rates and activities of microorganisms.

The extent of solvent toxicity to microorganisms is determined by various factors:

(a) Hydrophobic or lipophilic properties of solvents. The toxicity of solvents to microorganisms can be described by a partition coefficient ($\log P_{O/W}$) between organic compounds (solvents) and water which is specific to the applied substance. This partition coefficient is based on a standard octanol-water system model.[1,15,16]

The toxicity and the affinity of solvents to cell structures increase with hydrophobic properties of solvents, e.g., high toxicities with $P_{O/W}$ values of 1-5.[1,14] The partition coefficient correlates with the membrane-buffer partition coefficient between the membrane and aqueous system.[1,14,16] They also depend on membrane characteristics.[17,18]

(b) Accumulation, partitioning, and concentrations of solvents in cell structures (membranes). Dissolution and partitioning of solvents depend essentially on solvent properties, e.g., polarity (specific partition coefficients), or membrane characteristics (influence on partition coefficients). Both dissolution and partitioning can be influenced by additional factors, e.g., cosolvents. The effects on microorganisms can depend typically on solvent concentrations, e.g., dose-response effects.

(c) Biomass, ratio of concentrations of solvents and biomass. Effect of solvents depends on this ratio.

(d) Surrounding conditions, e.g., temperature which influences the proton leakage and microbial activities.[19]

The toxicity of solvents for microorganisms shows positive and negative consequences, e.g.:

- Positive aspects such as antibacterial effects[20] which are found in several products.
- Negative aspects such as reduced stability of biotransformation and bioremediation processes because of the inactivation of microorganisms.

13.4.2.3 Adaption of microorganisms to solvents – solvent-resistant microorganisms

13.4.2.3.1 Spectrum of solvent-resistant microorganisms

Different microorganisms are able to adapt and even to grow in the presence of solvents. Some relevant examples are given in Table 13.4.2.2.

Table 13.4.2.2. Solvent-tolerant microorganisms and their resistance to organic solvents

Solvent-tolerant microorganisms	Solvents	References
bacteria from deep sea (1.168 m, Japan)	benzene, toluene, p-xylene, biphenyl, naphthalene	Abe *et al*. (1995)[21]
deep sea isolates, *Flavobacterium* strain DS-711, *Bacillus* strain DS-994	hydrocarbons	Fukamaki *et al*. (1994)[23]
marine yeasts	n-alkanes	Fukamaki *et al*. (1994)[23]
Pseudomonas putida	toluene, m-, p-xylene, 1,2,4-trimethylbenzene, 3-ethyltoluene	Inoue and Horikoshi (1989)[24] Cruden *et al*. (1992)[25]
Pseudomonas sp.	α-pinene	Sikkema *et al*. (1995)[14]
E. coli K-12	p-xylene	Aono *et al*. (1991)[26]
Brevibacillus brevis	trichloroethylene	Moreno *et al*. (2009)[59]
Meiothermus sp. I40 (solvent-resistant keratinase)	dimethyl sulfoxide, ethanol, isopropanol, and acetonitrile	Kuo *et al*. (2012)[60]
Bacillus subtilis, Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa	deep eutectic solvents	Hayyan *et al*. (2013)[61]

The concentration of organic solvents which can be tolerated by the microorganisms varies extensively, e.g., growth of *Pseudomonas putida* in the presence of more than 50% toluene[27] but tolerance of *E. coli* K-12 in the presence of only up to 10% p-xylene.[26]

The tested deep eutectic solvents were not toxic to the studied bacteria (*Bacillus subtilis, Staphylococcus aureus, Escherichia coli,* and *Pseudomonas aeruginosa*) confirming their benign effects on these bacteria.[61] The cytotoxicity of deep eutectic solvents was much higher than their individual components (e.g. glycerine, choline chloride) indicating that their toxicological behavior is different.[61] The toxicity and cytotoxicity of deep eutectic solvents varied depending on the structure of components.[61]

The growth characteristics of different species can differ to a great extent, e.g., no growth, growth with or without metabolizing solvents. Generally higher solvent tolerance of Gram-negative bacteria compared to Gram-positive bacteria is observed.[28] Some solvent-tolerant microorganisms cannot use organic solvents as a substrate for growth and

need other substrates in complex media.[26,27] Other microorganisms can use organic solvents in minimal media as a source of energy or carbon, e.g., *Pseudomonas putida* in the presence of xylene or toluene.[25]

13.4.2.3.2 Adaption mechanisms of microorganisms to solvents

The mechanisms of solvent tolerance are only partially known.[29-31] Relevant microbial adaptation mechanisms are:

- *Changes in the composition of the cytoplasmatic membran*e. The compounds of the membranes such as lipids or proteins can influence the membrane characteristics and, therefore, the adaption to solvents. Mainly phospholipids in the membrane bilayer determine the partitioning of solutes and especially the resistance to solvents.[17,18] A reduction of the partition coefficient has been observed when the fatty acid composition was changed.[32] An increase of monounsaturated fatty acids and a decrease of saturated fatty acids correlated with a higher ethanol tolerance of *S. cerevisiae, E. coli*, and *Lactobacillus* strains.[33-35] An increase of unsaturated fatty acids is induced by polar solvents and low temperatures, an increase of saturated fatty acids is connected with more apolar solvents and high temperatures.[36] Even changes in the configuration of fatty acids, which are provoked by solvents, can lead to adaption mechanisms, e.g., *cis-trans* conversions.[29]
- *Changes in the microbial structure*. Various structural changes can cause a reduction of toxic solvent effects, e.g., the increase of membrane fluidity which is connected with an increase of unsaturated fatty acids (see above) and results in a decrease of the membrane permeability.
- *Specific structural characteristics of microorganisms*. Typical structures of microorganisms vary according to the microbial species, e.g., outer membrane characteristics of bacteria. For instance, Gram-negative bacteria such as *Pseudomonas sp.* tolerate higher concentrations of hydrophobic compounds compared to Gram-positive bacteria. The resistance of the outer membrane correlates with the solvent-tolerance.[28]
- *Alterations of the cell envelope structure (cell wall)*. Mechanical alterations and chemical modifications of the cell wall can reduce the microbial resistance to solvents. The most interesting chemical modification concerns hydrophobic or hydrophilic abilities of the cell wall.[37] Decreasing hydrophobicity of the cell wall enhances the adaption of microorganisms to solvents.[38]
- *Suppression of the effects of solvents on membrane stability*. – Limitation of solvent diffusion into the cell (see above).
- *Repairing mechanisms e.g. enhanced phospholipid biosynthesis*.
- *Limitation of solvent diffusion into the cell (see above)*.
- *Transport or export systems*. The excretion of compounds out of the microbial cell and the cytoplasmatic membrane is well known but only documented for some substances, e.g., for drugs.[39] Passive and active transport systems are relevant, e.g., ATP driven systems. Export systems for the several solvents must be assumed.

- *Immobilization and mobilization of microorganisms and solvents*. The adsorption of solvents to microorganisms can be reduced if the contact is decreased. For instance, immobilization of microorganisms or solvents minimizes the contact. An immobilization and reduction of toxicity was shown if adsorption materials were added.[40]
- *Surrounding conditions*, e.g., low temperature, which can induce higher solvent resistance of microorganisms (see above).

13.4.2.4 Solvents and microorganisms in the environment and industry – examples

Microorganisms frequently observed in organic-aqueous systems containing solvents are essential in natural and in industrial processes. The occurrence and role of microorganisms and organic compounds in these two-phase organic-aqueous systems are similar to the effects described above (see Section 13.4.2.2). Although toxic effects on microorganisms in these natural and industrial processes are well known, reliable data concerning solvent-resistant microorganisms are not available.

13.4.2.4.1 Examples

13.4.2.4.1.1 Biofilms, biofouling, biocorrosion

Important examples for organic-aqueous systems are surface-associated biofilms which are a form of existence of microorganisms. Microorganisms, mostly bacteria, are embedded into a glycocalyx matrix of these biofilms.[41,42] This biofilm matrix mediates the adhesion of microorganisms to surfaces, concentrates substances and protects microorganisms from antimicrobial agents.[41,42] Several organic-aqueous systems can be observed, especially surface of surrounding materials (pipes, etc.) in relation to water or ingredients (e.g., oil in pipes) related to water between ingredients and surrounding materials (pipes, etc.).

Some aspects of solvents in these organic-aqueous biofilm systems are studied. Solvents can occur in water systems emitted from surrounding organic materials.[43] It was shown that solvents are important concerning microbial biocorrosion and biofouling processes, e.g., by swelling and hydrolysis of materials.[44]

Despite these well-known aspects, reliable data and studies concerning solvent-resistant microorganisms in biofilm, biofouling, or biocorrosion processes are not shown. Nevertheless, similar mechanisms in biofilms must be assumed as described above (see Section 13.4.2.3) because similar conditions occur (organic-aqueous systems).

13.4.2.4.1.2 Antimicrobial effects, microbial test systems

The toxic mechanisms of solvents to microorganisms described above (see Section 13.4.2.2) are frequently used in effects of antimicrobial agents.

The damage of microbial biomembranes is fundamentally connected with the antimicrobial effects of several solvents on bacteria.[45] Biomembranes and other microbial structures can be affected by solvents *via* similar processes as described. Relevant examples are naked viruses which are generally less resistant to solvents because the envelopes of viruses are damaged by some solvents. Another example of solvent-like interactions are effects of antimicrobial agents to capsules of bacterial spores, e.g., *Bacillus* species.

Bacterial or enzymatic toxicity tests are used to assay the activity of organic compounds including solvents. A survey of environmental bacterial or enzymatic test systems is given by Bitton and Koopman.[46] The principles of these test systems are based on bacte-

rial properties (growth, viability, bioluminescence, etc.) or enzymatic activities and biosynthesis. The toxicity of several solvents was tested in bacterial or enzymatic systems, e.g., pure solvents such as phenol in growth inhibition assays (*Aeromonas sp.*),[46] solvents in complex compounds such as oil derivatives,[46,47] solvents in environmental samples such as sediments or solvents used in the test systems.[46,48,49] The efficiency of several test systems, e.g., Microtox tests or ATP assays, vary, e.g., looking at the effects of solvents.[46]

13.4.2.4.1.3 Industrial processes

In industrial processes the main microbial activities connected with solvents are:

- Processes in biotechnology, biotransformation, and biocatalysis,[50,51] e.g., production of chemicals from hydrophobic substrates or use of solvents as starting materials for microbiological reactions.
- Bioremediation: degradation of environmental pollutants, e.g., wastewater treatment or bioremediation in biofilm reactors.[52-55]

Various microorganisms and microbial mechanisms are relevant in these industrial processes. Examples are conversion processes of organic substances, e.g., by bacterial oxygenases.[56,57] Normally low-molecular-weight aromatic hydrocarbons including solvents are converted in these biotransformation processes.[58]

REFERENCES

1 J. Sikkema, J.A.M. de Bont, B.Poolman, *J. Biol. Chem*., **269**, 8022 (1994).
2 G.J. Salter, D.B. Kell, *Crit. Rev. Biotechnol*., **15**, 139 (1995).
3 S. Isken, A. Derks, P.F.G. Wolffs, J.A.M. de Bont, *Appl. Environ. Microbiol*., **65**, 2631 (1999).
4 D.T. Gibson, G.E. Cardini, F.C. Maseles, R.E. Kallio, *Biochemistry*, **9**, 1631 (1970).
5 R.E. Andrews, L.W. Parks, K.D. Spence, *Appl. Environ. Microbiol*., **40**, 301 (1980).
6 S. Uribe, J. Ramirez, A. Pena, *J. Bacteriol.*, **161**, 1195 (1985).
7 S. Hartman, M.J. van der Werf, J.A.M. de Bont, *Appl. Environ. Microbiol*., **56**, 1347 (1990).
8 S. Uribe, P. Rangel, G. Espinola, G. Aguirre, *Appl. Environ. Microbiol*., **56**, 2114 (1990).
9 J. Sikkema, B. Poolman, W.N. Konings, J.A.M. de Bont, *J. Bacteriol*., **174**, 2986 (1992).
10 C.P. Cartwright, J.R. Juroszek, M.J. Beavan, F.M.S. Ruby, S.M.F. DeMorais, A.H. Rose, *J. Gen. Microbiol*., **132**, 369 (1986).
11 C. Leao, N. van Uden, *Biochim. Biophys. Acta*, **774**, 43 (1984).
12 M.J. DeSmet, J. Kingma, B. Witholt, *Biochem. Biophys. Acta*, **506**, 64 (1978).
13 M.R. Smith in **Biochemistry of Microbial Degradation**, C. Ratledge, Ed, *Kluwer Academic Press*, Dordrecht, 1993, pp. 347-378.
14 J. Sikkema, J.A.M. de Bont, B. Poolman, B., *FEMS Microbiol. Rev*., **59**, 201 (1995).
15 A. Leo, C. Hansch, D. Elkins, *Chem. Rev*., 71, 525 (1971).
16 W.R. Lieb and W.D. Stein in **Transport and Diffusion Across Cell Membranes**, W.D. Stein, Ed., *Academic Press*, N.Y., 1986, pp. 69-112.
17 M.C. Antunes-Madeira, V.M.C. Madeira, *Biochim. Biophys. Acta,* **861**, 159 (1986).
18 M.C. Antunes-Madeira, V.M.C. Madeira, *Biochim. Biophys. Acta*, **901**, 61 (1987).
19 W. DeVrij, A. Bulthuis, W.N. Konings, *J. Bacteriol.*, **170**, 2359 (1988).
20 F.M. Harold, *Adv. Microb. Physiol.*, **4**, 45 (1970).
21 A. Abe, A. Inoue, R. Usami, K. Moriya, K. Horikoshi, *Biosci. Biotechnol. Biochem.*, **59**, 1154 (1995).
22 K. Moriya, K. Horikoshi, *J. Ferment. Bioeng.*, **76**, 168 (1993).
23 T. Fukamaki, A. Inoue, K. Moriya, K. Horikoshi, *Biosci. Biotechnol. Biochem*., **58**, 1784 (1994).
24 A. Inoue, K. Horikoshi, Nature, 338, 264 (1989).
25 D.L. Cruden, J.H. Wolfram, R. Rogers, D.T. Gibson, *Appl. Environ. Microbiol.*, **58**, 2723 (1992).
26 R. Aono, K. Albe, A. Inoue, K. Horikoshi, *Agric. Biol. Chem*., **55**, 1935 (1991).
27 A. Inoue, M. Yamamoto, K. Horikoshi, K., *Appl. Environ. Microbiol*., **57**, 1560 (1991).
28 A.J. Harrop, M.D. Hocknull, M.D. Lilly, *Biotechnol. Lett*., **11**, 807 (1989).
29 H.J. Heipieper, R. Diefenbach, H. Keweloh, *Appl. Environ. Microbiol*., **58**, 1847 (1992).
30 H.C. Pinkart, D.C. White, *J. Bacteriol.*, **179**, 4219 (1997).

31 J.L. Ramos, E. Duque, J. Rodriguez-Herva, P. Godoy, A. Haidour, F. Reyes, A. Fernandez-Barrero, *J. Biol. Chem*., **272**, 3887 (1997).
32 M.C. Antunes-Madeira, V.M.C., Madeira, *Biochim. Biophys. Acta*, **778**, 49 (1984).
33 P. Mishra, S. Kaur, *Appl. Microbiol. Biotechnol*., **34**, 697 (1991).
34 L.O. Ingram, *J. Bacteriol.*, **125**, 670 (1976).
35 K. Uchida, *Agric. Biol. Chem.*, **39**, 1515 (1975).
36 L.O. Ingram, *Appl. Environ. Microbiol.*, **33**, 1233 (1977).
37 V. Jarlier, H. Nikaido, *FEMS Microbiol. Lett*., **123**, 11 (1994).
38 Y.S. Park, H.N. Chang, B.H. Kim, *Biotechnol. Lett*., **10**, 261 (1988).
39 D. Molenaar, T. Bolhuis, T. Abee, B. Poolman, W.N. Konings, *J. Bacteriol*., **174**, 3118 (1992).
40 H. Bettmann, H.J. Rehm, *Appl. Microbiol. Biotechnol*., **20**, 285 (1984).
41 J.W. Costerton, *J. Ind. Microbiol. Biotechnol*., **22**, 551 (1999).
42 J.W. Costerton, *Int. J. Antimicrobial Agents*, **11**, 217 (1999).
43 K. Frensch, H.F. Scholer, D. Schoenen, *Zbl. Hyg. Umweltmed*., **190**, 72 (1990).
44 W. Sand, *Int. Biodeterioration Biodegradation*, **40**, 183 (1997).
45 K. Wallhäußer, **Praxis der Sterilisation, Desinfektion, Konservierung**, *Thieme Verlag*, Stuttgart, 1998.
46 G. Bitton, B. Koopman, *Rev. Environ. Contamin. Toxicol*., **125**, 1 (1992).
47 K.L.E. Kaiser, J.M. Ribo, *Tox. Assess*, **3**, 195 (1988).
48 B.J. Dutka, K.K. Kwan, *Tox. Assess*, **3**, 303 (1988).
49 M.H. Schiewe, E.G. Hawk, D.I. Actor, M.M. Krahn, Can. *J. Fish Aquat*., **42**, 1244 (1985).
50 O. Favre-Bulle, J. Schouten, J. Kingma, B. Witholt, *Biotechnology*, **9**, 367, 1991.
51 C. Laane, R. Boeren, R. Hilhorst, C. Veeger, in C. Laane, J. Tramper, M.D. Lilly, Eds., **Biocatalysis in organic media**, *Elsevier Publishers, B.V.,* Amsterdam, 1987.
52 C. Adami, R. Kummel, *Gefahrstoffe Reinhaltung Luft*, **57**, 365 (1997).
53 A.R. Pedersen, S. Moller, S. Molin, E. Arvin, *Biotechnol. Bioengn*., **54**, 131 (1997).
54 P.J. Hirl, R.L. Irvine, *Wat. Sci. Technol.,* **35**, 49 (1997).
55 M.W. Fitch, D. Weissman, P. Phelps, G. Georgiou, *Wat. Res*., **30**, 2655 (1996).
56 S.V. Ley, F. Sternfeld, S.C. Taylor, *Tetrahedron Lett*., **28**, 225 (1987).
57 G.M. Whited, W.R. McComble, L.D. Kwart, D.T. Gibson, *J. Bacterio*l., **166**, 1028 (1986).
58 M.R. Smith, *J. Bacteriol.*, **170**, 2891 (1990)
59 B. Moreno, A. Vivas, R. Nogales, E. Benitez, Excotoxicology Environ. Safety, 72, 8, 2109-2114, 2009.
60 J.-M. Kuo, J.-I. Yang, W.-M. Chen, M.-H. Pan, M.-L. Tsai, Y.-J. Lai, A. Hwang, B. S. Pan, C.-Y. Lin, *Int. Biodeter. Biodeg*., **70**, 111-6, 2012.
61 M. Hayyan, M. A. Hashim, A. Hayyan, M. A. Al-Saadi, I. M. AlNashef, M. E. S. Mirghani, O. K. Saheed, *Chemosphere*, **90**, 7, 2193-5, 2013.

13.4.3 CHOICE OF SOLVENT FOR ENZYMATIC REACTION IN ORGANIC SOLVENT

Tsuneo Yamane
Graduate School of Bio- and Agro-Sciences, Nagoya University, Nagoya, Japan

13.4.3.1 Introduction

The ability of enzymes to catalyze useful synthetic biotransformations in organic media is now beyond doubt. There are some advantages in using enzymes in organic media as opposed to aqueous medium, including

1. shifting the thermodynamic equilibrium to favor synthesis over hydrolysis,
2. reduction in water-dependent side reactions,
3. immobilization of the enzyme is often unnecessary (even if it is desired, merely physical deposition onto solid surfaces is sufficient),
4. elimination of microbial contamination,
5. suitable for reaction of substrates insoluble and/or unstable in water, etc.

Here organic media as the reaction system are classified into two categories: substrates dissolved in neat organic solvents and solvent-free liquid substrates. Although the latter seems preferable to the former, if it works, there are a number of cases where the former is the system of choice: for example, when the substrate is solid at the temperature of the reaction, when high concentration of the substrate is inhibitory for the reaction, when the solvent used gives better environment (accelerating effect) for the enzyme, and so forth.

Prior to carrying out an enzymatic reaction in an organic solvent, one faces the choice of a suitable solvent in the vast pool of organic solvents. From active basic research having been carried out in the past decades, there has been a remarkable progress in our understanding of properties of enzymes in organic media, and in how organic solvents affect them. Some researchers call the achievement “medium engineering”. A comprehensive monograph was published in 1996 to review the progress.[1]

In this section organic solvents often used for enzymatic reactions are roughly classified, followed by the influence of solvent properties on enzymatic reactions and the properties of the enzymes affected by the nature of the organic solvents are briefly summarized.

13.4.3.2 Classification of organic solvents

Among numerous kinds of organic solvents, the ones often used for enzymatic reactions are not so many and may be classified into three categories (Table 13.4.3.1),[2] in view of the importance of water content in the organic solvent concerned (see Section 13.4.3.3).

Water-miscible organic solvents. These organic solvents are miscible with water at the temperature of the reaction. Any cosolvent system having 0-100% ratio of the solvent/water can be prepared from this kind of solvent. Note that some organic solvents having limited water solubility at ambient temperature, and hence are not regarded as water-miscible, become miscible at elevated temperature.

Water-immiscible organic solvents. These organic solvents have a noticeable but limited solubility of water, ranging roughly 0.1-10% its solubility. The water solubility is, of course, increased as the temperature is raised.

Water-insoluble organic solvents. These solvents are also water-immiscible and have very low water solubility so that they are regarded as water-insoluble, i.e., water is practically insoluble in the organic solvents. Most aliphatic and aromatic hydrocarbons belong to this category.

Table 13.4.3.1. Classification of solvents commonly used for enzymatic reactions in organic media. [Adapted, by permission, from T. Yamane, *Nippon Nogeikagaku Kaishi*, **65**, 1104(1991)]

1) Water-miscible organic solvents (methanol, ethanol, ethylene glycol, glycerol, N,N'-dimethylformamide, dimethylsulfoxide, acetone, formaldehyde, dioxane)
2) Water-immiscible organic solvents (water solubility [g/l] at the temperature indicated)
alcohols ((n-, iso-) propyl alcohol, (n-, s-, t-) butyl alcohol, (n-, s-, t-) amyl alcohol, n-octanol)
esters (methyl acetate, ethyl acetate (37.8, 40°C), n-butyl acetate, hexyl acetate)
alkyl halides (dichloromethane (2, 30°C), chloroform, carbon tetrachloride, trichloroethane (0.4, 40°C)
ethers (diethyl ether (12, 20°C), dipropyl ether, diisopropyl ether, dibutyl ether, dipentyl ether)
3) Water-insoluble organic solvents (water solubility [ppm] at the temperature indicated)
aliphatic hydrocarbons (n-hexane (320, 40°C), n-heptane (310, 30°C), isooctane (180, 30°C))
allicyclic hydrocarbons (benzene (1200, 40°C), toluene (880, 30°C)
allicyclic hydrocarbons (cyclohexane (160, 30°C))

In Table 13.4.3.1 organic solvents often used for enzymatic reactions are listed together with their water solubilities (although not for all of them).

13.4.3.3 Influence of solvent parameters on nature of enzymatic reactions in organic media

Factors that influence the activity and stability of enzymes in organic media have been mostly elucidated. Several of them are mentioned below.

1) Water activity, a_w

Among factors, the amount of water existing in the reaction system is no doubt the most influential. To emphasize the effect of water, the author once proposed to say “enzymatic reaction in microaqueous organic solvent”, instead of merely say “enzymatic reaction in organic solvent”.[3-5]

A trace amount of water or nearly anhydrous state renders practically no enzymatic reaction. In this context, it should be reminded that commercially available enzyme preparations, or the enzymes even after lyophilization or other drying procedures, contain some water bound to the enzyme proteins. Whereas, excess water in the reaction system results in hydrolysis of the substrate, which is often unfavorable side-reaction, giving rise to a lower yield of product. Thus, there exists usually the optimal water content for each enzymatic reaction of concern.

Water molecules in the microaqueous system exist in three different states:

1. water bound to the enzyme protein,
2. water dissolved freely in the solvent (plus dissolved substrate),
3. water bound to impurities existing in the enzyme preparation or bound to the support materials if immobilized enzyme particles are used.

Therefore, the following equation with respect to water holds:

Total water = (Water bound to the enzyme) + (Water dissolved in the solvent) [13.4.3.1]

+ (Water bound to the immobilization support or to impurities of the enzyme preparation)

Water affecting most of the catalytic activity of the enzyme is the one bound to the enzyme protein.[6] From the above equation, it can be well understood that the effect of water varies depending on the amount of enzyme used and/or its purity, kind of solvent, and nature of immobilization support, etc. as far as the total water content is used as the sole variable. Also, it is often asked what is the minimum water content sufficient for enzymatic activity? It should be recognized that a relation between the degree of hydration of the enzyme and its catalytic activity changes continuously. There exist a thermodynamic isotherm-type equilibrium between the protein-bound water and freely dissolved water, and its relationship is quite different between water-miscible and water-insoluble solvents.[4]

A parameter better than the water content, water activity, a_w, was proposed to generalize the degree of hydration of a biocatalyst in organic media.[7] a_w is a thermodynamic parameter which determines how much water is bound to the enzyme and in turn decides the catalytic activity to a large extent among different kinds of the organic solvents. The a_w is especially useful when the water-insoluble organic solvent is used because the precise water content is hard to be measured due to its low solubility. It was shown that profiles between a_w and the reaction rate were similar for solvents having varying water contents.[8] In different solvents, the maximum reaction rate was observed at widely different water content, but if water content was qualified in terms of a_w, the optimum was observed at almost the same a_w (Figure 13.4.3.1). However, as seen from Figure 13.4.3.1, the profile does not lay on a single curve, and the absolute optimal reaction rate varies depending on the kind of the solvent, implying that a_w is not almighty.

2) Hydrophobicity (or polarity), logP

A hydrophobicity parameter, logP, was first proposed for microbial epoxidation of propene and 1-butene.[9,10] logP is the logarithm of P, where P is defined as the partition coefficient of a given compound in the standard n-octanol/ water two phase:

$$P = \frac{\text{solubility of a given compound in n-octanol phase}}{\text{solubility of a given compound in water phase}} \qquad [13.4.3.2]$$

Laane *et al.*[10] concluded as a general rule that biocatalysis in organic solvents is low in polar solvents having a logP < 2, is moderate in solvents having a logP between 2 and 4, and is high in apolar solvents having a logP > 4. They also stated that this correlation between polarity and activity paralleled the ability of organic solvents to distort the essential water layer bound to the enzyme that stabilized the enzyme. Since logP can easily be determined experimentally, or be estimated from hydrophobic fragmental constants, many

biotechnologists have tried since then to correlate effects of organic solvents on biocatalysts they studied with the logP approach. Their results have been successful only partially. A number of exceptions to the "logP rule" have been in fact reported.

3) relative permittivity (or dipole moment), ε (or D)

Interactions between an enzyme and a solvent, in which the enzyme is suspended, are mostly non-covalent ones as opposed to interactions with water. These strong non-covalent interactions are essential of electrostatic origin, and thus according to Coulomb's law, their strength is imposed dependent on the relative permittivity, ε, (which is higher for water than for almost all organic solvents). It is likely that enzymes are more rigid in anhydrous solvents of low ε than in those of high ε. Thus, ε of a solvent can be used as a criterion of the rigidity of the enzyme molecule. For the enzyme to exhibit its activity, it must be dynamically flexible during its whole catalytic action so that its activity in a solvent of lower ε should be less than in a solvent of higher ε. On the other hand, its selectivity or specificity becomes higher when its flexibility decreases so that the selectivity of a solvent of lower ε should be higher than in a solvent of higher ε.

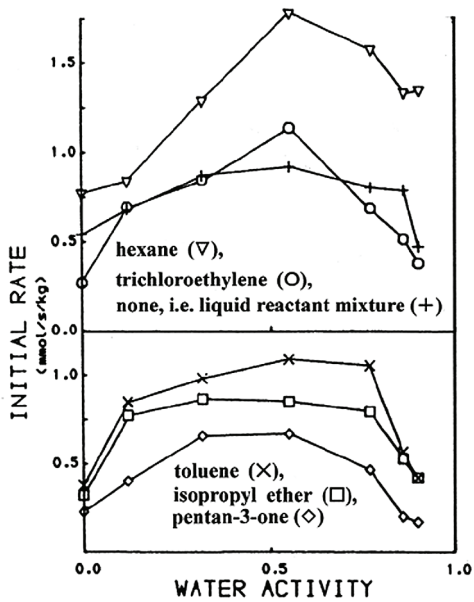


Figure 14.4.3.1 Activity of lipozyme catalyst as a function of water activity in a range of solvents. [Adapted, by permission, from R.H. Valivety, P.J. Halling and A.R. Macrae, *Biochim. Biophys. Acta*,

13.4.3.4 Properties of enzymes affected by organic solvents

1) Thermal stability (half-life), $t_{1/2}$

Stability of an enzyme in an organic solvent is estimated by its half-life, $t_{1/2}$, when its activity is plotted as a function of incubation time. Although $t_{1/2}$ during the enzymatic reaction is more informative for practical purposes, $t_{1/2}$ under no substrate is often reported because of its easiness of measurement. Inactivation of an enzyme is caused mostly by the change in its native conformation, or irreversible unfolding of its native structure. Water, especially enzyme-bound water makes a major contribution to the protein folding through van der Waals interaction, salt-bridges, hydrogen bonds, hydrophobic interaction, etc. When the enzyme molecule is put into organic solvent, water molecules bound to the enzyme molecule are more or less re-equilibrated, depending on the free water content. Therefore, both the nature of the organic solvent and the free water content have profound effects on its stability.

It has been shown that a number of enzymes suspended in anhydrous (dry) organic solvents exhibit thermal stability far superior to that in aqueous solutions (Table 13.4.3.2).[11] This is because most of the chemical processes that occur in the thermal inactivation involve water, and therefore do not take place in a water-free environment. Furthermore, increased rigidity in dry organic solvents hinders any unfolding process. The increased thermal stability in the dry organic solvent drops down to the stability in aqueous solution by adding a small amount of water as demonstrated by Zaks and Klibanov[12] and others. Thus, the thermal stability of an enzyme in organic solvent strongly depends on its free water content.

Table 13.4.3.2. Stability of enzymes in non-aqueous vs. aqueous media. [Adapted, by permission, from **Enzymatic Reactions in Organic Media**, A. M. P. Koskinen and A. M. Klibanov, *Blackie Academic & Professional* (An Imprint of Chapman & Hall), Glasgow, 1996, p. 84**]**

Enzyme	Conditions	Thermal property	References
PLL	tributyrin aqueous, pH 7.0	$t_{1/2}$ < 26 h $t_{1/2}$ < 2 min	Zaks & Klibanov (1984)
Candida lipase	tributyrin/heptanol aqueous, pH 7.0	$t_{1/2}$ = 1.5 h $t_{1/2}$ < 2 min	Zaks & Klibanov (1984)
Chymotrypsin	octane, 100°C aqueous, pH 8.0, 55°C	$t_{1/2}$ = 80 min $t_{1/2}$ =15 min	Zaks & Klibanov (1988) Martinek *et al*. (1977)
Subtilisin	octane, 110°C	$t_{1/2}$ = 80 min	Russell & Klibanov (1988)
Lysozyme	cyclohexane, 110°C aqueous	$t_{1/2}$ = 140 h $t_{1/2}$ < 10 min	Ahen & Klibanov (1986)
Ribonuclease	nonane, 110°C, 6 h aqueous, pH 8.0, 90°C	95% activity remains $t_{1/2}$ < 10 min	Volkin & Klibanov (1990)
F_1-ATPase	toluene, 70°C aqueous, 70°C	$t_{1/2}$ > 24 h $t_{1/2}$ < 10 min	Garza-Ramos *et al*. (1989)
Alcohol dehydrogenase	heptane, 55°C	$t_{1/2}$ > 50 days	Kaul & Mattiasson (1993)
HindIII	heptane, 55°C, 30 days	no loss of activity	Kaul & Mattiasson (1993)
Lipoprotein lipase	toluene, 90°C, 400 h	40% activity remains	Ottoline *et al*. (1992)
β-Glucosidase	2-propanol, 50°C, 30	80% activity remains	Tsitsimpikou *et al*. (1994)
Tyrosinase	chloroform, 50°C aqueous solution, 50°C	$t_{1/2}$ = 90 min $t_{1/2}$ = 10 min	Yang & Robb (1993)
Acid phosphatase	hexadecane, 80°C aqueous, 70°C	$t_{1/2}$ = 8 min $t_{1/2}$ = 1 min	Toscano *et al*. (1990)
Cytochrome oxidase	toluene, 0.3% water toluene, 1.3% water	$t_{1/2}$ = 4.0 h $t_{1/2}$ = 1.7 min	Ayala *et al*. (1986)

For References, refer to Ref. 11.

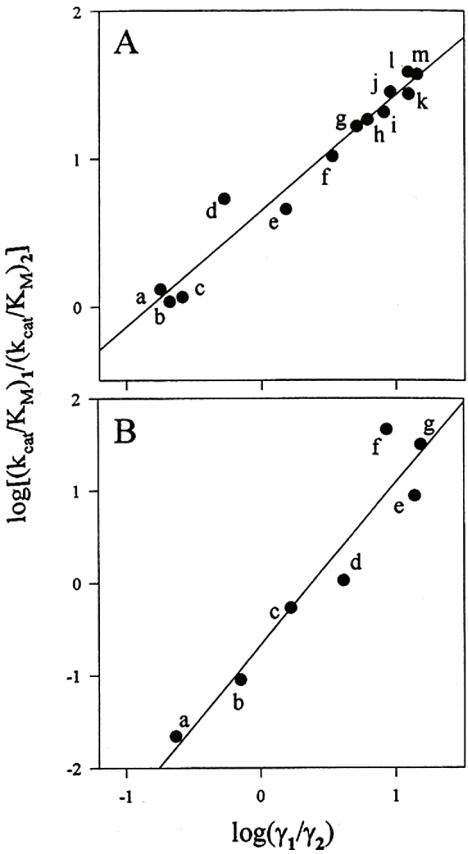


Figure 13.4.3.2. The dependence of (A) subtilisin, Carlsberg and (B) α-chymotrypsin substrate specificity for substrates 1 and 2 on the ratio of their Raoult's law activity coefficients. For the structures of the substrates 1 and 2, and the solvents a through m in (A) and a to g in (B), refer to Ref. 16. [Adapted, by permission, from C.R. Wescott and A.M. Klibanov, *Biotechnol. Bioeng.*, **56**, 343 (1997)].

2) Specificity and selectivity, k_{cat}/K_m

It is the most exciting and significant feature that the substrate specificity, enantioselectivity, and regioselectivity can be profoundly affected by nature of solvents in which the enzyme molecule exists. This phenomenon has opened an alternative approach for changing specificity and selectivity of an enzyme other than screening by nature and protein engineering in the field of synthetic organic chemistry. The ability of enzymes to discriminate substrate specificity among different, but structurally similar substrates, enantioselectivity among enantiomers, enantiofaces or identical functional groups linked to a prochiral center, and regioselectivity among identical functional groups on the same molecule, is expressed quantitatively by E value, which is the ratio of the specificity constants, k_{cat}/K_m, for the two kinds of substrate (or entiomers), i.e., $(k_{cat}/K_m)_1/(k_{cat}/K_m)_2$. For kinetic resolution of the racemic mixture by the enzyme, E is called enantiomeric ratio. The higher E, the higher the enantiomeric excess (i.e., the optical purity), ee, of the product (or remaining substrate). It is said that an E value higher than 100 is preferable for pharmaceutical or biotechnological applications. For an overview of this topic, see Refs. 13 and 14.

(2a) Substrate specificity

Zaks and Klibanov reported that the substrate specificity of α-chymotrypsin, subtilisin, and esterase changed with an organic solvent.[15] The substrate specificity in octane was reversed compared to that in water. A thermodynamical model that predicted the substrate specificity of subtilisin Carlsberg and α-chymotrypsin in organic media on the basis of specificity of the enzyme in water and physicochemical characteristics of the solvents was developed by Wescott and Klibanov.[16] They determined k_{cat}/K_m for transesterification of N-acetyl-L-phenylalanine and N-acetyl-L-serine with propanol in 20 anhydrous solvents, and correlated the data of $(k_{cat}/K_m)_{Ser}/(k_{cat}/K_m)_{Phe}$, first with the solvent to water partition coefficients for the substrate, P_{Phe}/P_{Ser}. Later they examined the selectivity of

subtilisin toward two different substrates with the Raoult's law activity coefficients, γ, using the following equation:[15]

$$\log[(k_{cat}/K_m)_1/(k_{cat}/K_m)_2] = \log(\gamma_1/\gamma_2) + \text{constant} \qquad [13.4.3.3]$$

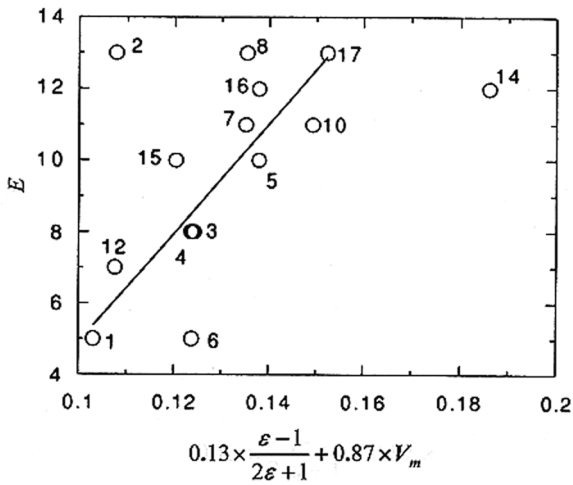


Figure 13.4.3.3. Linear relationship between f(ε, V_m) and E for lipase-catalyzed transesterification of *cis*- and *trans*-4-methylcyclohexanols with vinyl acetate in various organic solvents. For the organic solvents 1 through 18, refer to Ref. 20. [Adapted, by permission, from K. Nakamura, M. Kinoshita and A. Ohno, *Tetrahedron*, **50**, 4686 (1994)].

The correlation was unexpectedly high as seen in Figure 13.4.3.2,[16] implying that the change of substrate specificity of the enzyme in organic solvent stems to a large extent from the energy of desolvation of the substrate.

(2b) Enantioselectivity

Changes in enantioselectivity in various organic solvents was first discovered by Sakurai *et al.*[17] Later Fitzpatrick and Klibanov studied enantioselectivity of subtilisin, Carlsberg in the transesterification between the *sec*-phenethyl alcohol (a chiral alcohol) and vinyl butyrate to find that it was greatly affected by the solvent. Only the correlations with ε or with D gave good agreement.[18] The enzyme enantioselectivity was inverted by changing solvents.[19] Nakamura *et al.*[20] studied lipase (Amano AK from *Pseudomonas sp.*)-catalyzed transesterification of *cis*- and *trans*-methylcyclohexanols with vinyl acetate in various organic solvents and investigated the effect of solvent on activity and stereoselectivity of the lipase.[20] They correlated their stereoselectivity with good linearity (except for dioxane and dibutyl ether) by the following two-parameter equation (Figure 13.4.3.3):

$$E = a(\varepsilon - 1)/(2\varepsilon + 1) + bV_m + c \qquad [13.4.3.4]$$

where ε and V_m are relative permittivity and molar volume of the solvent, respectively, and a, b, and c are constants which should be experimentally determined.

Bianchi *et al.*[21] also reported that for the resolution of antitussive agent, Dropropizine, using both hydrolysis in aqueous buffer and transesterification techniques in various organic solvents, by a lipase (Amano PS from *Pseudomonas cepacia*), E depended very much on organic solvents (Table 13.4.3.3), with the highest E value (589) in n-amyl alcohol and the lowest one (17) in water.[21] In this case, however, there was no correlation between the enantioselectivity and the physicochemical properties of the solvents such as logP or ε.

Table 13.4.3.3. Effect of the solvent on enantioselectivity of lipase PS. [Adapted, by permission, from D. Bianchi, A. Bosetti, P. Cesti and P. Golini, *Tetrahedron Lett*., **33**, 3233 (1992)].

Solvent	logP	ε	Nucleophile	E
H_2O		78.54	H_2O	17
hexane	3.5	1.89	n-propanol	146
CCl_4	3.0	2.24	n-propanol	502
toluene	2.5	2.37	n-propanol	120
isopropyl ether	1.9	3.88	n-propanol	152
2-methyl-2-butanol	1.45	5.82	n-propanol	589
2-methyl-2-butanol	1.45	5.82	H_2O	63
n-propanol	0.28	20.1	n-propanol	181
acetonitrile	–0.33	36.2	n-propanol	82
1,4-dioxane	–1.1	2.2	n-propanol	164

As mentioned above, no correlation was reported in a large number of articles on the effects of solvents on the enzyme specificity/selectivity, although correlations between the specificity/selectivity and physicochemical properties of the solvents were successful in some combinations of an enzymatic reaction for a set of solvents. Therefore, attempts to rationalize the phenomena based on either physicochemical properties of solvents or on their structure, are at present clearly unsatisfactory from the point of view of predictive value. Further experiments carried out under more strictly defined condition are necessary to reach the quantitative explanation of the whole phenomena.

13.4.3.5 Concluding remarks

The use of deep eutectic solvents in biotransformations, including enzymatic and whole-cell, has gathered increasing interest.[22] Deep eutectic solvents enhance the activity and stability of several enzymes such as lipase, protease, and cellulase.[22] On the other hand, organic solvents such as hexane, acetone, and methanol cause denaturation of enzymes.[22]

Activity, stability, and selectivity of an enzyme are affected considerably by the nature of organic solvents as well as free water content in the enzyme-catalyzed reaction in the organic solvents. However, rational criteria for the selection of a proper solvent among a vast variety of the organic solvents are very limited so far. Researchers are obliged to resort to empirical approach by examining some kinds of solvent for the enzyme-catalyzed reaction concerned at the present state of the art.

REFERENCES

1 A. M. P. Koskinen and A.M. Klibasnov, Ed., **Enzymatic Reactions in Organic Media**, *Blackie Academic & Professional (An Imprint of Chapman & Hall), London, 1996.*
2 T. Yamane, *Nippon Nogeikagaku Kaishi*, **65**, 1103 (1991).
3 T. Yamane, *J. Am. Oil Chem. Soc*., **64**, 1657 (1987).
4 T. Yamane, Y. Kozima, T. Ichiryu and S. Shimizu, *Ann. New York Acad. Sci*., **542**, 282 (1988).
5 T. Yamane, *Biocatalysis*, **2**, 1 (1988).

6 J.A. Rapley, E. Gratton and G. Careri, *Trends Biol. Sci*., Jan., 18 (1983).
7 P. J. Halling, *Biochim. Biophys. Acta*, **1040**, 225 (1990).
8 R. H. Valivety, P.J. Halling, A.R. Macrae, *Biochim. Biophys. Acta*, **1118**, 218 (1992).
9 C. Laane, S. Boeren and K. Vos, *Trends Biotechnol*., **3**, 251 (1985).
10 C. Laane, S. Boeren, K. Vos and C. Veeger, *Biotechnol. Bioeng*., **30**, 81 (1987).
11 A. Zaks, in **Enzymatic Reactions in Organic Media** ed. by A.M.P. Koskinen and A.M. Klibanov, *Blackie Academic & Professional* (An Imprint of Chapman & Hall), London, 1996, p. 84.
12 A. Zaks and A.M. Klibanov, *Science*, **224**, 1249 (1984).
13 C. R. Wescott and A.M. Klibanov, *Biochim. Biophys. Acta*, **1206**, 1 (1994).
14 G. Carrea, G. Ottolina and S. Riva, *Trends Biotechnol.*, **13**, 63 (1995).
15 A. Zaks and A.M. Klibanov, *J. Am. Chem. Soc*., **108**, 2767 (1986).
16 C. R. Wescott and A.M. Klibanov, *J. Am. Chem. Soc.*, **108**, 2767 (1986).
17 T. Sakurai, A.L. Margolin, A.J. Russell and A.M. Klibanov, *J. Am. Chem. Soc*., **110**, 7236 (1988).
18 P. A. Fitzpatrick and A.M. Klibanov, *J. Am. Chem. Soc*., **113**, 3166 (1991).
19 S. Tawaki and A.M. Klibanov, *J. Am. Chem. Soc.*, **114**, 1882 (1992).
20 K. Nakamura, M. Kinoshita and A. Ohno, *Tetrahedron*, **50**, 4681 (1994).
21 D. Bianchi, A. Bosetti, P. Cesti and P. Golini, *Tetrahedron Lett.*, **33**, 3231 (1992).
22 I. Juneidi, M. Hayyan, M. A. Hashim, *Process Biochem*., in press, 2018.

13.5 COIL COATING

George Wypych
ChemTec Laboratories, Toronto, Canada

Steel, aluminum, or tin sheet, delivered in coils, is uncoiled, coated by rollers, dried in ovens at temperatures from 80 to 260°C. The coil coating industry is under pressure to eliminate the use of solvents. Polyester coil coatings contain up to 40% solvents such as alcohols (diacetone alcohol), glycol acetates (propylene glycol methyl ether acetate, ethyl diglycol acetate), glycols (butyl diglycol, propylene glycol monomethyl ether), aromatic hydrocarbons (e.g., Solvesso 150, xylol), and ketones (isophorone).[1,2,4] A book[1] predicted that the solvent-based technology will not change during the next decade because the industry heavily invested in equipment to deal with solvents. Such changes in technology require long testing before they can be implemented. The coil coating industry normally recovers energy from evaporated solvents either by at-source incineration or by a recycling process which lowers emissions. Because of a large amount of solvents used, the use of PVC and fluorocarbon resins in some formulations, and the use of chromates in pretreatment, the pressure remains on the industry to make improvements.[3] The coil coating industry was estimated to be consuming about 50,000 tons of solvents both in Europe and in the USA.[1] About half of these solvents are hydrocarbons. The 2007 estimate of solvent use in Europe is 80,000 to 100,000 tons of solvents.[4]

Two decades after prediction mentioned in the book,[1] solvents are used as previously described. In 2007 in Europe, out of 158 coating lines, only 7 used solvent-free powder coatings.[4] In 2007 in Europe, water-based products and powder coatings made up less than 1% of the total products used.[4] Current solvent emissions are 0.3% of the total solvent use on older equipment and 0.02% on new equipment or 0.006/m^2 (much less than 5% allowed by European Directive of 1999).[4]

According to the published studies,[3,5] efforts to change this situation did start in the early 1990s and by mid-nineties, research data were available to show that the technology can be changed. Two directions will most likely challenge the current technology: radiation curing and powder coating.

Coil coats are thin (about 30 μm wet thickness) but contain a high pigment loading. Consequently, UV curing is less suitable than electron beam curing. The application of this technology requires a change to the polymer system and acrylic oligomers are the most suitable for this application. This system can be processed without solvents. If a reduction of viscosity is required, it can be accomplished by the use of plasticizers (the best candidates are branched phthalates and linear adipates) and/or reactive diluents such as multifunctional monomers. Results[3] show that the UV stability of the system needs to be improved by using a polyester top coat or fluoropolymer. With top coat, material performs very well as learned from laboratory exposures and exposures in an industrial environment.[3] At the time of the study (about 20 years ago), the process of the coating was less efficient than solvent-based system because production speed was about 6 times slower than the highest production rates in the industry (240 m/min). At the same time, it is

known[2] that the quality of solvent-based coatings may suffer from excessive production rate, but it all depends on the equipment design. Radiation curing has a disadvantage because of its high capital investment but it does have an economic advantage because the process is very energy efficient. Previous experiences with radiation curing technology show that the process has been successfully implemented in several industries such as paper, plastic processing, and wood coating where long-term economic gains made the changes viable.

Comparison of solvent-based fluoropolymer and fluorocarbon powder coating developed in Japan[5] shows that elimination of solvent is not only good for the environment but also improves performance (UV stability was improved). The study was carried out with a very well designed testing program to evaluate the weathering performance of the material.

These two technologies show that there is an activity to improve coil coatings with simultaneous elimination of solvents. Two patents contribute some information on the developments in the coil coating industry.[6,7] One problem in the industry is with the poor adhesion of the coating to steel.[2,3] A primer developed contains dipropylene glycol methyl ether and PM acetate which allows the deposition of relatively thick layers (20-40 μm), without blistering, and at a suitable rate of processing. However, the primer has a low solids content (30-45%).[6] A new retroreflective coating was also developed[7] which is based on ethyl acrylate-styrene copolymer and contains a mixture of xylene with another aromatic hydrocarbon (Solvesso 150) at a relatively low concentration (11-12%).

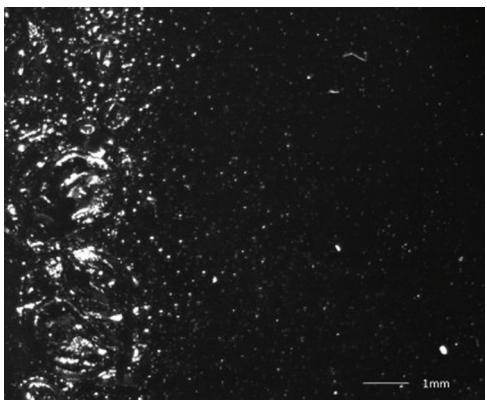


Figure 13.5.1. Solvent-boil defects in black polyester coating (left hand side of image). [Adapted, by permission, from I. Mabbett, J. Elvins, C. Gowenlock, P. Jones, D. Worsley, *Prog. Org. Coat.*, **76**, 9, 1184-90, 2013.]

Patented coil coating system used infrared radiation in curing oven with near-infrared emitters and oxidizing chamber for the destruction of volatile solvents.[8]

Limitation of volatile organic compound emissions led to the development of coil coating systems with reduced solvent content.[9] Reactive diluents derived from vegetable oils have been used to substitute up to 40% of the white spirit.[9] The concept can be described as a melamine crosslinkable alkyd which is formed in parallel to the crosslinking process.[9]

A NIR-crosslinkable coating which has absorbed too strongly in the NIR region was found to have solvent-boil defects due to crosslinking and film formation occurring prior to the solvent removal since too much absorption in the top few microns of a crosslinking polymer may initiate film formation prior to the full removal of any solvent.[10] Figure 13.5.1 shows solvent-boil defect.[10]

Due to the very high oven temperatures encountered in the curing of coil coatings, solvents with high boiling points are utilized to permit high coating speeds.[11] Several Dow glycol ether products meet this requirement; Dowanol™ DPM, TPM, PMA, DPMA, Butyl Cellosolve™, Butyl Carbitol™, and Methyl Carbitol.[11] These solvents provide a broad range of evaporation rates, high dilution ratios, and excellent solvency.[11] The coil coating lines incorporate incineration as a means of reducing solvent emissions while utilizing the fuel value of the solvents to maintain high oven temperatures.[11] Dow glycol ether products have relatively high BTU values.[11]

REFERENCES

1 B P Whim, P G Johnson, **Directory of Solvents**, *Blackie Academic & Professional,* London, 1996.
2 A L Perou, J M Vergnaud, *Polym. Testing*, **16**, No.1, 19-31 (1997).
3 G M Miasik, *Surface Coatings International*, **79**, No.6, 258-67 (1996).
4 Guidance 7. Coil coating. Guidance on VOC Substitution and Reduction for Activities Covered by the VOC Solvents Emissions Directive (Directive 1999/1/EC). European Commission - DG Environment Contract ENV/C.4/FRA/2007/001.
5 C Sagawa, T Suzuki, T Tsujita, K Maeda, S Okamoto, *Surface Coatings International*, **78**, No.3, 94-8 (1995).
6 M T Keck, R J Lewarchik, J C Allman, **US Patent 5,688,598**, *Morton International, Inc*., 1997.
7 G L Crocker, R L Beam, **US Patent 5,736,602**, 1998.
8 B Kai, **EP1790928**, *Advanced Photonics Technologies AG,* 30 May 2007.
9 K Ohlsson, T Bergman, P-E Sundell, T Deltin, I Tran, M Svensson, M Johansson, *Prog. Org. Coat*., **73**, 4, 291-3, 2012.
10 I. Mabbett, J. Elvins, C. Gowenlock, P. Jones, D. Worsley, *Prog. Org. Coat*., **76**, 9, 1184-90, 2013.
11 DOW. Glycol Ethers for Coil Coatings. Product information.

13.6 COSMETICS AND PERSONAL CARE PRODUCTS

George Wypych
ChemTec Laboratories, Toronto, Canada

Several cosmetic products contain solvents.[1-3] These include nail polish, nail polish remover, fragrances, hair dyes, general cleaners, hair sprays and setting lotions. In most cases, ethanol is the only solvent. Nail polish and nail polish remover contain a large variety of solvents. Several patents[3-9] give information on compositional changes in this area.

Nitrocellulose, polyester, acrylic and methacrylic ester copolymer, formaldehyde resin, rosin, cellulose acetate butyrate are the most frequently used polymers in nail polish formulations. Solvents were selected to suit the polymer used. These include acetone, methyl acetate, ethyl acetate, butyl acetate, methyl glycol acetate, methyl ethyl ketone, methyl isobutyl ketone, toluene, xylene, isopropyl alcohol, methyl chloroform, and naphtha. Solvents constitute a substantial fraction of the composition usually around 70%. Reformulation is ongoing to improve the flexibility and durability of the nail polish.[3] Other efforts are directed to improve antifungal properties,[4] to eliminate ketones and formaldehyde resin (ketones because of their toxicity and irritating smell and formaldehyde resins because they contribute to dermatitis),[5] and elimination of yellowing.[6] All efforts are directed towards improvements in drying properties and adhesion to the nails. These properties are partially influenced by solvent selection. The trend is towards greater use of ethyl acetate, butyl acetate, naphtha, and isopropanol which are preferable combinations to the solvents listed above.

Acetone used to be the sole component of many nail polish removers. It is still in use but there is a current effort to eliminate the use of ketones in nail polish removers. The combinations used most frequently are isopropanol/ethyl acetate and ethyl acetate/isopropanol/1,3-butanediol.

General cleaners used in hairdressing salons contain isopropanol and ethanol. Hair spray contains ethanol and propellants which are mixtures of ethane, propane, isobutane, and butane. The reported study[2] of chemical exposure in hairdresser salons found that, although, there were high concentrations of ethanol, the detected levels were still below the NIOSH limit. The concentrations were substantially higher in non-ventilated salons (about 3 times higher) than those measured in well ventilated salons. Small concentrations of toluene were found as well, probably coming from dye components.

Patents[7,8] show that solvents may enter cosmetic products from other ingredients, such as components of powders and thickening agents. Some solvents such as dichloromethane and benzene, even though they are present is smaller quantities are reason for concern.

In lipsticks, lip glosses, mascaras, hair care products, the following solvents are typically used isododecane, cyclopentasiloxane, and methyl trimethicone.[9] These solvents have low evaporation rates.[9] Addition of medium and high evaporation rate solvent gives instant skin formation.[9] although defects may arise if fast evaporation will cause shrinkage of the film. Hexamethyl disiloxane is used as fast evaporating solvent.[9]

Toluene is widely used as a solvent to help nail polish apply smoothly and adhere evenly to nails.[10] N-Methylpyrrolidone, a 5-membered lactam structure, is a clear-yellow liquid miscible with water and other common solvents such as ethyl acetate, chloroform, and benzene.[10] Due to its usefulness as an organic solvent, N-methylpyrrolidone has been used as a solvent and surfactant in the manufacturing of cosmetic products.[10] Out of 36 commercial cosmetic products tested toluene was detected in 26 products and N-methylpyrrolidone in 5 products.[10]

The natural deep eutectic solvents are promising as green solvents for foods, cosmetics and pharmaceuticals due to their unique solvent power which can dissolve many non-water-soluble compounds and their low toxicity.[11] The stability analysis shows that natural pigments from safflower are more stable in sugar-based natural deep eutectic solvents than in water or 40% ethanol solutions.[11] The high stabilizing ability of natural deep eutectic solvents was correlated with the strong hydrogen bonding interactions between solutes and solvent molecules.[11] The natural deep eutectic solvents are like liquid crystals in which the pigment molecules are fixed in the crystals.[11]

Methylal and 1,3-dioxolane are of interest in cosmetics production because they are no-mutagenic, non-carcinogenic, not toxic for reproduction, they do not cause allergic reaction, they are not dangerous to the environment, biomimetic, and amphiphilic. They are useful in hair and skin care products, toiletries, color cosmetics and paraphermaceuticals.

The composition enhancing the appearance of a keratinous substrates, in particular lashes contains a latex film-forming polymer (a styrene/acrylate copolymer), a hyperbranched functional polymer (C30+olefin/undecylenic acid copolymer), an organic solvent (non-aromatic hydrocarbon-based oil, e.g., isodecane, isododecane, isohexadecane), water, and pigment.

REFERENCES

1 B P Whim, P G Johnson, **Directory of Solvents**, *Blackie Academic & Professional*, London, 1996.
2 B E Hollund, B E Moen, *Ann. Occup. Hyg.*, **42** (4), 277-281 (1998).
3 M F Sojka, **US Patent 5,374,674**, *Dow Corning Corporation*. 1994.
4 M Nimni, **US Patent 5,487,776**, 1996.
5 F L Martin, **US Patent 5,662,891**, *Almell Ltd.*, 1997.
6 S J Sirdesai, G Schaeffer, **US Patent 5,785,958**, *OPI Products, Inc*., 1998.
7 R S Rebre, C Collete, T. Guertin, **US Patent 5,563,218**, *Elf Atochem S. A*., 1996.
8 A Bresciani, **US Patent 5,342,911**, *3V Inc*., 1994.
9 G A Sandstrom, J R Glynn, P Maitra, **WO2011056332**, *Avon Products, Inc*., 12 May 2011.
10 W. Zhou, P. G. Wang, J. B. Wittenberg, D. Rua, A. J. Krynitsky, *J. Chromat. A*, **1446**, 134-40, 2016.
11 Y. Dai, R. Verpoorte, Y. H. Choi, *Food Chem*., **159**, 116-21, 2014.
12 H. S. Bui, C. Pang, **US9622958**, *L'Oreal*, Apr. 18, 2017.

13.7 DRY CLEANING. TREATMENT OF TEXTILES IN SOLVENTS

Kaspar D. Hasenclever
Kreussler & Co.GmbH, Wiesbaden, Germany

Most processes in manufacturing and finishing of textiles are aqueous. In order to prevent water pollution, some years ago developments were made to transform dyeing-, cleaning- and finishing-processes from water to solvents. During 1970-1980 solvent processes for degreasing, milling, dyeing, and waterproofing of textiles could get limited economic importance. All these processes were done with tetrachloroethylene (TCE). After getting knowledge about the quality of TCE penetrating solid floors, stone and ground, contaminating groundwater, this technology was stopped.

Today the main importance of solvents in connection with textiles is given to dry cleaning, spotting and some special textile finishing processes.

13.7.1 DRY CLEANING

13.7.1.1 History of dry cleaning

Development of dry cleaning solvents

The exact date of discovery of dry cleaning is not known. An anecdote tells us that in about 1820 in Paris, a lamp filled with turpentine fell down by accident and wetted a textile. After the turpentine was vaporized, the wetted areas of the textile were clean, because the turpentine dissolved oily and greasy stains from it.

In 1825, Jolly Belin founded the first commercial “dry laundry” in Paris. He soaked textile apparel in a wooden tub filled with turpentine, cleaned them by manual mechanical action, and dried them by evaporating the turpentine in the air.

After getting the know-how to distill benzene from tar of hard coal in 1849, this was used as a solvent for dry cleaning because of its far better cleaning power. But benzene is a strong poison, so it was changed some decades later to petrol, which is explosive. In order to reduce this risk, petrol as dry cleaning solvent was changed to white spirit (USA: Stoddard solvent) with a flash point of 40-60°C (100-140°F) in 1925.

The flammability of the hydrocarbon solvents in dry cleaning plants was judged to be risky because of fire accidents. After finding the technology for producing inflammable chlorinated hydrocarbons, trichloroethane and tetrachloroethylene (TCE) were introduced in dry cleaning since about 1925. These solvents gave the opportunity for good cleaning results and economic handling. Up to 1980, TCE was the most important solvent for dry cleaning worldwide.

Compared to TCE, fluorinated chlorinated hydrocarbons (CFC) offer benefits to dry cleaning because of their lower boiling points and their more gentle action to dyestuffs and fabrics. So since 1960, these solvents have had some importance in North America, Western Europe, and the Far East. They were banned because of their influence on the ozone layer in the stratosphere by the UNESCO's Montreal Protocol in 1985.

At the same time, TCE was classified as a contaminant to groundwater and as a dangerous chemical to human health with the possible potential of cancerogenic properties.

As a result of this, hydrocarbon solvents on the basis of isoparaffins with a flash point higher than 55°C (130°F) were at first used in Japanese and German dry cleaning operations since 1990.

Also, alternatives to conventional dry cleaning were developed. Wet cleaning was introduced by Kreussler in 1991 (Miele System Kreussler) and textile cleaning in liquid carbon dioxide was exhibited by Global Technologies at the Clean Show Las Vegas in 1997.

Development of dry cleaning machines

In the beginning, dry cleaning was done manually in wooden tubs filled with turpentine or benzene. About 1860, the Frenchman Petitdidier developed a wooden cylindrical cage, which was rotated in a tub filled with solvent. The apparel to be dry cleaned was brought into the cage and moved through the solvent by the rotation of the cylinder. This machine got the name “La Turbulente”.

The next step was the addition of a centrifuge to the wooden machine. The dry cleaned apparel was transferred from the machine into the centrifuge and then dried by vaporizing the solvent into the open air.

About 1920, a tumble dryer was used for drying the dry cleaned textiles. Fresh air was heated up, blown through the dryer, where the air was saturated with solvent vapor and then blown out to be exhausted into the environment. The used solvent was cleaned to be recycled by separation of solid matter by a centrifugal power with a separator and to be cleaned from dissolved contamination by distilling.

In 1950, dry to dry machines were developed by Wacker in Germany for use with TCE. The principle of working is as follows: The cage, filled with textiles, is rotating in a closed steel cylinder. The dry cleaning solvent is pumped from the storage tank into the cylinder so that the textiles in the cage are swimming in the solvent. After ending the cleaning process, the solvent is pumped back into the storage tank and the cage rotates with high speed (spinning) in order to separate the rest of the solvent from the textile. Then air is circulated through a heat exchanger to be heated up. This hot air is blown into the rotating cage in order to vaporize the remaining solvent from the textiles. The air saturated with solvent vapor is cleaned in a condenser, where the solvent is condensed and separated from the air. The air now goes back into the heat exchanger to be heated up again. This circulation continues until textiles are dry. The separated solvent is collected in a tank to be reused.

In order to reduce solvent losses and solvent emissions, since 1970 charcoal filters have been used in the drying cycle of dry cleaning machines, so that modern dry cleaning systems are separated from the surrounding air.

13.7.1.2 Basis of dry cleaning

Dry cleaning means a cleaning process for textiles, which is done in apolar solvents instead of water. If water is used, such cleaning process is called “washing” or “laundering”.

Natural textile fibers, such as wool, cotton, silk, and linen, swell in water because of their tendency to absorb water molecules in themselves. This causes an increase in their

diameter and a change of the surface of yarns and fabrics. The result is shrinkage, felting, and creasing.

Apolar solvents, such as hydrocarbons, are not absorbed by natural textile fibers because of the high polarity of the fibers. So there is no swelling, no shrinkage, no felting and no creasing. From the solvent activity, dry cleaning is very gentle to textiles, with the result that the risk of damaging garments is very low.

Because of the apolar character of dry cleaning solvents cleaning activity also deals with apolar contamination. Oils, fats, grease and other similar substances are dissolved in the dry cleaning operation. Polar contamination, such as salt, sugar, and most nutrition and body excrements are not dissolved.

In the same way that water has no cleaning activity with regard to oils, fat, or grease, in dry cleaning there is no activity with regard to salts, sugar, nutrition and body excrements. And in the same way that water dissolves these polar substances, cleaning of textiles from these contaminants does not pose any problems in a washing process.

To make washing active to clean oils, fat and grease from textiles, soap (detergent) has to be added to water. To make dry cleaning active to clean salts, sugar and the like from textiles, dry cleaning detergent has to be added to the solvent.

In washing, fresh water is used in the process. After being used, the dirty washing liquid is drained off. In dry cleaning, the solvent is stored in a tank. To be used for cleaning it is pumped into the dry cleaning machine. After being used, the solvent is pumped back into the storage tank. To keep the solvent clean it is constantly filtered during the cleaning time. In addition to this, a part of the solvent is pumped into a distilling vessel after each batch to be cleaned by distilling.

Dry cleaning solvents are recycled. The solvent consumption in modern machines is in the range of about 1- 2 wt% of the dry cleaned textiles.

13.7.1.3 Behavior of textiles in solvents and water

Fibers used for manufacturing textiles can be classified into three main groups:

- Cellulosic fibers: cotton, linen, rayon, acetate.
- Albumin fibers: wool, silk, mohair, camelhair, cashmere.
- Synthetic fibers: polyamide, polyester, acrylic.

Textiles made from cellulosic fibers and synthetics can be washed without problems. Apparel and higher class garments are made from wool and silk. Washing very often bears a high risk. So these kinds of textiles are typically dry cleaned.

Dependent on the relative moisture of the surrounding air fabrics absorb different quantities of water. The higher the polarity of the fiber, the higher is their moisture content. The higher the swelling (% increase of fiber diameter) under moisture influence, the higher is the tendency of shrinkage in a washing or dry cleaning process.

Table 13.7.1. Water content (%) in textile fibers dependent on relative humidity

Fiber	Relative humidity, %			Swelling
	70	90	max.	
Viscose	14.1	23.5	24.8	115
Wool	15.6	22.2	28.7	39
Silk	11.2	16.2	17.7	31
Cotton	8.1	11.8	12.9	43
Acetate	5.4	8.5	9.3	62
Polyamide	5.1	7.5	8.5	11
Acrylic	2.1	4.0	4.8	9
Polyester	0.5	0.6	0.7	0

The same absorption of water occurs if textiles are immersed in a solvent in a dry cleaning machine. If the relative humidity in the air space of the cylinder of a dry cleaning machine is higher, textiles absorb more water. The water content of textiles in a solvent is equal to the water content of textiles in the open air if the relative humidity is the same.

If water additions are given to the dry cleaning solvent in order to intensify the cleaning effect with regard to polar contamination, then the relative humidity in the air space of the cylinder of the dry cleaning machine increases. As a result of this, the water content in the dry cleaned textiles increases, too, so that swelling begins and shrinkage may occur.

Woolen fabrics are particularly sensitive to shrinkage and felting because of the scales on the surface of the wool fiber. Not only in washing, but also in dry cleaning there is a risk of shrinkage on woolen garments. This risk is higher when the dry cleaning process is influenced by water addition. If the relative humidity in the air space of a dry cleaning machine is more than 70%, shrinkage and felting may occur, if the dry cleaning solvent is tetrachloroethylene (TCE). In hydrocarbon solvents, wool is safe up to 80% relative humidity, because of the lower density of hydrocarbons compared to TCE, which reduces mechanical action.

13.7.1.4 Removal of soiling in dry cleaning

"Soiling" means all the contamination on textiles during their use. This contamination is from very different sources. For cleaning purposes, the easiest way of classification of "soiling" is by the solubility of soiling components. The classification can be done by definition of four groups:

- Pigments: Substances are insoluble in water and in solvents. Examples are: dust, particles of stone, metal, rubber; soot, the scale of skin.
- Water soluble material: Examples are: salts, sugar, body excrements, sap and juice.

- Polymers: Substances are insoluble in solvents but can be soaked and swell in water. Examples are: starch, albumin and those containing material such as blood, milk, eggs, and sauce
- Solvent soluble material: Examples are: oil, fat, grease, wax, resins.

Table 13.7.2 Average soiling of garments (apparel) in Europe

Soil type	Proportion, %	Solubility	Components
Pigments	50	not	dust, soot, metal oxides, rub-off, pollen, aerosols
Water-soluble	30	water	sugar, salt, drinks, body excretions
Polymers	10	water	starch, albumin, milk, food
Solvent soluble	10	solvents	solvents skin grease, resin, wax, oils, fats

In practice, the situation is not so simple as it seems to appear after this classification. That is because soiling on garments almost always contains a mixture of different substances. For example, a spot of motor oil on a pair of trousers consists of solvent soluble oil, but also pigments of soot, metal oxides, and other particles. The oil works as an adhesive for the pigments, binding them to the fabric. In order to remove this spot, first, the oil has to be dissolved then pigments can be removed.

The removal of solvent soluble "soiling" in dry cleaning is very simple. It will be just dissolved by physical action. Polymers can be removed by the combined activity of detergents, water, and mechanical action. The efficiency of this process depends on the quality and concentration of detergent, the amount of water added into the system, and the operating time. Higher water additions and longer operating time increase the risk of shrinkage and felting of the textiles.

Water-soluble "soiling" can be removed by water, emulsified in the solvent. The efficiency here depends on the emulsifying character of the detergent and the amount of water addition. The more water is emulsified in the solvent, the higher is the efficiency of the process and the higher is the risk of shrinkage and felting of the textiles.

Pigments can be removed by mechanical action and by dispersing activity of detergents. The higher the intensity of mechanical action, influenced by cage diameter, rotation, the gravity of the solvent and operating time and the better the dispersing activity of the detergent, the better is the removal of pigments. The same parameters influence the care of the textiles. The better the cleaning efficiency, the higher the risk of textile damage.

13.7.1.5 Activity of detergents in dry cleaning

The main component of detergent is a surfactant. The eldest known surfactant is soap. Chemically soap is an alkaline salt of fatty acid. Characteristic of soap (and surfactant) is the molecular structure consisting of apolar – hydrophobic – part (fatty acid) and a polar – hydrophilic – part (–COONa), causing surface activity in aqueous solution.

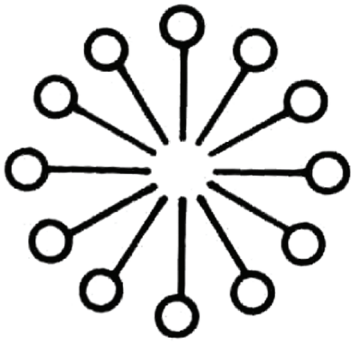


Figure 13.7.1. Schematic diagram of surfactants aggregated in micelle in aqueous solution.

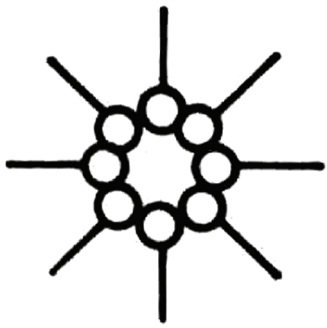


Figure 13.7.2. Schematic diagram of surfactants aggregated in micelle in solvent solution.

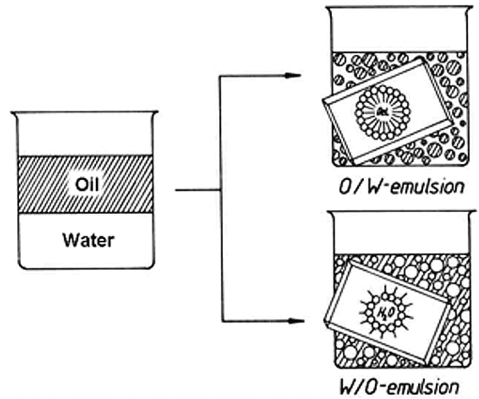


Figure 13.7.3. Aggregation of surfactants in emulsions of type oil in water (O/W) and water in oil (W/O).

Surface activity has its function in the insolubility of the hydrophobic part of molecule in water and the hydrophilic part of the molecule influences water solubility. This gives a tension within soap molecules in water forming layers on every available surface and forming micelles if there is a surplus of soap molecules compared to the available surface. This soap behavior stands as an example of the mechanism of action of surfactants in general.

Micelles of surfactants in water are formed by molecular aggregates of surfactants oriented in such a way that the hydrophobic parts are directed internally so that the hydrophilic parts are directed outwards. In this way, the aggregates form spheres, cylinders, or laminar layers, dependent on its concentration.

Because of this behavior, it is possible to remove oil, fat or grease from substrates in aqueous solutions, if surfactants are present. The surfactants act to disperse the oil into small particles and build up micelles around these particles so that oil, fat or grease incorporated inside the micelle (Figure 13.7.1). If aggregates are small, the solution is clear. If aggregates are larger, the solution (emulsion – type oil in water) becomes milky.

In the same way, but in the opposite direction, surfactants form micelles in solvents (Figure 13.7.2). In this case, not the hydrophobic, but the hydrophilic part is directed internally and the hydrophobic outwards. Emulsions, in this case, are not formed by oil in water, but by water in oil (solvent) (Figure 13.7.3).

Because of this behavior, it is possible to remove water-soluble (polar) material from substrates in solvents, if surfactants are at present. The surfactants disperse the polar material into very small particles and build up micelles around the particles so that the polar

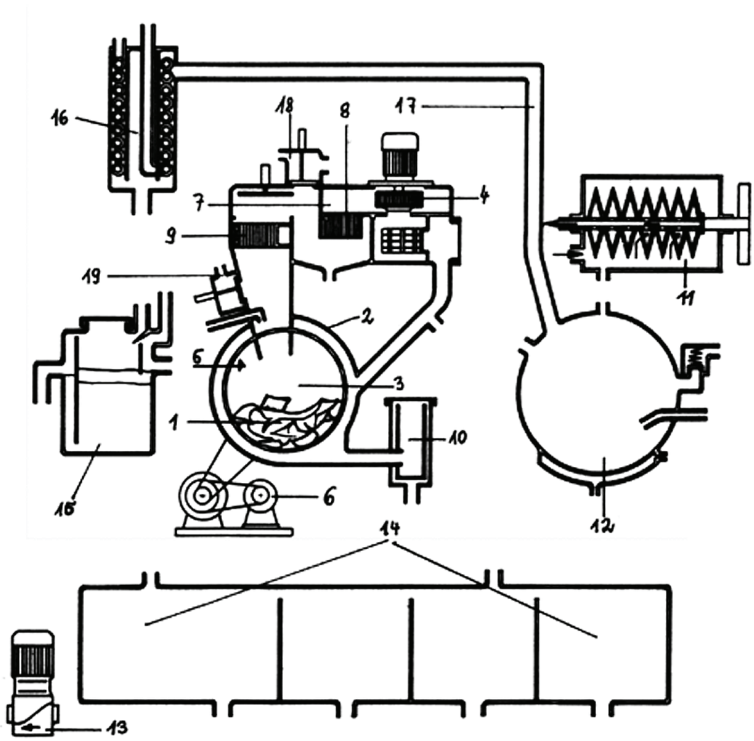


Figure 13.7.4. Scheme of a dry cleaning machine. 1 textiles to be cleaned, 2 cylinder, 3 cage, 4 fan, 5 heater, 6 drive for cage, 7 air canal, 8 cooler, 9 lint filter, 10 button trap, 11 filter, 12 distilling vessel, 13 pump, 14 solvent storage tanks, 15 water separator, 16 condenser, 17 steam pipe, 18 outlet to charcoal filter, 19 dosing unit.

material is totally incorporated into micelle. If the aggregates are small, the solution is clear. If they are large, the solution (emulsion – type water in oil) becomes milky. Drycleaning detergents consist of surfactants, cosolvents, lubricants, antistatic compounds and water. They are used in order to increase the cleaning efficiency, to improve the handle of dry cleaned textiles, and to prevent electrostatic charge on textiles They are formulated as liquids in order to be easily added to the solvent by automatic dosing equipment. In dry cleaning the drycleaning detergents play the same role as soap or laundry detergents in textile washing.

13.7.1.6 Dry cleaning processes

Process technology in dry cleaning has the target to clean garments as good as possible without damaging them, at lowest possible costs and with highest possible safety. Because of the environmental risks dependent on the use of TCE or hydrocarbon solvents, safe operation is the most important. Modern dry cleaning machines are hermetically enclosed, preventing infiltration of surrounding air, operating with electronic sensor systems, and they are computer-controlled. The main part is the cylinder with the cleaning cage, the sol-

vent storage tanks, the solvent recovering system, the solvent filter system and the distillation equipment (Figure 13.7.4).

Cylinder/cage:

A cage capacity is 20 liters per kg load capacity of the machine (about 3 gals per lb). That means an average sized dry cleaning machine with a load capacity of 25 kg (50 lbs) has a cage capacity of 500 liters (130 gals). This size is necessary because the same cage is used for cleaning and drying.

During the cleaning cycle, 3-5 liters of solvent per kg load (0.5-0.8 gal/lb) is pumped into the cylinder. In a 25 kg machine, it is 80-125 liters (25-40 gal). This solvent is filtered during the cleaning time.

Solvent storage tanks:

A dry cleaning machine has 2-3 solvent storage tanks. The biggest – the working tank – has a capacity in liters ten times the load capacity in kg. The clean solvent tank and optional retex tank have half the capacity. All the tanks are connected to each other with an overflow pipe.

The working tank with its inlet and outlet is connected to the cylinder of the machine. The inlet of the clean tank is connected to the distilling equipment, the outlet to the cylinder.

Filter system:

The filter is fed with solvent from the cylinder by pump pressure. The filtered solvent goes back into the cylinder. The filter has a further connection to the distilling equipment used as a drain for the residue.

Distilling equipment:

The distilling vessel has the same capacity as the biggest storage tank. The solvent to be distilled is pumped into the vessel from the cylinder or from the filter. The vessel is steam or electrically heated. The solvent vapor is directed into a condenser (water cooling) and then to a water separator, from where it flows into the clean solvent tank. The residue after distillation remains in the vessel and is pumped into special residue drums.

Recovering system:

In order to dry the dry cleaned garments from the solvent residue which remains after spinning, a fan extracts air out of the cylinder into a condenser, where the solvent vapor is condensed out of the air. From there the air is blown into a heater and directed by a fan back into the cylinder. In this way, the solvent is vaporized away from the garment and after condensing, reused for cleaning.

Dosing equipment:

In order to get the right additions of dry cleaning detergent into the solvent, a dry cleaning machine has dosing equipment working on the basis of a piston pump, which doses the right amount of detergent at the right time into the system.

Computer control:

All the processes are computer controlled. Drying/Recovering, Distilling/Filtration operate according to fixed programs; the cleaning cycle can be varied with regard to the requirements of the garment. The most common program works as follows:

Loading the machine, closing the door, starting computer control:

1 min	pumping solvent from the working tank into cylinder up to low dip level (3 l/kg);
3 min	pre-cleaning by rotating the cage in the cylinder;
1 min	pumping the solvent from the cylinder into the distillation vessel;
1 min	spinning;
2 min	pumping solvent from the working tank into cylinder up to high dip level (5 l/kg); addition of detergent (2-5 ml/l of solvent);
8 min	cleaning by rotating the cage in the cylinder together with filter action;
1 min	pumping the solvent from the cylinder back to the working tank (the solvent in working tank is filled by overflow from clean tank);
3 min	spinning
8 min	drying /recovering solvent with recovery system 5 min drying/ recovering solvent with charcoal filter.

After the sensor has indicated that the load is free of solvent residue, opening the door and unloading the machine. After the cleaning process, the garment is controlled for cleaning quality and can be finished or if necessary, it undergoes spotting/recleaning before finishing.

13.7.1.7 Recycling of solvents in dry cleaning

The recycling of solvents in dry cleaning is very important, because solvents are too expensive for single use and their disposal is not environmentally friendly, even is they are biodegradable. Three different systems are used for the cleaning of the solvent in order for it to be recycled:

- Filtration
- Adsorption
- Distillation

Filtration is a simple physical process, separating insoluble parts from the solvent. It is done during the cleaning cycle.

Adsorption is mainly used together with hydrocarbon solvents because their high boiling temperature is insufficient to separate lower boiling contaminants from the solvent. Adsorption systems use charcoal or bentonites. The solvent is pumped to filters where contaminants with higher polarity than solvent are adsorbed by the adsorbing material. The adsorbing material can adsorb contaminants in a quantity of about 20% of its own weight. After being saturated, the absorbing material must be replaced and changed to fresh material. The charged adsorbing material is disposed of according to regulations, which is cost intensive.

Distillation is the best cleaning method if the boiling point of the solvent is significantly lower than the boiling point of possible contaminants. With dry cleaning machines using TCE, distilling is the normal recycling method. The boiling point of TCE is 122°C, which makes steam heating possible so that the process can be done safely and cost-effectively. The distillation residue consists of removed soil and detergents. Its quantity is much lower than in the adsorption systems because there is no waste of adsorbing material. Disposal costs are much lower than with adsorption.

13.7.2 SPOTTING

13.7.2.1 Spotting in dry cleaning

Spotting is the removal of stains from textiles during professional textile cleaning. Correct cleaning, good lighting conditions, appropriate equipment, effective spotting agents, and expert knowledge are indispensable.

Lighting conditions

Lighting of the spotting table with composite artificial light consisting of a bluish and a yellowish fluorescent tube attached above the table approx. 80 cm from the standing point is better suited than daylight. This ensures high-contrast, the shadow-free lighting of the work surface and allows for working without fatigue.

Equipment

Basic equipment should comprise a spotting table with vacuum facility, sleeve board, steam and compressed air guns, and a spray gun for water. Spotting brushes should have soft bristles for gentle treatment of textiles. Use brushes with bright bristles for bright textiles and brushes with dark bristles for dark textiles. Use spatulas with rounded edges for removing substantial staining.

13.7.2.2 Spotting agents

In dry cleaning, normally three groups of spotting agents are used:

Brushing agents

Brushing agents containing surfactants and glycol ethers dissolved in low viscosity mineral oil and water. Brushing agents are used for pre-spotting to remove large stains from textiles. They are applied undiluted with a soft brush or sprayed onto the heavily stained areas before dry cleaning.

Special spotting agents

Special spotting agents are used for removing particular stains from textiles. The range consists of three different products in order to cover a wide range of different stains. The products are applied as drops directly from special spotting bottles onto the stain and are allowed to react. The three products are:

- An acidic solution of citric acid, glycerol surfactants, alcohol and water for removing stains originating from tannin, tanning agent, and fruit dye.
- The basic solution of ammonia, enzymes, surfactants, glycol ethers and water for removing stains originating from blood, albumin, starch, and pigments.
- A neutral solution of esters, glycol ethers, hydrocarbon solvents and surfactants for removing stains originating from paint, lacquer, resin, and adhesives.

Post-spotting agents

Stains that could not be removed during basic cleaning must be treated with post-spotting agents. Most common is a range of six products, which are used in the same way, as the special spotting agents:

- Alkaline spotting agent for stains originating from starch, albumin, blood, pigments
- Neutral spotting agent for stains originating from paint, lacquer, grease, and
- Acidic spotting agent for stains originating from tannin, fruits, beverages, and rust.

- Acidic rust remover without hydrofluoric acid.
- Solvent combination for removing oily and greasy stains from textiles.
- Bleaching percarbonate as color and ink remover.

13.7.2.3 Spotting procedure

Correct procedure for spotting

It is recommended to integrate the three stages of spotting

- Brushing
- Special spotting
- Post-spotting

into the process of textile cleaning. Perform brushing and special spotting when examining and sorting the textiles to be cleaned.

Brushing

Examine textiles for excessive dirt, particularly at collars, pockets, sleeves, and trouser legs. If textiles are to be dry cleaned check them particularly for stains originating from food or body secretions.

If the textiles are to be wet-cleaned check them particularly for greasy stains. Apply a small quantity of brushing agent onto the stained areas and allow to react for 10-20 minutes before loading the cleaning equipment.

Special spotting

Intensive staining found during the examination of the textiles can be treated with special spotting agents. The stain substance must be identified and related to one of the following categories:

- coffee, tea, fruit, red wine, grass, urine
- blood, food, pigments, sweat
- wax, paint, lacquer, make-up, pen ink, adhesives

Depending on the category of the stain substance, apply the special product with the dripping spouts in the work bottle onto the stain and tamp it gently with a soft spotting brush. Allow to react for 10-20 minutes before loading the cleaning equipment.

Post-spotting

Stains that could not be removed during dry-cleaning or wet cleaning with machines are subject to post-spotting. Proceed as follows:

- Place the garment with the stained area onto the perforated vacuum surface of the spotting table.
- Identify stain, drip appropriate product undiluted onto the stain and tamp it gently with the brush.
- For stubborn stains, allow the product to react for up to 3 minutes.
- Use a vacuum to remove the product and rinse the spotted area with a steam gun.
- Dry with compressed air, moving the air gun from the edges to the center of the spotted area.

Hidden spot test

If it is suspected that a stain cannot be removed safely due to the textile material, the compatibility of the spotting agent should be checked by applying a small quantity of the agent

at a hidden part of the garment. If the garment passes the test, the spotting agent is expected to be successful without damaging the garment.

13.7.3 TEXTILE FINISHING

The use of solvents for textile finishing has only some importance for the treatment of fully fashioned articles. The processes are done in industrial dry cleaning machines. The advantages are the same as in dry cleaning compared to washing: lower risk against shrinkage and damage of sensitive garments.

13.7.3.1 Waterproofing

In Northern Europe, North America and Japan, some kinds of sportswear need to be water-proofed. The treatment is done in dry cleaning machines with a load capacity larger than 30 kg (>60 lbs). The machines need to be equipped with a special spraying unit, which allows one to spray a solution of waterproofing agent into the cage of the machine.

The waterproofing agents consist of fluorocarbon resins dissolved in a mixture of glycol ethers, hydrocarbon solvents, and TCE. This solution is sprayed onto the garments, which are brought into the cage of the machine. The spraying process needs about 5-10 min. After spraying, the solvent is vaporized in the same way as drying in dry cleaning, so that the fluorocarbon resin will stay on the fibers of the garments. To get good results and the highest possible permanence of water resistance, the resin needs to be thermally fixed. To meet these requirements, a drying temperature of > 80°C (= 176°F) is necessary.

13.7.3.2 Milling

Solvent milling has some importance for the treatment of fully fashioned woolen knitwear. The process is very similar to normal dry cleaning. The specific difference is the addition of water together with the detergent, in order to force an exact degree of shrinkage and/or felting.

Milling agents are similar to dry cleaning detergent. They have specific emulsifying behavior, but no cleaning efficiency. The process runs like this: textiles are loaded into the machine, then solvent (TCE) is filled in before the milling agent diluted with water is added. After this addition, the cage rotates for 10-20 min. The higher the water addition, the higher the shrinkage; the longer the process time, the higher the felting. After this treatment, the solvent is distilled and textile load is dried. High drying temperature causes a rather stiff handle, low drying temperatures give more elastic handle.

13.7.3.3 Antistatic finishing

Antistatic finishing is used for fully fashioned knitwear – pullovers made from wool or mixtures of wool and acrylic. The process is equal to dry cleaning. Instead of dry cleaning detergent, the antistatic agent is added.

Antistatic agents for the treatment of wool consist of cationic surfactants such as dialkyl-dimethylammonium chloride, imidazolidione or etherquats. Antistatic agents for the treatment of acrylic fibers are based on phosphoric acid esters.

13.7.4 CURRENT SOLVENTS

With the advent of new technology, solvents were changed to account for health and environmental regulations. Some of the currently used systems are listed below.

Firma Kreussler developed an environmentally friendly system which includes new solvent, SolvonK4, which is halogen-free, synthetic, acetal-based solvent. Current patents[1,2] give information on physical and chemical properties of this solvent. In addition to the solvent, the system includes brushing agent, PrenettK4, detergent concentrate, ClipK4, and water and stain repellent agent, VinoyK4. This formulation is able to dissolve and absorb lipophilic and hydrophilic components of dirt. According to European regulations, the composition is not a hazardous substance. It is also biodegradable and dermatologically tested.

Another biodegradable solvent, Rynex-3E, is based on dipropylene glycol ether. It does not contribute to air pollution. It presents no danger to ground water. It can be used without risk to health and safety.

A dry cleaning composition comprising a volatile siloxane, a mixture of different classes of organic surfactants, and, optionally, water was also proposed and it is used until now.[3] Popular liquid silicone, GreenEarth (decamethylcyclopentasiloxane), was found to perform almost as previously used (banned now) tetrachloroethane.

High-pressure carbon dioxide is a potential solvent for textile dry cleaning.[4] However, the particulate soil (e.g. clay, sand) removal in CO_2 is generally insufficient.[4] The cleaning performance of CO_2 is 50% lower than that of perchloroethylene which is commonly used as cleaning solvent in the textile dry cleaning industry but it is toxic, classified as probable carcinogen, and harmful for the environment.[4] The washing results show that liquid CO_2 spray may be a suitable additional mechanism to provide textile movement.[5]

The State Coalition for Remediation of Drycleaners was established in 1998, with support from the U.S. EPA Office of Superfund Remediation and Technology Innovation. The organization presented a paper which analyzed details of the past and present solvents in drycleaning.[6]

The following alternative dry cleaning solvents have been approved by the Department of Environmental Conservation in New York State for use in non-vented, closed-loop drycleaning machines that are equipped with a refrigerated condenser, conform to local fire codes, and meet the additional specifications required by the alternative solvent manufacturer: Green Earth® (SB-32): decamethylcyclopentasiloxane, CAS 541-02-6, by General Electric; ExxonMobil DF-20001: synthetic hydrocarbon, CAS 64742-48-9; Chevron Philips EcoSolv®1: highly refined hydrocarbon, CAS 68551-17-7; Rynex 3™: dipropylene glycol tert-butyl ether, CAS 132739-31-2; Sasol (LPA-142)1: highly refined hydrocarbon, CAS 64742-47-8; R.R. Streets Solvair™2: dipropylene glycol n-butyl ether (DPGnBE), CAS 29911-28-2; SolvonK4™: dibutoxymethane, CAS 2568-90-3, by Kreussler; Green Earth® GEC-5: decamethylcyclopentasiloxane, CAS 541-02-6, by Shin-Etsu; DC-1421: aliphatic hydrocarbon solvent, CAS 64742-88-7, by Essential Solvents.

Perchloroethylene, PERC, is classified as a Toxic Air Contaminant by the Environment Protection Agency and it is being phased out of the dry cleaning process (in 2013, 85% US dry cleaners used PERC). The US EPA announced that all existing PERC dry

cleaning machines in co-residential facilities are prohibited in the US after Dec. 21, 2020, and the state of California is committed to phasing out PERC by 2023. Carbon dioxide and decamethylcyclopentasiloxane are perceived as suitable alternative solvents. The cost of machinery for implementation of liquid carbon dioxide is very high (about 3-4 times higher than machines for use of other solvents on the market).

This section was added by Editor to account for most recent changes characterizing new developments in dry cleaning following writing the original of this section.

REFERENCES

1 H Eigen, C Meyer, M Seiter, **CA2763392**, *Chemische Fabrik Kreussler & Co*., 29 Dec. 2010.
2 C Meyer, H Eigen, M Seiter, **US20120084928**, *Chemische Fabrik Kreussler & Co*., 12 Apr. 2012.
3 R J Perry, D A Riccio, L D Ryan, **WO2002050366**, *General Electric*, 27 Jun. 2002.
4 S. Sutanto, V. Dutschk, J. Mankiewicz, M. van Roosmalen, M. M. C. G. Warmoeskerken, G.-J. Witkamp, *J. Supercrit. Fluids*, **89**, 1-7, 2014.
5 S. Sutanto, M. J.E. van Roosmalen, G. J. Witkamp, *J. Supercrit. Fluids*, **93**, 138-43, 2014.
6 https://drycleancoalition.org/chemicals/chemicalsusedindrycleaningoperations.pdf

13.8 FABRICATED METAL PRODUCTS

GEORGE WYPYCH
ChemTec Laboratories, Toronto, Canada

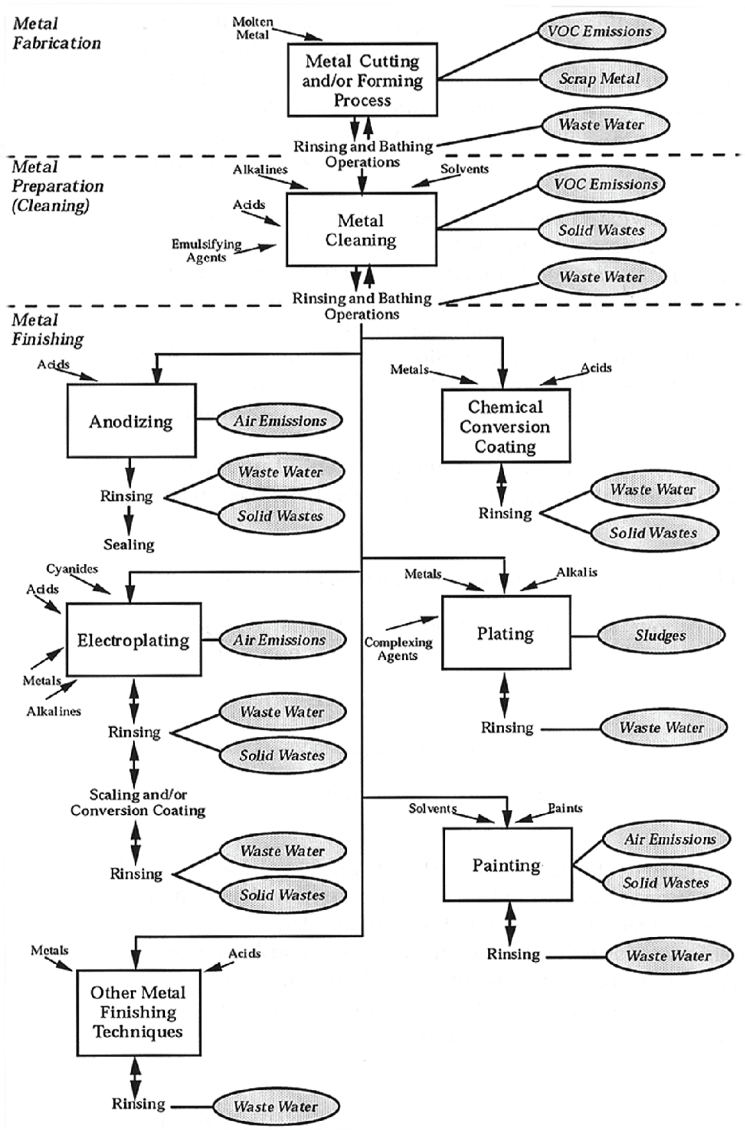


Figure 13.8.1. Schematic diagram of operations in fabricated metal products manufacturing process. [Reproduced from EPA Office of Compliance Sector Notebook Project. Profile of the Fabricated Metal Products Industry. US Environmental Protection Agency, 1995.]

Figure 13.8.1 shows a schematic diagram of the operations in a fabricated metal products manufacturing process.[1] The diagram shows that solvent emissions, wastewaters, and solid wastes are produced from three operations: the metal cutting and forming process, metal cleaning, and painting. In metal cutting and forming, the major solvents used are 1,1,1-trichloethane, acetone, toluene, and xylene. In surface cleaning, the straight solvents are used for cleaning or some solvents such as kerosene or glycols are emulsified in water and the emulsion is used for cleaning. When emulsions are used the amount of solvent is decreased. Solvents are released due to evaporation, volatilization during storage, and direct ventilation of fumes. Wastewaters are generated from rinse waters. These wastewaters are typically cleaned on-site by conventional hydroxide precipitation. Solid wastes are generated from waste-water cleaning sludge, still bottoms, cleaning tank residues, and machining fluid residues. In painting, two methods are used: spray painting and electrodeposition. Painting operations release benzene, methyl ethyl ketone, methyl isobutyl ketone, toluene, and xylene. Paint cleanup operations also contribute to emissions and waste generation. The predominant solvents used for equipment cleaning are tetrachloride, dichloromethane, 1,1,1-trichloroethane, and perchloroethylene. Sources of solid and liquid waste include components of emission controlling devices (e.g., paint booth collection system and ventilation filters), equipment washing, paint disposal, overspray, and excess paint discarded after expiration of paint's shelf-life.

Table 13.8.1. Reported solvent releases from the metal fabricating and finishing facilities in 1993 [Data from Ref. 1].

Solvent	Amount, kg/year	Solvent	Amount, kg/year
acetone	870,400	2-methoxyethanol	22,800
benzene	1,800	methyl ethyl ketone	4,540,000
n-butyl alcohol	495,000	methyl isobutyl ketone	934,000
sec-butyl alcohol	13,600	tetrachloroethylene	844,000
cyclohexanone	303,000	toluene	3,015,000
1,2-dichlorobenzene	10,900	1,1,1-trichloroethane	2,889,000
dichlorofluoromethane	10,800	trichloroethylene	3,187,000
dichloromethane	1,350,000	trichlorofluoromethane	82,000
ethylbenzene	299,000	1,2,4-trimethylbenzene	262,000
ethylene glycol	99,000	xylene (mixture)	4,814,000
2-ethoxy ethanol	18,600	m-xylene	8,800
isopropyl alcohol	23,400	o-xylene	17,000
methanol	199,000	p-xylene	10

Table 13.8.1 shows reported solvent releases from metal fabricating and finishing facilities and Table 13.8.2 shows reported solvent transfers from the same industry.

Xylene, methyl ethyl ketone, trichloroethylene, 1,1,1-trichloroethane, and dichloromethane are released in the largest quantities. Methyl ethyl ketone, xylene, toluene, tri-

chloroethylene, and methyl isobutyl ketone are transferred in the largest quantities outside the industry for treatment and disposal. The metal fabrication and finishing industry's contribution to reported releases and transfers in 1995 was 9.3% of the total for 21 analyzed industries. This industry is the fourth largest contributor to total reported releases and transfers.

Table 13.8.2. Reported solvent transfers from the metal fabricating and finishing facilities in 1993 [Data from Ref. 1]**.**

Solvent	Amount, kg/year	Solvent	Amount, kg/year
acetone	767,000	methyl ethyl ketone	5,130,000
n-butyl alcohol	282,000	methyl isobutyl ketone	846,000
sec-butyl alcohol	495	tetrachloroethylene	415,000
cyclohexanone	1,025	toluene	1,935,000
dichloromethane	237,000	1,1,1-trichloroethane	920,000
ethylbenzene	263,000	trichloroethylene	707,000
ethylene glycol	68,000	1,2,4-trimethylbenzene	42,000
2-ethoxy ethanol	1,800	xylene (mixture)	2,335,000
isopropyl alcohol	41,000	m-xylene	27,000
methanol	138,000	o-xylene	37
2-methoxyethanol	7,800	p-xylene	23

Among the potential actions to reduce pollution, these are the most effective: recycling of solvents, employing better waste control techniques, and substituting raw materials. For solvent cleaning, several techniques are suggested. Employees should be required to obtain solvent from their supervisor. It is estimated that this will reduce waste by 49%. Pre-cleaning (wipe, blow part with air, etc.) should be adopted or the parts should be first washed with used solvent. Equipment for vapor degreasing should be modified by increasing its headspace, covering degreasing units, installing refrigerator coils, rotating parts before removing, installing thermostatic controls, and adding filters. Trichloroethylene and other halogenated solvents should be replaced with liquid aqueous alkali cleaning compounds.

Other waste reduction can be realized by the better production scheduling, use of dry filters in the spray booth, prevention of leakage from the spray gun, separation of wastes, and recycling of solvents by distillation.

Such comprehensive data for present consumption are not any longer collected by EPA, which does not mean that there are no improvements. It is known from the literature that open systems are analyzed and modeled to reduce emissions and closed systems are popular in industrial applications.[3] Vapor degreasing is an example of enclosed systems which permits control of solvent emissions. n-Propyl bromide is a popular solvent used in metal cleaning.

Firma Kreussler developed an environmentally friendly system which includes a solvent, which is halogen-free, synthetic, acetal-based product.[4] In addition to metal parts, this solvent can also be used in cleaning textiles and electronics.[4]

The global impacts and local risks due to the use of organic solvents and aqueous agents were evaluated in a case study of metal cleaning processes.[5] The contribution of chlorinated solvents to photochemical ozone creation was much larger than that of the processes using aqueous detergents but the contribution of aqueous processes to eutrophication was significant, whereas that of the solvent processes was negligible.[5] The neighbors' health risks were small in all the scenarios developed in this case study for both solvent and aqueous agents.[5] The ecological risks in the river where wastewater from the cleaning site was discharged were not negligible for aqueous cleaning.[5] Wastewater treatment for removing surfactants was necessary for processes using aqueous detergents to reduce the contribution to the risk increase.[5] It was postulated that the decision makers who select an alternative substance should recognize the countervailing risk that may be posed as a result of the substitution.[5]

REFERENCES

1 EPA Office of Compliance Sector Notebook Project. Profile of the Fabricated Metal Products Industry. US Environmental Protection Agency, 1995.
2 EPA Office of Compliance Sector Notebook Project. Sector Notebook Data Refresh - 1997. US Environmental Protection Agency, 1998.
3 E Kikuchi, Y Kikuchi, M Hirao, Proceedings of the 22nd European Symposium on Computer Aided Process Engineering, 17-20 June 2012, London.
4 H Eigen, C Meyer, M Seiter, **WO2012000848**, *Chemische Fabrik Kreussler & Co. GmbH*, 5 Jan. 2012.
5 E. Kikuchi, Y. Kikuchi, M. Hirao, *J. Cleaner Production*, **19**, 5, 414-23, 2011.

13.9 FOOD INDUSTRY – SOLVENTS FOR EXTRACTING VEGETABLE OILS

Phillip J. Wakelyn* and Peter J. Wan**
National Cotton Council, Washington, DC, USA*
USDA, ARS, SRRC, New Orleans, LA, USA**

13.9.1 INTRODUCTION

Many materials including oils, fats, and proteins, for both food and nonfood use, are recovered from diverse biological sources by solvent extraction.[1,2] These materials include animal tissues (e.g., beef, chicken, pork and fish); crops specifically produced for oil or protein (e.g., soy, sunflower, safflower, rape/canola, palm, and olive); by-products of crops grown for fiber (e.g., cottonseed and flax); food (e.g., corn germ, wheat germ, rice bran, and coconut); confections (e.g., peanuts, sesame, walnuts, and almonds); nonedible oils and fats (castor, tung, jojoba); and other oil sources (oils and fats from microbial products, algae, and seaweed). There are many physical and chemical differences between these diverse biological materials. However, the similarities are that oils (edible and industrial) and other useful materials (e.g., vitamins, nutriceuticals, fatty acids, phytosterols, etc.) can be extracted from these materials by mechanical pressing, solvent extracting, or a combination of pressing and solvent extraction. The preparation of the various materials to be extracted varies. Some need extensive cleaning, drying, fiber removal (cottonseed), dehulling, flaking, extruding, etc., all of which affect the solvent-substrate interaction and, therefore, the yield, composition, and quality of the oils and other materials obtained.

Historically, the advancement of processing technology for recovering oils and other useful materials has been primarily driven by economics. For thousands of years stone mills, and for several centuries simple hydraulic or lever presses were used as batch systems. The continuous mechanical presses only became a reality during the early 1900s. It was not until the 1930s, that extraction solvents were used more widely, which greatly enhanced the recovery of oil from oilseeds or other oil bearing materials.

In solvent extraction, crude vegetable oil and other useful materials are dissolved in a solvent to separate them from the insoluble meal. Many solvents have been evaluated for commercial extraction. Commercial hexane has been the main solvent for the oilseed processing industry since the 1940s[1,2] because of its availability at a reasonable cost and its suitable functional characteristics for oil extraction. However, the interest in alternative solvents to hexane has continued and is motivated by one of a combination of factors: the desire for a nonflammable solvent, more efficient solvent, more energy efficient solvent, less hazardous and environmentally friendly solvent, a solvent with improved product quality, and solvents for niche/specialty markets. Commercial isohexane (hexane isomers) is replacing commercial hexane in a few oilseed extraction operations and other solvents (e.g., isopropanol, ethanol, acetone, etc.) are also being used for various extraction processes or have been evaluated for use as extracting solvents.[3-6]

With the greater flexibility of operating hardware and availability of various solvents with tailored composition, the oilseed industry does have expanded options to choose the

unique composition of solvents to obtain the desired final products. While the availability, cost, ease-of-use (i.e., no specialty processing hardware required and with low retrofitting costs), and acceptable product quality continue to be the principal factors used to choose a solvent for oil extraction, in recent years environmental concerns and health risk have become increasingly important criteria to be considered in selecting an oil extraction solvent.

This chapter presents information on solvents for extracting oilseeds and other biological materials for oils, fats, and other materials.

13.9.2 REGULATORY CONCERNS

Many workplace, environmental, food safety, and other regulations (see Tables 13.9.1 and 13.9.2 for summary information on U.S. laws and regulations) apply to the use of solvents for the extraction of oilseeds and other diverse biological materials. Some solvent may have fewer workplace and environmental regulatory requirements; offer benefits, such as an improved product quality and energy efficiency;[7] as well as other advantages, such as the ability to remove undesirable (e.g., gossypol from cottonseed) and desirable (e.g., vitamin E, tocopherols, lecithins, phytosterols, and long-chain polyunsaturated fatty acids) constituents of oilseeds and other biological materials more selectively. Some of the regulations required in the United States are discussed. Many other countries have similar requirements, but if they do not, it would be prudent to consider meeting these regulations in solvent extraction and to have environmental, health and safety, and quality management programs.[19,44]

Table 13.9.1. U.S. Worker health and safety laws and regulations

Laws:
Occupational Safety and Health Act of 1970 (OSHA) (PL 91-596 as amended by PL 101 552; 29 U.S. Code 651 et. seq. as amended through January 1, 2004)
OSHA Health Standards:
Air Contaminants Rule, 29 CFR 1910.1000
Hazard Communication Standard, 29 CFR 1910.1200, Revision 3, issued in the Federal Register, March 26, 2012.
OSHA Safety Standards:
Process Safety Management, 29 CFR 1910.119
Emergency Action Plan, 29 CFR 1910.38(a)(1)
Fire Prevention Plan, 29 CFR 1910.38(b)(1)
Fire Brigades, 29 CFR 1910.156
Personal Protection Equipment (General Requirements 29 CFR 1910.132; eye and face protection,.133; respiratory protection.134)

Table 13.9.2. U.S. Environmental laws and regulations

Law or Regulation	Purpose
Environmental Protection Agency (EPA) (established 1970)	To protect human health and welfare and the environment
Clean Air Act (CAA) (42 U.S. Code 7401 et seq.)	To protect the public health and welfare. Provides EPA with the authority to set NAAQS, to control emissions from new stationary sources, and to control HAP.
Federal Water Pollution Control Act (known as the Clean Water Act) (CWA) (33 U.S. Code 1251 et seq.)	The major law protecting the "chemical, physical and biological integrity of the nation's waters." Allows the EPA to establish federal Limits on the amounts of specific Pollutants that can be released by municipal and industrial facilities.
Toxic Substances Control Act (TSCA) (15 U.S. Code 2601 et seq.)	Provides a system for identifying and evaluating the environmental and health effects of new chemicals and chemicals already in commerce.
Resource Conservation and Recovery Act (RCRA) (42 U.S. Code 6901 et seq.)	A system for handling and disposal of non-hazardous and hazardous waste.
Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) (42 U.S. Code 9601 et seq.)	Known as "Superfund", gives the EPA power to recover costs for containment, other response actions, and cleanup of hazardous waste disposal sites and other hazardous substance releases.
Emergency Planning and Community Right-to-Know Act (EPCRA; also "SARA 313") (42 U.S. Code 1101 et seq.)	(Part of Superfund) Provides authority for communities to devise plans for preventing and responding to chemical spills and release into the environment; requires public notification of the types of hazardous substances handled or release by facilities; requires state and local emergency plans.

13.9.2.1 Workplace regulations

Workplace regulations (see Table 13.9.1) are promulgated and enforced in the U.S. by the Occupational Safety and Health Administration (OSHA), which is in the Department of Labor. The purpose of OSHA is to ensure that the employers maintain a safe and healthful workplace. Several workplace standards that affect extraction solvents are discussed.

13.9.2.1.1 Air Contaminants Standard (29 CFR 1910.1000)

The purpose of the air contaminants standard is to reduce the risk of occupational illness for workers by reducing permissible exposure limits (PEL) for chemicals. Table 13.9.3 lists the PELs [8-hr. time-weighted average (TWA) exposure] for the solvents discussed. To achieve compliance with the PEL, administrative or engineering controls must first be determined and implemented, whenever feasible. When such controls are not feasible to achieve full compliance, personal protective equipment, work practices, or any other protective measures are to be used to keep employee exposure below the PEL.

Table 13.9.3. U.S. Workplace regulations,[a] air contaminants

Chemical Name (CAS #)	Permissible Exposure Limit (PEL) [Health Risk: Basis for the PEL]
n-Hexane (110-54-3)	500 ppm/1800 mg/m^3; new PEL was 50 ppm/180 mg/m^3 same as ACGIH (TLV); [neuropathy]
Commercial hexane[b] (none)	(Same as n-hexane)
n-Heptane (142-82-5)	500 ppm/2000 mg/m^3; new PEL was 400 ppm/1600 mg/m^3, (500 ppm/2050 mg/m^3 STEL) same as ACGIH (TLV); [narcosis]
Cyclohexane (110-82-7)	300 ppm/1050 mg/m^3; ACGIH (TLV) 300 ppm/1030 mg/m^3; [sensory irritation]
Cyclopentane (287-92-3)	None; new PEL was 600 ppm, same as ACGIH (TLV); [narcosis]
Hexane isomers	None; new PEL was 500 ppm/1760 mg/m^3 (1000 ppm STEL) same as ACGIH (TLV); [narosis]
Commercial isohexane[c] (none)	(Same as hexane isomer)
2-Methyl pentane (isohexane) (2-MP) (107-83-5)	(Same as hexane isomer)
3-Methyl pentane (3-MP) (96-14-0)	(Same as hexane isomer)
Methyl cyclopentane (MCP) (96-37-7)	(Same as hexane isomer)
2,2 Dimethyl butane (neohexane) (2,2-DMB) (75-83-2)	(Same as hexane isomer)
2,3 Dimethyl butane (2,3-DMB) (79-29-8)	(Same as hexane isomer)
Methyl cyclohexane (108-87-2)	500 ppm; new PEL was 400 ppm/1610 mg/m^3, same as ACGIH (TLV); [narcosis]
Isopropyl alcohol (2-propanol) (IPA) (67-17-5)	400 ppm/980 mg/m^3; ACGIH (TLV) same plus 500 ppm/1225 mg/m^3 STEL; [sensory irritation]
Ethyl alcohol (ethanol) (64-17-5)	1000 ppm/1880 mg/m^3; ACGIH (TLV) same; [narcosis, irritation]
Acetone (67-64-1)	1000 ppm/2400 mg/m^3; ACGIH (TLV) 750 ppm (1780 ppm STEL); [sensory irritation]

[a]CAS No. is the Chemical Abstracts Service Registry Number; PEL is from 29 CFR 1910.1000, Table Z-1; American Conference on Governmental Industrial Hygienists (ACGIH), threshold limit value (TLV); under the HCS, MSDS is required for all of the compounds (physical and/or chemical hazard); all of the solvents are flammable liquids or gasses, under the OSHA definition, and are regulated under the PSM Standard.

[b]Commercial hexane as used in the U.S. is usually about 65% n-hexane, and the rest is hexane isomers (e.g., methyl cyclopentane (MCP), 2-methyl pentane (2-MP), and 3-methyl pentane (3-MP)), and it contains less than 10 ppm benzene.
[c]Mixture of 2-MP (45-50%), 3-MP, 2,2-DMB, and 2,3-DMB. (ref 7)

In the case of a mixture of contaminants, an employer has to compute the equivalent exposure when the components in the mixture pose a synergistic threat (toxic effect on the same target organ) to worker health.[8,9]

13.9.2.1.2 Hazard Communication Standard (HCS) (29 CFR 1910.1200)

The HCS requires information on hazardous chemicals to be transmitted to employees through labels, material safety data sheets (MSDS), and training programs. A written hazard communications program and record keeping are also required.

A substance is a "hazardous chemical" if it is a "physical hazard" or a "health hazard". A flammable or explosive liquid is a "physical hazard". A flammable liquid means "any liquid having a flash point below 110°F (37.8°C), except any mixture having components with flash points of 100°F (37.8°C) or higher, the total of which make up 99% or more of the total volume of the mixture". "Health hazard" means "a chemical for which there is statistically significant evidence based on at least one valid study that acute or chronic health effects may occur in exposed employees". Hexane and all the solvents listed in Table 13.9.3 would require MSDS since all are flammable liquids (physical hazards) as defined by OSHA and/or possible health hazards because all, except hexane isomers, have a U.S. OSHA PEL. However, hexane isomers have an American Conference of Industrial Hygienist (ACGIH) threshold limit value (TLV),[10] which many states and countries enforce as a mandatory standard.

Chemical manufacturers and importers are required to review the available scientific evidence concerning the hazards of chemicals they produce or import, and to report the information to manufacturing employers who use their products. If a chemical mixture has not been tested as a whole to determine whether the mixture is a hazardous chemical, the mixture is assumed to present the same hazards as do the components that comprise 1% or greater of the mixture or a carcinogenic hazard if it contains a component in concentration of 0.1% or greater that is a carcinogen. Commercial hexane containing 52% n-hexane has been tested and found not to be neurotoxic, unlike pure n-hexane.[11-13] So mixtures with less than 52% n-hexane should not be considered to be a neurotoxin, although n-hexane would have to be listed on the MSDS, if in greater quantity than 1% of the mixture.

13.9.2.1.3 Process Safety Management (PSM) Standard (29 CFR 1910.119)

PSM is for the prevention or minimization of the consequences of catastrophic releases of toxic, reactive, flammable, or explosive chemicals. This regulation applies to all processes that involve one or more of 137 listed chemicals (29 CFR 1910.119, Appendix A) above their threshold quantities or have 10,000 lbs. or more of a flammable liquid or gas, as defined by the U.S. OSHA HCS [29 CFR 1910.1200(c)]. This includes n-hexane, hexane isomers, and all solvents listed in Table 13.9.3.

In addition to the PSM standard, U.S. OSHA has been enforcing two other regulations for operations/processes with flammable liquids. First, under Personal Protective Equipment – General Requirements (29 CFR 1910.132), OSHA has cited or obtained voluntary agreement from organizations relative to flame-resistant (FR) clothing. Operators

and other employees working in the area of a flammable process are being required to wear flame-resistant work clothing. For facilities that use hexane and other flammable solvents, it would be prudent to require FR clothing for all personnel working in areas where there is an exposure to a flammable liquid. Second, OSHA has cited organizations for failure to meet related safety regulations under Fire Brigades (29 CFR 1910.156), specifically for standards such as: training, both initial and annual refresher training; protective equipment availability and testing; and fitness for duty including periodic physicals. If an on-site fire brigade is part of the site's Emergency Response Plan (29 CFR 1910.38), then these requirements must also be met. In addition, the requirement of the PSM standard for an Emergency Response Plan triggers the requirements of Emergency Action Plan [29 CFR 1910.38(a)].

13.9.2.2 Environmental regulations

The role of the U.S. Environmental Protection Agency (EPA) is to protect human health and welfare and the environment. The U.S. EPA administers all regulations affecting the environment and chemicals in commerce. The individual states and state environmental regulatory control boards implement and enforce most of the regulations. The legislation that serves as the basis for the regulations can be divided into: statutes that are media-specific [Clean Air Act (CAA) and Clean Water Act (CWA)]; statutes that manage solid and hazardous waste [Resources Conservation and Recovery Act (RCRA) and Comprehensive Environmental Response, Compensation and Liability Act (CERCLA; “Superfund”)]; and, statutes that directly limit the production rather than the release of chemical substance [Toxic Substances Control Act (TSCA) and Federal Insecticide, Fungicide and Rodenicide Act (FIFRA)]. See Table 13.9.2 for a summary of the information on environmental laws and regulations, and Tables 13.9.4 and 13.9.5 for an overview of environmental requirements that apply to each solvent.

Table 13.9.4. U.S. Environmental regulations, air, and water.

Chemical Name (CAS No.)	VOC	HAP	CWA	Solub. in H_2O
n-Hexane (110-54-3)	Yes	Yes	Yes	I
Commercial hexane(none)	Yes			
n-Heptane (148-82-5)	Yes	No	Yes	I
Cyclohexane (110-82-7)	Yes	No	Yes	0.01
Cyclopentane (287-92-3)	Yes	No	Yes	I
Hexane isomers (none)	Yes	No	Yes	
Commercial isohexane (none)	(same as hexane isomers)	No	Yes	
2-Methyl pentane (isohexane) (107-83-5)	(a hexane isomer) Yes	No	Yes	0.0014
3-Methyl pentane (96-14-0)	(a hexane isomer) Yes	No	Yes	0.0013
Methyl cyclopentane (96-37-7)	(a hexane isomer) Yes	No	Yes	0.0013
2,2-Dimethyl butane (neohexane) (75-83-2)	(a hexane isomer) Yes	No	Yes	0.0018

Table 13.9.4. U.S. Environmental regulations, air, and water.

Chemical Name (CAS No.)	VOC	HAP	CWA	Solub. in H_2O
2,3-Dimethyl butane (79-29-8)	(a hexane isomer) Yes	No	Yes	0.0011
Methyl cyclohexane(108-87-2)	Yes	No	Yes	0.0014
Isopropyl alcohol (2-propanol) (67-17-5)	Yes	No	Yes	Misc.
Ethyl alcohol (ethanol) (64-17-5)	Yes	No	Yes	Misc.
Acetone (67-64-1)	No[b]	No	Yes	Misc.

[a]Under the Clean Water Act there could be stormwater and NPDES permit requirements; none of the solvents are listed as priority toxic pollutants in 40 CFR 401.15.
[b]Acetone is considered by the U.S. EPA not be a VOC (60 FR 31643; June 16, 1995)
Abbreviations: CAS No., Chemical Abstracts Service Registry number; VOC, volatile organic chemical; HAP, hazardous air pollutant; CWA, Clean Water Act; I, insoluble in H_2O; MISC., miscible in H_2O; and 0.01, 0.01 parts soluble in 100 parts H_2O. Source for water solubility: Ref 47.

Table 13.9.5 U.S. Environmental regulations, waste.

Chemical Name (CAS #)	(RCRA)		(EPCRA/SARA Title III)[a]	
	RCRA Code[b]	Sec. 304 CERCLA RQ	Sec. 311/312	Sec. 313 (TRI)
n-Hexane (110-54-3)		5000[c]	Yes	Yes
Commercial hexane(none)			Yes	Yes[d]
n-Heptane (148-82-5)			Yes	No
Cyclohexane (110-82-7)	U056	1000	Yes	Yes
Cyclopentane (287-92-3)			Yes	No
Hexane isomers (none)			Yes	No[e]
Commercial isohexane (none)				No[e]
2-Methyl pentane (isohexane) (107-83-5)			Yes	No[e]
3-Methyl pentane (96-14-0)			Yes	No[e]
Methyl cyclopentane (96-37-7)			Yes	No[e]
2,2-Dimethyl butane (neohexane) (75-83-2)			Yes	No[e]
2,3-Dimethyl butane (79-29-8)			Yes	No[e]
Methyl cyclohexane(108-87-2)			Yes	No
Isopropyl alcohol (2-propanol) (67-17-5)			Yes	No[f]
Ethyl alcohol (ethanol) (64-17-5)			Yes	No
Acetone (67-64-1)	U002	5000	Yes	No

[a]From Title III Lists of Lists, U.S. EPA, EPA 740-R-95-001 (April 1995); 40 CFR 52-99; (59 FR 4478; January 31, 1994) hexane added to TRI list; (60 FR 31633; June 16, 1995) acetone removed from TRI list.

[b]40 CFR 261.33, listed hazardous waste - EPA RCRA Hazardous Waste Number. All the solvents that are on the RCRA list are listed because of Section 3001 of RCRA (part for identification and listing of hazardous waste) except hexane which is on because of CAA Section 112 (HAP).
[c]RQ for hexane finalized June 12, 1995 (60 FR 30939).
[d]Only the amount of commercial hexane that is n-hexane has to be reported (e.g., if the commercial hexane is 62% n-hexane, only 62% of the emissions have to be reported for TRI).
[e]The EPA clarified that the listing for hexane was only for n-hexane, other isomers of hexane are not included. (59 FR 61457; Nov. 30, 1994).
[f]The EPA has indicated (62 FR 22318, April 25, 1997) that IPA itself does not meet the criteria for listing on the TRI list. The EPA will remove IPA from the TRI list. Abbreviations: RQ, reportable quantity in pounds/24 h.

13.9.2.2.1 Clean Air Act (CAA; 42 U.S. Code 7401 et seq.)

To satisfy the CAA requirements, states and state air control boards are required to implement regulations and develop state implementation plans (SIP).[14,15] Criteria pollutants (e.g., ozone, oxides of nitrogen, carbon monoxide) are regulated with National Ambient Air Quality Standards (NAAQS) and hazardous air pollutants (HAP), such as hexane, with National Emissions Standards for Hazardous Air Pollutants (NESHAP).

The NAAQS are set at levels sufficient to protect public health (primary air quality standards) and welfare (secondary air quality standards; "welfare effects" include wildlife, visibility, climate, damage to and deterioration of property and effects on economic value and on personal comfort and well being) from any known or anticipated adverse effect of the pollutant with an adequate (appropriate) margin of safety. The 1990 CAA expanded the list of HAP to 188, including hexane, and more strictly regulates nonattainment areas for criteria pollutants such as ozone, particulate matter, carbon monoxide and oxides of nitrogen.

NAAQS: Volatile organic compounds (VOC) are essentially considered the same as the criteria pollutant ozone.[16,17] VOCs are very broadly defined by the U.S. EPA (40 CFR 51.100): any compound of carbon, excluding carbon monoxide, carbon dioxide, carbonic acid, metallic carbides or carbonates, and ammonium carbonate, that participates in atmospheric photochemical reactions. This includes any organic compound other than those specifically listed as having been determined to have negligible photochemical reactivity. Reactive VOCs are essentially all those judged to be clearly more reactive than ethane – the most reactive member of the "negligibly reactive" class. C_4-C_6 paraffins are of relatively low kinetic reactivity but produce NO_2, and potentially ozone.[18] Hexane and all of the solvents discussed, except acetone, would be considered VOCs (see Table 13.9.4) that can undergo photochemical oxidation in the atmosphere to form ozone. In the U.S., acetone was added to the list of compounds excluded from the definition of VOCs in 1995, because it was determined to have negligible photochemical reactivity.[19]

Most U.S. vegetable-oil extracting facilities would be major sources of VOCs and would be covered by the requirements for ozone emissions and attainment unless they used a solvent that was not classified as a VOC. (The definition of "major source" changes as the severity of the ozone nonattainment area increases. Plants in marginal and moderate areas are major if they emit 100 tons VOC/yr; in serious areas, 50 tons/yr; in severe areas, 25 tons/yr; and in extreme areas 10 tons/yr). All facilities in ozone non-attainment areas could be required to reduce emissions through implementing Reasonable Available Control Measures (RACM) standards or Best Available Control Measures (BACM). Any new

or significantly modified facility would have to comply with the new source review (NSR) requirements and prevention of significant deterioration (PSD) requirements.

Hazardous air pollutants (HAP) or air toxics: If a facility is a major emitter of any of the chemicals on the CAA list of HAPs, EPA requires sources to meet emissions standards.[14,16,17] n-Hexane is on the HAP list but isohexane, acetone and other solvents listed in Table 13.9.4 are not.

The air toxic requirements of the CAA for establishing control measures for source categories are technology-based emission standards (not health-based) established for major sources (10 tons/yr of one HAP or 25 tons/yr of total HAP) that require the maximum degree of reduction emissions, taking costs, other health and environmental impacts, and energy requirements into account. Standards are set based on known or anticipated effects of pollutants on the public health and the environment, the quantity emitted, and the location of emissions. Compliance involves the installation of Maximum Achievable Control Technology (MACT) – MACT essentially is maximum achievable emission reduction. For new sources, MACT standards must be no less stringent than the emission control achieved in practice by the best controlled similar source. The MACT standards for vegetable oil processing using n-hexane has been issued in 2001 (Rule and Implementation Information for Vegetable Oil Production; Solvent Extraction was issued on September 1, 2004). Once a standard has been promulgated for a source category, a source had three years after the due date to comply. The requirements cover normal operations and startup, shutdown, and malfunction (SSM). The allowable emissions for solvent extraction for vegetable oil production in the U.S., as a 12-month rolling average based on a 64% n-hexane content, will vary from 0.2 gal/ton to greater than 0.7 gal/ton depending on the oilseed (65FR34252; May 26, 2000). There are also variable emission requirements depending on the oilseed for allowable emissions for solvent extraction for vegetable oil production in Europe.

Table 13.9.6. Oilseed solvent loss factors for allowable HAP loss (12-mo. rolling ave.).

Type of Oilseed Process	A source that...	Oilseed Solvent Loss Factor (gal/ton)	
		Existing Sources	New Sources
Corn Germ, Wet Milling	processes corn germ that has been separated from other corn components using a wet process of centrifuging a slurry steeped in a dilute sulfurous acid solution	0.4	0.3
Corn Germ, Dry Milling	processes corn germ that has been separated from the other corn components using a dry process of mechanical chafing and air sifting	0.7	0.7
Cottonseed, Large	processes 120,000 tons or more of a combination of cottonseed and other listed oilseeds during all normal operating periods in a 12 operating month period	0.5	0.4

Table 13.9.6. Oilseed solvent loss factors for allowable HAP loss (12-mo. rolling ave.).

Type of Oilseed Process	A source that...	Oilseed Solvent Loss Factor (gal/ton)	
		Existing Sources	New Sources
Cottonseed, Small	processes less than 120,000 tons of a combination of cottonseed and other listed oilseeds during all normal operating periods in a 12 operating month period	0.7	0.4
Flax	processes flax	0.6	0.6
Peanuts	processes peanuts	1.2	0.7
Rapeseed	processes rapeseed	0.7	0.3
Safflower	processes safflower	0.7	0.7
Soybean, Conventional	uses a conventional style desolventizer to produce crude soybean oil products and soybean animal feed products	0.2	0.2
Soybean, Specialty	uses a special style desolventizer to produce soybean meal products for human and animal consumption	1.7	1.5
Soybean, Small Combination Plant	processes soybeans in both specialty and conventional desolventizers and the quantity of soybeans processed in specialty desolventizers during normal operating periods are less than 3.3 percent of total soy-beans processed during all normal operating periods in a 12 operating month period. The corresponding solvent loss factor is an overall value and applies to the total quantity of soybeans processed	0.25	0.25
Sunflower	processes sunflower	0.4	0.3

A health-based standard would be for a boundary line level of a solvent (e.g., n-hexane) based on the inhalation reference concentration (RfC).[20] The current RfC for n-hexane is 200 mg/m^3. Recent research suggests that the RfC for hexane should be at least 10 times higher (> 2000 mg/m^3).

Federal permits: All major sources of regulated solvents are required to have federally enforceable operating permits (FOP)[14,15] (also referred to as Title V permits).

State permits: Most states require state permits for facilities that emit listed air pollutants.[14,15] In some states federal permits and state permits are combined, while in other states facilities are required to have both a state or county (air district) permit and a federal permit. As part of annual emission inventory reporting requirements, many states already require reporting of HAP and VOC because of their state implementation plan (SIP).

13.9.2.2.2 Clean Water Act (CWA; 33 U.S. Code 1251 et seq.)

The CWA is the major law protecting the “chemical, physical and biological integrity of the nation's waters.” Under it, the U.S. EPA establishes water-quality criteria used to develop water quality standards, technology-based effluent limitation guidelines, and pretreatment standards and has established a national permit program [National Pollution Discharge Elimination System (NPDES) permits; 40 CFR 122] to regulate the discharge

of pollutants. The states have a responsibility to develop water-quality management programs.

For extraction solvents, vegetable oil extracting facilities are covered by basic discharge effluent limitations [direct discharges to receiving waters or indirect discharges to publicly owned treatment works (POTW)], and stormwater regulations.[15] The amount of solvent in effluent discharges and in stormwater (for those covered) needs to be determined and possibly monitored as part of an NPDES permit and as part of the visual examination or testing of stormwater quality.

13.9.2.2.3 Resource Conservation and Recovery Act (RCRA; 42 U.S.Code 6901 et seq.)

RCRA subtitle C (40 CFR 261) is a federal "cradle-to-grave" system to manage hazardous waste (including provisions for cleaning up releases and setting statutory and regulatory requirements). Subtitle D covers nonhazardous wastes. Materials or items are hazardous wastes if and when they are discarded or intended to be discarded. The act requires generators, transporters, and disposers to maintain written records of waste transfers, and requires the U.S. EPA to establish standards, procedures, and permit requirements for disposal. The act also requires states to have solid waste management plans, prohibits open dumping, and requires the EPA to establish criteria for sanitary landfills. EPA under RCRA also regulates underground storage tanks that store or have stored petroleum or hazardous substances.

Hazardous wastes are either listed wastes (40 CFR 261.30-.33) or characteristic wastes (40 CFR 261.21-.24). The U.S. EPA defines four characteristics for hazardous waste: ignitability (40 CFR 260.21); corrosivity (40 CFR 260.22); reactivity (40 CFR 260.23); and toxicity (40 CFR 260.24). Any waste that exhibits one or more of these characteristics is classified as hazardous under RCRA. The ignitability definition includes a liquid that has a flash point less than 60°C (140°F); the EPA included ignitability to identify wastes that could cause fires during transport, storage, or disposal (e.g., used solvents). All of the solvents in Table 13.9.5 have flash points less than 60°C, so all could be RCRA ignitability waste.

13.9.2.2.4 Emergency Planning and Community Right-to-Know Act (EPCRA; 42 U.S. Code 11001 et seq.)

Enacted as Title III of the 1986 Superfund Amendments and Reauthorization Act ("SARA"), the Act mandates the EPA to monitor and protect communities regarding releases of chemicals into the environment. It requires states to establish emergency planning districts with local committees to devise plans for preventing and responding to chemical spills and releases. ["Superfund" is the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) of 1980 that gives the U.S. EPA authority to force those responsible for hazardous waste sites or other releases of hazardous substances, pollutants, and contaminants to conduct cleanup or other effective response actions.]

Section 304 (40 CFR 355.40): Facilities are subject to state and local reporting for accidental releases, in quantities equal to or greater than their reportable quantities (RQ), of extremely hazardous substances (EHS) or CERCLA hazardous substances (40 CFR 302, Table 302.4) under Section 304. n-Hexane, cyclohexane, acetone, and some of the

other solvents discussed are CERCLA hazardous substances and have CERCLA RQ for spills (Table 13.9.5).

Section 311, 312 (40 CFR 370.20-.21): Business must make MSDSs, for chemicals that are required to have an MSDS, available to state and local officials. Since all of the solvents discussed require MSDSs under the OSHA HCS, all are covered by these requirements.

Section 313 (40 CFR 372), Toxic Release Inventory (TRI): Businesses are required to file annual reports with federal and state authorities of releases to air, water, and land above a certain threshold for chemicals on the TRI/Section 313 list (40 CFR 372.65) by July 1 each year for the previous year's releases.[21] TRI requirements are triggered if a facility is involved in manufacturing with 10 or more full-time employees, manufactures, processes, or otherwise uses one or more listed substance(s) in a quantity above the statutory reporting threshold of 25,000 lbs/yr (manufactured or processed) or 10,000 lbs/yr (otherwise used). Beginning with the 1991 reporting year, such facilities also must report pollution prevention and recycling data for such chemicals pursuant to Section 6607 of the Pollution Prevention Act (42 U.S. Code 13106).

n-Hexane was added to the TRI list in 1994 with reporting for 1995 emissions.[19] The other solvents discussed are not on the TRI list. The EPA can add new chemicals to or delete chemicals from the TRI list as it deemed necessary and any person may petition the EPA to add chemicals or delete chemicals from the list.

13.9.2.2.5 Toxic Substances Control Act (TSCA; 15 U.S. Code 2601 et seq.)

If a chemical's manufacture, processing, distribution, use, or disposal would create unreasonable risks, the U.S. EPA, under the TSCA, can regulate it, ban it, or require additional testing. TSCA mandates the U.S. EPA to monitor and control the use of toxic substances by requiring the Agency to review the health and environmental effects of new chemicals [referred to as “Premanufacturing Notice” or “PMN”; Section 5(a)(1) of TSCA] and chemicals already in commerce. The U.S. EPA also has Significant New Use Rules (SNUR) under Section 5(a)(2) of TSCA which provides a way for the U.S. EPA to restrict uses of a chemical substance already in commerce that are proposed for new uses. All of the solvents discussed are already commercially available, so a PMN would not apply; some could be subjected to SNUR (40 CFR 721, subpart A) since some are not presently being used as extraction solvents in large quantities.

Under Section 4(a) of TSCA, the U.S. EPA can require testing of a chemical substance or mixture to develop data relevant for assessing the risks to health and the environment. Section 8(d) of TSCA requires that lists of health and safety studies conducted or initiated with respect to a substance or mixture be submitted to the U.S. EPA. All new toxicological data of the effects of a chemical not previously mentioned must be reported immediately if the data reasonably supports the conclusion that such substance or mixture presents a substantial risk of injury to health or the environment [Section 8(e) of TSCA]. Testing (Section 4 test rule) was required for several of the solvents earlier (e.g., commercial hexane for which new toxicological information was reported to the U.S. EPA since 1992),[22] and any new toxicological information will have to be reported to the U.S. EPA under Section 8(e) and 8(d).

13.9.2.3 Food safety

In the U.S. the use of a solvent to extract oil, that is a human food product or used in a food product, from oilseeds and biological materials falls under the rules and regulatory jurisdiction of the U.S. Food and Drug Administration (FDA), which regulates all aspects of food, including food ingredients and labeling in the U.S. In order to be legally used as an oilseed extraction solvent in the U.S., a substance must have been subject to an approval by the U.S. FDA or the U.S. Department of Agriculture (USDA) during 1938-1958 for this use ("prior sanction"); be generally recognized as safe (GRAS) for this use; or be used in accordance with food additive regulations promulgated by the U.S. FDA.

Many prior sanctions and GRAS determinations are not codified in the U.S. FDA regulations. However, extracting solvents used in food manufacturing, such as n-hexane, have been labeled as a food additive, solvent, defoaming agent, component of a secondary food and color additives, minor constituent, or incidental additives (i.e., "additives that are present in a food at significant levels and do not have any technical or functional effect in that food") depending on the application. Incidental additives can be "processing aids," (i.e., "substances that are added to a food during processing but removed from the food before it is packaged"). Most food-processing substances, including solvents, can be regarded as "incidental additives" and thus are exempt from label declaration in the finished food product. Even if exempt from label declaration, all extraction solvents must be used in accordance with the U.S. FDA good manufacturing practices (GMP; 21 CFR 100).

In the U.S., the Flavor and Extract Manufacturers' Association (FEMA) has conducted a program since 1958 using a panel of expert pharmacologists and toxicologists to determine substances that are GRAS. This panel uses all available data, including experience based on common uses in food. This safety assessment program ("FEMA GRAS") is widely accepted and considered an industry/government partnership with the U.S. FDA.[23] A number of papers published in Food Technology since 1961[24,25] list the substances that the panel has determined to be GRAS and the average maximum levels in parts per million (ppm) at which each has been reported to be GRAS for different categories of food. The U.S. FDA has not incorporated these substances in their regulations but does recognize the findings of the Expert Panel of FEMA as GRAS substances.

Since vegetable oil and other human food grade oils undergo deodorization (steam distillation) and other purification processes (i.e., refining and bleaching) as part of the manufacturing process prior to being used as a food product, they should not contain any of the extraction solvent, if proper manufacturing practices are followed. (see Section 13.9.3.3 Processing crude oil, for more details.) Refining removes free fatty acids and other non-oil compounds (e.g., phospholipids, color, and trace metals); bleaching with acid-activated bleaching earth or clay (e.g., bentonite), removes color-producing substances and residual soaps; and deodorization, the last major processing step in edible oils refining removes volatile compounds (undesirable ingredients occurring in natural oils and those that may be imparted by prior unit processes or even storage, many of which are associated with undesirable flavors and odors).[26,27] Most commercial deodorizers operate at a temperature of 245-275°C (475-525°F) under a negative pressure of 2-10 mm Hg.[26,27] It has been reported that no hexane residue remains in the finished oil after processing due

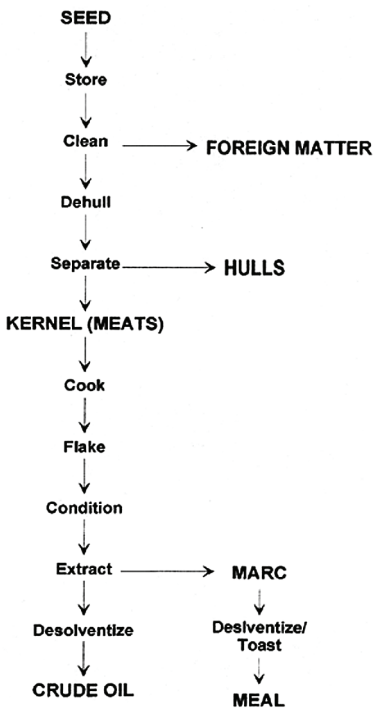


Figure 13.9.1a. Flow diagram of oilseed extraction process from seed to crude oil and meal.

to its high volatility.[28] In addition, animal-feeding studies with expeller and solvent-extracted meals have not indicated any adverse health effects related to the extraction solvent.[29]

Hexane has been used since the 1940s as an oilseed-extraction solvent on the determination that it is GRAS and it may also be subject to a prior sanction. However, like many other food-processing substances, there is no U.S. FDA regulation specifically listing hexane as GRAS or prior sanctioned.

GRAS status may be determined by a company ("GRAS self-determination"), an industry, an independent professional scientific organization (e.g., FEMA GRAS), or the U.S. FDA. The Federal Food, Drug, and Cosmetic Act (FFDCA; 21 U.S. Code 321 et seq.) does not provide for the U.S. FDA to approve all ingredients used in food, and the U.S. FDA explicitly recognizes that its published GRAS list is not meant to be a complete listing of all substances that are in fact GRAS food substances. Although there is no requirement to inform the U.S. FDA of a GRAS self-determination or to request FDA review or approval on the matter, the U.S. FDA has established a voluntary GRAS affirmation program under which such advice will be provided by the agency. Solvents that do not have a prior sanction, a GRAS determination, or a tolerance set, probably should be evaluated for compliance under food safety requirements, if a facility is considering changing its extracting solvent or using a solvent for the extraction of the various biological materials for specialty markets.

13.9.3 THE SOLVENT EXTRACTION PROCESS

Three types of processing systems are used to extract oil from oil-bearing materials: expeller pressing, prepress solvent extraction, and direct solvent extraction. Only prepress solvent extraction and direct solvent extraction, which remove the oil from the conditioned, prepared seed with an organic solvent, will be discussed here[1,27] (see Figures 13.9.1a&b). Oil-bearing materials have to be prepared for extraction to separate the crude oil from the meal. Careful control of moisture and temperature during processing must be exercised to maintain the quality of the protein in the meal and to minimize the damage to the oil. Crude oils are refined by conditioning with phosphoric acid and treating with sodium hydroxide (alkali-refining) (see Figure 13.9.2). Refined oil is bleached with activated clay to remove color pigments. Bleached oils are then deodorized by steam distillation. The refined, bleached, and deodorized oil (RBD oil) is used to produce finished products, e.g., salad and cooking oils, shortening and margarine. Some of the finished

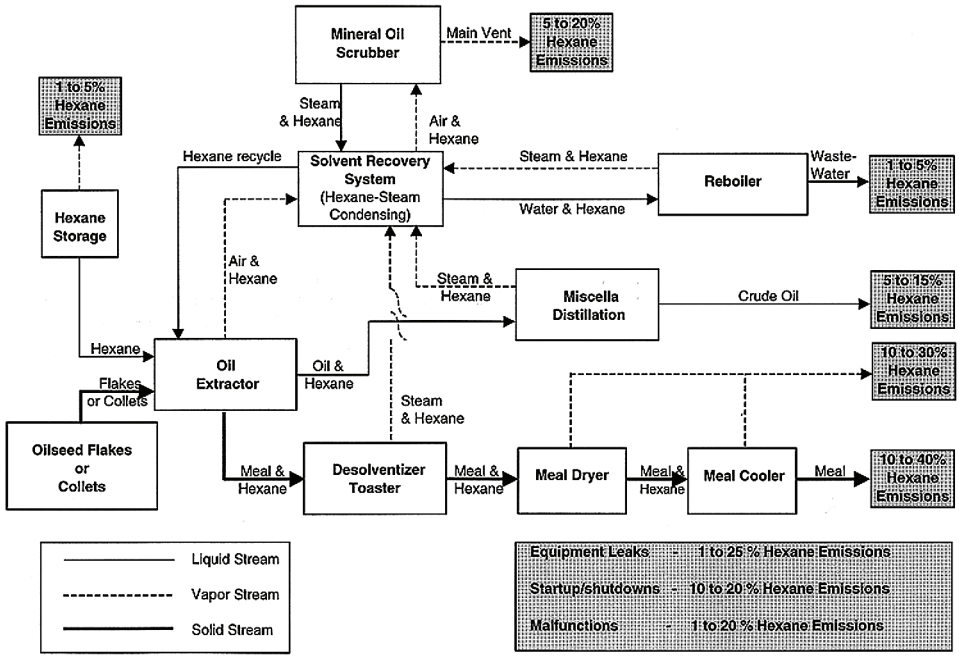


Figure 13.9.1b. Flow diagram of oilseed extraction process. Overview of extraction operation and identification of emission sources.

products also require the oil to be hydrogenated, which changes the consistency of the oil, and increases stability to oxidation, which extends the shelf life of the finished products. Also, some of the oils are winterized to remove the higher melting constituents, which can be used in confectionary products; the winterized oil is less likely to become cloudy in refrigerated storage.

13.9.3.1 Preparation for extraction

Storage: For optimum extraction and quality of oil, the oil-bearing material should be stored so that it remains dry and at relatively low temperature. If it is wet, it should be processed as soon as possible after harvest. Oils in the presence of water can deteriorate rapidly, forming free fatty acids and causing greater refining loss.

Seed cleaning: The first step in the commercial processing of oilseeds is "cleaning", to remove foreign materials, such as sticks, stems, leaves, other seeds, sand, and dirt using dry screeners and a combination of screens and aspiration. Permanent electromagnets are also used for the removal of trash iron objects. Final cleaning of the seed usually is done at the extraction plant just prior to processing.

Dehulling: After cleaning, it may be necessary to remove the seed's outer seed- coat (hull). The seedcoat contains little or no oil, so its inclusion makes the extraction less efficient. Also, the next processing step is grinding to reduce particle size, and any tough seedcoats would interfere with this process. If the hulls are not removed prior to

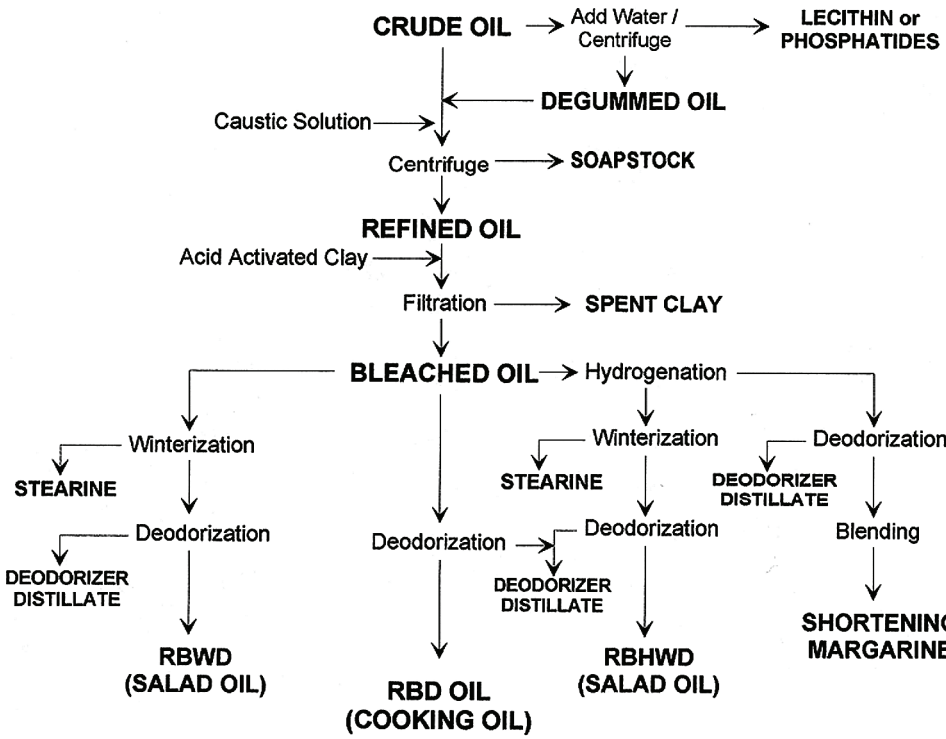


Figure 13.9.2. Flow diagram of edible oil processing.

extraction, they will reduce the total yield of oil by absorbing and retaining oil in the press cake. An acceptable level of hull removal must be determined, depending on the desired protein level of the final meal. Hulls are removed by aspirator and undehulled seeds are removed from the kernels by screening and returned to the huller. Some meats still adhere to the hulls, which are beaten, then screened again to obtain the meat.

Grinding, rolling, or flaking: After dehulling, the meats are reduced in size, or "flaked," to facilitate oil removal. The proper moisture content of the seeds is essential for flaking, and if the moisture level is too low, the seeds are "conditioned," with water or steam, to raise the moisture to about 11%. For solvent extraction, flakes are commonly not less than 0.203-0.254 mm (0.008-0.010 inch), which can be solvent extracted efficiently with less than 1% residual oil. Thinner flakes tend to disintegrate during the solvent extraction process and reduce the miscella percolation rate.

Cooking: Prior to extraction, the flakes are heated. The purpose of cooking the flakes is: (1) cell walls are broken down, allowing the oil to escape; (2) oil viscosity is reduced; (3) moisture content is controlled; (4) protein is coagulated; (5) enzymes are inactivated and microorganisms are killed; and (6) certain phosphatides are fixed in the cake, which helps to minimize subsequent refining losses. Flakes are cooked in stack cookers to over

87.8°C (190°F) in the upper kettle. Flakes with high phosphatide content may benefit from being cooked at slightly lower temperatures to avoid elevating refining losses. The temperature of the flakes is raised to 110-132.2°C (230-270°F) in the lower kettles. The seeds are cooked for up to 120 min. Overcooking lowers the nutritional quality of the meal and can darken both the oil and meal. Poor-quality seeds with high levels of free fatty acids cannot be cooked for as long a period as high-quality seeds because of darkening. Darker oil requires additional refining to achieve a certain bleach color.

Expanders: Sometimes low shear extruders called expanders are used. This equipment has the capability to process both low- and high-oil content materials. The meats are fed into an extruder after dehulling, flaking, and cooking and are heated as they are conveyed by a screw press through the extruder barrel. The meats are under considerable pressure and temperature when they reach the exit of the extruder. The change in pressure as the material leaves the extruder causes it to expand and the oil cells are ruptured, releasing the oil, which is rapidly reabsorbed. The expanded "collets" produced are then cooled and extracted with a solvent.

13.9.3.2 Oil extraction

Prepress solvent extraction: In this process, the oil-bearing material is first mildly pressed mechanically by means of a continuous screw press operation to reduce the oil by half to two-thirds of its original level before solvent extraction to remove the remaining oil in the pre-pressed cake. Pressing followed by solvent extraction is more commonly used when high oil content materials (e.g., canola/rapeseed, flaxseed, corn germ) are processed.

Direct solvent extraction: This process involves the use of a nonpolar solvent, usually hexane, to dissolve the oil without removing proteins and other non-oil soluble compounds. Solvent extraction yields about 11.5% more oil than does the screw press method, and less oil remains in the meal. The cooked flakes or collets (if expanders are used) are mixed with hexane in a batch or continuous operation. The hexane vapor pressure limits the practical operating temperature of the extraction and its contents to about 50-55°C. The resulting miscella (oil-solvent mixture) and the marc (solvent laden collets) are heated to evaporate the solvent, which is collected and reused. The oil is freed from the miscella, by using a series of stills, stripping columns, and associated condensers. The hexane-free oil (i.e., crude oil) is cooled and filtered before leaving the solvent-extraction plant for storage or further treatment. This is the crude oil normally traded in the commodity market. Occasional over-heating of the oil-solvent miscella will cause irreversible color changes in the oil.

13.9.3.3 Processing crude oil

Most crude edible oils, obtained from oil-bearing materials, consist primarily of triglycerides (triacylglycerols). The triglycerides (approximately 95% of the crude oil) are the constituents recovered for use as neutral oil in the manufacture of finished products. The remaining nontriglyceride portion contains variable amounts of other lipophilic compounds, such as free fatty acids (FFA), nonfatty materials generally classified as "gums," phospholipids (phosphatides), tocopherols, color pigments, trace metals, sterols, meal, oxidized materials, waxes, moisture, and dirt. Most of these minor lipid components are detrimental to finished product color, flavor, and smoking stability, and so must be

removed from the neutral oil by a processing/purification process. The object of the processing/purification steps is to remove the objectionable impurities while minimizing possible damage to the neutral oil and tocopherols and loss of oil during such processing.

Lecithin and cephalin are common phosphatides found in edible oils. Soybean, canola/rapeseed, corn, and cottonseed are the major oils that contain significant quantities of phosphatides. The alkaline treatment used for FFA reduction is also capable of removing most of the phosphatides from these crude oils. Tocopherols are important minor constituents of vegetable oils, which are a natural antioxidant that retard the development of rancidity.

Refining, bleaching, and deodorization are the steps that are necessary if the oil is to be used in food applications. Oil that has only gone through these three steps is called "RBD" oil. Figure 13.9.2 illustrates the processing pathways.

Refining: Refining involves the removal of nonglyceride materials (phospholipids, color, and trace materials) and FFA. The goal is to produce a high-quality refined oil with the highest yield of purified triglycerides. Refining is by far the most important step in processing. An improperly refined oil will present problems in bleaching and deodorization and reduce quality.

Some solvent-extracted crude oils, including soybean or canola/rapeseed, contain approximately 2-3% gums, which are mainly phosphatides and require degumming. The principal phosphatides are lecithin and cephalin. Gums can cause problems through higher than necessary refining losses, or by settling out in storage tanks. The degumming operation exploits the affinity of most phosphatides for water, converting them to hydrated gums that are insoluble in oil and readily separated by centrifugal action. Lecithin can be recovered and concentrated from the gums in a separate solvent extraction process, usually with acetone.

Either water-degummed oil or crude oil can be treated with sodium hydroxide solution to saponify free fatty acids that are subsequently removed as soapstock by a primary refining centrifuge. Conventional alkali refining is by far the most widespread method of edible oil refining. The success of the alkali refining operation is the coordination of five prime factors: (1) use of the proper amount of reagent (sodium hydroxide), (2) proper mixing, (3) proper temperature control, (4) proper residual contact time, and (5) efficient separation.

Oil is alkali-refined by the addition of sodium hydroxide solution at a level sufficient to neutralize the FFA content of the oil. An excess of sodium hydroxide is required to reduce the color of the refined oil and to ensure the completion of the saponification reaction and to remove other trace elements. The amount and strength of the sodium hydroxide solution needed to neutralize the FFA depend on the amount of both FFAs and phosphatides present in the crude oil. Water-soluble soaps are formed in the primary reaction between the sodium hydroxide and FFAs. The hydratable phosphatides react with the caustic forming oil-insoluble hydrates. The caustic used in alkali refining is normally diluted to about 8-14% NaOH, although higher concentrations are occasionally used to reduce color. The proper amount of NaOH solution added to the oil will produce an adequately refined oil with the minimum of triglyceride oil loss. The amount of NaOH solu-

tion (neutralizing dose plus excess) is determined by experience and adjusted according to laboratory results.

After the NaOH solution is injected, it is mixed for 6-10 minutes to ensure thorough contact. The treated oil is then heated to assist in breaking the emulsion prior to separation of the soapstock from oil in continuous centrifuges.

Any soap remaining, after the primary soapstock separation, is removed through continuous hot water washings. In this step, water is added at 10-15% at a temperature sufficient to prevent emulsification, generally 82-90.5ºC (180-195ºF). The oil is again separated from the soapy phase in water wash separators and drier prior to bleaching.

Bleaching: The oil is further purified by "bleaching", which removes color bodies and trace metals as well as entrained soaps, and products of oxidation that are adsorbed onto the surface of bleaching agents or adsorbents. Types of adsorbents most commonly used include neutral clay, acid activated clay, and activated carbon. The choice of adsorbent will depend on a balance between the activity of the adsorbent, oil retention loss, and adsorbent cost.

The process is generally carried out *via* batch or continuous bleaching. The adsorbent is mixed with the refined oil creating a slurry that is agitated to enhance contact between the oil and the adsorbent. This is generally carried out under a vacuum at 90-95ºC (194-203ºF) for 15-30 minutes. Vacuum bleaching offers the advantages of an oil with improved oxidative and flavor stability. Finally, the adsorbent is filtered from the oil using pressure leaf filters precoated with diatomaceous earth. Spent clay is steamed for efficient oil recovery.

Deodorization: Deodorization, which removes the volatile compounds along with residual FFA, is a critical step in ensuring the purity of any vegetable oil and improves flavor, odor, color, and oxidative stability. Many of the volatile compounds removed are formed by the autooxidation of fat, which produces aldehydes, ketones, alcohols, and hydrocarbons that are associated with undesirable flavors and odors. The process is also effective in removing any remaining pesticide residues or metabolites that may be in the oil.

Deodorization, which can be conducted as a batch operation in smaller plants or as a continuous or semicontinuous process by larger deodorizing facilities, consists of a steam distillation process in which the oil is heated to 230ºC (446ºF) under a vacuum of 2-10 mm Hg. Steam is sparged through the oil to carry away the volatiles and provide agitation. The odor and flavor compounds, which are more volatile than the triglycerides, are preferentially removed. After deodorization and during the cooling stage, 0.005-0.01% citric acid is generally added to chelate trace metals, which can promote oxidation. Deodorized oils preferably are stored in an inert atmosphere of nitrogen to prevent oxidation. Tocopherols and sterols are also partially removed in the deodorization process. Tocopherols can be recovered from the deodorizer distillate in a separate operation.

13.9.4 REVIEW OF SOLVENTS STUDIED FOR EXTRACTION EFFICIENCY

Research on solvents for extraction has been carried out for more than 150 years and has intensified since the first patent was issued to Deiss of France in 1855.[1,3,48] In the early effort of selecting an extraction solvent, the availability, operation safety, extraction effi-

ciency, product quality and cost were the major concerns. In recent decades, toxicity, biorenewability, environmental friendliness have been added to the solvent selection criteria. Among the solvents tested, a majority of the candidate solvents were excluded on the ground of toxicity and safety. Only a handful of solvents are used to any degree. These are acetone, alcohol, hexanes, heptane, and water.[1,4-7,49] Water is used in rendering of fat from animal tissues and fish and in coconut processing,[49] alcohol for spice and flavorings extraction,[5,49] acetone for lecithin separation and purification.[4] For commodity oils derived from vegetable sources, only hydrocarbon solvents have been used since 1930s. Acetone was used by an Italian cottonseed oil mill during the 1970s.[4] Aqueous acetone and acetone-hexane-water azeotrope were studied by the scientists at the Southern Regional Research Center of Agricultural Research Service, USDA during the 1960s and 1970s.[4] The effort was stopped due to the cost of retrofit required, the difficulties in managing the mixture of solvents with the presence of water and product quality concerns – a strong undesirable odor associated with the acetone extracted meals.[4] Ethanol and isopropanol were studied in the 1980s as a potential replacement of hexane for oil extraction. Both were proven technically feasible but economically unacceptable.[5,6] n-Hexane is listed as a HAP under the CAA[14,15] (See Section 13.9.2.2.1 CAA) and there are other regulatory requirements. As a way to meet environmental regulations, a short-term option to commercial hexane appears to be hydrocarbons with significantly reduced n-hexane content.

13.9.4.1 Hydrocarbon solvents

Extraction of oils has largely relied on mechanical or heat rendering process for centuries.[50] Increased demand of productivity to separate oils from oilseeds has been the principal factor driving the changes of oilseed processing from the ancient hydraulic press to a continuous screw press or expeller in early 1900s.[51,52] This operation still left more than 4-5% residual oil in the pressed cake.[51] More complete recovery of oil can only be effectively accomplished by solvent extraction.[53,54]

Solvent extraction of oils had an early beginning. Deiss in France received a patent to extract fat from bone and wool with carbon bisulfide in 1855.[53] A year later, Deiss received additional patents covering the extraction of oil-bearing seeds. Large-scale solvent extraction was already established in Europe in 1870.[55] The earliest extractors were unagitated single-unit batch extractors of small capacity and not very efficient.[56,57] These extractors were gradually modified by the addition of agitation. They were organized in a battery of ten batch extractors which can be operated in a counter-current principle. Extractors of this type operated in European plants during the last three decades of the 19th century.[57]

Further development in solvent extraction technology was relatively slow until early twentieth century. Solvent extraction spread from Europe to various parts of the world including the United States and South America.[57] The first extraction plant in the United States was used to recover grease from garbage, bones, cracklings, and other packinghouse wastes and to recover residual oil from castor pomace.[57] Wesson[58] reported his efforts applying solvent extraction to recover cottonseed oil from 1889 till the close of World War I. During the 1930s solvent extraction was introduced in the United States for

the recovery of oil from soybeans and the German equipment of the continuous type was used almost exclusively.[57-61] Just prior to World War II the installation of continuous solvent extraction equipment was greatly accelerated and throughout the period of the War new plants were erected in an effort to keep pace with the constantly increasing production of soybeans. All of the later installations have been of American manufacture and in a number of cases of American design.[57-61]

Solvents used in the early effort to extract grease and oils were diverse. Besides carbon bisulfide used by Deiss,[53] chlorinated hydrocarbons, benzene, and alcohols were all being tried. Extracting oil from corn and cottonseed with both aviation gasoline and petroleum distillate was performed in the United States in 1915 and 1917 respectively.[62] The hydrocarbon paraffins became the preferred solvents for oilseed extraction during 1930s through the process of elimination.[63-71] Due to the prominent defects of early solvent extraction: dark crude oil, strong solvent odor in meal and high cost associated with solvent loss, low boiling hydrocarbons such as propane and butane were recommended as oil extraction media.[72] The flammability of hydrocarbons also prompted much research in 1940s using chlorinated hydrocarbons as the extraction solvents[73,75] before its meal was found unsafe as feed.[75-77] For the purpose of improved protein and oil quality[75,78] and of processing safety and biorenewable solvents,[75,79,80] both ethanol and isopropanol were investigated as the oil extracting solvents. While these alcohols offer various advantages in product quality and process safety and are renewable, they are still not economically feasible to replace hydrocarbons as oilseed extraction solvents.[81] Hexane-rich solvent became popular in the oilseed industry,[54,57,82,83] because it is the most efficient solvent, extracts minimum non-oil material and is easy to separate from the crude oil and marc.[63] A thorough comparison of various hydrocarbon solvents for cottonseed oil extraction on a laboratory scale basis was reported by Ayers and Dooley in 1948.[84] A more recent study by Wan *et al*.[85] used a laboratory scale dynamic percolation extractor which operates at conditions similar to those applied in the oil mill practice. Plant trials of isohexane and heptane solvents versus hexane in a 300 tons/day cottonseed factory revealed some interesting findings.[7]

13.9.4.1.1 Nomenclature, structure, composition and properties of hydrocarbons

Petroleum and natural gas are the most abundant and affordable sources of hydrocarbon. Sometimes naphtha is used to describe the low boiling liquid petroleum and liquid products of natural gas with a boiling range from 15.6°C (60°F) to 221°C (430°F). This large group of compounds can be structurally classified as aliphatic and aromatic. Aliphatic hydrocarbons include saturated alkanes (paraffins), unsaturated alkenes (olefins) and alkynes (acetylenes), and cycloparaffins (naphthenes). Paraffins can be linear such as n-butane, n-pentane, and n-hexane, and branched such as isobutane, isopentane, isohexane, etc. Example of olefins is ethylene; of cycloparaffins, cyclopentane and cyclohexane; and of an aromatic, benzene.[8,86,87] These compounds are derived from natural gas and petroleum oils which normally contain thousands of hydrocarbons with molecular weight ranging from methane to about 50,000-100,000 Daltons. Upon refining, the crude petroleum is divided into hydrocarbon gases (methane, ethane, propane and butane), light distillates (naphthas and refined oils), intermediate distillates (gas oil and absorber oil), heavy distil-

lates (technical oils, paraffin wax and lubricating oils), residues (petroleum grease, residual fuel oil still wax, asphalts and coke), and refinery sludges (acid coke, sulfonic acid, heavy fuel oils and sulfuric acid).[88] Historically, various fractions of petroleum naphthas, pentane and hexane from the light naphthas, aviation gasoline and benzol from the intermediate naphthas, and aromatic hydrocarbon, benzene, have been tested for oil extraction.[62-71]

13.9.4.1.2 Performance of selected hydrocarbon solvents

Factors affecting extraction: There is little theoretical basis to be followed for the extraction of oilseeds.[66,89-91] The study of the extraction of oilseeds is complicated by the fact that the total extractible material is variable in quantity and composition.[66,89] Composition of the early extracted material is nearly pure triglyceride. As the extraction progresses, increasing amount of non-glyceride material will be extracted.[66,89] It is believed that the majority of the oil from oilseed flakes is easily and readily extracted.[66,90] While the thickness of flakes affects extraction rate, the concentration of miscella below 20% does not greatly increase the amount of time to reduce the residual oil in flakes to 1%.[89] Good[91] summarized much of the early effort in soybean extraction: (1) The first oil extracted is superior in quality to the last small fraction; (2) While other solvents have been used in the past, hexane has become the primary solvent due to a combination of properties; (3) Flake thickness is the most important factor in achieving good extraction results; (4) Higher extractor temperatures up to nearly the boiling point, improve extraction results; (5) Moisture control is important throughout the extraction process; (6) Heat treatment affects the total extractibles; and (7) The soaking theory of extraction indicates that weak micelles are very effective in helping to achieve good extraction results.

Particle size, which relates to the surface area available for extraction is obviously one of the most important factors for extraction study. Coats and Wingard[92] noticed that particle size was more influential when the seed grit was being extracted. When oilseed flakes were being extracted, the flake thickness would be a more important factor instead of the size of the flakes. Moisture content in oilseed can affect the extraction results.[93-95] The optimum moisture content of cottonseed meats for extraction was first reported by Reuther *et at*.[94] to be from 9 to 10%. Work by Arnold and Patel[95] indicated 7 to 10% to be the optimum moisture for cottonseed flakes and very little variation in extraction rate for soybean with a moisture content between 8 and 12%.

Wingard and Phillips[96] developed a mathematical model to describe the effect of temperature on extraction rate using a percolation extractor as follows:

$$\log(\text{time,min}) = n \log(\text{temp., }^{o}\text{F}) + \log k \text{ or } \text{time} = k(\text{temp.})^{n} \qquad [13.9.1]$$

where time is defined as the number of minutes required to reach 1% residual oil in the oil-seed flakes. For all practical purposes, they concluded that the time in minutes required to reduce the oilseed to 1% residual oil content on a dry basis varied inversely with the square of the extraction temperature in degrees Fahrenheit.

Evaluation methods: Except for the pilot plant batch or counter-current extraction described by various laboratories,[54,74,78] most of the solvent extraction evaluation work found in the literature was done in one or several of the laboratory scale devices. The per-

colation batch-extraction apparatus of the Soxhlet type has often been used to evaluate the rate of extraction of hydrocarbon solvents such as the one described by Bull and Hopper.[89] Wingard and Shand[97] described a percolation type of extractor and a cocurrent batch extractor and claimed to be useful to study the factors influencing equipment design and plant operation as well as fundamental studies contributing to a general understanding of extraction. Wan, *et al*. modified the design of percolation type extractor to closely simulate a single stage counter current miscella extraction conditions as practiced in the factory.[85] Cocurrent batch extractor with numerous variations was also frequently applied for the extraction properties of selected solvents which were often operated at room temperature.[75,97] Soxhlet extraction[84,85] and Soxtec System HT6 (Perstorp Analytical, Herndon, VA) were also frequently used to evaluate solvents.[98] Soxhlet extractor allows vaporized and condensed pure solvent to percolate through oilseed sample. The temperature of the condensed solvent is normally lower than its boiling point. Depending upon the cooling efficiency of the condenser and the room temperature, the temperature of the condensed solvent and the temperature of the extracting solvent in the extractor largely varied from the laboratory to laboratory. This extraction temperature variability was minimized with the Soxtec method by refluxing the oilseed sample in the boiling solvent for 15 minutes followed by Soxhlet type of rinsing for 35 minutes. In theory, the Soxtec method is more efficient and better reproduced. However, the Soxtec method only utilized a 3 g oilseed sample. The heterogeneity of an oilseed sample could be a significant source of variation.

Flakes of oilseeds were most frequently used for the solvent extraction studies. Sometimes, ground oilseed kernels of a specified sieve size were used.[98] Residual oil content in the extracted flakes after a certain specified extraction condition or oil content in miscella (mixture of oil and solvent) was examined and the percentage of total oil extracted was calculated.[89-97] The total extractable oil of flakes was determined by four hours Soxhlet extraction. Wan *et al*.[85] used a precision densitometer to determine the miscella concentration (percent of oil in miscella by weight) after a given time of extraction from which the percentage of oil extracted from cottonseed flakes was calculated. From these data, Wan *et al*.[85] was also able to estimate the initial rate of extraction and final extraction capacity for each solvent as fresh and at selected initial miscella concentrations up to 30%.

Bull and Hopper[89] conducted extraction of soybean flakes in a stainless steel batch-extraction apparatus of the Soxhlet type with petroleum solvents, Skellysolve F (boiling range, 35 to 58°C) at 28°C and Skellysolve B (boiling range, 63 to 70°C) at 40°C. The extraction was carried out to permit the miscella obtained by each flooding of the flakes with a solvent to be recovered separately. Their results showed that iodine number decreased and refractive index increased slightly with the extraction time which implied that more saturated fat was extracted during a later stage of the extraction. Oils extracted during the later stages of the extraction were found to contain greater amounts of unsaponifiable matter and were rich in phosphatides, as high as 18% of the last fraction. Skellysolve B which is a hexane-rich solvent demonstrated a much faster initial rate of extraction than that of Skellysolve F which is a pentane rich solvent and therefore, it took longer to complete the extraction for Skellysolve F. The fatty acid profile of each fraction showed a

slight increase of saturated and a slight decrease of unsaturated fatty acid in the later fractions.

Arnold and Choudhury[82] reported results derived from a lab scale extraction of soybean and cottonseed flakes in a tubular percolation extractor at 135-140°F with pure, high purity and commercial hexane, and reagent grade benzene. They claimed that pure hexane extracted soybean slower than high purity and commercial hexane. During the first 60 minutes of extraction, benzene extracted more oil than the hexanes. However, at the end of 80 minutes, benzene extracted only slightly more than pure hexane but definitely less than the commercial hexanes. Similar results were obtained for the four solvents when cottonseed flakes were extracted.

A laboratory extraction study of cottonseed flakes using various hydrocarbon solvents was reported by Ayers and Dooley.[84] Soxhlet extractor and Waring blender were used for these experiments. Among the petroleum hydrocarbon solvents tested were branched, normal and cycloparaffins as well as aromatic hydrocarbons with various degrees of purity. They were: pure grade (99 mole percent purity) n-pentane, isopentane, cyclohexane, benzene, and n-heptane; technical grade (95 mole percent purity) neohexane, diisopropyl, 2-methylpentane, 3-methylpentane, n-hexane, and methylcyclopentane; technical grade (90 mole percent purity) cyclopentane; and commercial grade n-heptane, isohexanes, n-hexane, isoheptane and n-heptane. To assess the performance of these solvents, they used the following empirical formula:

$$\text{Quality-Efficiency Rating} = 0.4\ (\text{Oil Yield Factor}) + 0.4\ (\text{Refining Loss Factor}) + \\ + 0.2\ (\text{Refined and Bleached Oil Color Factor}) \qquad [13.9.2]$$

When comparing the oil yield factor alone, 3-methylpentane was rated the best. When comparing the solvents based on the empirical Quality-Efficiency Rating formula, they concluded that methylpentanes (3- and 2-methylpentane) were superior extraction solvents for cottonseed oil. The normal paraffins, highly-branched isohexanes, cycloparaffins, and aromatics were progressively rated as less efficient than methylpentanes. Therefore, they recommended a tailor-made solvent for the extraction of cottonseed should exclude aromatic hydrocarbons, have low limits on cycloparaffin content, and consist largely of normal and isoparaffin hydrocarbons.

A study by Wan *et al.*[85] using a laboratory scale dynamic percolation type of extractor (Figure 13.9.3) operated at the following conditions such as, temperature (5°C below the boiling point of each solvent) and miscella flow rate (9 gal/min/ft^2), similar to those applied in the oil mill practice. Commercial grade hexane, heptane, isohexane, neohexane, cyclohexane, and cyclopentane were used to extract cottonseed flakes which had 5.8% moisture and 31.4% oil. When these solvents were tested near their boiling points, hexane apparently extracted cottonseed oil at a higher initial rate, > 94% oil extracted after 2 minutes, than all other solvents. Both heptane and hexane were able to extract more oil at the end of 10 minutes of extraction. Isohexane demonstrated to have adequate initial extraction rate (80% oil extracted after 2 minutes) and extraction capacity (93% oil extracted after 10 minutes of extraction) but it is noticeably less effective than hexane. Similar to findings by Ayers and Dooley,[84] results from the study by Wan *et al.*[85] also

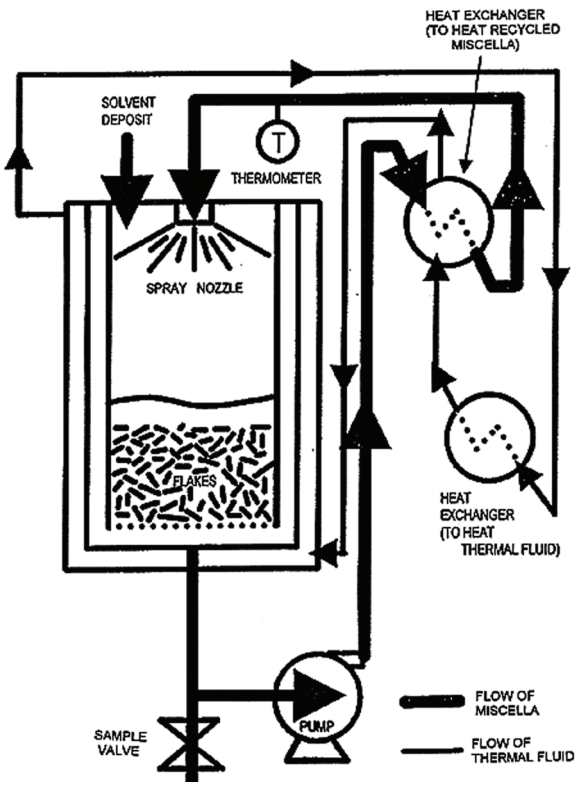


Figure 13.9.3. Schematic of bench-scale dynamic percolation extractor.

demonstrates that neohexane, cyclohexane, and cyclopentane performed distinctly less efficiently than hexane, heptane and isohexane. Conkerton *et al.*[98] tested commercial heptane versus hexane in a Soxtec extractor. Under this extraction condition, heptane actually extracted more oil than hexane from ground cottonseed kernel passed through a 20 mesh screen. The oil and meal quality were not appreciably affected by the higher temperature extraction of heptane.

Plant scale results: Although hydrocarbon solvents have been used for oilseed extraction since the 1930s, very little in plant operating data is available. During the spring of 1994, Wan *et al.*[7] conducted plant trials with commercial heptane and isohexane at a 300 tons/day cottonseed crushing plant which routinely used hexane as the extraction solvent. Test results indicated that heptane performed well as an extraction solvent. However, it required extra energy and time to recover and it consequently reduced the throughput rate of cottonseed being processed. Isohexane, on the other hand, was termed as an "easier" solvent by the plant engineers than hexane to operate. The plant also experienced a 40% steam savings and better than 20% throughput increase when it was operating with isohexane.[7] This encouraging result prompted a second plant trial with commercial isohexane.[45] The second plant trial was carried out at a cottonseed oil mill with a relatively new extraction and miscella refining facility which was constructed in 1988 with a designed capacity of 500 tons/day but operated at only 270 tons/day due to limited delinting capacity. After a week-long testing with commercial isohexane, this plant experienced more than 20% natural gas usage and easily increased the throughput rate by close to 10% when compared with commercial hexane. These energy savings with commercial isohexane over commercial hexane may be largely attributed to the difference in the amount of water present in their corresponding azeotropes. Isohexane requires an additional step – isomerization to manufacture and will always be priced higher than hexane. But based on the two cottonseed oil mill trials, isohexane can be a cost-efficient solvent.[99] One additional benefit, the shorter residence time

of the extracted cottonseed marc in the desolventizer/toaster because of the lower boiling range of isohexane will likely preserve more vegetable protein in the final meals which has been observed for both plants during the tests.[7,45] The benefit of improved quality of oils was not obvious in both plant trials but might be realized with extended trials.

Further evaluation of hydrocarbon solvents: As indicated in the study conducted by Wan *et al.*,[85] the commercial cyclic hydrocarbons are less effective extraction solvents than the branched and linear hydrocarbons. The comparison of extraction efficiency of pure isomers of hexane was conducted with the same single stage extractor as displayed in Figure 13.9.3. This was done to identify any unique structure-function characteristics of these pure components of commercial hexane and provide some guidance to the selection and tailored formulation for future commercial isohexane for the oilseed extraction industry. The extraction results for various pure isomers of six carbon paraffins using the single stage extractor indicated the following: (a) cyclohexane is noticeably less efficient in extracting cottonseed flake than all the other isomers; (b) slightly branched isomers, such as, 2-methyl and 3-methyl pentane, and methyl-cyclopentane are very slightly less efficient than n-hexane; and (c) highly branched isomers, 2,2-dimethyl and 2,3-dimethyl butane, are slightly less efficient than slightly branched isomers in extraction (unpublished data).

13.9.5 FUTURE TRENDS

In future, there will be new demands for highly specialized extraction solvents for newly domesticated species that make useful novel oils[30] and other products and new or altered biological products with enhanced nutritional and industrial properties will be developed through conventional breeding and genetic engineering for use such as "functional foods"[31] (e.g., phytosterols to achieve cholesterol lowering); oils with altered lipid profiles[32] (e.g., for lower saturated fat) or with more vitamin E; new drugs/nutraceuticals, industrial chemicals (e.g., fatty acids for lubricants, as cosmetics, coatings, detergents, surfactants, flavors, polymers, etc.); sources for specialty chemicals; and value added products; etc.[31-38]

Genetically enhanced (GE)/biotech crops make up a growing share of the agricultural output.[39] Biotechnology is the most powerful tool ever put in the hands of agricultural scientists. The ability to breed desirable traits or eliminate problematic ones can yield potentially spectacular benefits, such as various chemicals of importance including improved fats and oils, and vaccines and medicine, improved nutrition (e.g., in casaba, oilseeds, rice, sweet potatoes), and improved yields with the use of less agricultural chemicals. GE/biotech crops could be increasingly developed as biofactories for a wide range of products, including nutrients pharmaceuticals, and plastics. There is much promise for being able to produce products that would protect millions from disease, starvation, and death. However, problems in Europe, particularly in the UK,[40] Europe,[41] Japan, Korea, and Australia/New Zealand already have some restrictions and require some labeling. The U.S. is reviewing the issue.[42] Thus even though this technology has great promise for the increased use of new and existing solvents for extraction of products from diverse biological materials, there are also many potential problems because of misperceptions and misinformation.

Commercial hexane, which is a HAP and a VOC, is presently the solvent used.[16,17] To meet new and existing CAA requirements it is likely that extraction facilities will become much more efficient chemical engineering operations with upgraded equipment,[43] more computerized monitoring and control for better quality management,[44] and better environmental management/stewardship.[19] In addition, it is possible that alternate solvents (e.g., isohexane[3,7,45]) or lower n-hexane content commercial hexane (30-50% vs. 64%) will be used to meet these regulations. It is also possible that solvents like acetone, which is not a HAP or VOC and is not on the TRI list, will be more strongly investigated.[16,17,46]

The separation of low volatility liquid mixtures by counter-current or semibatch fractionation with a supercritical fluid solvent opens new alternatives for separation with respect to distillation, absorption, or liquid extraction.[100] A new monographic source evaluates various aspects of this technology. Method of oil extraction determines the volatile profile of virgin olive oil.[101] Analytical methods are available to discriminate between different technological methods.[101] Hydrodistillation, simultaneous distillation/extraction and supercritical fluid extraction methods were found to be the most suitable for studying the effect of processing on aroma.[101]

Oil-containing material is heated and subjected to sonication, which increases extraction efficiency and extraction yield.[102] Polyol-containing solvent, such as glycerol, and alkalizing agent are used for selective extraction of free fatty acids in the process of refining vegetable oil.[103] Many solvents are patented for removal of various components of oils in processes of refining.

The oil extraction process from Australian native beauty leaf seed has been optimized in terms of seed preparation and cracking, seed kernel treatment, moisture content, and oil extraction methods.[104] The mechanical oil extraction using an electric powered screw press and chemical oil extraction using n-hexane as an oil solvent have been applied to extract oil from the seed kernel.[104] The mechanical oil extraction was ineffective due to relatively lower oil yields compared to the chemical extraction which was a very effective method for oil extraction because of its consistent performance and high oil yield, but the cost of production was relatively higher due to the cost of solvent.[104]

Several technologies for microalgae oil extraction are being evaluated in order to find the most adequate for large-scale microalgae processing, taking as feedstock a composition of *Chlorella* sp. microalgae biomass.[105] Energetic efficiencies, total process irreversibilities, energy consumption, and energy loss were calculated for all solvent-based microalgae oil extraction pathways evaluated.[105] The energy analysis identified the hexane-based oil extraction as the most adequate alternative, presenting a maximum energy efficiency of 51% and energetic losses of 982,000 MJ considering a production of 104,000 t of microalgae oil per year.[105]

A liquid CO_2/propane mixtures were used to extract jojoba oil from oilseeds.[106] A solvent mixture containing 30 wt% CO_2 exhibited good solvent power.[106] Oil extraction yielded 98% oil recovery using a minimum solvent to oilseed mass ratio of 5 and operating the extractor at 313 K and 70 bar.[106]

The numerous extraction techniques for oils and lipids have been studied and employed.[107] But, hexane extraction method is still widely used on the commercial

scale.[107] Application of three-phase partitioning has emerged as a greener alternative to the hexane extraction that simultaneously yields separation of other valuable biomolecules like proteins.[107] Three phases formed in three-phase partitioning are oil in upper organic phase, proteins in the middle precipitate phase, and hydrophilic moieties, such as polysaccharides in bottom phase.[107] In an industrial process, the upper phase consists of oil dissolved in t-butanol, middle phase consists of proteins precipitated with salts while the end phase contains an aqueous phase with water-soluble biomolecules such as carbohydrates, soluble fibers, gums, etc.[107]

A variety of oil raw materials results in multitude of steps involved, such as seed pretreatment which deals with the stages prior to the extraction stage, such as cleaning, crushing, and scorching; extraction, this step involves the separation of the raw material into oil and residue (cake); and finally refining steps.[108] Five fundamental specialized alternatives exist for oil extraction: hot water flotation, ghanis, manual presses, powered expellers, and solvent extraction.[108] The selection of steps depends on the raw material and required oil quality.[108]

REFERENCES

1 **Technology and Solvents for Extracting Oilseeds and Non-petroleum Oils**, P.J. Wan and P.J. Wakelyn, Eds., *AOCS Press*, Champagne, IL, 1997.

2 M.A. Williams and R.J. Hron, **Bailey's Industrial Oils and Fat Products**, 5th edn., Vol. 4: **Edible Oil and Fat Products: Processing Technology, Y.H Hui,., Ed., *John Wiley and Sons, Inc.*, 1996, p. 119.**

3 P.J. Wan, **Hydrocarbon Solvents**, in **Technology and Solvents for Extracting Oilseeds and Non-petroleum Oils**, P.J. Wan and P.J. Wakelyn, Eds., *AOCS Press*, Champaign, IL, 1997, p.170-185.

4 R.J. Hron, **Acetone**, *Ibid*, p.186-191.

5 R.J. Hron, **Ethanol**, *Ibid*, p.192-197.

6 E.W. Lucas and E. Hernandez, **Isopropyl Alcohol**, *Ibid*, p. 199-266.

7 P.J. Wan, R.J. Hron, M.K. Dowd, M.S. Kuk, and E.J. Conkerton, *J. Am. Oil Chem. Soc*., **72**, 661 (1995).

8 **Occupational Health and Safety Administration Field Operations Manual**, Chapter IV: **Violations**, **C. Health Standards Violations**, (OSHA Instruction 2.45B CH-4, Dec.13, 1993), *The Bureau of National Affairs, Washington*, DC, 1994, pp. 77:2513-18.

9 **Occupational Health and Safety Administration Technical Manual**, **Section I- Sampling, Measurement Methods, and Instruments, Chapter 1 - Personal Sampling for Air Contaminants**, Appendix I:1-6. Sampling and Analytical Errors (SAEs) (Issued by OSHA Instruction TED 1.15, September 22, 1995; amended *by OSHA Instruction* TED 1.15 CH-1, May 24, 1996).

10 1997 TLVs and BEIs, **Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices**, *The American Conference of Governmental Industrial Hygienists*, Cincinnati, OH, 1997, pp. 12-40.

11 J.B Galvin, C.J. Kirwin, D.W. Kelly, *INFORM*, **6**(8), 951 (1995).

12 H.H. Schaumberg and P.S. Spencer, *Brain*, **99**, 183 (1976).

13 J.B. Galvin, **Toxicity Data for Extraction Solvents Other Than Isohexane/Hexane Isomers**, in **Technology and Solvents for Extracting Oilseeds and Nonpetroleum Oils**, P.J.Wan and P.J.Wakelyn, Eds., *AOCS Press*, Champaign, IL, 1997, p. 75-85.

14 P.J. Wakelyn, *Cotton Gin and Oil Mills Press*, **92**(17), 12 (1991).

15 P.J. Wakelyn and L.A. Forster, Jr., *Oil Mill Gaz.*, **99**(12), 21 (1994).

16 P.J. Wan and P.J. Wakelyn, *INFORM*, **9**(12),1155 (1998).

17 P.J. Wan and P.J. Wakelyn, *Oil Mill Gaz*., **104**(6), 15 (1998).

18 **U.S. EPA, Study of Volatile Organic Compound Emissions from Consumer and Commercial Products**, *U.S. Environmental Protection Agency, Office of Quality Planning and Standards*, Research Triangle P*ark*, NC 27711, EPA - 453/R-94-066-A, March 1995.

19 P.J. Wakelyn and P.K. Adair, **Assessment of Risk and Environmental Management**, in **Emerging Technologies, Current Practices, Quality Control, Technology Transfer, and Environmental Issues**, Vol. 1, Proc. of the World Conference on Oilseed and Edible Oil Processing, S.S. Koseoglu, K.C. Rhie, and R.F. Wilson, Eds. *AOCS Press*, Champaign, IL, 1998, pp. 305-312

20 **n-Hexane, U.S. EPA Integrated Risk Information System (IRIS) Substance File**, U.S. *EPA*, 1999 (www.epa.gov/ngispgm3/IRIS/subst/0486.htm).
21 **U.S. EPA, Toxic Chemical Release Inventory Reporting Form R and Instructions** (Revised 1995 Version), U.S. *EPA, Office of Pollution Prevention and Toxics*, Washington, DC, EPA 745-K-96-001, March 1996, Table II, p. II-1
22 J.K. Dunnick, **Toxicity Studies of n-Hexane** in F344/N Rats and B6C3F1 Mice, National Toxicology Programs, *U.S. Dept. of Health and Human Services*, NTP TOX 2, NIH Publication No. 91-3121, 1991.
23 A. H. Allen, **GRAS Self-Determination: Staying Out of the Regulatory Soup, Food Product Design**, (April 1996 supplement to Food Product Design, 6 pages) (1996).
24 B.L. Oser and R.A. Ford, *Food Technol.*, **27**(1), 64 (1973).
25 R.L. Hall and B.L. Oser, *Food Technol*., **19**, 151 (1965).
26 A.M. Galvin, in **Introduction to Fats and Oils Technology**, P.J. Wan, Ed., *AOCS Press,* Champagne, IL, 1991,pp. 137-164.
27 L.A. Jones and C.C. King, in **Bailey's Industrial Oil and Fats Products**, 5th edn., **Vol. 2 Edible Oil and Fat Products: Oils and Oil Seeds**, Y.H. Hui, Ed., *John Wiley and Sons, Inc*., 1996, pp. 177-181.
28 H.W. Lawson, **Standards for Fat and Oils**, *The AVI Publishing Co., Inc*., Westport, CT, 1985, p. 34.
29 S.W. Kuhlmann, M.C. Calhoun, J.E. Huston and B.C. Baldwin, Jr., Total (+)- and (-)- Gossypol in Plasma and Liver of Lambs Fed Cottonseed Meal Processed by Three Methods, *J. Anim. Sci.*, **72** (suppl. 1), 145 (1994).
30 D.J. Murphy, *INFORM*, **11**(1), 112 (2000)
31 M.A. Ryan, *Today's Chemist at Work,* **8**(9), 59 (1999).
32 B.F. Haumann, *INFORM*, **8**(10), 1001 (1997).
33 B. Flickinger and E. Hines, *Food Quality*, **6**(7), 18 (1999).
34 C.T. Hou, Value Added Products from Oils and Fats through Bio-processes, Int. Symp. On New Approaches to Functional Cereals and Oils, Beijing, China, Nov. 9-14, 1997, Chinese Cereals and Oils Association, Beijing, China, 1997, p. 669.
35 D.J. Kyle, **New Specialty Oils: Development of a DHA-rich Nutraceutical Product**, *Ibid*, p. 681.
36 J.K. Daum, **Modified Fatty Acid Profiles in Canadian Oilseeds**, *Ibid*, pp. 659-668.
37 C.M. Henry, *Chemical Eng. News*, **77**(48), 42 (1999).
38 R. Ohlson, *INFORM*, **10**(7), 722 (1999).
39 G.J. Persley and J.N. Siedow, **Applications of Biotechnology to Crops: Benefits and Risks**, CAST Issue Paper No. 12, *Council for Agricultural Science and Technology*, December 1999.
40 M. Heylin, *Chem. Eng. News*, 77(49), 73 (1999).
41 Anom., *Official J. European Communities*, **43**(L6), 13 (2000).
42 B. Hileman, *Chem. Eng. News*, 77(50), 31 (1999).
43 P. Delamater, *Oil Mill Gaz*., **104**(11), 34 (1999).
44 P.J. Wakelyn, P.K. Adair, and S.R. Gregory, *Oil Mill Gaz*., **103**(6), 23 (1997).
45 M. Horsman, *Oil Mill Gaz*., **105**(8), 20 (2000).
46 R.J. Hron, P.J. Wan, and P.J. Wakelyn, *INFORM*, *In Press*, (2000).
47 J.A. Dean, **Dean's Handbook of Chemistry**, Thirteenth Edition, *McGraw-Hill, Inc*., New York, NY, 1985.
48 R.D. Hagenmaier, **Aqueous Processing, in Technology and Solvents for Extracting Oilseeds and Non-petroleum Oils**, P.J. Wan and P.J. Wakelyn, Eds., *AOCS Press*, Champaign, IL, 1997, p.311-322.
49 L. A. Johnson, **Theoretical, Comparative, and Historical Analyses of Alternative Technologies for Oilseed Extraction**, *Ibid*, p.4-47.
50 D.K. Bredeson, *J. Am. Oil Chem. Soc*., **60**, 163A (1983).
51 **Cottonseed and Cottonseed Products**, A.E. Bailey, Ed., *Interscience Publishers Inc*., New York, pp. 5, 615-643,(1948).
52 V.D. Anderson, **U.S. Patent 647,354** (1900).
53 Anonymous. *J. Am. Oil Chem. Soc.*, **54**, 202A (1977).
54 J. Pominski, L.J. Molaison, A.J. Crovetto, R.D. Westbrook, E.L.D'Aquin, and W.F. Guilbeau, *Oil Mill Gaz*., **51**(12), 33 (1947).
55 O.K. Hildebrandt, *Fette Seifen Anstrichm*, **46**, 350 (1939).
56 M. Bonotto, *Oil & Soap*, **14**, 310 (1937).
57 K.S. Markley, *Oil Mill Gaz.*, **51**(7), 27 (1947).
58 D. Wesson, *Oil & Soap*, **10**, 151 (1933).
59 E. Bernardini, *J. Am. Oil Chem. Soc*., **53**, 275 (1976).
60 K.W. Becker, *ibid*., **55**, 754 (1978).
61 K.W. Becker, *Oil Mill Gaz.*, **84**, 20 (1980).

62 W.E. Meyerweissflog, *Oil & Soap*, **14**, 10 (1937).
63 W.H. Goss, *ibid*, **23**, 348 (1946).
64 W.H. Goss, *J. Am. Oil Chem. Soc*., **29**, 253 (1952).
65 R.P. Hutchins, *ibid*, **54**, 202A (1977).
66 G. Karnofsky, *ibid*, **26**, 564 (1949).
67 A.E. MacGee, *Oil and Soap*, **14**, 322 (1937).
68 A.E. MacGee, *ibid*, **14**, 324 (1937).
69 A.E. MacGee, *J. Am. Oil Chem. Soc*., **26**, 176 (1949).
70 A.E. MacGee, *Oil Mill Gaz.*, **52**, 17,35 (1947).
71 A.E. MacGee, *ibid*, **67**, 22 (1963).
72 H. Rosenthal, and H.P. Trevithick, *Oil and Soap*, **11**, 133 (1934).
73 I.J. Duncan, *J. Am. Oil Chem. Soc*., **25**, 277 (1948).
74 O.R. Sweeney, and L.K. Arnold, *ibid*, **26**, 697 (1949).
75 A.C. Beckel, P.A., Belter, and A.K. Smith, *ibid*, **25**, 7 (1948).
76 L.L. McKinney, F.B. Weakley, R.E. Campbell, A.C. Eldridge, J.C. Cowan, J.C. Picken, and N.L. Jacobson, *ibid*, **34**, 461 (1957).
77 T.A. Seto, M.O. Shutze, V. Perman, F.W. Bates, and J.M. Saulter, *Agric. Food Chem.*, **6**, 49 (1958).
78 F.K. Rao, and L.K. Arnold, *J. Am. Oil Chem. Soc*., **35**, 277 (1958).
79 E. W. Lusas, L.R. Watkins and K.C. Rhee, in **Edible Fats and Oils Processing: Basic Principles and Modern Practices**, D. R. Erickson, Ed., *AOCS Press*, IL, p. 56, 1990.
80 R.J. Hron, Sr., S. P. Koltun and A. V. Graci, *J. Am. Oil Chem. Soc*., **59**(9), 674A (1982).
81 R.J. Hron, Sr., M.S. Kuk, G. Abraham and P. J. Wan, *ibid*, **71**(4), 417 (1994).
82 L.K. Arnold and R.B.R. Choudhury, *ibid*, **37**, 458 (1960).
83 K.S. Olson, *Oil Mill Gaz*., **85**, 20 (1980).
84 A.L. Ayers and J.J. Dooley, *J. Am. Oil Chem. Soc*., **25**, 372 (1948).
85 P.J. Wan, D. R. Pakarinen, R. J. Hron, Sr., and E. J. Conkerton, *ibid*, **72**(6), 653 (1995).
86 M.P. Doss, **Physical Constants of the Principal Hydrocarbons**, *The Texas Company*, Third Edition, New York. (1942).
87 L.A. Johnson and E. W. Lusas, *J. Am. Oil Chem. Soc*., **60**(2), 229 (1983).
88 McGraw-Hill Encyclopedia of Science and Technology, **10**, 71 (1960).
89 W.C. Bull and T.H. Hopper, *Oil and Soap*, **18**, 219 (1941).
90 H.B. Coats and G. Karnofsky, *J. Am. Oil Chem. Soc*., **27**, 51 (1950).
91 R.D. Good, *Oil Mill Gaz.*, **75**, 14 (1970).
92 H.B. Coats and M.R. Wingard, *J. Am. Oil Chem. Soc*., **27**, 93 (1950).
93 W.C. Bull, *Oil and Soap*, **20**, 94 (1943).
94 C.G. Reuther, Jr., R.D. Westbrook, W.H. Hoffman, H.L.E. Vix and E.A. Gastrock, *J. Am. Oil Chem. Soc*., **28**, 146 (1951).
95 L.K. Arnold and D.J. Patel, *ibid*, **30**, 216 (1953).
96 M.R. Wingard and R.C. Phillips, *ibid*, **28**, 149 (1951).
97 M.R. Wingard and W.C. Shand, *ibid*, **26**, 422 (1949).
98 E.J. Conkerton, P.J. Wan and O.A. Richard, *ibid*, **72**, 963 (1995).
99 P.J. Wan, *INFORM*, **7**, 624 (1996).
100 E. Brignole, S. Pereda, **High-Pressure Fractionation and Extraction of Natural Oils** in **Supercritical Fluid Science and Technology**, *Elsevier*, Vol. 3, 239-61 (2013).
101 S. Vichi, **Extraction Techniques for the Analysis of Virgin Olive Oil Aroma** in **Olives and Olive Oil in Health and Disease Prevention**, *Elsevier*, 2010.
102 M. Augustin, **WO2012167315**, *Commonwealth Scientific and Industrial Research Organization*, 13 Dec. 2012.
103 L.P. Nielsen, V.C.Norn, **WO2012035020**, *Palsgaard A/S*, 22 Mar. 2012.
104 M. M. K. Bhuiya, M. G. Rasul, M. M. K. Khan, N. Ashwath, A. K. Azad, M. Mofijur, *Ener. Procedia*, **75**, 56-61, 2015.
105 Y. Peralta-Ruiz, A.-D. González-Delgado, V. Kafarov, *Appl. Ener.*, **101**, 226-36, 2013.
106 C. Palla, P. Hegel, S. Pereda, S. Bottini, *J. Supercrit. Fluids*, 91, 37-45, 2014.
107 D. C. Panadare, V. K. Rathod, *Trends Food Sci. Technol*., **68**, 145-51, 2017.
108 A. A. Mariod, M. E. S. Mirghani, I. Hussein, **Principles of Oil Extraction, Processing, and Oil Composition** in **Unconventional Oilseeds and Oil Sources**, *Academic Press*, 2017, pp. 347-50

13.10 GROUND TRANSPORTATION

George Wypych
ChemTec Laboratories, Toronto, Canada

The ground transportation industry in the USA is dominated by truck freight (78.6%). Other methods of transportation include rail (7.9%), water (5.2%), air (4%), pipeline (2.2%), and other (2.1%). Solvents are used and solvent wastes and emissions are generated during refurbishing and maintenance.

Railcar refurbishing involves stripping and painting. Paint is usually removed by mechanical means (steel grit blast system) but solvents are occasionally used. Solid wastes are generated from latex paint wastes but hazardous wastes are also generated from solvent-based paints and thinners. Parts cleaning is mostly done using mineral spirits. Waste solvents are sent off-site for reclamation.

Truck maintenance work usually requires a parts washer which may involve either a heated or ambient temperature solvent, hot tank, or a spray washer. In the solvent tank washer, solvent (usually mineral spirits, petroleum distillates, and naphtha) is recirculated from the solvent tank. Spent solvent is usually replaced monthly. Carburetor cleaning compounds contain dichloromethane. Tanker cleaning often involves a solvent spray.

The ground transportation industry employs a large number of people (more than 4 million in transportation and warehousing in 2014; 1,678,280 heavy-duty truck drivers, 826,510 truck delivery, 505,560 school bus drivers in 2015 in the USA).[2] It is one of the less polluting industries. It generates 0.3% of VOC released by all major industries combined (about half of that of the aerospace industry). Most solvents used are of low toxicity. A good system of collection and reclamation of solvent wastes is done effectively and this is the major reason for the relatively good performance of the industry.

The hydrocarbons derived from terpenes are structurally similar to the compounds in petroleum distillate fuels and often share similar combustion properties.[3] Blending of hydrogenated sesquiterpenes, caryophyllene and its stereoisomers, which have a moderate cetane number and only moderately high viscosity, with synthetic branched paraffins can raise cetane number and reduce the viscosity of biosynthetic fuels that meet applicable jet and diesel specifications.[3] Compared with fuel alcohol, the terpene mixtures of caryophyllene, caryophyllene alcohol, and other caryophyllene stereoisomers are either oxygen-free or have very low oxygen hydrocarbon and hydrocarbon-like compounds (C:O>10), making them particularly attractive candidate as "drop-in" replacements for non-renewable ground transportation and aviation fuels.[3] *Escherichia coli* was engineered to yield terpene enriched in caryophyllene and caryolan-1-ol and algae hydrolyzate was converted to terpene at high yields using engineered strains.[3]

REFERENCES

1 **EPA Office of Compliance Sector Notebook Project. Profile of the Ground Transportation Industry**. Trucking, Railroad, and Pipeline. *US Environmental Protection Agency*, 1997.
2 **EPA Office of Compliance Sector Notebook Project. Sector Notebook Data Refresh** – 1997. *US Environmental Protection Agency*, 1998.
Chapter 4: Transportation Employment. *Bureau of Transportation Statistics*.
3 W. Wu, F. Liu, R. W. Davis, *Metabolic Eng. Commun*., **6**, 13-21, 2018.

13.11 INORGANIC CHEMICAL INDUSTRY

George Wypych
ChemTec Laboratories, Toronto, Canada

This industry has two major sectors: inorganic chemicals and chloralkali. Inorganic chemicals are often of mineral origin processed to basic chemicals such as acids, alkalies, salts, oxidizing agents, halogens, etc. The chloralkali sector manufactures chlorine, caustic soda, soda ash, sodium bicarbonate, potassium hydroxide and potassium carbonate. The major processes in this industry do not use solvents but there are many specialized auxiliary processes which use solvents. Tables 13.11.1 and 13.11.2 give information on the reported solvent releases and transfers from inorganic chemical industry.

Table 13.11.1. Reported solvent releases from the inorganic chemical plants in 1995 [Data from Ref. 2].

Solvent	Amount, kg/year	Solvent	Amount, kg/year
benzene	33,000	hexane	2,000
carbon tetrachloride	3,000	methanol	574,000
chloromethane	2,600	methyl ethyl ketone	460
dichloromethane	12,500	N-methyl-2-pyrrolidone	180
ethyl benzene	110	toluene	12,000
ethylene glycol	1,800	xylene	1,500

Table 13.11.2. Reported solvent transfers from the inorganic chemical plants in 1995 [Data from Ref. 2].

Solvent	Amount, kg/year	Solvent	Amount, kg/year
benzene	780	methyl ethyl ketone	9,000
carbon tetrachloride	6,400	N-methyl-2-pyrrolidone	8,700
dichloromethane	5,000	toluene	6,000
ethylene glycol	12,000	xylene	96,000

The tables show that the industry, which operates almost 1,500 plants and employs over 110,000 people, has minimal impact on global emission of VOCs. Consequently, the industry does not have any major initiative to deal with solvent emissions or wastes. Future safety improvements concentrate on non-solvent issues.

Solvent extraction is a well-established process within the inorganic chemical and hydrometallurgical industries for transfer of cations or anions from an aqueous phase into an organic phase.[3] Because direct extraction of ionic species is energetically very unfavorable, the transfer is accomplished by forming organic-soluble neutral complexes in the aqueous phase by reactions between the ionic species of interest and an appropriate

organic compound (extractant).[3] There are three major types of extractants which are cation exchangers, anion exchangers, and solvating extractants.[3] The cation exchangers are either acidic or chelating extractants.[3] Types of acidic cation extractants include organic acids such as carboxylic, sulfonic, phosphoric, and phosphinic acids. Common examples are di-2-ethylhexyl phosphoric acid and alkyl monocarboxylic acids with 10–20 carbons in various branched or cyclic structures.[3] On the other hand, chelating extractants contain two functional groups that form bidentate complexes with metal ions.[3] Aromatic β-hydroxyoximes are the most commonly utilized chelating agents in a wide variety of industries.[3] A book chapter discusses this subject.[3]

REFERENCES

1 **EPA Office of Compliance Sector Notebook Project. Profile of the Inorganic Chemical Industry**. *US Environmental Protection Agency*, 1995.
2 **EPA Office of Compliance Sector Notebook Project. Sector Notebook Data Refresh – 1997**. *US Environmental Protection Agency*, 1998.
3 C. Erkey, **Extraction of Metals Using Supercritical Fluids** in **Supercritical Fluid Science and Technology**, Vol. 1, *Elsevier*, 2011, pp. 121-60.

13.12 IRON AND STEEL INDUSTRY

George Wypych
ChemTec Laboratories, Toronto, Canada

The US iron and steel industry is very diverse industry having total sales of $113 billion and over 149,000 employees in 2014. Figure 13.12.1 is a schematic diagram of the iron and steel making process. Only one stage – finishing – employs solvents. The finishing stage includes processes to remove mill scale, rust, oxides, oil, grease, and soil prior to

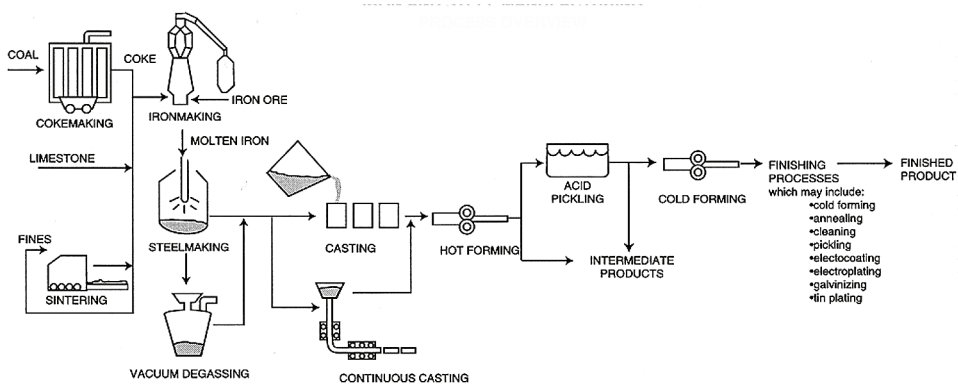


Figure 13.12.1. Schematic diagram of operations in the iron and steel manufacturing process. [Reproduced from EPA Office of Compliance Sector Notebook Project. Reference 1.]

coating. Methods used include solvent cleaning, pressurized water or air blasting, cleaning with abrasives, and alkaline or acid pickling.

Tables 13.12.1 and 13.12.2 give information on the reported solvent releases and transfers from the iron and steel industries. Not all the solvents listed in the tables are used in processing. Some are by-products of coke manufacture from coal. Benzene and polycyclic aromatics compounds are by-products. Strong solvents such as methyl ethyl ketone, toluene, xylene, and trichloroethylene are typical of those used in cleaning processes. There is no program formulated by the industry to reduce amounts of solvents used.

Table 13.12.1. Reported solvent releases from the iron and steel plants in 1995.
[Data from Ref. 2].

Solvent	Amount, kg/year	Solvent	Amount, kg/year
benzene	321,000	N-methyl-2-pyrrolidone	3,600
n-butyl alcohol	26,000	polycyclic aromatic compounds	2,400
cresol	1,800	tetrachloroethylene	91,000
dichloromethane	318,000	1,2,4-trimethylbenzene	17,000
ethylbenzene	5,000	trichloroethylene	620,000

Table 13.12.1. Reported solvent releases from the iron and steel plants in 1995. [Data from Ref. 2].

Solvent	Amount, kg/year	Solvent	Amount, kg/year
methanol	241,000	toluene	261,000
methyl ethyl ketone	358,000	xylene	168,000

Table 13.12.2. Reported solvent transfers from the iron and steel plants in 1995. [Data from Ref. 2].

Solvent	Amount, kg/year	Solvent	Amount, kg/year
benzene	3,000	N-methyl-2-pyrrolidone	11,500
n-butyl alcohol	1,400	polycyclic aromatic compounds	3,820,000
cresol	12	tetrachloroethylene	20,000
dichloromethane	14,500	1,2,4-trimethylbenzene	3,600
ethylene glycol	197,000	trichloroethylene	165,000
ethylbenzene	550	toluene	11,500
methanol	25	xylene	14,000
methyl ethyl ketone	66,000		

Out of three studied processes of carbon dioxide capture to reduce CO_2 emissions by the steel industry, the DMX™ process (Demixing solvent) was found useful for production of supercritical CO_2 solvent.[3] Considering an available steam at 21 €/t, it would be possible to produce CO_2 from blast furnace gases at around 40 €/t by using the DMX™ process.[3] The DMX™ process is based on the use of specific solvents (blend of amines) which are characterized by a critical solubility temperature (LCST) above which two non-miscible liquid phases are formed.[3]

Cyanex 923 extractant is a liquid phosphine oxide which has potential applications in the solvent extraction recovery of both organic and inorganic solutes from aqueous solution.[4] It was successfully applied to the recovery of zinc and iron from the waste chloride solution.[4]

REFERENCES

1 **EPA Office of Compliance Sector Notebook Project. Profile of the Iron and Steel Industry. Trucking, Railroad, and Pipeline**. *US Environmental Protection Agency*, 1995.
2 **EPA Office of Compliance Sector Notebook Project. Sector Notebook Data Refresh – 1997.** *US Environmental Protection Agency*, 1998.
3 M. Dreillard, P. Broutin, P. Briot, T. Huard, A. Lettat, *Ener. Procedia*, **114**, 2573-89, 2017.
4 M. K. Sinha, S. Pramanik, S. K. Sahu, L. B. Prasad, M. K. Jha, B. D. Pandey, *Separation Purification Technol.*, **167**, 37-44, 2016.

13.13 LUMBER AND WOOD PRODUCTS – WOOD PRESERVATION TREATMENT: SIGNIFICANCE OF SOLVENTS

Tilman Hahn, Konrad Botzenhart, Fritz Schweinsberg
Institut für Allgemeine Hygiene und Umwelthygiene, Universität Tübingen, Tübingen, Germany
Gerhard Volland
Otto-Graf-Institut, Universität Stuttgart, Stuttgart, Germany

13.13.1 GENERAL ASPECTS

Wood preservation is based on various fundamental principles, e.g., construction aspects such as exposure to humidity, selection of different types of wood products according to their durability, and chemistry of wood preservatives. Important groups of chemical wood preservatives are water-soluble and solvent-based substances.[1]

The main requirements of chemical wood preservatives are:[1]

- Stability, especially chemical stability.
- Resistance to environmental conditions, e.g., light or heat.
- Penetration into the wood products.
- Effectiveness against wood attacking agents (e.g., insects, fungi, bacteria).
- Compatibility with other construction components, e.g., paints, adhesives, and fasteners.
- Construction aspects, e.g., corrosion.
- Minimal environmental impact, e.g., minimum emissions or minimum environmental pollution.
- Ability to work with a range of wood products.
- Case applications, e.g. fundamental differences of indoor and outdoor coatings.
- Having favorable visual aspects, e.g., surface properties, color, uniformity, influence on grain pattern, etc.

All requirements cannot be fulfilled completely by various wood preservatives. Therefore wood preservatives should be selected according to the particular case.

13.13.2 ROLE OF SOLVENTS

13.13.2.1 Occurrence

Various solvents are added to wood preservatives. Only a limited number of wood preservatives are authorized by governmental agencies, e.g., in Germany "Institut für Bautechnik (DIBt)".[2] But there is a large grey market for wood preservatives other than the authorized substances. As a result, a large variety of solvents can occur in wood preservatives.

Different systems of classification are used worldwide. In Germany, authorized wood preservative substances are published in an index of wood preservatives ("Holz-

schutzmittelverzeichnis")[2] which is elaborated by the DIBt and the central German environmental authority ("Umweltbundesamt").

A systematic survey of wood preservatives is shown in Table 13.13.1, including wood preservatives containing solvents. Solvents are normally found in wet systems of wood preservatives. Commonly used solvents are substances which are applied in connection with normally used binders (aldehyde resins, acrylates, and polyurethanes). Water or the appropriate solvents are added to binders.

Table 13.13.1. Systems of wood preservatives.

Purpose and base	Terms	Active components
Water-soluble agents as preventive treatment against fungi and insects	"CF-salts"	chromium and fluorine compounds
	"CFA-salts"	alkali fluorides, alkali arsenate, and bichromate (no longer permitted)
	"SF-salts"	silicofluorides
	"HF-salts"	hydrogen fluorides
	"B-salts"	inorganic boron compounds
	"Single CK-salts"	copper salts, bichromate
	"CKA-salts"	copper salts, bichromate with arsenic compounds
	"CKB-salts"	copper salts, bichromate with boron compounds
	"CKF-salts"	copper salts, bichromate with fluorine compounds
	"CFB-salts"	chromium, boron and fluorine compounds
	collective group	other compounds, e.g., bis(N-cyclohexyl-diazeniumdioxyl)-copper
Oily agents as preventive treatment against fungi and insects	tar oil preparations	distillates of bituminous coal tar (carbolineum)
	preparations containing solvents	organic fungicides and insecticides
	pigment-free preparations containing binders & solvents	organic fungicides and insecticides
	preparations with stained pigments containing solvents	organic fungicides and insecticides
	special preparations only used in stationary installations	organic fungicides and insecticides
	preparations containing coal tar oil	organic agents, special distillates containing coal tar oil, solvents, and pigments
Preparations used for special applications	pastes	
	wood preservatives used in particle board in manufacturing plants	
	agents used as a preventive treatment against insects contain organic insecticides	

Solvent-borne wood preservatives contain mainly nonpolar, organic solvents apart from other substances such as fungicides and insecticides.[1] These solvents are classified as VOCs.

13.13.2.2 Technical and environmental aspects

Solvent-based wood preservatives show several advantages, especially in their application and technical effectiveness.[1] They can be applied repeatedly and do not alter the structure of the wood products. The application is faster and the characteristics of the final product are improved, e.g., the visual appearance of the surface.

Nevertheless, there are some disadvantages, especially environmental ones. Most solvents are released quickly (VOCs) and can cause severe environmental effects. This is especially true if toxic solvents are employed.

Emissions of solvents from wood products are described under various conditions, e.g., indoor air emissions from furniture or emissions in test chambers.[3,4] Solvents can be emitted as primary or reactive products of the wood product or the coating system; solvents can also be investigated as secondary emission products.[3,5] The emission characteristics depend on solvent properties and surrounding conditions, e.g., air velocity and air exchange rate.[6]

In the indoor air, solvents from wood products follow various pathways. Examples of interactions are possible reactions of solvents (e.g., styrene) with air components (e.g., hydroxyl radicals),[3] transport into and through indoor materials[7] or sorption processes.[5] The emitted solvents can be reduced by ventilation processes or they may be absorbed by organisms.

For humans, absorption of the wood preservatives or ingredients (e.g., solvents) can cause various toxic effects. It is often difficult to pinpoint the causative agents (see Chapter 19).

13.13.3 CURRENT DEVELOPMENTS

Solvents and diluents used in wood preservatives and coatings included: hydrocarbons (aliphatic, cyclic, and aromatic), oxygenated solvents (ketones, esters, alcohols, and glycol ethers), and water.[8]

Water-borne wood preservatives, based on hinokitol[9] and crude tall oil[10] have been patented. The solubility of active ingredient has been enhanced by the addition of a base.[9,10] Hydrocarbon solvent is used in a composition comprising an ester of boric acid and pentachlorophenol.[11] Ester is used as cosolvent capable to dissolve active component.[12] Also, micronized solid particles of preservative can be suspended in liquid organic carrier, such as toluene, xylene, mineral oil, vegetable oil, etc.[13]

The feasibility of manufacturing cross-laminated timber using fast-grown small diameter eucalyptus timber was explored in the preliminary studies.[14] The eucalyptus bonded with commercial one-component polyurethane adhesive usually provides poor resistance to delamination and shear force.[14] Hydroxymethylated resorcinol priming treatment was effective to enhance bond performance and mechanical properties of eucalyptus cross-laminated timber.[14] After hydroxymethylated resorcinol priming, the wood failure percentage values of eucalyptus cross-laminated timber at wet state bonded with phenol resorcinol formaldehyde and polyurethane adhesives increased by 27.8%, 12.4%.[14]

Solvent- and water-based wood stains were monitored using a small test emission chamber in order to characterize their emission profiles in terms of total and individual VOCs.[15] The solvent-based wood stain had the highest total VOCs emission level (5.7 mg/m^3) that decreased over time more slowly than those related to water-based stains. The same was true for solvents involved, such as benzene, toluene, ethylbenzene, xylenes, styrene, α-pinene, and camphene.[15] The highest level of limonene was emitted from a water-based wood stain.[15] The concentration-time profile showed that water-based product gave a remarkable reduction of the time of maximum and minimum emission.[15] Only one of the investigated water-based wood stains can be classified as a low-emitting product whose use may not have any potential adverse effect on human health.[15]

The above examples show that the selection of medium in which active components are either suspended or dissolved is not of primary importance.

REFERENCES

1 **Ullmann`s Encyclopedia of Industrial Chemistry**, 1998.
2 DIBt (Deutsches Institut für Bautechnik). **Holzschutzmittelverzeichnis. Index of wood preservatives** (1999).
3 T. Salthammer, A. Schwarz, F. Fuhrmann, *Atmospher. Environ.*, 33, 75 (1999).
4 T. Salthammer, *Atmospher. Environ*., 7, 189 (1997).
5 M. Wensing, H.J. Moriske, T. Salthammer, *Gefahrstoffe Reinhaltung der Luft*, 58, 463 (1998).
6 E. Uhde, A. Borgschulte, T. Salthammer, *Atmospher. Environ*., 32, 773 (1998).
7 R. Meininghaus, T. Salthammer, H. Knoppel, *Atmospher. Environ*., 33, 2395 (1999).
8 F. Bulian, J.A. Graystone, *Raw Materials for Wood Coatings* in *Wood Coatings*, *Elsevier*, 2009, 95-135.
9 **CN103168777**, 26 Jun. 2013.
10 H. Boren, **WO2008017730**, *Hoeljaekkae Oy*, 14 Feb. 2008.
11 G. Murray, **WO2013098579**, *Stella-Jones, Inc*., 4 Jul. 2013.
12 F.W. Frazer, **EP2373464**, *Tim Tech Chemicals Limited*, 12 Oct., 2011.
13 J. Zhang, R.M. Leach, **EP1799776**, *Osmose, Inc*., 2 Jan. 2013.
14 Z. Lu, H. Zhou, Y. Liao, C. Hu, *Constr. Build. Mater*., **161**, 9-15, 2018.
15 G. de Gennaro, A. D. Loiotile, R. Fracchiolla, J. Palmisani, M. R. Saracino, M. Tutino, *Atmosph. Environ.,* **115**, 53-61, 2015.

13.14 MEDICAL APPLICATIONS

George Wypych
ChemTec Laboratories, Toronto, Canada

Industries manufacturing medical devices use a wide variety of technological processes which likely take advantage of many available solvents. The range of solvent use is so wide that a complete description of each solvent and its application is not possible in this book. It is questionable if such analysis is even possible given that many processes are guarded by trade secrets where there is no patent disclosure. Some examples are given, more to show that, although solvents do contribute to pollution, they also help to produce materials which are needed for health and well-being.

Polyurethanes are materials which have the required properties and biocompatibility which makes them a good candidate for use in medical devices. Common applications include pacemaker leads, peripheral and central catheters, feeding tubes, balloons, condoms, surgical gloves, instrument and appliance covers, wound dressings, and many other.[1-4] Several methods are used to process polyurethanes. These include injection molding, extrusion, and solution processing. In solution processing film casting and dip molding are the most frequent techniques.

Dimethylacetamine, tetrahydrofuran, dichloromethane, methyl ethyl ketone, N,N-dimethylformamide, N-methylpyrrolidone, cyclopentanone, cyclohexanone, dioxane, and chloroform are the most commonly used solvents. Most of these are hazardous but used because they contribute to highly transparent products which are very desirable in medical devices. Transparent materials can only be made from transparent solutions.[1] These solvents can dissolve polymers well and form clear solutions. Ease of solvent removal from the material is very important in formulation design. Obviously, no traces of solvents should remain in the medical devices since even trace amounts may interfere with the treatment and the patient's health. An inappropriate solvent selection may cause the formation of the crust as the solvent evaporates. This leads to the material discontinuity (e.g., pinholes) which renders inferior products. This brings a discussion of solvent evaporation, the rheological properties of the formulation, and formation of multilayer materials.

Good solvents can be used in lower concentrations but they result in viscous solutions which, in dip coating, form thick films which have the potential of blistering on evaporation. If the solution is diluted, film continuity suffers which increases the number of pinholes. Rapid evaporation causes a formation of a crust of gelled solidified polymer which makes solvent removal more difficult and damages the integrity of the layer. Also, the material does not have time to adjust and leveling suffers. On the other hand, slow evaporation may cause dissolution of the layer below the coating in multilayered products and bubbling between the layers.

The selection of solvents for dip coating is usually a complex process ultimately requiring multicomponent solvent mixtures which include a good solvent, a poor solvent, and a solvent of lower boiling point (sometime called “blush resistor”) to balance viscosity and rate of evaporation.[2] In wound dressings, the solvents selected to affect the mate-

rial microstructure which controls the evaporation of exuded body fluids but prevents bacteria and pathogens from entering the wound.[3] In infection-resistant medical devices, the antimicrobial agent must be uniformly distributed over all areas of the medical device which may come into contact with a patient. Otherwise, there is a risk of infection.[4] Not all solvents dissolve antimicrobial agents or swell surface of medical device.

Cleaning of penetrable septa, tubing systems, and infusion and dialysis systems is another application in which solvents are used. The solvents which are suitable for elastomer cleaning are dichloromethane, perchloroethylene, halogenated hydrocarbons, and freons.[5] This cleaning method extracts undesirable organic materials from medical devices which might otherwise be extracted by body fluids. Heat treatment of catheters followed by washing with a polar solvent increases its surface lubricity. Catheter with poor surface lubricity often causes frictional pain upon its insertion into the body cavity and damages the mucosal tissue resulting in cross-infection.[6] Film dressings contain two types of solvents: solvents to dissolve the polymer and propellant solvents. These must be selected to achieve technological goals related to solubility and compatibility.[7]

Solvents, such as tetrahydrofuran, toluene, dimethylacetamide, acetone, chloroform, and alcohol, are used for improving the coating quality and performance of a drug-coated device, such as a stent by respraying the coating with a solvent to reflow the coating.[8]

A method of modulating drug release from a coating on a medical device has been patented.[9] A stent is an example of an implantable medical device that can benefit from improvements such as a coating that can be used as a vehicle for delivering pharmaceutically active agents in a predictable manner.[9] Selection of solvent composition contributes to the microstructure of the coated film. The structure obtained by invention permits control of drug delivery to tissue in contact with the stent.[9]

The intravascular catheter is used for providing central venous nutrition and performing dialysis treatment.[10] Antimicrobial layers may be formed with an antimicrobial agent such as antibiotic-coated on the surface.[10] The antimicrobial agent may be continually released from the surface while inside the body.[10] Most antibiotics are very polar and do not dissolve in organic solvents.[10] Aprotic polar solvents, such as dimethylformamide, dimethyl sulfoxide, dimethylacetamide, 2-butanone, acetone, acetonitrile, and N-methylpyrrolidone are useful in this application.[10]

Medical and surgical devices (such as stents) can be coated with compositions containing supercritical fluids.[11] Thin polymer film, containing a therapeutic agent uses a supercritical fluid deposition process.[11]

The compound is capable of being solvent bonded or welded to another thermoplastic material using cyclohexanone alone or with methyl ethyl ketone.[12] The compound is especially useful as medical tubing connected to other parts of medical equipment.[12]

Method of making polymeric devices, such as stents, using solvent-based processes, particularly, a method of making bioabsorbable stents (stents used in the treatment of blood vessels) have been patented.[13]

These examples show that the many technological considerations place constraints on in solvent selection. Solvent replacement in complex products and technological processes is a long-term, expensive proposition which usually results in a need for complete

reformulation of the material with failure to achieve the objective a possible outcome. Many solvent applications in medical devices are crucial for their performance.

REFERENCES

1 A J Walder, *Plast. Eng*., **54**, No.4, 29-31 (1998).
2 M T Shah, **US Patent 5,571,567**, *Polygenex International, Inc*., 1996.
3 J Delgado, R J Goetz, S F Silver, D H Lucast, **US Patent 5,614,310**, *3M*, 1997.
4 S Modak, L Sampath, **US Patent 5,567,495**, *Columbia University*, 1996.
5 S H Smith, J M Brugger, H W Frey, **US Patent 5,639,810**, *COBE Laboratories, Inc.*, 1997.
6 L Mao, Y Hu, D Piao, **US Patent 5,688,459**, *China Rehabilitation Research Center*, 1997.
7 A J Tipton, S M Fujita, R L Dunn, **US Patent 5,792,469**, *Atrix Laboratories, Inc*., 1998.
8 E B Stenzel, **CA2585700**, *Boston Scientific Limited*, 4 May 2006.
9 Y Tang, G Zhang, **US20070286882**, *Abbott Cardiovascular Systems*, 13 Dec. 2007.
10 K Amano, Y Akaike, **EP1908485**, *Covidien AG*, 27 Feb. 2013.
11 D B Mehta, M Corbo, **CA2409003**, *Ortho-Mcneil Pharmaceutical, Inc*., 19 Oct. 2010.
12 S Kim, W Thornton, **EP2358806**, *PolyOne Corporation*, 24 Aug. 2011.
13 S. D. Pacetti, N. Dong, **US9675478B2**, *Abbott Cardiovascular Systems Inc.,* Jun. 13, 2017.

13.15 METAL CASTING

George Wypych
ChemTec Laboratories, Toronto, Canada

The metal casting industry had 3,100 facilities in the USA and employed 250,000 people. Most plants are small and technological processes are very diverse. The processes do share common phases, including pattern making, mold and core preparation, furnace charge and metal melting, mold charging, cooling, and finishing. Most steps use solvents. In the mold-making process, many chemical binding systems are used, some of which contain methanol, benzene, toluene, and cresol. The metal is most often recycled and it typically requires cleaning before it is charged to the furnace. This is accomplished either by precombustion or solvent cleaning. In die casting operations, solvent-based or water-based lubricants are used. Die casters also use die fluxes which contain solvents. Some solvent replacement additives in water-based lubricants contain hazardous solvents. Finishing operations involve casting cleaning to remove scale, rust, oxides, oil, grease, and dirt. Solvents are typically chlorinated solvents, naphtha, toluene, and methanol. Cleaning can also be done by emulsifiers, abrasives, alkaline agents, and acid pickling. The cleaning operation is usually followed by painting which frequently involves solvent-based paints and thinners.

Tables 13.15.1 and 13.15.2 contain information on the reported solvent releases and transfers from metal casting industry. The data show that solvent use is not excessive relative to other industries. The industry plans to further improve its environmental record by developing environmentally improved materials which meet regulations. The solvent cleaning and die lubrication are processes under study.

Table 13.15.1. Reported solvent releases from the metal casting industry in 1995
[Data from Ref. 1].

Solvent	Amount, kg/year	Solvent	Amount, kg/year
benzene	110,000	methyl ethyl ketone	22,000
n-butyl alcohol	15,000	methyl isobutyl ketone	22,000
cresol	20,000	N-methyl-2-pyrrolidone	41,000
dichloromethane	50,000	tetrachloroethylene	13,000
ethylbenzene	10,500	1,1,1-trichloroethane	111,000
ethylene glycol	64,000	trichloroethylene	75,000
hexachloroethane	16,000	toluene	233,000
methanol	5,860,000	xylene	388,000

Table 13.15.2. Reported solvent transfers from the metal casting industry in 1995
[Data from Ref. 1].

Solvent	Amount, kg/year	Solvent	Amount, kg/year
benzene	115	N-methyl-2-pyrrolidone	22,000
ethylbenzene	340	1,1,1-trichloroethane	500
ethylene glycol	50,000	trichloroethylene	1,000
methanol	10,000	toluene	4,000
methyl ethyl ketone	8,000	xylene	82,000

The lost pattern casting of metals employs an erodable mold including a particulate material and a binder.[3] After a molten metal is poured into the mold, the erodable backing and the mold are contacted with a solvent.[3] This cools the molten metal so that it, at least partially, solidifies to form a casting. Water is usually used as a solvent.[3]

Casting composition comprises a monomer and/or a polymer, a metal or ceramic powder and a solvent.[4] Polymer used is polycarbonate, but many other polymers can be successfully used. Water and polar protic solvents can be used.[4] Cycloalkanes are used as a solvent of foundry binders.[5]

The invention provides a method for preparing a powder metallurgy complex shape part by using a 3D printing mold.[6] A 3D printing technology and a gel-casting forming technology are combined, namely a 3D printer is used for printing a thin-wall hollow part minus mold in a complex shape, the gel-casting technology is used for preparing metal slurry, after a catalyst and an initiator are added, the metal slurry is injected into the part minus mold, the metal slurry is solidified and dried, then organic solvent is used for dissolving a plastic mold or the plastic mold is subjected to thermal decomposition to be removed, so that a formed part blank body is obtained.[6]

841 Core Oil is a solvent containing alkyd oil, petroleum resins, solvents and drying agents. It is used in metal-casting foundries with green sands that require rapid development of high strengths. An added benefit of 841 Core Oil is low viscosity that allows a shorter mixing time or the use of a less efficient mixer.

REFERENCES

1 **EPA Office of Compliance Sector Notebook Project. Profile of the Metal Casting Industry**. *US Environmental Protection Agency*, 1998.
2 **EPA Office of Compliance Sector Notebook Project. Sector Notebook Data Refresh – 1997**. *US Environmental Protection Agency*, 1998.
3 J R Grassi, J Campbell, G W Kulman, **CA2496791**, *Alotech Ltd. Llc*, 1 Apr. 2004.
4 J T Leman, T F Mcnulty, C-P Lee, H-P Wang, **CA2612051**, *GE*, 6 Jun 2008.
5 M R Stancliffe, J Kroker, X Wang, **CA2766997**, *Ask Chemicals*, 20 Jan. 2011.
6 **CN103801696B**, Feb. 8, 2017.

13.16 MOTOR VEHICLE ASSEMBLY

George Wypych
ChemTec Laboratories, Toronto, Canada

The automotive industry in 2017 in the US employed 955,000 in manufacturing, 3,323,000 in sales and service. It is a large contributor to the gross national product. In European Union, 12.6 million people or 5.7% of total employment accounts for the automotive industry, The 3.3 million high-skilled jobs in automotive manufacturing represent 10.9% of EU's manufacturing employment. The automotive industry uses large quantities of solvents and it is perceived to contribute to pollution by solvents and other materials.[1-6] Solvents are used in a variety of cleaning, preparation, and painting operations. Automotive finishing process may be divided into four main categories: anti-corrosion operations (cleaning, phosphate treatment, and chromic acid treatment), priming operations (electrodeposition of primer, anti-chip coating application, and primer application), joint sealant application, and other finishing operations (color coat, clear coat). These main operations employ many materials which contain solvents.

The cleaning process involves acid/alkaline and solvent cleaning. Typical solvents involved are acetone, xylene, toluene, and 1,1,1-trichloroethylene. The primer bath is water-based but, usually, some organic solvents are present (5-10%). These solvents are the same as those listed above. After the application of primer, the car body is baked and then undergoes waterproofing with an application of polyvinylchloride sealant which contains a small amount of solvents. Following waterproofing, the automotive body proceeds to the anti-chip booth, where urethane or epoxy solvent-coating systems are applied. This process is followed by application of the primer-surfacer coating which is either a polyester or an epoxy ester in a solvent system. The primer-surfacer coating is applied by spraying and provides a durable finish which can be sanded. After the sanding step, the primary color coating is applied also by spraying. These primary color formulations contain about twice as much solvent as the primer-surfacer coating. Solvents are flashed-off (no heating) and a clear coat is applied. Then the entire car body is baked for about 30 min. Solvents used include butanol, isobutanol, methanol, heptane, mineral spirits, butyl acetate ethyl acetate, hexyl acetate, methyl ethyl ketone, acetone, methyl amyl ketone, toluene, and xylene.

Several finishing operations also employ solvents. After baking, a sound-deadener is applied to certain areas of the underbody. It is a solvent based material with a tar-like consistency. A trim is applied with adhesives which contain solvents (see section on adhesives and sealants). After the installation of trim and after the engine is installed, car undergoes an inspection. Some repainting is required in about 2% of the production. If the damage is minor then repainting is done by a hand operated spray gun. If the damage is substantial, a new body is installed. Equipment cleaning solvents are also used. Spraying equipment is cleaned with a “purge solvent” which may consist of a mixture of dimethylbenzene, 4-methyl-2-pentanone, butyl acetate, naphtha, ethylbenzene, 2-butanone, toluene, and 1-butanol.

Car-repair painters are exposed to many different solvents, including toluene, ethylbenzene, 1,2-dichloropropane, n-butylacetate, n-amylacetate, xylene isomers, ethylacetate, and benzene.[8]

Tables 13.16.1 and 13.16.2 contain information on the reported solvent releases and transfers from the motor vehicle assembly industry. The data show that solvent use is very large compared with all industries covered so far in our discussion except for the steel and iron industry. The motor vehicle assembly industry is the sixth largest producer of VOC and also the sixth largest industry in reported emissions and transfers.

Table 13.16.1. Reported solvent releases from the motor vehicle assembly industry in 1995 [Data from Ref. 2].

Solvent	Amount, kg/year	Solvent	Amount, kg/year
benzene	13,000	methyl ethyl ketone	2,320,000
n-butyl alcohol	2,260,000	methyl isobutyl ketone	3,060,000
sec-butyl alcohol	86,000	N-methyl-2-pyrrolidone	193,000
tert-butyl alcohol	4,200	methyl tert-butyl ether	32,000
cyclohexane	35,000	tetrachloroethylene	140,000
dichloromethane	380,000	1,1,1-trichloroethane	730,000
ethylbenzene	1,370,000	trichloroethylene	1,300,000
ethylene glycol	180,000	1,2,4-trimethylbenzene	1,120,000
isopropyl alcohol	9,000	toluene	2,610,000
hexane	95,000	xylene	10,800,000
methanol	1,550,000	m-xylene	25,000

Table 13.16.2. Reported solvent transfers from the motor vehicle assembly industry in 1995 [Data from Ref. 2].

Solvent	Amount, kg/year	Solvent	Amount, kg/year
benzene	3,400	methyl ethyl ketone	2,100,000
n-butyl alcohol	1,030,000	methyl isobutyl ketone	4,700,000
sec-butyl alcohol	9,000	N-methyl-2-pyrrolidone	330,000
tert-butyl alcohol	1,000	methyl tert-butyl ether	2,300
cyclohexane	670	tetrachloroethylene	49,000
dichloromethane	450,000	1,1,1-trichloroethane	140,000
ethylbenzene	1,740,000	trichloroethylene	480,000
ethylene glycol	605,000	1,2,4-trimethylbenzene	330,000
isopropyl alcohol	2,000	toluene	2,020,000
hexane	25,000	xylene	9,200,000
methanol	760,000	m-xylene	2,100

The data in Tables 13.16.1 and 13.16.2 are data from 1995 the most recent available. The automotive industry and associated paint companies conduct extensive work on replacement of VOC containing paint systems. These efforts are mainly directed to water-based systems and powder coatings. Until recently, water-based systems were preferred but now attention is shifting to powder coatings which eliminate VOC. Changes are dynamic and kept protected by trade secrets which makes it difficult to comment on specific progress. The 10 kg solvents was used by the European industry[5] in 1999 to produce one car. Solvents use is not the only problem the industry is facing. 16% of the total energy used in car production is required by painting and finishing operations. Both energy conservation and reduction of solvent consumption must be pursued to meet environmental objectives. Not only can these issues be addressed through material reformulation but the design of equipment used in applying and drying the coating can also reduce emission and save energy.

A new trend is apparent as plastics are introduced to automotive production. Plastic parts must also be painted. Paint systems are difficult to select. Chlorinated polyolefins provide good adhesion of paints and reduce VOC but are also under scrutiny because of presence of chlorine. Powder coatings are available[7] but they require a high energy input. These problems are apparent but the solution to them will take several years to implement due, in large part, to the long-term testing needed to confirm coating performance (up to 5 years in Florida).[8]

Automotive technicians are commonly exposed to organic and chlorinated solvents, particularly through use of cleaning products.[9] Occupational solvent exposures have been associated with deficits in cognitive function.[9] The main known neurologic effect of n-hexane among San Francisco area workers was peripheral neuropathy.[9]

Paint sludge constitutes a major fraction of the hazardous waste from automotive industry.[10] Major disposal routes are incineration or combustion at cement kilns.[10]

REFERENCES

1 **EPA Office of Compliance Sector Notebook Project. Profile of the Motor Vehicle Assembly Industry**. *US Environmental Protection Agency*, 1995.
2 **EPA Office of Compliance Sector Notebook Project. Sector Notebook Data Refresh - 1997**. *US Environmental Protection Agency*, 1998.
3 G. Wypych, Ed., **Weathering of Plastics. Testing to Mirror Real Life Performance**, *Plastics Design Library, Society of Plastics Engineers*, New York, 1999.
4 M Harsch, M Finkbeiner, D Piwowarczyk, K Saur, P Eyerer, *Automotive Eng.*, **107**, No.2, 211-4 (1999).
5 C A Kondos, C F Kahle, *Automotive Eng*., **107**, No.1, 99-101 (1999).
6 D C Shepard, *J. Coat. Technol.*, **68**, No.857, 99-102 (1996).
7 T Hosomi, T Umemura, T Takata, Y Mori, **US Patent 5,717,055**, *Mitsubishi Gas Chemical Company, Ltd.*, 1998.
8 M Vitali, F Ensabella, D Stella, M Guidotti, *Ind. Health*, **44** (2), 310-17 (2006).
9 M. N. Bates, B. R. Reed, S. Liu, E. A. Eisen, S. K. Hammond, *NeuroToxicol*., **57**, 22-30, 2016.
10 G. Salihoglu, N. K. Salihoglu, *J. Environ. Manag*., **169**, 223-35, 2016.

13.17 ORGANIC CHEMICAL INDUSTRY

George Wypych
ChemTec Laboratories, Toronto, Canada

The US chemical output value in 2016 was $767 billion.[1] The chemical industry worldwide output in 2016 was $5,195 billion with Asia-Pacific producing half of it. The US chemical industry employed in Jan. 2018 826,000 and European Union chemical industry employed in 2017 1,140,000 people. There are point source solvent emissions (e.g., laboratory hoods, distillation units, reactors, storage tanks, vents, etc.), fugitive emissions (e.g., pump valves, flanges, sample collectors, seals, relief devices, tanks), and secondary emissions (waste water treatment units, cooling towers, spills). Organic liquid wastes containing solvent are generated from processes such as equipment washing, surplus chemicals, product purification, product reaction, housekeeping, etc.

Tables 13.17.1 and 13.17.2 give the reported solvent releases and transfers from the organic chemical industry. Large quantities of solvents are involved. The organic chemical industry produced the second largest quantity of VOC and the second largest releases and transfers. The industry is actively working to reduce solvent use because of the high costs (waste treatment, fines, liabilities, etc). There are many efforts under way to reduce environmental emissions and improve safety practices. The initiatives include process modifications such as a reduction in non-reactive materials (e.g., solvents) to improve process efficiency, a reduction in the concentration of chemicals in aqueous solution, and improved R&D and process engineering. Equipment modifications are planned to reduce leaks, prevent equipment breakdown, and improve the efficiency of emission control devices.

Table 13.17.1. Reported solvent releases from the organic chemical industry in 1995
[Data from Ref. 3].

Solvent	Amount, kg/year	Solvent	Amount, kg/year
allyl alcohol	31,000	ethylbenzene	370,000
benzene	690,000	ethylene glycol	6,050,000
n-butyl alcohol	850,000	hexane	600,000
sec-butyl alcohol	63,000	isopropyl alcohol	150
tert-butyl alcohol	430,000	methanol	8,750,000
carbon disulfide	85,000	methyl ethyl ketone	260,000
carbon tetrachloride	10,000	methyl isobutyl ketone	520,000
chlorobenzene	27,000	N-methyl-2-pyrrolidone	350,000
chloroform	7,000	methyl tert-butyl ether	64,000
cresol	280,000	pyridine	120,000
m-cresol	320,000	tetrachloroethylene	20,000

Table 13.17.1. Reported solvent releases from the organic chemical industry in 1995
[Data from Ref. 3].

Solvent	Amount, kg/year	Solvent	Amount, kg/year
o-cresol	270,000	toluene	1,040,000
p-cresol	162,000	1,2,4-trichlorobenzene	41,000
cyclohexane	450,000	1,1,1-trichloroethane	130,000
cyclohexanol	1,100,000	trichloroethylene	18,000
dichloroethane	120,000	xylene	350,000
1,2-dichloroethylene	70	m-xylene	59,000
dichloromethane	310,000	o-xylene	34,000
N,N-dimethylformamide	25,000	p-xylene	660,000
1,4-dioxane	12,000		

Table 13.17.2. Reported solvent transfers from the organic chemical industry in 1995.
[Data from Ref. 3]

Solvent	Amount, kg/year	Solvent	Amount, kg/year
allyl alcohol	210,00	ethylbenzene	980,000
benzene	420,000	ethylene glycol	6,800,000
n-butyl alcohol	1,500,000	hexane	770,000
sec-butyl alcohol	1,700,000	isopropyl alcohol	85,000
tert-butyl alcohol	12,500,000	methanol	23,000,000
carbon disulfide	96,000	methyl ethyl ketone	800,000
carbon tetrachloride	12,000	methyl isobutyl ketone	390,000
chlorobenzene	130,000	N-methyl-2-pyrrolidone	110,000
chloroform	92,000	methyl tert-butyl ether	210,000
cresol	430,000	pyridine	33,000
m-cresol	720,000	tetrachloroethylene	138,000
o-cresol	57,000	toluene	4,400,000
p-cresol	870,000	1,2,4-trichlorobenzene	8,000
cyclohexane	900,000	1,1,1-trichloroethane	290,000
cyclohexanol	3,700	trichloroethylene	42,000
dichloroethane	230,000	xylene	4,000,000
1,2-dichloroethylene	1,000	m-xylene	51,000
dichloromethane	870,000	o-xylene	460,000
N,N-dimethylformamide	370,000	p-xylene	1,700

Germany's Evonik Industries AG and the Sinopec Beijing Research Institute of the Chemical Industry are to build a process development laboratory for organic solvent nanofiltration membrane technology.[4]

Ionic liquids are suitable for use as entrainers in extractive distillation.[5] This permits a more environmentally friendly operation, reduces exposure of chemicals to workers, increases ease of reuse and recycling by striping evaporation or drying, and consequently reducing total operating costs.[5] The book chapter discusses the use of ionic liquids for extractive and azeotropic distillation.[5]

To minimize the environmental impact of volatile organic solvents, a deep eutectic solvent consisting of choline chloride and urea (1:2 molar ratio) was used as the co-solvent for the preparation of gem-bisamides starting from aldehydes.[6] The deep eutectic solvent performed a triple role of a solvent, a catalyst, and a reagent, providing a green, safe, and cost-effective chemical process.[6]

The ultrasound-assisted extraction of various compounds was performed using clean, green solvents.[7] This technology may help in enhancing extraction yields, reducing solute degradation, and preserve the environment.[7]

The above selected are just some examples of efforts which aim at the decreasing use of solvents and application of safer solvents for people and environment.

REFERENCES

1 Statista
2 **EPA Office of Compliance Sector Notebook Project. Profile of the Organic Chemical Industry**. *US Environmental Protection Agency*, 1995.
3 **EPA Office of Compliance Sector Notebook Project. Sector Notebook Data Refresh - 1997**. *US Environmental Protection Agency*, 1998.
4 *Filtration Ind. Analyst*, **2017**, 7, 5, 2017.
5 N. Litombe, **Separation Science and Technology** in **Novel Catalytic and Separation Processes Based on Ionic Liquids**, *Elsevier*, 2017, pp. 193-202.
6 N. Azizi, M. Alipour, *J. Mol. Liquids*, **206**, 268-71, 2015.
7 B. K. Tiwari, *TrAC Trends Anal. Chem*., **71**, 100-9, 2015.

13.18 PAINTS AND COATINGS

13.18.1 ARCHITECTURAL SURFACE COATINGS AND SOLVENTS

*Tilman Hahn, *Konrad Botzenhart, *Fritz Schweinsberg,
**Gerhard Volland
***Institut für Allgemeine Hygiene und Umwelthygiene, Universität Tübingen, Tübingen, Germany**
****Otto-Graf-Institut, Universität Stuttgart, Stuttgart, Germany**

13.18.1.1 General aspects

Coating materials and coating techniques can be distinguished and systematized in various ways. The fundamental principles of common coating systems are:[1]

- *Physical drying*. A solid surface film is formed after the evaporation of water or organic solvents.
- *Physico-chemical drying/curing*. Polycondensation or polyaddition are combined
- *Chemical curing*. Solvents, e.g., styrene or acrylic monomers, react with the curing system.

The actual effects depend on the surrounding conditions and the ingredients of the coating system, e.g., solvents.

Solvents contribute many essential properties to the coating systems. Solvents can improve technical factors such as application or surface properties. Solvents also bring negative qualities to coating materials, especially with respect to environmental conditions (e.g., toxic effects of emitted organic solvents).

13.18.1.2 Technical aspects and properties of coating materials

Application techniques for coatings can be considered in various ways. The stability and durability of the coating are essential. Coatings that have normal wear and tear requirements are mainly based on oils and aldehyde resins. Higher durability or stability can be achieved by the use of one of the following one- or two-component systems.

One-component:

- Bituminous materials
- Chlorinated rubber
- Polyvinylchloride
- Polyacrylic resin
- Polyethylene
- Saturated polyester
- Polyamide

Two-component:

- Epoxy resin
- Polyurethane
- Mixtures of reactive resins and tar

A survey of the performance of different coating materials together with an assessment of various environmental factors is given in Table 13.18.1.1.

Table 13.18.1.1. Environmental performance of some coating materials.

Material	Abbreviation	Weathering response	Acid atmosphere	Humidity	Under water	Chemical stress		Solvent	Temperature <60°C	Mechanical	
						acid	alkali			abrasion	scratch
plant oil (linseed oil)	OEL	+y,s,f	+/-	+/-	-	-	-s	-	+	-	-
alkyd resin	AK	+	+/-	+/-	-	-	-s	-	+	-	-
bitumen	B	+/-e,f	+	+	+	+/-	+	-	+/-	-	-
chlorinated rubber	RUC	+/-b,c,f	+	+	+	+	+	-	+	+/-	+/-
PVC-soft	PVC	+/-e,f	+	+/-	+/-	+	+/-	-	+	+/-	+/-
Polyacrylic resin	AY	+	+	+	+	+	+	-	+	+	+/-
polyethene	PE	+/-e	+	+	+	+	+	+	+	+	+
polyester (saturated)	SP	+	+	+/-	+/-	+	+/-(s)	+	+	+	+
epoxy resin	EP	+/-c,g	+	+	+	+/-	+	+	+	+	+
polyurethane	PU	+	+	+/-	+/-	+	+/-	+/-	+	+	+
epoxy resin tar	EP-T	+/-c,e	+	+	+	+/-	+	+/-	+	+	+
polyisobutylene	PLB	+/-	+	+	+	+	+	-	+	+	+

+ = suitable, +/- = limited suitability, - = unsuitable, () = less distinct; b = bleaching, c = chalking, e = embrittlement, f = acid fragments, g = loss of gloss, s = saponification, y = yellowing

The following are the examples of architectural surface coatings.

13.18.1.2.1 Concrete coating materials

According to DIN 1045 concrete must be protected against aggressive substances if the chemical attack is severe and long-term. These are the requirements:

- Good adhesion
- Waterproof and resistant to aggressive substances and resistant to the alkalinity of the concrete
- Deformable

To realize these requirements, the following technical solutions can be applied:

- The use of paint coatings based on duroplast or thermoplastic substances
- Surface treatment – impregnation

Protective coatings based on polymers are used in construction with and without fillers and with or without reinforcing materials (fibers).

The following techniques are generally used:

- The film forming paint coatings (brushing, rolling, spraying).
- Coating (filling, pouring).

During application, the coating materials are normally liquid and subsequently harden by evaporation of solvents or as a result of chemical reactions.

The common coating systems for concrete are listed in Table 13.18.1.2. Synthetic resins (e.g., chlorinated rubber, styrene resins, acrylic resins) normally contain 40-60% solvents and form a thin film. Several coats must be applied. Reactive resins may require little or no solvent.

Table 13.18.1.2. Survey of often used coating systems for concrete.

Film-forming agents	Hotmelts	Film-forming agents dissolved	Film-forming agents emulsified	Reaction resin liquid
Bituminous substances	+	+	+	
Synthetic resin		+	+	
Reactive resins		(+)	(+)	+

13.18.1.2.2 Coating materials for metals

Wet coating processes are detailed in Table 13.18.1.3.

Table 13.18.1.3. Wet coatings – coating materials for metals.

		Abbreviation	Application	State	Curing method
Natural substances	oil	OEL	binders for wet coating	liquid	oxidizing
	bitumen	B			physical
	tar	T			physical
Plastic materials	alkyd resin	AK	binder for wet coating		oxidizing
	polyurethane	PU			chemical
	epoxy resin	EP			chemical
	acrylic resin	AY			physical
	vinyl resin	PVC			physical
	chlorinated	RUC			physical
	rubber				

The chemical properties of binders are not affected by the drying process if coatings are of a physically drying type. After the solvent has evaporated, the polymer molecules become intermeshed, thus producing the desired coating properties.

In contrast to physical drying, binders based on reactive resins such as epoxy resins, polyurethanes or polyesters consist of two components (liquid resin and curing agent)

which are either mixed shortly before the coat is applied, or, in the case of a one-component system, one which is applied as slow reacting mixture. The setting reaction begins at the surface of the coated material. The final products are normally more resistant and more compact than products based on physically drying binders. Pretreatment of the substrate is more critical for applications where chemically hardening products are applied. Coatings can be more or less permeable to water vapor and oxygen. Damage to the metal substrate can occur if water and oxygen reach the reactive surface simultaneously. This is normally impossible if the coatings adhere well and the coated surface is continuous. The adhesion of the coating also prevents the penetration of harmful substances *via* diffusion processes. Adhesion is enhanced by adsorption and chemical bonds.

13.18.1.2.3 Other coating materials

The market offers a wide spectrum of coating systems. Examples of common industrial coating materials are listed in Table 13.18.1.4 and relevant aspects concerning application and environmental or health risks are also included.

Table 13.18.1.4. Examples of coating materials containing hazardous ingredients, especially solvents[3]

Product group/ compounds	Application	Hazardous ingredients, especially solvents	Relevant health and environmental risks
zinc dust coating based on epoxy resin	corrosion protection/ primer, application by brush, spray, airless spraying	xylene 2,5-25%, ethylbenzene 2,5-10%, solvent naphtha 2,5-10%, 1-methoxy-2-propanol 1-2,5%	irritations (respiratory, skin, eyes), neurological (narcotic) effects, absorption (skin), flammable, explosive mixtures
reactive PUR-polymers containing solvents	corrosion protection/coating	solvent naphtha 10-20%, diphenylmethane isocyanate 2,5-10%	sensitization (respiratory) irritation (skin, eyes, gastrointestinal tract), neurological effects (narcotic effects, coordination), absorption (skin), flammable, water polluting
modified polyamine containing solvents	corrosion protection/coatings/ rigid system	4-tert-butylphenol 10-25%, M-phenylene-bis 2,5-10%, trimethylhexane, 1,6-diamine 10-25%, nonylphenol, 10-25% xylene 10-25%, ethylbenzene 2,5-10%	sensitization (skin, respiratory), irritations (skin, eye, respiratory, gastrointestinal tract), neurological (narcotic) effects (coordination), flammable, water polluting
modified epoxy resin containing solvents	corrosion protection/ coatings/ rigid system	bisphenol A (epichlorohydrin) 25-50% oxirane, mono(C_{12} -C_{14}-alkyloxy)methyl derivatives 2,5-10%, cyclohexanone 1-2,5%, 2-methylpropane-1-ol 2,5-10%, xylene 10-25%, ethylbenzene 2,5-10%, benzyl alcohol 1-2,5%, 4-methylpentane- 2-one 1-2,5%	irritations (skin), sensitization (skin, contact), neurological (narcotic) effects, absorption (skin), flammable, water polluting
modified epoxy resin containing solvent	corrosion protection/ top layer	bisphenol A (epichlorohydrin) 50-100%, 3-amino-3,5,5-trimethyl ethylbenzene 10-25%, xylene 10-25%	irritation (skin, eyes, respiratory), sensitization (skin), flammable, explosive gas/air mixtures, hazardous reactions (with acids, oxidizers), water polluting
filled and modified epoxy resin	coatings and corrosion prevention/ pore sealer	bisphenol A (epichlorohydrin) 50-100%, P-tert-butylphenyl-1-(2,3-epoxy)propyl-ether 1-2,5%	irritations, sensitization, water polluting

Table 13.18.1.4. Examples of coating materials containing hazardous ingredients, especially solvents[3]

Product group/ compounds	Application	Hazardous ingredients, especially solvents	Relevant health and environmental risks
filled and modified epoxy resin	coatings and corrosion prevention/pore sealer	trimethylhexamethylendiazine-1,6-diamine 10-25%, trimethylhexamethylendiamine-1,6-cyanoethylene 50-100%	irritations, sensitization, water polluting
filled and modified epoxy resin	flooring/mortar screen	bisphenol A (epichlorohydrin) 25-50%, benzyl butyl phthalate 2,5-10%, xylene 2,5-10%	irritation (eye, skin, respiratory), sensitization (contact, skin), explosive gas/air mixtures (with amines, phenols), water polluting
modified polyamine	flooring/mortar screen	benzyl alcohol 10-25%, nonylphenol 25-50%, 4,4´-methylene-bis (cyclohexylamine) 10-25%, 3,6,9-triazaundecamethylendiamine 10-25%	irritation (eye, skin, respiratory), sensitization (contact, skin), hazardous reactions (with acids, oxidizers), flammable, water polluting
filled and modified epoxy resin	corrosion protection/top layer	naphtha 2,5-10%, 2-methoxy-1-methylethylacetate 2,5-10%, 2-methylpropane-1-ol 1-2,5%, xylene 10-25%, ethylbenzene 2,5-10%	irritation (skin, eyes, respiratory), neurological (narcotic) effects, flammable, explosive, hazardous reactions (with oxidizers), water polluting
copolymer dispersion	walls, especially fungicidal properties, good adhesion in damp environment, resistant against condensed water	isothiazolone 1-2,5%, 3-methoxybutylacetate 1-2,5%	irritations (skin, eyes, gastrointestinal tract), water polluting
coating of synthetic resin containing solvents	corrosion protection/coating (steel)	solvent naphtha (petroleum) 25-50%, xylene 2,5-10%, ethylbenzene 1-2,5%	irritations (eyes, skin, respiratory, gastrointestinal tract), neurological (narcotic) effects, flammable, explosive gas/air mixtures, hazardous reactions (with oxidizers), water polluting
bituminous emulsion (phenol-free, anionic)	corrosion protection/coating (steel, drinking water tanks)	naphtha (petroleum) 25-50%	irritations (skin, eyes, respiratory), neurological effects (coordination), flammable, water polluting
modified, filled anthracene oil and polyamine	corrosion protection/top layer	solvent naphtha 2,5-10%, biphenyl-2-ol 2,5-10%, 3-amino-3,5,5-trimethylcyclohexamine 1-2,5%, xylene 1-2,5%	irritations (skin, eyes, respiratory), flammable, water polluting
partially neutralized composition of aminoalcohols	sealants and adhesives/elastic products (floor joints, joints)	2-aminoethanol 2,5-10%	sensitization, irritations, slight water pollution
filled, reactive PUR-polymers	sealants and adhesives/elastic products (floor joints, joints)	3-isocyanatemethyl-3,5,5-trimethylcyclohexylisocyanate 0,1-1%, N,N-dibenzylidenepolyoxypropylene diamine 1-2,5%, xylene 2,5-10%, ethylbenzene 1-2,5%	sensitization, irritations, hazardous reactions (with amines, alcohols)
solvent-based composition, based on PVC	coatings and corrosion prevention/ impregnation, sealer	solvent naphtha 50-100%, 1-methoxy-2-propanol 2,5-10%	irritations, flammable, neurological effects

Table 13.18.1.4. Examples of coating materials containing hazardous ingredients, especially solvents[3]

Product group/ compounds	Application	Hazardous ingredients, especially solvents	Relevant health and environmental risks
acrylate dispersion, water dispersed adhesion, promoter	coatings and corrosion protection/ rigid coat (for concrete and dense mineral substrates)	water-borne so-called solvent-free systems	irritations (long-term contact), slightly water polluting

13.18.1.3 Recent advances

A model paint containing resin dissolved in butanol was sprayed onto horizontal glass substrates to form films varying from 100 μm to 450 μm in thickness.[4] The substrates were photographed at 5 s intervals and image analysis software used to measure the number, diameter, and velocity of air bubbles trapped in the paint layer.[4] Also, the painted substrates were weighed to determine the rate of solvent evaporation.[4] Bubbles escaped from the paint in 100-900 s, the time increasing with paint thickness.[4] The Sauter mean diameter of bubbles, in films having a thickness of fewer than 300 μm, decreased with time because larger bubbles escaped faster than small bubbles.[4] The mean diameter of bubbles in a 450 μm thick layer increased due to bubble coalescence.[4] Bubble velocities due to movement of the liquid increased with paint thickness and reached 30 μm/s.[4] Concentration gradients due to solvent evaporation in a paint film created surface tension variations, causing Marangoni flow, which was bringing bubbles to the paint surface.[4]

The use of CO_2 for spray coating is a promising technique in the paint industry.[5] The polymer precipitation might be induced by the addition of CO_2 into solvent because CO_2 is a poor solvent for most polymers.[5] A solvent selection guide based on the solubility parameter is proposed to prevent the polymer precipitation.[5] Precipitation of the polymer (acrylic resin) from the diluent solution (methanol, butanol, and diethyl ketone) will occur, when solubility parameter of solvent and CO_2 mixture differs by 6 $MPa^{0.5}$.[5]

Ground-level ozone produced from VOC reaction with NO_x have been quantified using Maximum Incremental Reactivities (MIR).[6] MIR-based calculation of ozone formation potential of VOCs emitted from an aromatic solvent-containing paint that was used for marking of roads in Kraków, Poland has been estimated.[6] The evaporation of 240 kg of aromatic solvents from one tonne of paint caused the formation of 550 kg of ozone (up to 42 tonnes of tropospheric ozone annually in Kraków alone).[6] Elimination of the aromatic solvent would have decreased ozone production capability by about 50% and the use of waterborne paint would decrease ozone formation by 93%.[6] The life-cycle assessment results, i.e. considering the whole life-cycle from manufacturing to disposal, showed that a global warming potential reduction of more than 50% can be achieved by a more durable road marking system.[7] Methylmethacrylate Cold Plastics in agglomerate form (also known as structure marking, “3D” marking) provide an environmentally friendly road marking solution. Cold Plastic considerably reduces VOC emissions in comparison to solvent-borne paints, thus reducing photochemical ozone creation at the ground level.[7]

The recovery of industrially valuable organic solvents from liquid waste, generated by paint industry has been studied using ionic liquids.[8] The concentrations of aromatics recovered from the spent solvents were 13-33% and 23-49%, respectively for imidazolium and pyridinium based ionic liquids.[8] There is a correlation between π-character of ionic liquids and the level of extraction.[8] The ionic liquids have the potential for macro-scale recovery of re-useable solvents present in liquid waste of paint manufacture.[8]

The paints containing volatile organic components have been prohibited by the European Commission for professional indoor use.[9]

REFERENCES

1 **Ullmann´s Encyclopedia of Industrial Chemistry**, *Wiley*, 2014.
2 DIN 1045 (Deutsches Institut für Normung), Concrete and Reinforced Concrete. Beton und Stahlbeton, Beuth Verlag, Berlin, part 1 (2008), part 2 (2008).
3 Sika TechnoBauCD, Sika Chemie GmbH, Stuttgart (2000).
4 A. Dalili, S. Chandra, J. Mostaghimi, H. T. C. Fan, J. C. Simmer, *Prog. Org. Coat*., **97**, 153-65, 2016.
5 Y. Sato, T.i Shimada, K. Abe, H. Inomata, S.-i. Kawasaki, *J. Supercrit. Fluids*, **130**, 172-5, 2017.
6 T. E. Burghardt, A. Pashkevich, L. Żakowska, *Transp. Res. Procedia*, **14**, 714-23, 2016.
7 M. Cruz, A. Klein, V. Steiner, *Transp. Res. Procedia*, **14**, 869-75, 2016.
8 K. Moodley, M. Mabaso, I. Bahadur, G.G. Redhi, *J. Mol. Liquids*, **219**, 206-10, 2016.
9 A. Ronzino, V. Corrado, *Energy Procedia*, **78**, 1507-12, 2015.

13.18.2 RECENT ADVANCES IN COALESCING SOLVENTS FOR WATERBORNE COATINGS

DAVID RANDALL
Chemoxy International pcl, Cleveland, United Kingdom

13.18.2.1 Introduction

The role of coalescing solvents in coating formulations, the factors which affect the choice of coalescing solvents, and the recent developments in esters of low volatility, low odor and rapid biodegradability for use in coating formulations are discussed.

The term "paint" is widely used to describe a coating applied to a variety of substrates for protective or decorative purposes. "Paint" also implies a pigmented species, whereas "surface coatings" is a broader term for coating systems with or without pigments used for any coating purpose.

All paint systems may be considered as a combination of a small number of constituents. These are continuous phase or vehicle (polymer and diluent), discontinuous phase or pigment and extender, and additives.

This paper is not concerned with the detail of paint formulation, but the polymer types most widely encountered are alkyds, polyurethanes, and nitrocellulose in solvent-based systems, and acrylics, styrene-acrylics, and copolymers of vinyl acetate in water-based coatings.

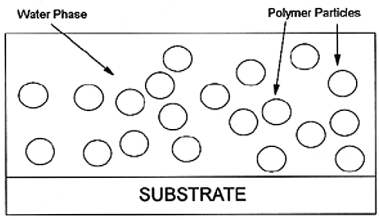
13.18.2.2 Water-based coatings

Not long ago, most paints were solvent-based. Since many polymers were produced in solution, it was natural that the coating system, derived from these polymers, would use the solvent as the diluent for the polymer. These were almost invariably organic species. The objections to the use of organic solvents in paint formulations were at first confined to those with strong views regarding the loss of significant quantities of organic species to the environment. Latter, these opinions have been reinforced by the role of some organic species in damage to the ozone layer, or to the production of smog in the lower atmosphere. This is a result of the reaction between organic species present catalyzed by sunlight and exacerbated by the presence of other pollutants associated with motor vehicles, etc. Flammability of paints also poses a significant problem in storage and use.

All this tended to reinforce the need to develop aqueous-based systems, for which these problems would be eliminated.

13.18.2.3 Emulsion polymers

Of course, the manufacture of polymers need not be carried out in solution; emulsion polymerization has a long and honorable tradition in the field of macromolecular chemistry. This polymerization technique is performed using water-insoluble monomers, which are caused to form an emulsion with the aqueous phase by the addition of a surfactant. Polymerization may be effected by the use of a variety of radical generating initiating species, and the molecular weight of the polymer is controlled by the use of chain transfer agents and the concentration of initiator employed. The final polymer dispersion is often



F

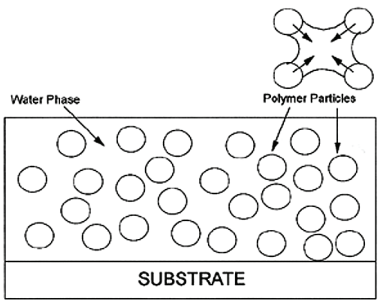


Figure 13.18.2.2. Initial water evaporation and film formation.

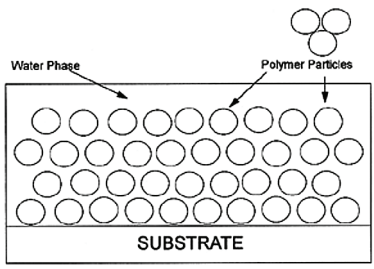


Figure 13.18.2.3. Close packing of latex particles.

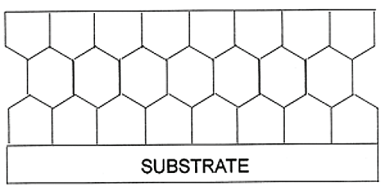


Figure 13.18.2.4. Coalescence to form a polymeric film.

described as a latex, named after natural rubber, which is also an emulsion polymer!

This polymerization technique allows for the formation of copolymers in which the addition of relatively small quantities of comonomer may have a significant effect on the final properties of the polymer. This is particularly the case with the glass transition temperature, T_g, of the polymer. This is a physical transition, which occurs in the polymer when the amorphous structure of that polymer begins to change from a glassy to a rubbery state. At temperatures below a polymer's T_g, it will be relatively brittle and will be unlikely to form a coherent film.

This effect has a major impact on the use of polymers in aqueous systems. In the case of a polymer in solution, the presence of the solvent plasticizes the polymer during film formation. A polymer with a high T_g, i.e., one greater than ambient temperature, can, when in solution, be applied at temperatures below its T_g. In the case of an emulsion polymer, water is a non-solvent in the system and film formation below the polymer T_g is unlikely. The temperature at which a coherent film may be formed from a solution or emulsion based system is known as the Minimum Film Forming Temperature (MFFT or MFT).

Figures 13.18.2.1-13.18.2.4 describe the formation of a discrete film from an emulsion system.

When the film is applied onto the substrate, discrete polymer particles are dispersed in the aqueous phase. The system is stabilized by the presence of the surfactant at the water-particle interface. The particles are spherical, with an average diameter of 0.1-0.2 μm.

As water is lost from the system, the mutually repulsive forces associated with the surfactants present inhibit the close packing of the particles and a cubic arrangement of the particles is formed.

As the water continues to evaporate, the particles become close-packed with a solids volume of around 70%. Capillary forces continue to force the particles together.

The final stage is achieved when most of the water is lost from the system. Here, the interparticular repulsive forces are overcome by increasing surface tension and the particles coalesce into a discrete film. This will only occur at temperatures in excess of the MFFT.

13.18.2.4 Role of a coalescing solvent

Most coatings based on emulsion polymers are used in environments where they will be expected to form a coherent film at temperatures as low as 0°C. However, other physical properties besides film-forming capability are required from the polymer. These include abrasion resistance, hardness, chemical resistance, impact performance, etc. These can often be impossible to achieve with a polymer of low T_g. The polymers, which most clearly meet these criteria are acrylics or copolymers of vinyl acetate or styrene. These would, without additions of coalescing species, be brittle, forming incoherent films with little adhesion to the substrate at normal application temperatures.

Coalescing solvents allow these polymeric systems to form films at ambient or subambient temperatures. The presence of the coalescing solvent has the following effects.

- It reduces the total surface energy of the system by reducing polymer surface area
- It increases the capillary forces by the controlled evaporation of water
- It reduces the repulsive forces between the polymeric particles
- It allows deformation of the particles in contact with each other by effectively lowering the T_g of the polymer.

An emulsion polymer consists of a dispersion of polymeric particles varying in size from 0.05-1 μm, dispersed in an aqueous environment. The coalescing solvent may be found in several different locations depending on their nature. They are classified according to their preferred location in the aqueous system.

Hydrophobic substances such as hydrocarbons will prefer to be within the polymer particle; these are described as A Group coalescents. These tend to be inefficient coalescing agents. Molecules, which are more hydrophilic than hydrocarbons tend to be preferentially sited at the particle – aqueous interface, along with the surfactant system. These are described as AB Group coalescents. These exhibit the best efficiency as coalescing solvents.

In the third group are the hydrophobic glycol ethers and similar species. These exhibit good coalescing power but are partitioned between the polymer particle, the boundary layer, and the aqueous phase. More of these are required than AB Group coalescents, they are called ABC Group coalescents. Finally, hydrophilic species such as glycols and the more polar glycol ethers are inefficient coalescing agents and are more commonly used as freeze-thaw stabilizers. These are described as C Group coalescents.

13.18.2.5 Properties of coalescing agents

13.18.2.5.1 Hydrolytic stability

A coalescing agent should have good hydrolytic stability (a high degree of resistance to hydrolysis) so that it can be used successfully in both low and high pH latex systems.

13.18.2.5.2 Water solubility

It is desirable for a coalescing aid to have low water miscibility for the following reasons:

- When added to a coating formulation, a coalescing aid with low water miscibility partitions into the polymer phase and softens the polymer; this improves pigment binding and polymer fusion
- There is less tendency for the evaporation of the coalescing aid to be accelerated by evaporation of the water during the early stages of drying.
- The early water resistance of the coating is not adversely affected
- When a latex coating is applied to a porous substrate, water immiscible coalescing aids are not lost into the porous substrate along with the water; i.e., more coalescing aid will be available to coalesce the coating.

13.18.2.5.3 Freezing point

The freezing point of a coalescing agent should be low (below –20°C) as materials with a high freezing point may require specialized (therefore more expensive) handling techniques in transport and storage.

13.18.2.5.4 Evaporation rate

The evaporation rate of a coalescing aid should be slow enough to ensure good film formation of the emulsion coating under a wide range of humidity and temperature conditions; however, it should be fast enough to leave the coating film in a reasonable length of time and not cause excessive film softness. The evaporation rate of the coalescing aid should be less than that of water but not so slow that it remains in the film for an extended period of time causing dirt pickup.

13.18.2.5.5 Odor

The odor of a coalescing agent should be minimal. This is especially important for interior coatings applications.

13.18.2.5.6 Color

A coalescing agent should be colorless, to prevent discoloration of the product.

13.18.2.5.7 Coalescing efficiency

The effectiveness of a coalescing agent is based upon the MFFT test.

13.18.2.5.8 Incorporation

A good coalescing agent should be capable of addition during any stage of paint manufacture. Any particular coalescing agent may need premixing prior to addition with varying amounts of the water and surfactant used in the paint stage.

13.18.2.5.9 Improvement of physical properties

A good coalescing agent can provide a significant improvement in scrub resistance, stain resistance, flexibility, and weatherability.

13.18.2.5.10 Biodegradability
A good coalescing agent should exhibit acceptably rapid biodegradation quickly.

13.18.2.5.11 Safety
The use of the coating system requires that the nature of the coalescing agent should permit use in the domestic environment. The suitability of such a material is, therefore, obviously dependent on its toxicity, flash point, vapor pressure and VOC classification.

13.18.2.6 Comparison of coalescing solvents

From the above, it may readily be seen that AB type coalescing solvents give the best performance in use. These are the high molecular weight esters and ester alcohols. Other species have some of the benefits of these materials but have side effects, which render them less suitable. Minimization of the quantity used tends to be a key financial issue, as well as offering the best environmental option. In virtually all cases, the efficiency of the AB group in the application is so marked, that they have become the industry standards. Several other properties, perhaps less important, than efficiency must then be considered when selecting between these.

These products are usually used in enclosed spaces, where product odor will be vital for acceptance to the consumer. The dibasic esters are virtually odor free. For legislative reasons, a solvent not classified as a VOC will be of definite benefit, given the current attitude to organics in consumer products. Again, the dibasic esters have initial boiling points considerably above the VOC threshold of 250°C.

The stability of the product towards hydrolysis is also a significant factor in the selection of the optimum coalescing agent. Effectively, this parameter determines the storage stability of the product. Again, dibasic esters, particularly those produced from higher molecular weight alcohols appear to have an advantage.

The efficiency of the AB group of coalescents towards almost all polymer types has already been mentioned. For styrene-acrylics and vinyl acetate – Veova copolymers, the diesters have a significant edge in performance compared with other members of that group. This advantage is shown in the reduction in the amount required to attain a particular minimum film forming temperature, MFFT or the actual MFFT for a given addition level.

Coasol manufactured by Chemoxy is the blend of di-isobutyl esters of the dibasic acids; adipic, glutaric and succinic. These acids are produced as a by-product in the production of adipic acid in the manufacture of Nylon 6,6. The ratio of the acids is 15-25% adipic, 50-60% glutaric, 20-30% succinic. Esterification using isobutanol is then performed and the product is isolated following distillation. Coasol was introduced in the 1990s as a coalescing agent to the aqueous based coatings industry.

Coasol has excellent coalescing properties and is compatible with virtually all paint systems. It has a very low vapor pressure at ambient temperature which ensures excellent plasticization throughout the film forming and drying process. Its extremely low odor also significantly improves the general view that aqueous systems have unpleasant odors. This is almost always as a result of the coalescing solvent. Its resistance to hydrolysis allows its

use in a wide variety of formulations, including those, which require adjustment of pH to basic conditions.

It rapidly biodegrades, both aerobically and anaerobically, since, as an ester, it is readily attacked by ubiquitous biospecies. Finally, its toxicological profile is virtually benign, so in use, it can be handled with confidence in most working environments. Its properties are summarized in Table 13.18.2.1.

Table 13.18.2.1. Properties of Coasol.

Physical characteristic	Coasol	Comments
Boiling point	> 275°C	Not a VOC
Evaporation rate	< 0.01 (Butyl acetate = 1.0)	Slow, allowing excellent coalescence
Freezing point	< -55°C	No freeze-thaw issue
Water solubility	600 ppm	
Hydrolytic stability	Very good	No hydrolysis in normal use
Color	5 Hazen units	Imparts no color to coatings
Coalescing efficiency	Excellent for most polymer systems	
Biodegradability	80% in 28 days	Biodegradable
Odor	None discernible	
Toxicology	Oral LD50 (Rat) >16,000 mg/kg	Essentially non toxic

13.18.2.7 Advances in diester coalescing solvents

The di-isopropyl esters of the higher adipic content stream is also useful. This has a vapor pressure similar to that of Coasol but is slightly more water soluble. Di-isopropyl adipate has the highest boiling point, the lowest vapor pressure, and the lowest water solubility of this range of products. These preparations were undertaken to add to the repertoire of products to suit the diverse requirements of the formulators of aqueous based systems.

In virtually all cases, the dibasic esters gave a significant improvement in efficiency in reducing the MFFT for a given quantity of additive. The attempts are made to offer a tailor-made solution to each individual polymer system employed in the development of aqueous based systems. The dibasic esters of the AGS acids group offer the opportunity for fine tuning, with the added advantage of low odor, low toxicity and “excellent” VOC status.

Literature brings new research data regarding the use of coalescent solvents. Low VOC waterborne coatings were developed using fatty acid derivatives.[1] These coatings did not contain volatile coalescent solvents, instead of an allylic fatty acid derivative (AFAD) and an acrylic fatty acid derivative (AcFAD), either as reactive (non-volatile) coalescing agents or as co-monomers.[1] The minimum film-forming temperatures of the coatings were lower than the reference, confirming that AFAD and AcFAD act as coalescing agents.[1]

Transparent protective coatings for metals, when soaked in water suffered from a visible whitening of their basecoats, when high load of coalescing agent (dipropylene glycol monomethyl ether) was used.[2] FTIR study of whitened layer indicated the presence of coalescent in the basecoat, suggesting that coalescent migrated from the topcoat into the primer basecoat.[2] Annealing reversed or inhibited water whitening.[2]

Development of binders, such as polyurethanes, that have expected performance at low VOC is the major direction of coatings research and development.[3] Such systems require reduced amounts of coalescing solvents.[3]

Additive FT-100 and Additive OTE-500 are added either to the resin or to the paint formulation to provide a finished coating formulation that exhibits five cycles of freeze-thaw stability.[4] These additives also improve other properties such as gloss, scrub resistance, and stain resistance.[4]

A coalescing agent for three-dimensional printing includes a co-solvent, a surfactant having a hydrophilic/lipophilic balance value that is less than 10, a carbon black pigment, a polymeric dispersant, and a balance of water.[5] The cosolvent is present in an amount ranging from about 15 to 30 wt% of a total coalescing agent.[5] The cosolvent is selected from the group consisting of 2-pyrrolidinone, 1,5-pentanediol, triethylene glycol, tetraethylene glycol, 2-methyl-1,3-propanediol, 1,6-hexanedol, and tripropylene glycol methyl ether.[5]

A glycol ether was reacted with phosphoric acid to produce a glycol ether ester product having low color, low odor, and low VOC content.[6] The product of reaction is useful as a low VOC coalescing agent.[6]

REFERENCES

1 J V Barbosa, E Veludo, J Moniz, A Mendes, F D Magalhaes, M M S M Bastos, *Prog. Org. Coat.*, **76**, 1691-96, 2013.
2 N A Swartz, K A Wood, T L Clare, *Prog. Org. Coat.*, **75**, 215-23, 2012.
3 J K Oh, J Anderson, B Erdem, R Drumright, G Meyers, *Prog. Org. Coat.*, **72**, 253-59, 2011.
4 Z Zong, S Wall, Y-Z Li, J Ruiz, H Adam, C Badre, F Trezzi, *Prog. Org. Coat.*, **72**, 115-19, 2011.
5 K. A. P. A. Emamjomeh, G. T. Haddick, **US20170247552A1**, *Hewlett-Packard Development Co LP*, Aug. 31, 2017.
6 G. J. Frycek, F. A. Donate, E. D. Daugs, R. J. Wachowicz, J. L. Trumble, **US9809529B2**, *Dow Global Technologies LLC*, Nov. 7, 2017.

13.18.2.2. Appendix – Classification of coalescing solvents.

Coalescent type	Type of species	Examples	Comments
Type A	hydrocarbons	white spirit	
Type AB	diesters	dimethyl ester diisobutyl ester	Estasol, DOW
		di-isobutyl adipate	Chemoxy, BASF
		di-isopropyl adipate	Chemoxy
		di-butyl phthalate	
Type AB	ester alcohols	diol monoesters (e.g., Texanol)	Eastman Chemical

13.18.2.2. Appendix – Classification of coalescing solvents.

Coalescent type	Type of species	Examples	Comments
Type ABC	glycol esters & glycol ester ethers	propylene glycol diacetate butyldiglycol acetate	DOW BASF
Type ABC	ether alcohols, & diethers	glycol ether 2-butoxyethanol MPG diethers	DOW BASF and others proglides and glymes
Type C	glycols	diethylene glycol dipropylene glycol triethylene glycol	DOW and others DOW and others DOW and others

13.19 PETROLEUM REFINING INDUSTRY

GEORGE WYPYCH
ChemTec Laboratories, Toronto, Canada

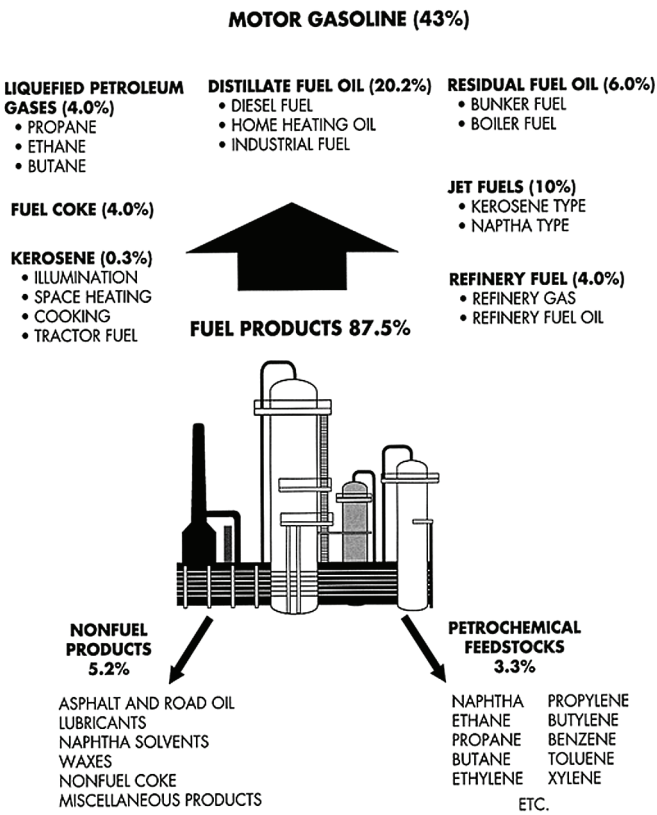


Figure 13.19.1. Diagram of production outputs from refineries. [Reproduced from EPA Office of Compliance Sector Notebook Project. Profile of the Petroleum Refining Industry, US Environmental Protection Agency, 1995.]

The US petroleum refining industry generates sales of over $730 billion with only about 143 plants.[1] It employs 62,000 people.[1] About 90% of the products used in the US are fuels of which 43% is gasoline. Figure 13.19.1 illustrates the products breakdown. The process is described in detail in Chapter 3. Emissions of hydrocarbons to the atmosphere occur at almost every stage of the production process. Solvents are produced in various processes and they are also used to extract aromatics from lube oil feedstock, deasphalting of lubricating base stocks, sulfur recovery from a gas stream, production of solvent additives for motor fuels such as methyl tert-butyl ether and tert-amyl methyl ether, and various cleaning operations. Emissions to atmosphere include fugitive emissions of the volatile components of crude oil and its fractions, emissions from incomplete combustion of fuel in the heating system, and various refinery processes. Fugitive emissions arise from thousands of valves, pumps, tanks, pressure relief valves, flanges, etc. Individual leaks may be small but their combined quantity results in the petrochemical industry contributing the largest quantity of emissions and transfers.

Tables 13.19.1 and 13.19.2 give solvent releases and transfers data for the petroleum refining industry. Transfers are a small fraction of releases which means that most wastes are processed on-site.

In addition to the emissions to the atmosphere, some plants have caused contamination of groundwater by releasing cooling and process water.

Table 13.19.1. Reported solvent releases from the petroleum refining industry in 1995
[Data from Ref. 3].

Solvent	Amount, kg/year	Solvent	Amount, kg/year
benzene	1,750,000	methyl isobutyl ketone	110,000
n-butyl alcohol	23,000	N-methyl-2-pyrrolidone	280,000
tert-butyl alcohol	28,000	methyl tert-butyl ketone	1,380,000
carbon tetrachloride	17,000	tetrachloroethylene	21,000
cresol	75,000	1,1,1-trichloroethane	50,000
cyclohexane	960,000	trichloroethylene	730
dichloromethane	8,000	1,2,4-trimethylbenzene	420,000
ethylbenzene	600,000	toluene	4,360,000
ethylene glycol	46,000	xylene	2,330,000
hexane	3,000,000	m-xylene	170,000
methanol	540,000	o-xylene	150,000
methyl ethyl ketone	2,100,000	p-xylene	1,000,000

Table 13.19.2. Reported solvent transfers from the petroleum refining industry in 1995
[Data from Ref. 3].

Solvent	Amount, kg/year	Solvent	Amount, kg/year
benzene	160,000	N-methyl-2-pyrrolidone	4,000
tert-butyl alcohol	900	methyl tert-butyl ketone	34,000
carbon tetrachloride	1,000	tetrachloroethylene	900
cresol	130,000	1,1,1-trichloroethane	6,500
cyclohexane	10,000	1,2,4-trimethylbenzene	31,000
ethylbenzene	61,000	toluene	270,000
ethylene glycol	58,000	xylene	340,000
hexane	13,000	m-xylene	11,000
methanol	180,000	o-xylene	30,000
methyl ethyl ketone	30,000	p-xylene	7,000
methyl isobutyl ketone	3,500		

Toluene, xylenes, and benzene constitute the majority of solvent emissions since they are native components of crude oil. Methyl ethyl ketone is also emitted in large quantities because of its use in lube oil dewaxing.

Pollution prevention will become increasingly important to the petroleum industry as federal, state and municipal regulations become more stringent and waste disposal cost rises. The industry estimates that to comply with 1990 Clean Air Act Amendments it will require an investment of $35-40 billion. Actions required to decrease pollution include process equipment modification, waste segregation and separation, recycling, and better training and supervision.

REFERENCES

1 **Petroleum Refining in the USA. Market Research Report**. *IBISWorld*, Nov. 2013.

2 **EPA Office of Compliance Sector Notebook Project. Profile of the Petroleum Refining Industry**. *US Environmental Protection Agency*, 1995.

3 **EPA Office of Compliance Sector Notebook Project. Sector Notebook Data Refresh - 1997**. *US Environmental Protection Agency, 1998*.

13.20 PHARMACEUTICAL INDUSTRY

13.20.1 USE OF SOLVENTS IN THE MANUFACTURE OF DRUG SUBSTANCES (DS) AND DRUG PRODUCTS (DP)

*Michel Bauer, **Christine Barthélémy
***International Analytical Department, Sanofi-Synthélabo, Toulouse, France**
****Laboratoire de Pharmacie Galénique et Biopharmacie, Faculté des Sciences Pharmaceutiques et Biologiques, Université de Lille 2, Lille, France**

13.20.1.1 Introduction

The manufacturing of a pharmaceutical drug is almost totally the responsibility of:

- the chemical industry for the preparation of the drug substance (active principle) and the excipients used for preparing the DP (finished product)
- the pharmaceutical industry for the preparation of the DP itself.

For a reader who is not familiar with the pharmaceutical industry, a reminder of the key points is given below.

One or several active compounds (DS) are prepared by organic synthesis, extracted from vegetables, animals, microorganisms or obtained by biotechnology. The DS is generally associated with several excipients of chemical, mineral or biological nature either as monomers or as polymers.

The goal is to formulate a processable DP stable over the time and allowing the active substance to be released *in vitro* and *in vivo*. Obviously, the formulation is designed according to the route of administration:

- oral route – solid dosage forms (e.g., tablets, capsules, etc.) drinkable solutions etc.
- ORL route (nasal solutions, spray)
- local route (suppositories, transdermal systems, eye-drop formulation, spray)
- intravenous and intramuscular route (injectable solution, lyophilizate, etc.)

At practically every step of the manufacture of the drug substance and the excipients, solvents, including water, are utilized. This is equally true for the preparation of the pharmaceutical formulations.

Ideally, we would like to have available a universal stable solvent, ultrapure, nontoxic, which does not affect the solutes. This is an old dream of the alchemists who searched for a long time for the “Alkahest” or “Menstruum universal” as it was named by Paracelsus.[1]

The fact that a solvent is not a totally inert species allows it to play an important role in chemical equilibria, rates of chemical reactions, the appearance of new crystalline forms, etc. and consequently contributes to the great wealth of compounds which the chemists are able to produce.

But of course, there are drawbacks in using solvents. Because they are not totally inert they may favor the formation of undesirable impurities in the intermediates of synthesis and in the DS. Regarding the manufacture of the DP, the solvents, including water,

may induce either polymorphic transformations or formation of solvates (hydrates) which, after drying, could lead to a desolvated solvate with quite different physical properties impacting potentially either positively or negatively the DP performance.[2]

Another crucial aspect which deserves to be discussed is the notion of purity. Impurities present in solvents could have an impact on the stability of drugs, for example, or on the crystallization process.

Last, but not least, the toxicological aspects should be taken into account. Numerous solvents show different kinds of toxicity and this should be a matter of concern in relation to the health of workers exposed to them.[3] But ultimately residual solvents still present in the DS and DP have to be assessed and systematically limited.

We are now going to consider several aspects of the use of solvents in the manufacture of drug substances (DS) and drug products (DP) including their quality (purity) and influence on the quality, stability and physicochemical characteristics of pharmaceutical products.

The issue of residual solvents in pharmaceutical products will be considered in Chapter 15.2 and will focus amongst other things on the corresponding ICH Guideline.[4]

13.20.1.2 Where are solvents used in the manufacture of pharmaceutical drugs?

13.20.1.2.1 Intermediates of synthesis, DS and excipients

13.20.1.2.1.1 General points

Raw materials are now produced by the chemical industry and involve the use of solvents at different steps in their production. These materials are usually produced by:

- chemical synthesis
- an extraction process
- a fermentation process
- or a biotechnology process

The goal of this chapter is, of course, not to deal with the criteria for selection in relation to their use in particular chemical reactions or extraction processes but rather to stress that impurities present in solvents could have an impact on the purity of the substances obtained, on their stability and potentially on their safety. These three concepts are of paramount importance in the pharmaceutical field.

A list of solvents which are commonly used in the chemical industry[5] is presented in Table 13.20.1.1.

Table 13.20.1.1. Solvents commonly used in the chemical industry

Alcohols	**Esters**	**Ketones**
Ethanol	Ethyl acetate	Acetone
Butanol		Methyl ethyl ketone
2-Ethylhexanol	**Ethers**	Methyl isobutyl ketone
Isobutanol	1.4-Dioxane	Methyl isopropyl ketone
Isopropanol	Butyl ether	Mesityl oxide
Methanol	Ethyl ether	
Propanol	Diisopropyl ether	**Nitriles**
Propyleneglycol	Tetrahydrofuran	Acetonitrile
	Tert-butyl methyl ether (MTBE)	
Amide		**Sulfur-containing**
Dimethylformamide		Dimethylsulfoxide
	Halogenated solvents	
Amine	Ethylene bromide	Water
Pyridine	Chloroform	
	Ethylene chloride	
Aliphatic hydrocarbons	Methylene chloride	
Cyclohexane	Tetrachloroethylene (perchlorethylene)	
Hexane	Carbon tetrachloride	
	Trichlorethylene	
Aromatics hydrocarbons		
Toluene		
Xylene		

It is relatively easy to know for pharmaceutical industry the nature of solvents to be looked for in a DS because it produces itself the active component or because it can have by contract an access to the DS Mater File or because there is a compendial monograph giving occasionally some indications (e.g., search for benzene in carbomers).

As a consequence of the ICH Guideline Q3C[4] dealing with the residual solvents in pharmaceutical products (see Chapter 15.2), the use of solvents of class I (solvents to be avoided) like benzene is no more possible. It is known that carbopol resins (carbomer), used to modify the rheology of polar systems and as a binder in sustained-release tablets, were polymerized in the benzenic medium. In the current quality of poloxamers, it was possible to retrieve up to 1000 ppm of benzene. With ICH limit being 2 ppm, it was impossible to achieve this goal. The manufacturers have consequently developed new polymerization media[6] containing either ethyl acetate alone or a mixture of ethyl acetate and cyclohexane, the first one belonging to class III (no safety concern), the second one belonging to class II (ICH limit 3880 ppm).

13.20.1.2.1.2 Criteria of purity

This is a difficult matter. Purity in chemistry is an ideal concept referring to a situation where a product consists of one type of molecules only. This is a theoretical situation which can only be EXPERIMENTALLY approached more or less closely.[7]

The purity of a product is a relative notion and it depends on the analytical methods used and their performance. More practically the quality finally chosen for a solvent will depend on the specific use for which this solvent is intended to be utilized.[8]

A solvent is considered sufficiently pure if it does not contain impurities able in nature and in quantity to interfere with the admissible quality of the product in the manufacture in which it participates.[7]

13.20.1.2.1.3 Solvents as reaction medium

In this case, the solvents should have a range between the melting point and the boiling point as extended as possible and a good thermal and chemical stability. The purity should be of high degree but could depend on the step considered in the global synthesis.

As an example let us consider the case of the dimethylformamide (DMF).[5] If it is used in reactions evolving in anhydrous media, it will be mandatory to control the level of water on the ppm level. The specification regarding the water content will be of course loosened if DMF is used in the chemical step including water as the reaction medium.

We will see further that solvents contain actually a lot of chemical impurities which could be reactive *vis a vis* the main molecule undergoing the chemical reaction and leading to additional impurities other than those coming from the mechanism of the reaction itself.

13.20.1.2.1.4 Solvents for crystallization

Solvents should be carefully chosen in such a way that they show a high solubility at high temperature and a low solubility at a low temperature of the substance to be crystallized or recrystallized.

Of course, the solvent should be absolutely inert and of the highest achievable purity

- The first one being identical to the one mentioned for solvents as reaction media: possibility to produce other impurities.
- The second one being linked to the crystallization process itself. It is well-known that the presence of impurities, whatever the origin, could have serious effects on the nucleation and growth process. We will discuss this subject a little bit further in the text.

13.20.1.2.1.5 Solvents used for extraction and preparative chromatography

As in the precedent cases they have to be absolutely inert (as far as it is possible) and with a high degree of purity for the reasons already evoked. In case of preparative chromatography, a special care will be taken concerning the chemical inertness to adsorbate[9] of the solvents constituting the mobile phase and the fact that impurities or additives contained in the solvents in a way not under control could impair significantly the reproducibility of the retention times.

13.20.1.2.1.6 Nature and origin of impurities contained in solvents[10]

It should be reminded here that a solvent used on the industrial level is rarely pure (we mean here no impurity analytically detectable).

- impurities coming from their origin or their manufacturing process
- impurities originating from the container during transportation
- stabilizers
- denaturing agents

- impurities resulting from a transformation of the solvent during the chemical reaction

These impurities or side products should be searched as long as possible when assessing the purity of the solvent. In fact, they could be less volatile than the main solvent and could finally concentrate in the pharmaceutical product.

We will now review briefly the nature of all these kinds of impurities of the most often used solvents.

13.20.1.2.1.6.1 Impurities coming from the origin or the manufacturing process of solvents[1,10] (see Table 13.20.1.2)

Table 13.20.1.2. Solvent impurities

Solvents	Possible impurities (according to the manufacturing process)
Hydrocarbons	
Toluene	Methylthiophene, benzene, paraffinic hydrocarbons
Xylene	Mixture of ortho, meta and para isomer, paraffinic hydrocarbons, ethylbenzene, sulfur compounds
Cyclohexane	Benzene, paraffinic hydrocarbons, carbonyl compounds
Halogenated compounds	
Dichloromethane	Chloroform, carbon tetrachloride, chloromethane
Chloroform	Chlorine, carbonyl chloride (phosgene), dichloromethane, carbon tetrachloride, hydrogen chloride
Carbon tetrachloride	Chlorides, chlorine, carbon disulfide
Alcohols	
Methanol	Water, acetone, formaldehyde, ethanol, methyl formate, dimethyl ether, carbon dioxide, ammonia
Ethanol	Aldehydes, ketones, esters, water, ethyl ether, benzene (if anhydrous ethanol)
2-propanol	Water, peroxides
N.B.: Some alcohols obtained by fermentation could contain pesticides. It is necessary to obtain from the seller some guaranty regarding limiting concentrations (expressed, for instance, in Parathion).	
Aliphatic ethers/cyclic ethers	
Ethyl ether/isopropyl ether/monoalkylated ethers/ethylene glycol/ diethylene glycol/etc.	Alcohols (from which they are prepared), water, corresponding aldehydes, peroxides
Tetrahydrofuran	Water, peroxides
Dioxane	Acetaldehyde, water, acetic acid, glycol acetal paraldehyde, crotonaldehyde/peroxides
Ketones	
Acetone	Methanol, acetic acid, water

Table 13.20.1.2. Solvent impurities

Solvents	Possible impurities (according to the manufacturing process)
Esters	
Methyl acetate	Acetic acid, water, methanol
Ethyl acetate	Acetic acid, ethanol, water
Amides	
Formamide	Formic acid, ammonium formate, water
N,N-Dimethylformamide	N-Methylformamide, formic acid, water
Nitriles	
Acetonitrile	Acetamide, ammonium acetate, ammonia, water, toluene
Nitro-compounds	
Nitrobenzene	Nitrotoluene, dinitrothiophene, dinitrobenzene, aniline

13.20.1.2.1.6.2 Impurities originating from the container during transportation
They relate to contamination coming from tankers or drums not correctly cleaned. These concerns especially solvents of low quality. In case of utilization of such solvents, the user has to bear in mind that some incidents or uncommon behavior may find an explanation based on this consideration.
13.20.1.2.1.6.3 Stabilizers
It is very difficult to know every stabilizer used. There is here an important problem of confidentiality. We quote, thereafter, some stabilizers which are well-known (see Table 13.20.1.3).

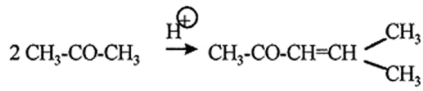
Table 13.20.1.3 Stabilizers used in selected solvents

Solvents	Stabilizers
Dichloromethane	Ethanol, 2-methyl-but-2-ene
Chloroform	Ethanol (1 vol%) for avoiding the phosgene formation, 2-methyl-but-2-ene
Diethyl ether	2,6-di-tert-butyl-4 methylphenol (BHT)
Tetrahydrofuran	BHT, p-cresol, hydroquinone, calcium hydride

13.20.1.2.1.6.4 Denaturing agents
This process is relevant primarily to ethanol. Common denaturing agents are methanol, isopropanol, ethyl acetate, and toluene.
13.20.1.2.1.6.5 Transformation of solvent during the chemical reaction
Solvents are rarely chemically inert. During the reactions in presence of solvents, they can undergo chemical transformation generating impurities which can be found, for example, in the DS.

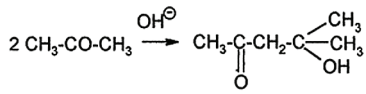
This is a huge field which cannot be exhaustively covered. We give a few examples of well-known side reactions.

- Acetone in acidic media is easily transformed into mesityl oxide:

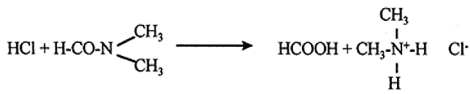


So products should be tested for their presence when performing residual solvents analysis on drugs.

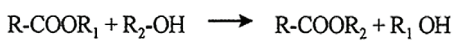
- In basic medium the diketone-alcohol is obtained:



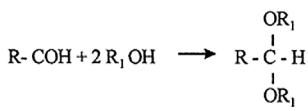
- DMF can be hydrolyzed in the presence of a hydrochloric acid:



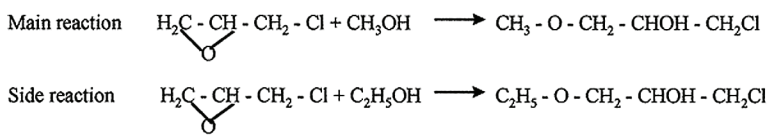
- Acids undergoing reaction in alcoholic media can be partially transformed into esters
- Transesterification reaction occurs, for example, when recrystallization has to be performed on a molecule containing an ester group:



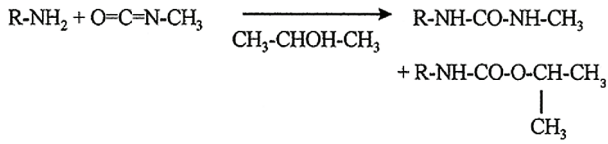
- Aldehydes (even ketones) can be transformed in alcoholic solutions into ketals:



From time to time the solvent can react *in lieu* of the reagent. In a synthesis aimed at preparing 3-chloro 1-methoxy-2-propan-2-ol from chloromethyloxirane and the methanol, traces of ethanol present in methanol gave the corresponding ethoxylated compound:



Another example concerns the preparation of a urea derivative using the action of an amine on isocyanate in the presence of isopropanol:



Many other examples could be found. They stress the need for close collaboration between chemists and analysts when planning chemical syntheses and assessing quality control monographs.

13.20.1.2.2 Drug products[11,12]

13.20.1.2.2.1 General points

Because ultimately it is the DP which is administered to the patient, it is necessary to have the quality of the solvents potentially used in the design of pharmaceutical formulations under control.

13.20.1.2.2.2 *Areas of utilization*

Solvents including water are used in different ways in pharmaceutical formulation:

- either as a part of the final drug product: injectables, drinkable solutions, patches, sprays, microemulsions
- or used as an intermediary vehicle which is removed at the end of the process:
  - granulation
  - coating
  - sugar coating
  - microencapsulation

We have listed in Table 13.20.1.4 the most commonly used solvents.

Table 13.20.1.4 Solvents used in formulation

Water	Methylene chloride
Ethyl acetate	Chloroform
Ethyl alcohol (denaturated with butanol and isopropanol)	Hexane
Isopropyl alcohol (denaturated with methyl ethyl ketone)	Cyclohexane
Methanol	Polyethyleneglycol (low molecular weight)
Acetone	

Manufacturers try progressively to replace the formulations using organic solvents such as chloroform, dichloromethane, cyclohexane belonging to the class 2 (ICH classification see Chapter 15.2), for example by developing aqueous coatings.

13.20.1.2.2.3 What should be the quality?

Taking into account the fact that the solvents used in the DP manufacturing process, either as a component of the formulation or as a residual solvent, will be absorbed by the patient, their quality must be of the highest standard. From a regulatory point of view, in almost every country if not all, it is mandatory to use solvents covered by a pharmacopoeial

monograph (e.g., European Pharmacopoeia, USP, JP, local Pharmacopoeias). Some examples are given below.

13.20.1.3 Impacts of the nature of solvents and their quality on the physicochemical characteristics of raw materials and DP.

13.20.1.3.1 Raw materials (intermediates, DS, excipients)

The impurities contained in the solvents could have several effects on the raw materials:

- When the solvents are removed, non-volatile or less volatile impurities will be concentrated in the raw materials.
- They can induce chemical reactions leading to side products.
- They can affect the stability of the raw material considered.
- They can modify substantially the crystallization process.

13.20.1.3.1.1 Concentration of less volatile impurities

Due to the potential concentration of these impurities, they should be tested for in both DS and excipients and even in intermediates of synthesis if the latter constitute the penultimate step of the synthesis and if solvents belong to class 1 or class 2 solvent.

13.20.1.3.1.2 Side reactions

This case has already been illustrated (see paragraph 13.20.1.2.1.6.5). The skills of the chemist together with those of the analyst are needed to ensure that the presence of unexpected impurities can be detected. By way of example, the reactions involving the keto-enol tautomerism deserve to be mentioned. The equilibrium is very sensitive to the solvent so that the presence of other solvents as impurities in the main solvent can modify the keto-enol ratio leading to irreproducibility in the chemical process.[13,14]

13.20.1.3.1.3 Consequences for stability

Some solvents, as mentioned in the paragraph 13.20.1.2.1.5, can contain very active entities such as aldehydes and peroxides. For example, if the raw material contains primary or secondary amines and/or is susceptible to oxidation or hydrolysis, it is likely that degradants will be formed over the time, reducing potentially the retest date of the raw material. The same situation could affect the DP and, therefore, two examples are given in paragraph 13.20.1.3.2.

13.20.1.3.1.4 Solvent purity and crystallization

This issue is may be less known except for chemists working in this specialized area. Because the consequences can be important for the processability, stability and occasionally bioavailability of the drug substance in its formulation, it is relevant to comment on this subject.

13.20.1.3.1.4.1 Role of nature and the quality of solvent on crystallization

Most of the drugs on the market are obtained as a defined crystalline structure and formulated as solid dosage forms. It is well known that a molecule can crystallize to give different crystalline structures displaying what is called polymorphism. The crystal structures may be anhydrous or may contain a stoichiometric number of solvent molecules leading to the formation of solvates (hydrates in case of water molecules). Pseudopolymorphism is the term used to describe this phenomenon.

Another characteristic which plays a major role in the overall processability of the DS for DP manufacture is the “crystal habit”. This term is used[15,16] to describe the overall

shape of crystals, in other words, the differing external appearance of solid particles which have the same internal crystalline structure.

Both structures (internal, external) are under the control of different parameters including the nature of the solvent used and its quality. The role of the solvent itself in the overall crystallization process, including the determination of the crystal structure and the crystal habit, is well known.[17] But it is equally worth noting that impurities coming from:

- the product to be crystallized
- the solvent used
- the environment

can selectively affect the nucleation process and the growth rates of different crystal faces.[17-21] They can be selectively adsorbed to certain faces of the polymorphs thereby inhibiting their nucleation or retarding their growth to the advantage of others. Crystal shape (habit) can also be modified by a solvent without polymorphic change. Additives or impurities can block, for a defined polymorph, the growth rate of certain faces leading to, for instance, needles or plates. It is possible to introduce deliberately additives to "steer" the crystallization process. An interesting example of this crystal engineering strategy has been published for adipic acid[22] or acetaminophen.[23]

13.20.1.3.1.4.2 Solvent-solid association/overview

After the crystallization of the product, solvents must be removed in order to obtain the minimum amount of residual solvents compatible with safety considerations and/or physicochemical considerations including stability, processability, and occasionally microbiological quality. Different situations can be encountered.

13.20.1.3.1.4.2.1 Solvent outside the crystal

The solvent remains outside the crystals at the time of crystal formation. It is adsorbed on the surface or onto the crystal planes. In the first case, the solvent is easily removed. But in the second case, if a cleavage plane exists, the drying process can be very difficult. Two methods can be used to try to remove this type of residual solvent almost completely.

- Displacement by water vapor in an oven, keeping in mind that this method may introduce some degradation leading to processability problems.[11,24]
- Extraction by supercritical CO_2[25,26] that the extraction power of CO_2 is basically limited to slightly polar solvents.

13.20.1.3.1.4.2.2 Solvent inside the crystal

The solvent remains inside the crystalline structure. Three situations can arise.

13.20.1.3.1.4.2.2.1 Occluded solvents

During rapid crystallization, some degree of disorder (amorphous phases, crystalline defects) can arise, creating pockets where residual solvent can be occluded. Through a process of dissolution/recrystallization, this "hole" moves towards the external faces of the crystal releasing the solvent at the end. This phenomenon is more frequent for large crystals (500-600 μm) but rare for smaller crystals (1-100 μm). The solvent odor which is detected when opening a drum or a bag containing a substance which was dried in the normal way can be explained by this mechanism.

13.20.1.3.1.4.2.2.2 Solvates

At the end of the crystallization process, the substance can be isolated as a solvate (hydrate), i.e., as a pseudopolymorph. The solvates generally have quite different physico-chemical properties than the anhydrous form. Their stability can be questionable and, in any case, deserves to be investigated. In some cases, it is possible to remove the solvent from the crystal without changing the structure of the lattice leading to an isomorphic desolvate which displays a similar X-ray diffraction pattern to that of the parent compound.[2,27] The lattice of the desolvated solvate is at a high energy state relative to the original solvate structure. A better dissolution rate and compressability can be expected,[28] but the drawbacks are hygroscopicity and physico-chemical instability. The lattice could undergo a relaxation process over time which increases the packing efficiency of the substance by reducing the unit cell volume.

When developing a new chemical entity, all these aspects have to be considered to avoid unpleasant surprises during development or once the drug is on the market. Due to the need for process scale-up and to make the manufacturing process more industrial, changes are introduced especially in the crystallization and the drying processes, (e.g., change from static drying to dynamic drying). Because the drying is a particularly disturbing process for the integrity of the lattice, defects and/or amorphous phases may be created favoring subsequent polymorphic or pseudopolymorphic transformations of the crystalline form developed so far if it is not the most stable one.

13.20.1.3.1.4.2.2.3 Clathrates

In contrast to solvates, clathrates do not show any stoichiometric relationship between the number of molecules of the substance and the number of molecules of solvent. Clathrates actually correspond to a physical capture of solvent molecules inside the crystal lattice without any strong bonds including hydrogen bonds. Molecules of one or several solvents can be trapped within the crystalline structure as long as the crystallization has been performed with a pure solvent or a mixture. The case of the sodium salt of warfarin giving "mixed" clathrates with water and isopropyl alcohol is well known and the existence of 8/4/0 or 8/2/2 proportions has been shown.[11]

It is fairly obvious that some powder properties like wettability can be modified by the formation of clathrates. Because their formation is not easy to control, some batch to batch inconsistency may be expected in this situation.

In order to demonstrate the internal character of the clathrate relative to the crystal lattice, the example of a molecule developed in the laboratory of one of the authors is given below.

Figure 13.20.1.1 shows the DSC pattern of a molecule with the melting event at 254°C and the corresponding TG pattern obtained at the same temperature scanning rate. At the time the melting occurs, a loss of weight is observed corresponding to the loss of 0.2% of isopropanol. The nature and the amount of the solvent have been confirmed by GC after dissolving the substance.

13.20.1.3.2 Drug product

As for the DS, the solvents used for DP manufacture can produce some negative effects by themselves or through their own impurities.

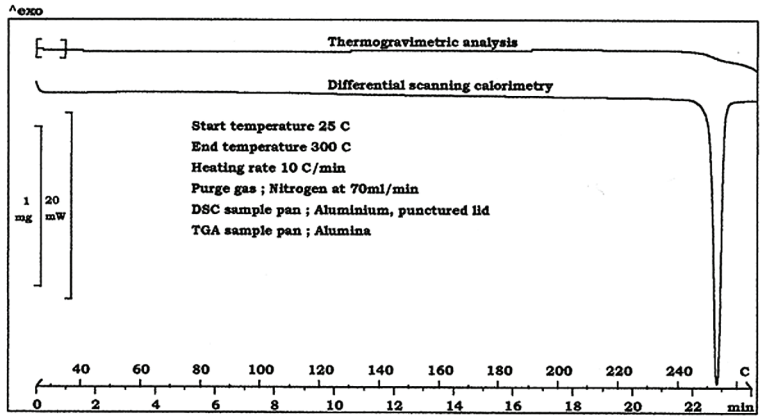
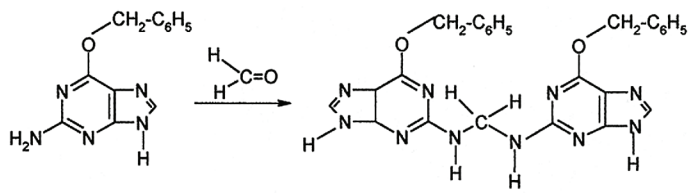


Figure 13.20.1.1. DSC and TG patterns.

For liquid or semi-liquid formulations, the formulator has to ensure that the solvents themselves do not display chemical interactions with DS or excipients. Everything which has been said in paragraphs 13.20.1.2.1.5 and 13.20.1.3.1 remains true here.

13.20.1.3.2.1 Interaction of impurities contained in the solvent

As said in paragraph 13.20.1.3.1 with the DS, impurities contained in the solvent, especially if they are strongly reactive, like aldehydes or peroxides, can promote the formation of degradants. Regarding aldehydes, the publication of Bindra *et al.*[29] should be mentioned. It relates to the degradation of the o-benzylguanine in an aqueous solution containing polyethylene glycol 400 (PEG 400). This type of solvent very often contains formaldehyde, which can lead to the formation of a precipitate over time:



PEG can also contain peroxides which can initiate over time, the formation of degradants *via* an oxidation process. Several publications have dealt with this phenomenon.[30,31]

13.20.1.3.2.2 Interaction with the container

When the formulation is a solution which is prepared from water and different organic solvents, it is mandatory to investigate possible interactions between the medium and the container especially if the latter is of polymeric nature (PVC-PVDC, polyethylene, etc.) with or without elastomeric stoppers. A thorough investigation is necessary including:

- an examination of the solution for plasticizers, antioxidants, monomers, and oligomers, mineral impurities, potentially extracted from the container,

- the evaluation of the absorption by the container of components (DS, excipients) contained in the solution.

In the first case, the migration of impurities into the solution could initiate physico-chemical instability and possibly some potential toxicity.

In the second case, a decrease in the content of the DS and/or some excipient (e.g., organic solvents added to promote the solubility) could lead to some loss of therapeutic efficacy and in some case to physical instability (precipitation).

13.20.1.3.2.3 Solvates formation during the solid dosage form manufacture

During the granulation process, it is possible that the DS (occasionally the excipient) could transform into a solvated crystalline structure (solvate, hydrate). During the drying process, different situations can occur:

- The solvate is poorly stable and the solvent is easily removed leading to either the original polymorphic form but creating a certain degree of disorder in the crystalline structure or to what is called a "desolvate solvate" form. In this last case, also named "isomorphic desolvate", the desolvated solvate retains the structure of its parent solvated form. The x-ray diffraction patterns look similar between the parent and the daughter forms. In this situation, we have the creation of a molecular vacuum which could substantially impact on the stability, hygroscopicity and mechanical characteristics of the DS and finally of the DP.
- The solvate is stable and within the formulation: we then have in a sense a new chemical entity. The properties of the solvate could be entirely different (solubility, kinetics of dissolution, stability, processability, etc.) and the consequence could be either positive or negative. The case where the kinetics of dissolution are affected by the formation of solvates should always be investigated. Papers on this subject have been published for molecules such as lorazepam,[32] hydrocortisone,[33] cephalexin,[32] etc.
- Obviously, as in the case of raw materials, the clathrate formation should be considered in order to explain possible batch to batch inconsistency.

12.28.3.3 Conclusions

We have seen that the solvent, far from being inert, plays a key role by itself and occasionally *via* its own impurities in different ways which are important for pharmaceutical development. We will now discuss how to set up sound specifications for solvents in relation to their field of use.

13.20.1.4 Setting specifications for solvents

13.20.1.4.1 Solvents used for the raw material manufacture

For the raw materials we should distinguish between solvents:

- used during the synthesis
- those used for the last step of the manufacture corresponding very often to the crystallization process.

As a rule of thumb, the specifications set for solvents used for the crystallization step will be more stringent than those used during the synthesis.

For the intermediates of synthesis, if the origin of the solvent is under control (e.g., existence of contracts/Quality Assurance audits) a simplified monograph is completely

Table 13.20.1.5. Example of monographs.

Solvents used during the synthesis (of well controlled origin)
Character/Appearance
Identification (IR, GC or n_D^{20})
Purity GC (generally not less than 98%)

Table 13.20.1.6. Example of monographs.

Final crystallization solvents (of well controlled origin)
Character/Appearance
Identification (IR, GC or n_D^{20})
Tests:
Water content (0.1 to 0.5 according to the solvents)
Residue on evaporation: not more than 0.01 per cent
Purity GC not less than 99% and examine for denaturing agents and other potential impurities

Table 13.20.1.7. Example of monograph applied to a new solvent: Ethyl acetate. Specifications

Controls	
Character	Clear liquid, colorless
Identification	
A – Infrared spectrum	Complies
or	
B – Refractive index	1.370 to 1.373
or	
C – Gas chromatography	Complies
Assay	
Ethyl acetate (purity)	Not less than 99.5%

Table 13.20.1.8. Example of monograph applied to the recycled solvent: Ethyl acetate. Specifications

Controls	Standards
Characters	Clear liquid, colorless
Identification	
Gas chromatography	Complies
Tests	
Water content	Not more than 2.0%
Related substances	
Methanol	Not more than 1.0%
Ethanol	Not more than 2.0%
Ethyl chloride	Not more than 2.0%
Others impurities (sum)	Not more than 2.0%
Assay	
Ethyl acetate (purity)	Not less than 99.5%

adequate (see Table 13.20.1.5) as long as the supplier provides a detailed certificate of analysis where impurities (including solvents) are properly specified with acceptable limits. If the same solvent is used for the crystallization step, the additional purity tests are necessary (see Table 13.20.1.6).

For economic reasons, it may be necessary to recycle solvents. If so, the containers should be fully identified in terms of storage:

- If solvents can be efficiently purified (e.g., by redistillation) they must comply with the same specification as than those of fresh solvents and consequently can be used in any synthesis.
- If they still contain volatile impurities resulting from the reaction they come from, they can be recycled only for this reaction. In this case, the impurities should be identified and their possible impact on the reaction evaluated. In tables 13.20.1.7 and 13.20.1.8 we have summarized possible specifications for a fresh batch of ethyl acetate used for a defined chemical reaction and those for the recycled solvent.

Table 13.20.1.9. Water quality

European Pharmacopoeia- Suppl. 2000		**USP 24**	
WATER, PURIFIED		**PURIFIED WATER**	
Controls	Standards	Controls	Standards
• Purified water in bulk		• Purified water produced on site for use in manufacturing	
Production . Total viable aerobic count . Total organic carbon . Conductivity . Packaging and storage Characters Tests . Nitrates . Heavy metals . Aluminium . Bacterial endotoxins	 Not more than 100 micro organisms per ml Not more than 0.5 mg/ml Not more than 4.3 µ5-cm^{-1} In conditions designed to prevent growth of micro organisms A clear, colourless and tasteless liquid Not more than 0.2 ppm Not more than 0.1 ppm Not more than 10 µg/l Not more than 0.25 I.U. of endotoxin per ml	 Cf. Tests Cf. Tests . Total organic carbon . Water conductivity	 Complies Complies
• Purified water in containers		• Purified water packaged in bulk for industrial use	
Characters Tests . Nitrates . Heavy metals . Aluminium . Bacterial endotoxins . Acidity or alkalinity . Oxidisable substances . Chlorides . Sulphates . Ammonium . Calcium and magnesium . Residue on evaporation . Microbial contamination - - Packaging and storage	A clear, colourless and tasteless liquid Not more than 0.2 ppm Not more than 0.1 ppm Not more 10 µg/l Not more than 0.25 I.U of endotoxin per ml Complies Complies Complies Complies Not more than 0.2 ppm Complies Not more than 0.001 % Not more than 10^2 micro organisms per ml - - Stored in conditions designed to assure the required microbiological quality	 . Oxidisable substances . Chlorides . Sulphates . Ammonia . Calcium . pH . Carbon dioxide Packaging and storage	 Complies Complies Complies Complies Complies 5.0 to 7.0 Complies Preserve in suitable, tight containers

Table 13.20.1.10. Specification for acetone.

European Pharmacopoeia, Suppl. 2000		NF 19	
ACETONE			
Controls	Standards	Controls	Standards
			Not less than 99 % calculated on the anhydrous basis
Characters	A volatile clear, colourless, miscible with water, alcohol and ether. The vapour is flammable		
Identification			
. A	Complies		
. B	Complies		
		IR	Complies
Tests			
. Appearance of solution	Complies		
. Acidity or alkalinity	Complies		Not more than 0.789
. Relative density	0.790 to 0.793	. Specific gravity	
. Related substances :			
- Methanol	Not more than 0.05 % (V/V)		
- 2-propanol	Not more than 0.05 % (V/V)		
- Additional impurity	Not more than 0.05 % (V/V)		
. Matter insoluble in water	Complies		Complies
. Reducing substances	Complies	. Readily oxidizable substances	Not more than 2 mg
. Residue on evaporation	Not more than 1 mg (50 ppm)	. Non volatile residue	(0.004 %) Not more than 0.5 %
. Water (semi-micro determination)	Not more than 3 g/l	. Water (GC)	
		Assay (GC)	Not less than 99.0 % calculated on the anhydrous basis
Storage	Store protected from light	Packaging and storage	Preserve in tight containers remote from fire
Impurities			
. A	Methanol		
. B	2-propanol		

We recommend working with reliable solvent suppliers who can give every assurance of the quality of solvents provided to avoid any "unpleasant surprises".

Water should be mentioned separately. If it is used during the synthesis of intermediates the quality "drinking water" can be used without any problems. But if water is used during the last step of the process, its quality must be in compliance with the requirements of purified water as they are described in several pharmacopeias. In Table 13.20.1.9 the requirements for the Ph. Eur and USP are given as examples. Purified water is generally obtained from the drinking water. It undergoes demineralization by either distillation or an ion-exchange process. Particular attention has to be paid to microbiological quality.

Table 13.20.1.11. Specification for ethanol.

European Pharmacopoeia, Suppl. 2000		USP 24	
ETHANOL (96 %)		ALCOHOL	
Controls	Standards	Controls	Standards
Definition	Not less than 95.1 % V/V (92.6 % m/m) and not more than 96.9 % V/V (95.2 % m/m) of ethanol at 20°C and water	Definition	Not less than 92.3 % and not more than 93.8 % by weight, corresponding to not less than 94.9 % and not more than 96.0 %, by volume at 15.56°
Characters	A colourless, clear, volatile, flammable liquid, hydroscopic, miscible with water and methylene chloride. It burns with a blue, smokeless flame. It boils at about 78°C.		
Identification			
A - Relative density	0.8051 to 0.8124		
B - IR	Complies		
C	Complies	A	Complies
D	Complies	B	Complies
Tests		Tests	
. Appearance	Complies		
. Acidity or alkalinity	Complies	. Acidity	Complies
. Relative density	0.8051 t o 0.8124	. Specific gravity	0.812 to 0.816 indicating between 92.3% and 93.8% by weight or between 94.9% and 96.0% by volume
. Absorbance	Complies		
. Volatile impurities (GC)			
- methanol	Not more than 200 ppm (v/v)	- methanol	Complies
- sum of acetaldehyde and acetal	Not more than 10 ppm v/v expressed as acetaldehyde	- aldehydes and other foreigh organic substances	Complies
- benzene	Not more than 2 ppm v/v		
- 4-methyl pentan-2-ol	Not more than 300 ppm		
		. Amyl alcohol and non volatile, carbonizable substance	Complies
		. Limit of acetone and isopropyl alcohol	Complies
		. Limit of non volatile residue	Not more than 1 mg
		. Water insoluble substances	Complies
Storage	Store in a well-closed container, protected from light	Packaging and storage	Preserve in tight containers, remote from fire

Impurities as per European Pharmacopoeia, Supplement 2000:
A – 1,1-diethoxyrethane (acetal); B – Acetaldehyde; C – Acetone; D – Benzene; E – Cyclohexane;
F – Methanol; G – Butan-2-one (methyl ethyl ketone); H – 4-methylpentan-2-one (methyl isobutyl ketone);
I – Propanol; J – Propan-2-ol; K – Butanol; L - Butan-2-ol; M – 2-methylpropanol (isobutanol);
N – Furan-2-carbaldehyde (furfural); O – 2-methylpropan-2-ol (1,1-dimethyl alcohol); P – 2-methylbutan-2-ol;
Q – Pentan-2-ol; R – Pentanol; S – Hexanol; T – Heptan-2-ol; U – Hexan-2-ol; V – Hexan-3-ol

13.20.1.4.2 Solvents used for the DP manufacture

There is no other choice than to use the quality of solvents defined by a Pharmacopoeia. It is true that there are still discrepancies between the pharmacopeias of different countries. It is hoped that the ICH process dealing with the harmonization of quality, safety, and efficacy amongst three main zones of the world (EU, USA, Japan) will progressively reduce the remaining differences in dossiers submitted to Regulatory Authorities and the way the data are evaluated.

As examples, Tables 13.20.1.10, 13.20.1.11, and 13.20.1.12 summarize specifications for acetone, ethanol, and isopropanol given by the Ph. Eur. and USP. As can be seen only the Ph. Eur. monograph makes reference to volatile impurities to be tested for by GC.

13.20.1.5 Quality of solvents and analysis

The solvents, including water, are used in almost every area of analytical sciences: spectroscopy, chromatography, potentiometry, electrochemistry. They should be characterized by a set of properties making them suitable for use for their intended purpose.

13.20.1.5.1 Quality of solvents used in spectroscopy

As a general requirement, the solvents used in spectroscopy should be transparent and stable towards the relevant range of wavelengths. They should be able to dissolve the substance to be examined and not contain impurities affecting the stability of the substance or the validity of the method (selectivity, repeatability, limit of detection, analytical response). Theoretically, the solvent chosen should have minimal interaction with the solute. But, what could be seen as a disadvantage could also be an important source of structural information. What is called the solvent effect can help in UV, IR and NMR spectroscopies,[34] e.g., in structure elucidation. In the book by Reichardt,[1] data regarding the cut-off points of solvents commonly used in UV/visible spectroscopy are provided. The cut-off point is defined as the wavelength in the ultraviolet region at which the absorbance approaches 1.0 using a 1-cm cell path with water as the reference. In the same way, the ranges of transparency for IR-solvents are given. Complete IR-spectra of organic solvents can be found in the “Stadler IR spectra handbook of common organic solvents”. The solvents suppliers usually provide catalogs including a “spectroscopic grade” allowing the user to make a sound choice.

In the case of the NMR spectroscopy, problems arise with the residual protonated part of deuterated solvents (^{1}H-NMR) and the ^{13}C-NMR absorption bands of compounds used as solvents. References can be found[1] where detailed data are given regarding these points.

A common problem which can be met regularly in chemistry is the identification of signals from common contaminants in solvents of medium quality (see paragraph 13.20.1.2.1.6.1). Gottlieb and Col[35] have published data on NMR chemical shifts of trace

impurities contained in common laboratory solvents, making NMR spectroscopy the instrument of choice as a tool for routine quality control.

Table 13.20.1.12. Specification for isopropanol.

European Pharmacopoeia, Suppl. 2000		USP 24	
ISOPROPYL ALCOHOL			
Controls	Standards	Controls	Standards
			Not less than 99.0 %
Characters	A clear, colourless liquid, miscible with water, alcohol and ether		
Identification		Identification	
A - Relative density	0.785 to 0.789	A - Specific gravity	0.783 to 0.787
B - Refractive index	1.376 to 1.379	B - Refractive index	1.376 to 1.378
C	Complies		
Tests			
. Appearance	Complies		
. Acidity or alkalinity	Complies	Acidity	Complies
. Benzene and related substances (GC)			
- 2-butanol	Not more than 0.1 %		
- others impurities	Not more than 0.3 %		
- benzene	Not more than 2 ppm		
. Peroxides	Complies		
. Non volatile substances	Not more than 2 mg (20 ppm)	. Limit of non volatile residue	Not more than 2.5 mg (0.005 %)
. Water	Not more than 0.5 %		
		Assay	Not less than 99.0 %
Storage	Store protected from light	Packaging and storage	Preserve in tight containers remote from heat
Impurities			
A -	Acetone		
B -	Benzene		
C -	Di isopropyl ether		
D -	Diethyl ether		
E -	Methanol		
F -	Propanol		

13.20.1.5.2 Quality of solvents used in chromatography

The aim of this paragraph is not to focus on strategies for solvent selection in order to achieve extraction or liquid chromatography. A detailed literature review has been published by Barwick[36] on this matter allowing the user to design relevant methodology in any particular case. It is preferable to focus on the impact of impurities present in the solvent on the chromatographic performances.

Impurities and solvent additives can cause several problems and artifacts in liquid and gas chromatography.[37-39] Primarily, they can be the origin of irreproducible separations, enhanced UV-background and even of mechanical problems. De Schutter and Col[37]

have investigated this problem in the purity of solvents used in high-performance thin-layer chromatography.

A way to improve the stability of the chromatographic system by minimizing the role of solvent impurities is to add deliberately a controlled amount of organic modifier. For example, Lauren and Col[40] have applied this technique, using decanol for improving the stability of the LC used for analyzing carotenoids. Middleditch and Zlatkis[41] have listed an impressive range of stabilizers and additives which can be found in solvents which may help the chromatographer in explaining the occurrence of artifacts in chromatography. Zelvensky et al.[38] have determined by gas chromatography the most common impurities contained in solvents for liquid chromatography. The series of solvents investigated include acetonitrile, methanol, ethanol, dichloromethane, formic acid, dimethylformamide, pyridine, tetrahydrofuran, and dimethyl sulfoxide. Parsons et al.[39] have performed a search for trace impurities in solvents commonly used for gas chromatographic analysis of environmental samples.

13.20.1.5.3 Quality of solvents used in titrimetry

For titrimetric determinations performed in an aqueous medium, it is highly recommended to use distilled water and to perform a blank determination if necessary.

For determinations performed in non-aqueous media, the solvents should be as anhydrous as possible and, of course, inert to the titrant and the substance. Their purity should be such that they do not contain impurities which could react with the substance to be analyzed. A blank titration should be performed if necessary.

13.20.1.6 Conclusions

Far from being inert and not affecting the molecules dissolved in it, the solvent can affect the behavior of the solute in different ways. This chapter has aimed to support the idea that it is important for the chemist and the pharmacist to control the quality of the solvents used in the different areas of pharmaceutical activity. As we have tried to show, many pitfalls can be avoided during the development of a drug if a thorough investigation of the quality of the solvents used is carried out.

REFERENCES

1 C. Reichardt, **Solvents and solvents effect in organic chemistry**, 4th edition, 2011, *John Wiley & Sons*.
2 G.A. Stephenson, E.G. Groleau, R.L. Kleemann, W. Xu and D.R. Rigsbee, *J. Pharm. Sci*., **87**, 536 (1998).
3 A. Picot, **Le bon usage des solvants, Information Toxicologique n° 3, Unité de prévention du risque chimique - CNRS** (France) (1995).
4 **ICH guideline Q3C (R6) on impurities: guideline for residual solvent**, 2016.
5 M. Gachon, *STP Pharma Pratiques,* **1**, 531 (1991).
6 **Carbomer Monograph - Eur. Ph. Addendum 2000**, p 494.
7 J.A. Riddik and W.B. Bungler, **Organic Solvent**s, *Wiley Intersciences,* New-York, 1970, pp 552-571.
8 G.P.J. Ravissot, *STP Pharma Pratiques*, **9**, 3 (1999).
9 See Reference 1 p 427.
10 M. Debaert, *STP Pharma Pratiques*, **1**, 253 (1991).
11 A.M. Guyot-Hermann, *STP Pharma Pratiques*, **1**, 258 (1991).
12 D. Chulia, M. Deleuil, Y. Pourcelot, **Powder Technology and Pharmaceutical Processes**, *Elsevier*, Amsterdam, 1994.
13 J.L. Burdett and M.T. Rodgers, *J. Am. Chem. Soc*., **86**, 2105 (1964).
14 M.T. Rodgers and J.L. Burdett, *Can. J. Chem.*, **43**, 1516 (1965).
15 J. Haleblian and W. McCrone, *J. Pharm. Sci*., **58**, 911 (1969).
16 P. York, *Int. J. Pharm*., **14**, 1 (1983).
17 S. Khoshkhoo and J. Anwar, *J. Phys. D.; Appl. Phys*., **26**, B90 (1993).

18 J. Shyh-Ming, *Diss. Abst. Int*., **57** (10), 6402-B (1997).
19 W. Beckmann and W.H. Otto, *Chem. E. Res. Des*., **74**, 750 (1996).
20 N. Rodriguez-Hornedo and D. Murphy, *J. Pharm. Sci.*, **88**, 651 (1999).
21 R. David and D. Giron in **Powder Technology and Pharmaceutical Processes, Handbook of Powder Technology**, *Elsevier Sciences, Ed*., Amsterdam 1994, pp 193-241.
22 A.S. Myerson, S.M. Jang, *J. Cryst. Growth*, **156**, 459 (1995).
23 A.H.L. Chow, D.J.W. Grant, *Int. J. Pharm.*, **42**, 123 (1988).
24 C. Lefebvre-Ringard, A.M. Guyot-Hermann, R. Bouché et J. Ringard, *STP Pharma Pratiques*, **6**, 228 (1990).
25 D.C. Messer, L.T. Taylor, W.N. Moore and W.E. Weiser, *Ther. Drug Monit.*, **15**, 581 (1993).
26 M. Perrut, *Information Chimie,* **321**, 166 (1990).
27 R.R. Pfeiffer, K.S. Yang and M.A. Tucker, *J. Pharm. Sci*., **59**, 1809 (1970).
28 R. Hüttenrauch, *Pharm. Ind*., **45**, 435 (1983).
29 D.S. Bindra, T.D. William and V.J. Stella, *Pharm. Res*., **11**, 1060 (1994).
30 J.W. McGinity and J.A. Hill, *J. Pharm. Sci.*, **64**, 356 (1975).
31 D.M. Johnson and W.F. Taylor, *J. Pharm. Sci.*, **73**, 1414 (1984).
32 J. Joachim, D.D. Opota, G. Joachim, J.P. Reynier, P. Monges and L. Maury, *STP Pharma Sci*., **5**, 486 (1995).
33 S.R. Byrn, C.T. Lin, P. Perrier, G.C. Clay and P.A. Sutton, *J. Org. Chem*., **47**, 2978 (1982).
34 J. Wiemann, Y. Pascal, J. Chuche, **Relations entre la structure et les propriétés physiques**, *Masson edit*, Paris, 1965.
35 H.E. Gottlieb, V. Kotlyar and A. Nudelman, *J. Org. Chem*., **62**, 7512 (1997).
36 V.J. Barwick, *Trends in An. Chem*., 16, 293 (1997).
37 J.A. de Schutter, G. Van der Weken, W. Van den Bossche and P. de Moerloose, *Chromatographia*, **20**, 739 (1985).
38 V.Y. Zelvensky, A.S. Lavrenova, S.I. Samolyuk, L.V. Borodai and G.A. Egorenko, *J. Chromatogr*., **364**, 305 (1986).
39 W.D. Bowers, M.L. Parsons, R.E. Clement, G.A. Eiceman and F.W. Rarasek, *J. Chromatogr.*, **206**, 279 (1981).
40 D.R. Lauren, M.P. Agnew, D.E. McNaughton, *J. Liq. Chromatogr*., **9**, 1997 (1986).
41 B.S. Middleditch, A. Zlatkis, *J. Chromatogr. Sci*., **25**, 547 (1987).

13.20.2 PREDICTING COSOLVENCY FOR PHARMACEUTICAL AND ENVIRONMENTAL APPLICATIONS

An Li
School of Public Health, University of Illinois at Chicago, 2121 W. Taylor Street, Chicago, IL 60612, USA

13.20.2.1 Introduction

Cosolvency refers to the effects of adding one or more solvents (cosolvents), which are different from the existing solvent in a solution, on the properties of the solution or behavior of the solute. Cosolvency has found its applications in numerous scientific and engineering disciplines. The discussion in this section will be limited to aqueous phase cosolvency (a significant portion of the solvent mixture is water), and cosolvents will include only pure organic solvents which are miscible with water either completely (in any proportion) or partially (in only certain proportions). The extent of cosolvency will be quantitatively described by the difference in solute solubilities in pure water and in a mixture of water and cosolvent(s).

Since the first edition of this book was published in 2001,[1] progress has been made in both applying cosolvency in practice and in its prediction using computer models. A literature search of "cosolvency" found >110 journal papers published since the year 2000, and more than a thousand if the word "cosolvent" was searched. The application of cosolvency has expanded largely, driven by the needs in emerging fields such as nanotechnology in the material revolution, alternative fuels to meet the energy demand, development in polymer and other industrial materials, etc., in the rapidly evolving human society. For example, numerous patents involve the use of cosolvents in the formulations of flame retardant products, which have been added for fire protection purposes to almost all types of consumer goods ranging from fabric products such as carpets and upholsteries to electronics and batteries. In this revision, the effort has been made to update the knowledge in pharmaceutical and environmental applications of aqueous phase cosolvency. The list of reviewed publications is by no measure exhaustive. In addition, a new section on the thermodynamics of cosolvency is added, which examines the enthalpy, entropy, and free energy of solubilization of hydrophobic substances in the presence of cosolvents.

13.20.2.2 Applications of cosolvency in pharmaceutical sciences and industry

Cosolvency has been studied in pharmaceutical sciences and industry for many decades. Although many drugs are formulated and administrated in solid, vapor, powder, or other forms, using solutions as drug delivery vehicle has significant advantages. Most parenterally administered medicines are in the form of a liquid solution, and for intravenous injection, liquid form dosage is the only possible form. However, drugs are usually designed with little concern about their level of solubility in solution. It is the task of pharmaceutical formulators to find appropriate forms for the drug to be effectively delivered into biological systems.

The phenomena of cosolvency have been studied for more than a century by pharmaceutical scientists. Numerous experimental data are published in the literature, and most of

the models to be discussed in later sections have been developed from pharmaceutical research. In addition to the need of solubilizing drugs which are poorly water-soluble, controlling the dissolution of drugs administered as solids to optimize therapeutic activity also demands an improved understanding of drug solubilization. Approaches that may be pursued to enhance drug solubility in a liquid dosage formulation include adjusting pH, adding surfactants, cosolvents, or complexation agents. Choice of these techniques depends primarily on the drug's chemical structure and physicochemical properties. For example, control of pH is applicable only when the drug is an electrolyte. To solubilize nonelectrolyte drugs, the use of cosolvents outweighs surfactants and complexing agents.[2]

Cosolvents that are routinely used in drug formulation include ethanol, propylene glycol, polyethylene glycol, and glycerin. Examples of pharmaceutical products containing these cosolvents are summarized in Table 13.20.2.1. A large amount of solubility data can be found for drugs in various solvents including binary and ternary solvent mixtures.[3] Additional data are provided for many drugs in the recent literature.[4-20]

The purpose of using cosolvents in drugs is almost exclusively for solubility and dissolution enhancement. Cosolvent addition increases the drug solubility roughly logarithmically with a linear increase in the amount of cosolvent used, although only a few volume percent may not be effective. However, the absorption of drugs in the intestines of human and animals may not be increased with the same proportion. Transfer across membranes is more controlled by membrane-aqueous phase partitioning coefficient, which tends to be lowered by the presence of organic cosolvents.[21] Additionally, the amount of cosolvent(s) in a drug formulation should be minimized to avoid possible side effects or the lowering of the drug effectiveness.

Table 13.20.2.1. Selected pharmaceutical products containing cosolvents.

Trade Name	Cosolvent	% (v)	Manufacturer	Type
Aclovate cream	Propylene glycol		Schering	Topical
Alurate elixir	Ethanol	20	Roche	Oral liquid
Amidate	Propylene glycol	35	Abbott	Parenteral
Amphojel	Glycerin		Wyeth-Ayerst	Oral
Apresoline	Propylene glycol	10	Ciba	Parenteral
Aristocort cream	Propylene glycol		Fujisawa	Topical
Ativan	Polyethylene glycol Propylene glycol	20 80	Wyeth-Ayerst	Parenteral
Bentyl syrup	Propylene glycol		Lakeside	Oral
Brevibioc	Ethanol	25	DuPont	Parenteral
Cleocin T lotion	Glycerin		Upjohn	Topical
Comtrex cough	Ethanol	20	Bristol	Oral liquid
Cyclocort lotion	Polyethylene glycol		Lederle	Topical
Delsym	Propylene glycol		McNeil Consumer	Oral
Depo-Medrol	Polyethylene glycol		Upjohn	Parenteral

Table 13.20.2.1. Selected pharmaceutical products containing cosolvents.

Trade Name	Cosolvent	% (v)	Manufacturer	Type
Dilantin	Ethanol Propylene glycol	10 40	Parke-Davis	Parenteral
Dramamine	Propylene glycol	50	Searle	Parenteral
Elocon lotion	Propylene glycol		Schering	Topical
Entex liquid	Glycerin		Norwich-Eaton	Oral
Fluonid solution	Propylene glycol		Herbert	Topical
Halog cream	Propylene glycol		Westwood-Squibb	Topical
Halog ointment	Polyethylene glycol		Westwood-Squibb	Topical
Kwell cream	Glycerin		Reed & Carnrick	Topical
Lanoxin	Ethanol Propylene glycol	10 40	Burroughs Wellcome	Parenteral
Librium	Propylene glycol	20	Roche	Parenteral
Lidex	Propylene glycol		Syntex	Topical
Luminal Sod	Propylene glycol	67.8	Winthrop	Parenteral
MVI-12	Propylene glycol	30	Armour	Parenteral
Nembutal	Ethanol Propylene glycol	10 40	Abbott	Parenteral
Neoloid	Propylene glycol		Lederle	Oral
Nitro-BID IV	Ethanol	70	Marion	Parenteral
Novahistine DH	Glycerin		Lakeside	Oral
Paradione	Ethanol	65	Abbott	Oral liquid
Pentuss	Propylene glycol		Fisons	Oral
Psorcon ointment	Propylene glycol		Dermik	Topical
Rondec DM	Glycerin		Ross	Oral
S-T Forte syrup	Ethanol	5	Scot-Tussin	Oral liquid
Sulfoxyl lotion	Propylene glycol		Stiefel	Topical
Tinactin	Polyethylene glycol		Schering	Topical
Trideslon cream	Glycerin		Miles	Topical
Tussar	Propylene glycol		Rorer	Oral
Tussionex	Propylene glycol		Fisons	Oral
Tylenol	Propylene glycol		McNeil Consumer	Oral
Valium	Ethanol Propylene glycol	10 40	Roche	Parenteral
Vepesid	Ethanol	30.5	Bristol-Myers	Parenteral

(Data are from reference 22)

13.20.2.3 Applications of cosolvency in environmental sciences and engineering

The significance of cosolvency research in environmental sciences stems from the need for accurate modeling the distribution and movement of organic pollutants and cleaning up the polluted soils and sediments.

In environmental cosolvency studies, the majority of the solutes are hydrophobic organic compounds (HOCs), including benzene and its derivatives, polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), polychlorinated dibenzo-p-dioxins and furans (PCDDs and PCDFs), and various pesticides. The 1990 Clean Air Act Amendment has stimulated research on gasoline additives such as methyl t-butyl ether (MTBE) and formulated fuels like gasohol, and their cosolvent effects on the solubility and sorption of a few pollutant groups have also been examined.[23-25,29] Since the late 1970s, most published environmental research papers have focused on the effects of adding cosolvents on the aqueous solubility[26-40] and soil sorption[32,41-60] of these HOCs, as they are generally highly persistent, bioaccumulative and toxic. A few researchers have also examined cosolvent effects on liquid phase partitioning,[61,62] and chemical reactions.[63] In recent years, "emerging pollutants" such as halogenated and organophosphate flame retardants, perfluorinated compounds, personal care and pharmaceutical products, etc., have caused tremendous attention due to their widespread contamination of the environment. However, cosolvent effects on the environmental behavior of these new pollutants have hardly been investigated.

In the cases of industrial waste discharges, liquid fuel and paint spills, storage tank leakage, landfill leaching, and illegal dumping, various organic solvents may find their way into the natural environment. These solvents may not only act as pollutants themselves, but also bring substantial changes on the distribution, movement, and fate of other environmental pollutants of high concern. With the insertion of ethanol into gasoline in recent years, concerns on its effects have led to investigations on the sorption and degradation of PAHs, BTEX (benzene, toluene, ethylbenzene, and xylenes) and other hydrocarbons in the subsurface environment when "gasohol" was added.[64,65] However, some studies found minimal impact of ethanol on the transport and fate of hydrocarbons in the subsurface environment.[66,67] Ethanol itself appears to be lost relatively rapidly due to evaporation and microbial degradation, with limited transport in the groundwater.[67]

Meanwhile, environmental engineers have put cosolvents to work in cleaning up contaminated sites. As a consequence of the failure of using traditional pump-and-treat remediation for soils contaminated with organic pollutants, a few new approaches have been experimented since the late 1980s. Among those involving cosolvents, *Ex situ* solvent extraction was developed to treat excavated soils, sediment, or sludge. A typical one is the basic extractive sludge treatment (B.E.S.T.) process certified by USEPA.[53,68] Triethylamine was selected as the extracting solvent due mainly to its inverse miscibility property – it is completely miscible with water below 60°F but separates from water above 90°F. This property makes it easier to recycle the solvents after separating the treated solids from liquids containing the solvent, pollutants, and water. For PCBs in various soils, it is typical to achieve an extraction efficiency higher than 99% using the B.E.S.T technique.

Among the emerging pollutants, decabromodiphenyl ether (DBDE) is a major flame retardant, with its production peaked in the 1990s and ceased in 2012 in the western world. Remediation of contaminated sites frequently counts on its debrominative transformations *via* chemical, photochemical, or microbiological methods. Its extremely low water solubility requires the use of cosolvents for any experiments in aqueous phase. In addition, cosolvents were used to eliminate the confounding factors of bioavailability in DBDE debromination in sediment.[69] In an experiments of DBDE debromination on clay particles embedded with nano-size, zero-valent ions, the use of cosolvent tetrahydrofuran (THF) at high volume fractions in water was found to reduce the reaction rates due to enhanced aggregation of clay particles and/or diminished adsorption of DBDE to smectite surfaces, while adding tetramethylammonium (TMA) attenuated the cosolvent effect.[70]

More attractive are *in situ* remediation approaches, which often cost less. Cosolvents promote the mobilization of organic chemicals in soils, thus accelerating the cleanup of contaminated site. Cosolvent flushing has been developed using the same principles as those used in solvent flooding, a technique to enhance petroleum recovery in oil fields. It involves injecting a solvent mixture, mostly water plus a miscible cosolvent, into the vadose or saturated zone upgradient of the contaminated area. The solvent with the removed contaminants is then extracted downgradient and treated above ground. Precise formulations for the water/cosolvent mixture need to be determined by laboratory and pilot studies in order to achieve the desired removal.[71-77]

A few field-scale evaluations of this technique were carried out at Hill Air Force Base, Utah, where the aquifer had been severely contaminated by jet fuel, chlorinated solvents, and pesticides during 1940s and 1950s. These contaminants had formed a complex non-aqueous phase liquid (NAPL) containing more than 200 constituents, which covered the surfaces of soil particles and was trapped in pores and capillaries over the years. One of the evaluations consisted of pumping ternary cosolvent mixture (70% ethanol, 12% n-pentanol, and 18% water) through a hydraulically isolated test cell over a period of 10 days, followed by flushing with water for another 20 days.[78,79] The removal efficiency varied from 90-99% at the top zone to 70-80% at the bottom near a confining clay layer. Similar removal efficiencies were obtained from another test cell using a combination of cosolvent n-pentanol and a surfactant at a total of 5.5 wt% of the flushing solution.[80] In order to remove gasoline residuals at a US Coast Guard base in Traverse City, Michigan, it was demonstrated that the contaminants were mobilized when cosolvent 2-propanol was used at 50% concentration, while methanol at either 20% or 50% showed little effect.[81] Cosolvent flushing was also proven to be effective in treating NAPLs which were denser than water. Methanol, isopropanol, and t-butanol were used in treating soils contaminated with tri- and tetra-chlorinated ethylenes.[82]

The applicability of solvent flushing, however, is often limited by the characteristics of the soil, especially the particle size distribution. While sandy soils may result in uncontrolled fluid migration, clayey soils with particles size less than 60 μm are often considered unsuitable for *in-situ* solvent flushing due to low soil permeability. In an attempt to remove PAHs from poorly permeable soils, Li, *et al*.[83] investigated the possibility of combining cosolvent flushing with the electrokinetic technique. Electrokinetic remediation

involves application of a low direct electrical current to electrodes that are inserted into the ground. As water is continuously replenished at anodes, dissolved contaminants are flushed toward the cathode due to electroosmosis, where they can be extracted and further treated by various conventional wastewater treatment methods. Their column experiment of removing phenanthrene from soil was moderately successful with the assistance of cosolvent n-butylamine at 20%(v). Retardation factor (ratio of the water linear velocity to that of the chemical) of phenanthrene was reduced from 753 in pure water to 11 by the presence of n-butylamine, and 43% of the phenanthrene was removed after 127 days or 9 pore volumes. However, significant removal of phenanthrene was not attained in their experiments with acetone and hydrofuran as cosolvents.

13.20.2.4 Experimental observations

Numerous experimental data exist in the literature on the solubility of organic solutes, including both drugs and environmental pollutants, in various mixtures of water and cosolvents. Experimental observations are often illustrated by plotting the logarithm of solubility of the solute versus the volume fraction of cosolvent in the solvent mixture. A few examples of solubilization curves are shown in Figure 13.20.2.1, which shows three typical situations for solutes of different hydrophobicity in the mixture of water and ethanol.

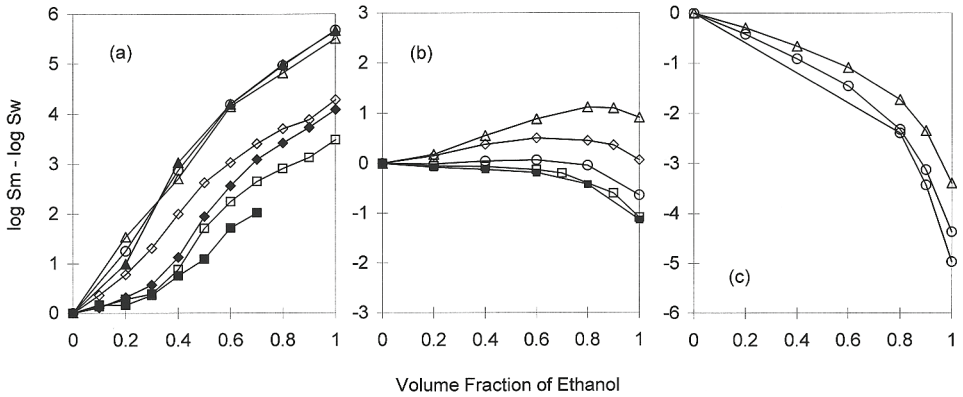


Figure 13.20.2.1. Effects of ethanol on the solubilities of selected organic compounds (a): ■ benzene, □ naphthalene, ◆ biphenyl, ◊ anthracene, ▲ benzo(a)pyrene, △ perylene, O chrysene. (b): ■ hydantoic acid, □ hydantoin, O methyl hydantoic acid, ◊ 5-ethyl hydantoin, △ 5-isobutyl hydantoin. (c): □ triglycine, O diglycine, △ glycine. [Adapted, by permission, from Li and Yalkovsky, *J. Pharm. Sci.*, **83**, 1735 (1994).]

The classification of solute/cosolvent/water systems based on their relative polarity was suggested by Yalkowsky and Roseman.[85] Solutes which are less polar than both water and the cosolvent are considered as “nonpolar”, those which have a polarity between those of water and the cosolvent as “semipolar”, and those which are more polar than both water and cosolvent as “polar”. Figure 13.20.2.1-a illustrates the behavior of relatively hydrophobic compounds, which tend to have monotonically increasing solubilization curves. The solubility enhancement is greater for the more hydrophobic solutes. Curves with opposite trends were mostly observed for polar solutes. The monotonical desolubilization

is greater for more hydrophilic solutes, as evidenced by the curves in Figure 13.20.2.1-c. In-between are semipolar solutes with slightly parabolic curves shown in 13.20.2.1-b. The impact of adding cosolvents is much less profound for the semipolars than for the other two groups. On a linear solubility scale, the parabola tends to be more obvious than on the log scale. The same general trends were seen for the cosolvents glycerine[85] and propylene glycol[85,86] and presumably many other water-miscible cosolvents.

It is more difficult to evaluate the effects of cosolvents which have limited miscibility with water. These organic solvents have limited miscibility with water. In the literature, they have been termed as both cosolvents and cosolutes, and there is no clear criteria for the distinction. Cosolvent is usually miscible with water, or to be used in an attempt to increase the aqueous solubility of the solute. Cosolute, on the other hand, may be organic chemicals which have a similar chemical structure or behave similarly with the solute when they exist in water alone. The effects of cosolutes have been examined in a limited number of published papers.[87-97]

Partially water-miscible organic solvents (PMOSs) may act as either cosolvents or cosolutes, and the past research has shown the complexity of their effects.[27,31-34,97-99] It was demonstrated that in order to exert effects on solubility or sorption of HOCs, PMOSs must exist as a component of the solvent mixture in an appreciable amount: Munz and Roberts[27] suggested a mole fraction of greater than 0.005 and Rao and coworkers[31,32] proposed a volume percent of 1% or a concentration above 10^4 mg/L. Cosolvents with relatively high water solubility are likely to demonstrate observable effects on the solubilities of solutes, up to their solubility limits, in a similar manner to cosolvents of complete miscibility with water. A few experimental examples of the effects of PMOSs include 1-butanol and 1-pentanol acting on PCB congeners[34] and naphthalene,[30] and butanone on anthracene and fluoranthene.[99]

Even more hydrophobic organic solvents produce a little or even negative influence on the solubility of HOCs. For instance, the presence of benzene does not increase the aqueous solubility of PCBs up to their saturation concentration.[33] Solubility of a few PCB congeners in water were found to be depressed by dissolved methylene chloride and chloroform.[97] On the other hand, PCB solubility showed little change when cosolvent benzyl alcohol, 1-hexanol, 1-heptanol, or 1-octanol was present.[33,34] Similar “no change” observations were made for naphthalene with cosolvents methylene chloride and chloroform,[97] and for solutes benzene and hexane with cosolvent MTBE.[32] Much of the complexity with hydrophobic cosolvents, or rather, cosolutes, can be explained by the fact that these cosolvents may partition into the solute phase, thus the physical state of the solute is no longer the same as is in pure water. Instead of a basically pure crystalline or liquid phase of solute, the solute and the cosolvent form an organic mixture, and the composition and ideality of this mixture will very much determine the concentrations of its components in the aqueous phase. Such a situation may be better investigated along the line of phase partitioning, where Raoult's law defines an ideal system.

13.20.2.5 Predicting cosolvency in homogeneous liquid systems

Although progress has been made in recent decades, cosolvency remains a poorly understood phenomenon today due in large measure to our limited awareness of the liquid structure and the intermolecular forces. In fact, solubility in a pure solvent, particularly in water, is difficult to predict, although large databases are available.[100,101] A review of the cosolvency models can be found in the Handbook of Solubility Data for Pharmaceuticals[3] and others.[102] For solvent mixtures containing water, the molecular interactions among solute, solvent and cosolvent are further complicated by the presence of hydrogen bond if the solute or cosolvent has significant hydrogen donating or accepting capabilities.

At present, practical approaches to predicting aqueous phase cosolvency are to develop models based on established theories and to make use of the correlation between experimental observations and properties of the substances involved. As with all modeling efforts, it is essential to make judicious simplifications at various levels. The efforts to date have given rise to several models, including the extended regular solution theory[103-105] and its modification,[106] excess free energy model,[107-110] the phenomenological model,[111,112] modified Wilson model,[113,114] the combined nearly ideal binary solvent (NIBS) model,[115] the mixture response surface model,[116] the fluctuation theory of solutions,[39] and likely others. Some models are built upon the thermodynamic properties of the mixed solvents, while others focus on direct predicting the solute solubility or its activity coefficient in solution which is infinitely diluted with regard to the solute.

Many models, however, are considered to be more descriptive than predictive, because they inevitably involve one or more model parameters which are usually specific to a particular solute/solvent/cosolvent(s) system, and must be estimated from experimental data of solubility obtained for that system. On the other hand, purely empirical models, e.g., the double-log exponential equation,[117] aim at satisfying mathematical descriptions of measured data, and often offer little insight into the process. Comparisons among cosolvency models have been made in several published papers.[118-122] This discussion is intended to provide an easy approach for predicting the effect of cosolvents, which are frequently involved in pharmaceutical and environmental applications, on the solubility of organic chemicals. The starting point is the widely used log-linear model.

The log-linear model

Yalkowsky and Roseman[85] introduced the log-linear model in 1984 to describe the phenomenon of the exponential increase in aqueous solubility for nonpolar organic compounds as the cosolvent concentration is increased. They showed that

$$\log S_m^i = f\log S_c + (1 - f)\log S_w \qquad [13.20.2.1]$$

Rearranging equation [13.20.2.1] results in

$$\log(S_m^i/S_w) = f\log(S_c/S_w) = \sigma f \qquad [13.20.2.2]$$

The left side of equation [13.20.2.2] reflects the extent of solubilization; f defines how much cosolvent is required to reach the desired solubilization. The constant σ is the end-to-end slope of the solubilization curve and defined by:

$$\sigma = \log S_c - \log S_w = \log(S_c/S_w) \quad [13.20.2.3]$$

The model can be extended to systems containing a number of cosolvents:

$$\log(S_m^i/S_w) = \sum \sigma_i f_i \quad [13.20.2.4]$$

where the subscript i denotes the ith component of the solvent mixture.

Two measured solubilities will define the value of σ that is specific to a solute/cosolvent pair. The value of σ is also dependent on the solubility unit selected and on whether 10-based or e-based logarithm is used. The magnitude of σ reflects the difference in molecular interactions between solute/cosolvent and solute/water. When applied to describe cosolvency, σ is like a microscopic partition coefficient if water and cosolvent are thought of as two independent entities. There had been other definitions of σ, such as the partial derivative $(\log S_m)/\partial f$,[123] or the regressional (not end-to-end) slope of the solubilization curve.[124] The σ defined in these ways will depend on the range of f and on the accuracy of all data points over the entire range of f. These definitions are not desirable because they make σ difficult to predict and interpret in light of the concept of the ideal solvent mixture on which the log-linear model is based. Note also that σ is not related to the crystalline structure of the solute since the contributions from the free energy of melting to the two solubilities cancel out. However, it may change if the solute exists in pure cosolvent with a chemical identity different from that in water, as in the cases where solute degradation, solvation, or solvent-mediated polymorphic transitions occur in either solvent.

Estimation of σ

Laboratory measurements of S_w and S_c can be costly and difficult. Various methods, including group contribution technique and quantitative structure (or property) property relationships (QSPRs or QPPRs),[125] are available to estimate S_w and S_c, from which σ values can be derived. A direct approach to predicting σ has also been established based on the dependence of cosolvency on solute hydrophobicity. Among a number of polarity indices, octanol/water partition coefficient, K_{ow}, was initially chosen by Yalkowsky and Roseman[85] for correlation with σ, due mainly to the abundance of available experimental K_{ow} data and the wide acceptance of the Hansch-Leo fragment method[126] for its estimation. K_{ow} is a macroscopic property which does not necessarily correlate with microscale polarity indices such as dipole moment, and only in a rank order correlates with other macroscopic polarity indicators such as surface tension, relative permittivity, and solubility parameter.

Correlation between σ and solute K_{ow} takes the form:

$$\sigma = a + b\log K_{ow} \quad [13.20.2.5]$$

where a and b are constants that are specific for the cosolvent but independent of solutes. Their values have been reported for various cosolvents and are summarized in Table 13.20.2.2.

From Table 13.20.2.2, the slopes of equation [13.20.2.5], b, are generally close to unity, with few below 0.6 or above 1.2. Most of the intercepts a are less than one, with a

few negative values. In searching for the physical implications of the regression constants a and b, Li and Yalkowsky[127] derived equation [13.20.2.6]:

$$\sigma = \log K_{ow} + \log(\gamma_o^{\infty *}/\gamma_c) + \log(\gamma_w/\gamma_w^{\infty *}) + \log(V_o^*/V_c) \qquad [13.20.2.6]$$

According to this equation, σ~$\log K_{ow}$ correlation will indeed have a slope of one and a predictable intercept of $\log(V_o^*/V_c)$ if both $\gamma_o^{\infty *}/\gamma_c$ and $\gamma_w/\gamma_w^{\infty *}$ terms equal unity. V_o^* = 0.119 L mol^{-1} based on a solubility of water in octanol of 2.3 mol L^{-1}, and V_c ranges from 0.04 to 0.10 L^3 mol^{-1}, thus log (V_o^*/V_c) is in the range of 0.08 to 0.47, for the solvents included in Table 13.20.2.2 with the exclusion of PEG400. However, both $\gamma_o^{\infty *}/\gamma_c$ and $\gamma_w/\gamma_w^{\infty *}$ are not likely to be unity, and their accurate values are difficult to estimate for many solutes. The ratio $\gamma_o^{\infty *}/\gamma_c$ compares the solute behavior in water-saturated octanol under dilute conditions and in pure cosolvent at saturation, while the $\gamma_w/\gamma_w^{\infty *}$ term reflects both the effect of dissolved octanol on the aqueous activity coefficient and the variation of the activity coefficient with concentration. Furthermore, the magnitudes of both terms will vary from one solute to another, making it unlikely that a unique regression intercept will be observed over a wide range of solutes. Indeed, both a and b were found to be dependent on the range of the solute $\log K_{ow}$ used in the regression. For instance, for solutes with $\log K_{ow} \leq 0$, 0.01 to 2.99, and ≥ 3, the correlation of σ versus $\log K_{ow}$ for cosolvent ethanol have slopes of 0.84, 0.79, and 0.69, respectively, and the corresponding intercepts increase accordingly; the slope of the overall correlation, however, is 0.95. Much of the scattering on the σ~$\log K_{ow}$ regression resides on the region of relatively hydrophilic solutes. Most polar solutes dissociate to some extent in aqueous solutions, and their experimental $\log K_{ow}$ values are less reliable. Even less certain is the extent of specific interactions between these polar solutes and the solvent components.

According to equation [13.20.2.6], σ may not be a linear function of solute $\log K_{ow}$ on a theoretical basis. However, despite the complexities caused by the activity coefficients, quality of the regression of σ against $\log K_{ow}$ is generally high, as evidenced by the satisfactory R^2 values in Table 13.20.2.2. This can be explained by the fact that changes in both γ ratios are much less significant compared with the variations of K_{ow} for different solutes. In addition, the two γ terms may cancel each other to some degree for many solutes, further reducing their effects on the correlation between σ and $\log K_{ow}$. It is convenient and reliable to estimate σ from known $\log K_{ow}$ of the solute of interest, especially when the $\log K_{ow}$ of the solute of interest falls within the range used in obtaining the values of a and b.

Dependence of σ on the properties of cosolvents has been less investigated than those of solutes. While hundreds of solutes are involved, only about a dozen organic solvents have been investigated for their cosolvency potentials. A few researchers examined the correlations between σ and physicochemical properties of cosolvents for specific solutes, for instance, Li and Yalkowsky for naphthalene,[35] and Rubino and Yalkowsky for drugs benzocaine, diazepam, and phenytoin.[128] In both studies, hydrogen bond donor density (HBD), which is the volume normalized number of proton donor groups of a pure cosolvent, is best for comparing cosolvents and predicting σ. Second to HBD are the solubility parameter and interfacial tension (as well as log viscosity and $E_T(30)$ for naphtha-

lene systems), while $\log K_{ow}$, relative permittivity, and surface tension, correlate poorly with σ. The HBD of a solvent can be readily calculated from the density and molecular mass with the knowledge of the chemical structure using equation [13.20.2.7] The disadvantage of using HBD is that it cannot distinguish among aprotic solvents which have the same HBD value of zero.

$$\text{HBD} = (\text{number of proton donor groups})\,(\text{density})/(\text{molecular mass}) \quad [13.20.2.7]$$

In an attempt to generalize over solutes, Li and Yalkowsky investigated the possible correlations between cosolvent properties and slope of the σ~$\log K_{ow}$ regressions (b). Among the properties tested as a single regression variable, octanol-water partition coefficient, interfacial tension, and solubility parameter, are superior to others in correlating with b. Results of multiple linear regression show that the combination of $\log K_{ow}$ and HDB of the cosolvent is best (equation [13.20.2.8]). Adding another variable such as solubility parameter does not improve the quality of regression.

$$b = 0.2513 \log K_{ow} - 0.0054 HBD + 1.1645 \quad [13.20.2.8]$$

$(N = 13, R^2 = 0.942, SE = 0.060, F = 81.65)$

where $\log K_{ow}$ (range: $-7.6 \sim 0.29$) and HBD (range: $0 \sim 41$) are those of the cosolvent.

Equation [13.20.2.8] can be helpful to obtain the b values for cosolvents not listed in Table 13.20.2.2. In order to estimate cosolvency for such cosolvents, values of the intercept a are also needed. However, values of a can be found in Table 13.20.2.2 for only about a dozen cosolvents, and there is no reliable method for its estimation. To obtain a for a cosolvent, a reasonable starting value can be $\log(V_o^*/V_c)$, or $-(0.92 + \log V_c)$. The average absolute difference between a values listed in Table 13.20.2.2 and $\log (V_o^*/V_c)$ is 0.18 ($N = 7$) for alcohols and glycols, 0.59 ($N = 6$) for aprotic cosolvents, and >1 for n-butylamine and PEG400.[129]

This empirical approach using equations [13.20.2.8], [13.20.2.5], and [13.20.2.2] can produce acceptable estimates of $\log(S_m/S_w)$ only if the solubilization exhibits a roughly log-linear pattern, such as in some HOC/water/methanol systems. In addition, it is important to limit the use of equations [13.20.2.5] and [13.20.2.8] within the ranges of $\log K_{ow}$ used in obtaining the corresponding parameters.

Table 13.20.2.2. Summary of regression results for the relationship between σ and solute log K_{ow}.

Cosolvent	N	a	b	R^2	logK_{ow}	Ref.
Methanol	79	0.36 ± 0.07	0.89 ± 0.02	0.96	-4.53 ~ 7.31	80
Methanol	16	1.09	0.57	0.83	2.0 ~ 7.2	29
Methanol	16	1.07	0.68	0.84	n.a.	24
Ethanol	197	0.30 ± 0.04	0.95 ± 0.02	0.95	-4.90 ~ 8.23	80
Ethanol	107	0.40 ± 0.06	0.90 ± 0.02	0.96	-4.9 ~ 6.1	60
Ethanol	11	0.81	0.85	0.94	n.a.	24
1-Propanol	17	0.01 ± 0.13	1.09 0.05	0.97	–3.73 ~ 7.31	80
2-Propanol	20	–0.50 ± 0.18	1.11 ± 0.07	0.94	–3.73 ~ 4.49	80
2-Propanol	9	0.63	0.89	0.85	n.a.	24
Acetone	22	–0.10 ± 0.24	1.14 ± 0.07	0.92	–1.38 ~ 5.66	80
Acetone	14	0.48	1.00	0.93	0.6 ~ 5.6*	24
Acetonitrile	10	–0.49 ± 0.42	1.16 ± 0.16	0.86	–0.06 ~ 4.49	80
Acetonitrile	8	0.35	1.03	0.90	n.a.	24
Dioxane	23	0.40 ± 0.16	1.08 ± 0.07	0.91	–4.90 ~ 4.49	80
Dimethylacetamide	11	0.75 ± 0.30	0.96 ± 0.12	0.87	0.66 ~ 4.49	80
Dimethylacetamide	7	0.89	0.86	0.95	n.a.	24
Dimethylformamide	11	0.92 ± 0.41	0.83 ± 0.17	0.73	0.66 ~ 3.32	80
Dimethylformamide	7	0.87	0.87	0.94	n.a.	24
Dimethylsulfoxide	12	0.95 ± 0.43	0.79 ± 0.17	0.68	0.66 ~ 4.49	80
Dimethylsulfoxide	7	0.89	0.87	0.95	n.a.	24
Glycerol	21	0.28 ± 0.15	0.35 ± 0.05	0.72	–3.28 ~ 4.75	80
Ethylene Glycol	13	0.37 ± 0.13	0.68 ± 0.05	0.95	–3.73 ~ 4.04	80
Ethylene Glycol	7	1.04	0.36	0.75	n.a.	24
Propylene Glycol	62	0.37± 0.11	0.78 ± 0.04	0.89	–7.91 ~ 7.21	80
Propylene Glycol	47	0.03	0.89	0.99	–5 ~ 7	61
Propylene Glycol	8	0.77	0.62	0.96	n.a.	24
PEG400	10	0.68 ± 0.43	0.88 ± 0.16	0.79	–0.10 ~ 4.18	80
Butylamine	4	1.86 ± 0.30	0.64 ± 0.10	0.96	–1.69 ~ 4.49	80

*estimated from Figure 3 in Reference 24.
n.a. = not available.

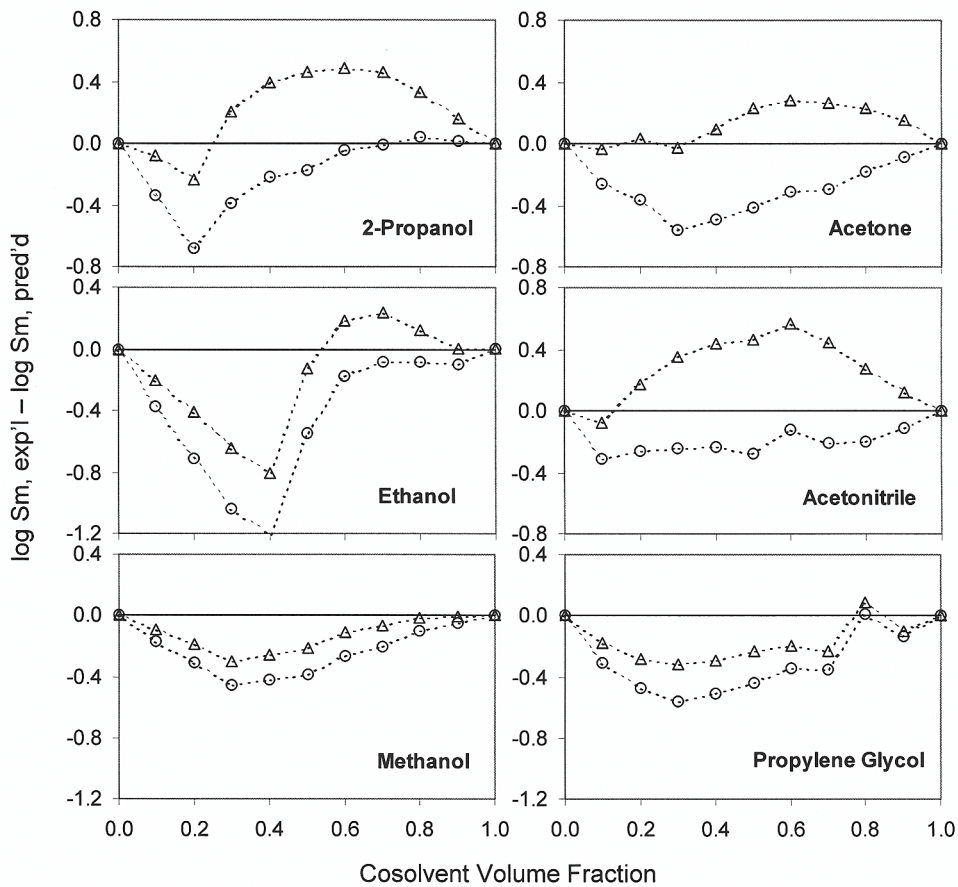


Figure 13.20.2.2a. Deviations from the log-linear model (equation [13.20.2.2], triangle) and the modified log-linear model (equation [13.20.2.10], circle) for solute naphthalene in various water/cosolvent systems. Experimental data are from Reference 130.

13.20.2.6 Predicting cosolvency in non-ideal liquid mixtures

Deviations from the log-linear model

Most solubilization curves, as shown in Figure 13.20.2.1, exhibit significant curvatures which are not accounted for by the log-linear model. A closer look at the solubilization curves in Figure 13.20.2.1 reveals that the deviation can be concave, sigmoidal, or convex. In many cases, especially with amphiprotic cosolvents, a negative deviation from the end-to-end, log-linear line is often observed at low cosolvent concentrations, followed by a more significant positive deviation as cosolvent fraction increases.

The extent of the deviation from the log-linear pattern, or the excess solubility, is measured by the difference between the measured and the log-linearly predicted $\log S_m$ values:

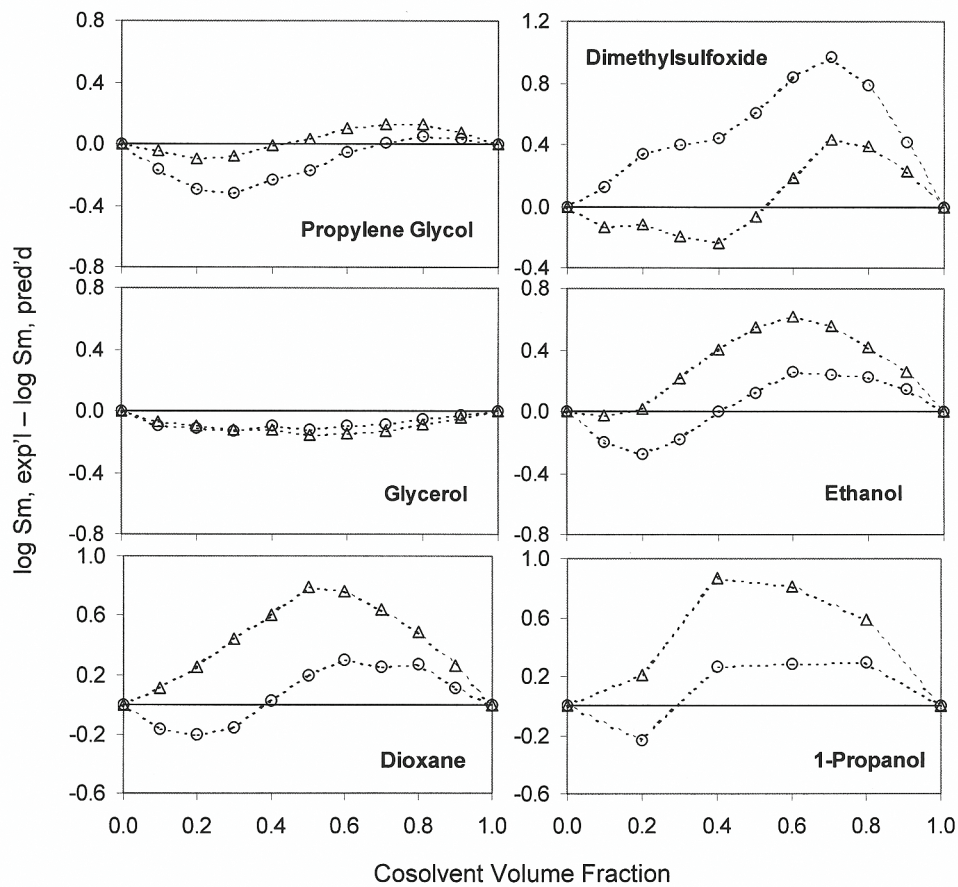


Figure 13.20.2.2b. Deviations from the log-linear model (equation [13.20.2.2], triangle) and the modified log-linear model (equation [13.20.2.10], circle) for solute benzocaine in various water/cosolvent systems. Experimental data are from References 131 and 132.

$$\log(S_m/S_m^i) = \log S_m - (\log S_w + \sum \sigma_i f_i) \qquad [13.20.2.9]$$

The values of $\log(S_m/S^i_m)$ for naphthalene, benzocaine, and benzoic acid in selected binary solvent mixtures are presented in Figures 13.20.2.2-a, -b, and -c, respectively.

The log-linear model is based on the presumed ideality of the mixtures of water and cosolvent. The log-linear relationship between $\log(S_m/S_w)$ and f is exact only if the cosolvent is identical to water, which cannot be the case in reality. The deviation is fortified as any degradation, solvation, dissociation, or solvent-mediated polymorphic transitions of the solute occur. The problem is compounded if the solute dissolves in an amount large enough to exert significant influence on the activity of solvent components. Due to the complexity of the problem, efforts to quantitatively describe the deviations have achieved only limited success.

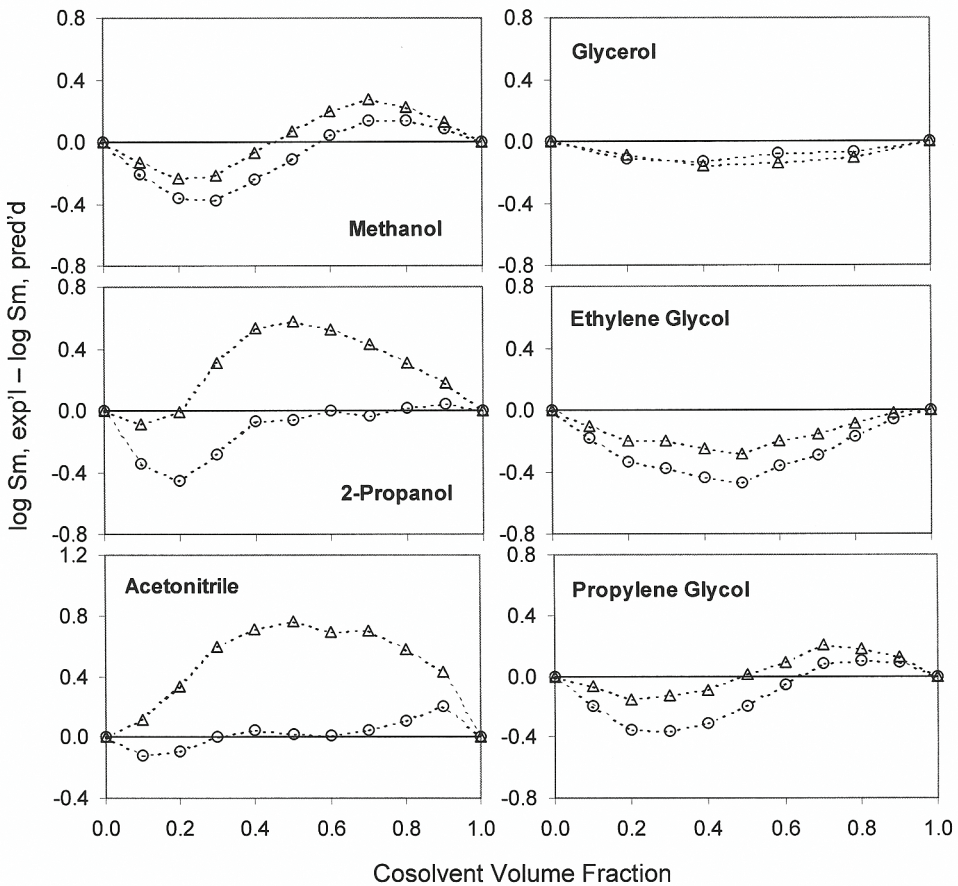


Figure 13.20.2.2c. Deviations from the log-linear model (equation [13.20.2.2], triangle) and the modified log-linear model (equation [13.20.2.10], circle) for solute benzoic acid in various water/cosolvent systems. Experimental data are obtained from References 85 and 133.

A generally accepted view is that the deviation from the log-linear solubilization is mainly caused by the non-ideality of the solvent mixture. This is supported by the similarities in the patterns of observed $\log S_m$ and activities of the cosolvent in the solvent mixture, when they are graphically presented as functions of f. Based on the supposition that solvent non-ideality is the primary cause for the deviation, Rubino and Yalkowsky[134] examined the correlations between the extent of deviation and various physical properties of solvent mixtures. However, none of the properties consistently predicted the extrema of the deviation, although density corresponded in several cases.

Non-ideality of a mixture is quantitatively measured by the excess free energy of mixing. From this standpoint, Pinal *et al.*[99] proposed that a term $\Sigma(f_i \ln \gamma_i)$ be added to equation [13.20.2.4] to account for the effect of the non-ideality of the solvent mixture:

$$\log(S_m^{ii}/S_w) = \sum \sigma_i f_i + 2.303 \sum f_i \log \gamma_i \qquad [13.20.2.10]$$

where γ_i is the activity coefficient of solvent component i in the solute-free solvent mixture. Values of γ's can be calculated by UNIFAC, a group contribution method for the prediction of activity coefficients in nonelectrolyte, nonpolymeric liquid mixtures.[135] UNIFAC derived activity coefficients are listed in Table 13.20.2.3 for selected cosolvent-water mixtures. They are calculated with UNIFAC group interaction parameters derived from vapor-liquid equilibrium data.[136,137]

The difference between the experimental $\log S_m$ and that predicted by the modified log-linear model, i.e., equation [13.20.2.10], is

$$\log(S_m/S_m^{ii}) = \log S_m - (\log S_w + \sum \sigma_i f_i + 2.303 \sum f_i \log \gamma_i) \qquad [13.20.2.11]$$

Results of equation [13.20.2.11] for naphthalene, benzocaine, and benzoic acid in selected binary solvent mixtures are also included in Figure 13.20.2.2. A few other examples can be found in Pinal *et al*.[99]

The modified log-linear model outperforms the log-linear model in more than half of the cases tested for the three solutes in Figure 13.20.2.2. The improvement occurs mostly in regions with relatively high f values. In the low f regions, negative deviations of solubilities from the log-linear pattern are often observed as discussed above but are not accounted for by the modified log-linear model as presented by equation [13.20.2.10]. In some cases, such as naphthalene in methanol and propylene glycol, and benzoic acid in ethylene glycol, the negative deviations occur over the entire f range of 0~1. In these cases, the modified log-linear model does not offer better estimates than the original log-linear model. With the activity coefficients listed in Table 13.20.2.3, the modified log-linear model generates worse estimates of $\log(S_m/S_w)$ than the log-linear model for systems containing dimethylacetamide, dimethylsulfoxide, or dimethylformamide. There is a possibility that the UNIFAC group interaction parameters involved in these systems are incorrect. With all the systems tested in this study with solute naphthalene, benzocaine, or benzoic acid, it is also found that replacing f_i in the last term of equation [13.20.2.11] with mole fraction x_i offers a slight improvement in only a few cases. Dropping the logarithm conversion constant 2.303 results in larger estimation errors for most systems.

An apparent limitation of this modification is the exclusion of any active role the solute may play in the observed deviation. Little understanding of the influence of solute structure and properties on deviations from the log-linear equation has been obtained. Although the patterns of deviations tend to be similar among solutes, as mentioned above, the extent of deviation is solute-dependent. For instance, C1~C4 alkyl esters of p-hydroxybenzoates and p-aminobenzoates demonstrated similar characteristics of solubilization by propylene glycol, with a negative deviation from the log-linear pattern occurring when f is low, followed by a positive one when f increases.[138] The magnitude of the negative deviation, however, was found to be related to the length of the solute alkyl chain in each group, while that of the positive deviation to the type of the polar groups attached.[138] Both the hydrophobicity and hydrogen bonding property of the solutes seem to be important in influencing the extent of the deviation from the ideal log-linear pattern.

Additional deviations related to the solute's behavior may occur. For strong electrolytes, the acid dissociation constant K_a may decrease as cosolvent fraction f increases.[49,99,139] This, in turn, will affect the patterns of solubilization by cosolvents. Furthermore, a high concentration of solutes may invalidate the log-linear model, which presumes negligible volume fraction of solute and no solute-solute interactions. For solid solutes, solvent induced polymorphism may also bring additional changes in their solubilization profile.

Another approach to quantitatively address the deviations of solubilization from the log-linear model makes use of an empirical parameter β:

$$\beta = \log(S_m/S_w)/\log(S_m^i/S_w) \qquad [13.20.2.12]$$

The modified log-linear equation then takes the form:

$$\log(S_m/S_w) = \beta\sum\sigma_i f_i \qquad [13.20.2.13]$$

Under the assumptions that the solute is chemically stable and has little influence on the activity of solvent component, β reflects the extent of deviation caused by the nonideality of the solvent mixture, as suggested by Rao *et al*.[32] However, since β itself is a complicated function of f, equation [13.20.2.13] does not provide additional aid for predicting cosolvency.

Some mathematical treatments are considered useful to predict a wide range of physicochemical properties in addition to solute solubility. This commonality may more likely result from mathematical treatment than be based on chemistry. For example, the Jouyban-Acree model, which was involved from the equation treating nearly idea binary solvents (NIBS), has been applied to predict the physicochemical properties such as density, viscosity, relative permittivity, surface tension, solvatochromic parameter, refractive index, etc., of mixed solvent systems.[102] For solute solubility, the model takes the form:

$$\log X_m = f_1\log X_1 + f_2\log X_2 + f_1 f_2 \sum i^2 S_i (f_1 - f_2)^i \qquad [13.20.2.14]$$

where X is the mole fraction solubility in cosolvent (1), water (2), or water-cosolvent mixture (m); while f_1 and f_2 are the mole fractions of cosolvent and water, respectively. The S_i values are model parameters representing the non-ideality caused by various solute-solvent and solvent-solvent interactions in the mixture and must be obtained by regressions.[102] Both experimental X_1 and X_2 are needed to guide the model performance. Such models can easily be expanded to systems with more than two solvent components.

Table 13.20.2.3. UNIFAC derived activity coefficients for selected binary water-cosolvent systems.

f	0.1	0.2	0.4	0.6	0.8	0.9
Methanol	MW = 32.04 Density = 0.7914					
mol/L	2.4700	4.9401	9.8801	14.8202	19.7603	22.2303
x	0.0471	0.100	0.2286	0.4001	0.6401	0.8001
γ, cosolvent	1.972	1.748	1.413	1.189	1.052	1.014
γ, water	1.003	1.013	1.055	1.14	1.298	1.424
Ethanol	MW = 46.07 Density = 0.7893					
mol/L	1.7133	3.4265	6.8530	10.2796	13.7061	15.4194
x	0.0331	0.0716	0.1705	0.3163	0.5523	0.7351
γ, cosolvent	5.550	4.119	2.416	1.564	1.152	1.050
γ, water	1.005	1.022	1.097	1.256	1.57	1.854
1-Propanol	MW = 60.01 Density = 0.8053					
mol/L	1.3399	2.6799	5.3597	8.0396	10.7195	12.0594
x	0.0261	0.0569	0.1385	0.2657	0.4910	0.6846
γ, cosolvent	12.77	8.323	3.827	2.001	1.248	1.077
γ, water	1.006	1.024	1.111	1.301	1.706	2.093
2-Propanol	MW = 60.01 Density = 0.7848					
mol/L	1.3058	2.6116	5.2233	7.8349	10.4466	11.7524
x	0.0255	0.0555	0.1355	0.2607	0.4846	0.6790
γ, cosolvent	12.93	8.488	3.921	2.040	1.258	1.080
γ, water	1.006	1.023	1.107	1.294	1.695	2.084
Acetone	MW = 58.08 Density = 0.7899					
mol/L	1.3600	2.7200	5.4401	8.1601	10.8802	12.2402
x	0.0265	0.0577	0.1403	0.2686	0.4947	0.6878
γ, cosolvent	8.786	6.724	3.952	2.370	1.484	1.196
γ, water	1.004	1.015	1.075	1.222	1.616	2.211
Acetonitrile	MW = 41.05 Density = 0.7857					
mol/L	1.9140	3.8280	7.6560	11.4840	15.3121	17.2261
x	0.0369	0.0793	0.1868	0.3407	0.5795	0.7561
γ, cosolvent	10.26	7.906	4.550	2.536	1.501	1.126
γ, water	1.005	1.021	1.11	1.366	2.076	3.571
Dioxane	MW = 88.11 Density = 1.0329					
mol/L	1.1723	2.3446	4.6891	7.0337	9.3783	10.5506
x	0.0229	0.0501	0.1233	0.2404	0.4577	0.6551
γ, cosolvent	14.71	8.743	3.616	1.833	1.171	1.124
γ, water	1.006	1.026	1.112	1.284	1.604	1.666

Table 13.20.2.3. UNIFAC derived activity coefficients for selected binary water-cosolvent systems.

f	0.1	0.2	0.4	0.6	0.8	0.9
DMA	MW = 87.12 Density = 0.9429					
mol/L	1.0823	2.1646	4.3292	6.4938	8.6584	9.7407
x	0.0212	0.0464	0.1149	0.2261	0.4380	0.6368
γ, cosolvent	0.121	0.141	0.204	0.330	0.602	0.826
γ, water	0.999	0.994	0.962	0.872	0.651	0.453
DMF	MW = 73.1 Density = 0.9445					
mol/L	1.2921	2.5841	5.1683	7.7524	10.3365	11.6286
x	0.0252	0.0549	0.1342	0.2586	0.4819	0.6767
γ, cosolvent	0.833	0.873	0.930	0.962	0.983	0.985
γ, water	0.999	0.997	0.991	0.984	0.972	0.969
DMSO	MW = 78.13 Density = 1.10					
mol/L	1.4079	2.8158	5.6316	8.4475	11.2633	12.6712
x	0.0274	0.0596	0.1445	0.2754	0.5034	0.6952
γ, cosolvent	0.07956	0.110	0.211	0.399	0.715	0.899
γ, water	0.996	0.981	0.913	0.774	0.540	0.386
Glycerol	MW = 92.1 Density = 1.2611					
mol/L	1.3693	2.7385	5.4771	8.2156	10.9542	12.3235
x	0.0267	0.0580	0.1411	0.2699	0.4964	0.6893
γ, cosolvent	1.257	1.066	0903	0.899	0.969	0.996
γ, water	1.003	1.010	1.027	1.025	0.979	0.942
Ethylene glycol	MW = 62.07 Density = 1.088					
mol/L	1.7864	3.5727	7.1455	10.7182	14.2910	16.0773
x	0.0345	0.0744	0.1765	0.3254	0.5626	0.7432
γ, cosolvent	2.208	1.923	1.494	1.214	1.053	1.013
γ, water	1.002	1.01	1.047	1.12	1.247	1.338
Propylene glycol	MW = 76.09 Density = 1.0361					
mol/L	1.3617	2.7234	5.4467	8.1701	10.8934	12.2551
x	0.0265	0.0577	0.1405	0.2688	0.4951	0.6881
γ, cosolvent	3.392	2.498	1.567	1.177	1.044	1.019
γ, water	1.005	1.018	1.069	1.145	1.224	1.267
Butylamine	MW = 73.14 Density = 0.7414					
mol/L	1.0137	2.0273	4.0547	6.0820	8.1094	9.1231
x	0.0199	0.0436	0.1084	0.2149	0.4219	0.6215
γ, cosolvent	6.532	4.498	2.318	1.391	1.042	0.998
γ, water	1.004	1.016	1.071	1.175	1.326	1.384

13.20.2.7 Thermodynamics of aqueous phase cosolvency

One of the basic experimental approaches to understanding the thermodynamics of a process is to investigate the effect of temperature. It allows the estimations of the enthalpy and, sometimes, the entropy of the process, thus provides insights on the microscopic

molecular interactions. Theoretically, the mole fraction solubility (x) of a hydrophobic solute in a solvent or solvent mixture is

$$\ln x = -\Delta G/RT = -\Delta H/RT + \Delta S/R \quad [13.20.2.15]$$

where R is the gas constant, and T is the experimental temperature in Kelvin. ΔG, ΔH, and ΔS are the free energy, the apparent enthalpies, and the apparent entropy, respectively, of the dissolution process. The reference state for the solute is its pure state and can be either liquid, subcooled liquid, or solid. The mole fraction solubility x can be converted from the experimental molar solubility S:

$$x = S \times V \quad [13.20.2.16]$$

assuming that the presence of solute results in negligible change in the molar volume of the solution V. For pure solvent, the molar volume V can be calculated from the molecular mass and density at specified temperatures. Approximation of the molar volume of solvent mixtures is often made based on those of the solvent, water (w) in this case, and the cosolvent (c):

$$V = x_w V_w + x_c V_c \quad [13.20.2.17]$$

Equation [13.20.2.15] is used to derive the standard apparent thermodynamic functions. ΔG can be estimated from experimental x directly. To obtain ΔH, the van't Hoff regression is used in which the experimental ln x is plotted against the reciprocal absolute temperature in Kelvin (1/T), and

$$\Delta H = -R \times \text{slope} \quad [13.20.2.18]$$

This approach assumes the constancy of ΔH over the temperature range; that is, its accuracy depends largely on the linearity of the van't Hoff regression. Estimation of ΔS from R $\times$ intercept of the regression, as implied by equation [13.20.2.15], is invalid due to the large propagation of measurement errors encountered in extrapolating the 1/T (x-axis) to zero.[140,141] The widely reported enthalpy-entropy compensation, or strongly linear correlation, could be a "phantom phenomenon"[142] which reveals little information on the mechanisms of solute dissolution.

The enthalpy-entropy relationship has been examined using another approach. First, ln x is plotted again ($1/T - 1/T_{mh}$) where T_{hm} is the harmonic mean of the experimental temperatures. The ΔH is estimated using equation [13.20.2.18] as the slope remains the same as when 1/T is used as the independent variable, and

$$\Delta G = -RT_{hm} \times \text{intercept} \quad [13.20.2.19]$$

Then, a plot of ΔH versus ΔG is made, and the position of the peaks is used to indicate the shift of dominance from entropy at low cosolvent fractions due to the lessening of the water structure, to enthalpy at high cosolvent content. Thus, this approach is considered to be able to detect a true enthalpy-entropy relationship independent of a statistical compensation.[143-145]

Cosolvent effect on aqueous solubility at different temperatures have been reported mostly in pharmaceutical studies, which report the thermodynamics of drug dissolution for ibuprofen, naproxen, oxolinic acid, probenecid, phenacetin, etc. in water mixed with cosolvents such as ethanol, propylene glycol, or dioxane.[107,143-148] Few such studies have been done in environmental research, although many have focused on either the effect of cosolvents at a specific temperature or the effect of temperature on solubility in water without involving cosolvents. Due to the needs of environmental remediation, cosolvent effects on the sorption and Henry's law constant under different temperatures have been reported.[149,150]

The available reports revealed van Hoff's plots with little curvature for several solid drugs in water-cosolvent systems within the experimental temperature ranges up to 40°C. The ΔH values are positive suggesting endothermic dissolution which includes the melting and mixing processes. The experimentally derived ΔH values in many cases peak in the mid-ranges of the cosolvent fraction. For example, the highest ΔH values for ibuprofen and naproxen were found in 80:20 and 60:40 mass ratios of propylene glycol:water mixtures, respectively,[143] and those for naproxen, probenecid and salicylic acid in about 30:70 ethanol:water mixtures.[144,145] Similar observation was made for 4-chlorobiphenyl in water-alcohol mixtures.[151] Due to the scarcity of data, it is currently difficult or impossible to predict the thermodynamic functions of the cosolvent effects, particularly in hydrogen-bonded solvent systems.

Summary

Applications of cosolvency in pharmaceutical and environmental research and industries are briefly summarized. Using ethanol as an example, the effects of adding a cosolvent on the solubilities of various organic solutes are presented in Figure 13.20.2.1. The log-linear solubilization model, equation [13.20.2.2] or [13.20.2.4], is the simplest theory of cosolvency developed so far. It discovers general trends and major determinant actors of cosolvency, thus providing guidelines for predicting the solubility of organic chemicals in mixed solvents. The cosolvency power of a specific cosolvent towards a solute of interest, σ, can be estimated with equation [13.20.2.5] with the knowledge of the solute octanol-water partition coefficient K_{ow}. Sources of error associated with this estimation method are discussed based on equation [13.20.2.6]. The slope of the σ~logK_{ow} regression, b, can be estimated from the logK_{ow} and hydrogen bond donor density of the cosolvent, as presented by equation [13.20.2.8]. One of the previously published modifications to the log-linear model, equation [13.20.2.10], is evaluated. The difference between the measured logS_m and those predicted by the log-linear and the modified log-linear model are presented in Figure 13.20.2.2 for solutes naphthalene, benzocaine, and benzoic acids in selected water and cosolvent mixtures. Recently published Jouyban-Acree model is introduced. A new section is added to this version to demonstrate the thermodynamic approach which is expected to be useful in further our understanding of aqueous cosolvency.

NOTATIONS

a	intercept of $\log\sigma \sim \log K_{ow}$ regression
b	slope of $\log\sigma \sim \log K_{ow}$ regression
f	volume fraction of cosolvent in mixed solvent with water
K_{ow}	n-octanol/water partition coefficient
R	gas constant
S_c	solubility in pure cosolvent
S_m	solubility in the mixture of water and cosolvent
$S^i_{m_i}$	solubility in the mixture of water and cosolvent, predicted by the log-linear model (Eq. [13.20.2.2])
$S_{m^{ii}}$	solubility in the mixture of water and cosolvent, predicted by the modified log-linear model (Eq. [13.20.2.10])
S_w	solubility in pure water
T	temperature in Kelvin
T_{hm}	the harmonic mean of the experimental temperatures in Kelvin
V	molar volume of the solvent
V_o^*	molar volume of 1-octanol saturated with water, 0.119 L mol^{-1} (based on a solubility of water in octanol of 2.3 mol L^{-1})
V_c	molar volume of cosolvent
V_w^*	molar volume of water saturated with 1-octanol, 0.018 L mol^{-1}
V_w	molar volume of water, 0.018 L mol^{-1}
x	mole fraction solubility
ΔG	free energy of dissolution
ΔH	enthalpy of dissolution
ΔS	entropy of dissolution
β	empirically obtained water-cosolvent interaction parameter
σ	cosolvency power, $\sigma = \log(S_c/S_w)$
$\gamma_o^{\infty *}$	infinite dilution activity coefficient of solute in 1-octanol saturated with water
γ_c	activity coefficient of solute in cosolvent
$\gamma_{w_{\infty}}^*$	activity coefficient of solute in water
$\gamma_w^{\infty *}$	infinite dilution activity coefficient of solute in water saturated with 1-octanol

REFERENCES

1 A. Li. **Predicting cosolvency for pharmaceutical and environmental applications.** In: **Handbook of Solvents**. G. Wypych, Ed.; *ChemTec Publishing*, Toronto, Canada, 2001, 997-1016.
2 S. H. Yalkowsky, in **Techniques of solubilization of drugs**; S. H. Yalkowsky, Ed.; *Dekker*, New York, 1984, Chapter 1.
3 Jouyban. A. **Handbook of Solubility Data for Pharmaceuticals**. *CRC Press*, Boca Raton, Florida, 2010.
4 A. V. Tithing, C. K. Mohan, and M. Vimalchand, *Indian J. Pharm. Sci*., **70**, 66-70 (2008).
5 M. Longman, and V. Venkateswarlu, Internat. *J. Pharm. Sci. Nanotechnol.*, **1**, 349-356 (2009).
6 S. Chilukala, C. Aparna, N. Shastri, and M. Sadanandam, *J. Pharmacy Res.*, **4**, 4135-4138 (2011).
7 S. Agrawal, N. Soni, N. K.Jain, and G. P. Agrawal, *Internat. J. Pharm. Sci. Res*., **3**, 2325-2336 (2012).
8 B. Sree Giri Prasad, V. R. M. Gupta, N. Devanna, M. Rama Devi, G. Vishnu Vardhan Rao, and N. Harish, *Internat. J. Pharma. Chem. Biol. Sci.*, **2**, 338-342 (2012).
9 S. S. Tous, A. M. El Saye d, M. G. Abd El Mohsen, M. N. Agban, M. F. Boushra, *J. Drug Delivery Sci. Techno*l., **22**, 341-346 (2012).
10 S. Agrawal, N. Soni, N. K. Jain, and G. P. Agrawal, Internat. *J. Current Pharm. Res*., **4**, 128-137 (2012).
11 E. A.Cantillo, D. R. Delgado, and F. Martinez, *J. Molec. Liquids*, **181**, 62-67 (2013).
12 N. Soltani, A. Shaynafar, D. Djozan, and A. Jouyban, *J. Drug Deliv. Sci. Technol.*, **23**(2), 187-190 (2013).
13 S. Chilukala, C. Aparna, N. Shastri, and M. Sadanandam, *J. Pharm. Res*., **4**, 4135-4138 (2011).
14 V. Panahi-Azar, S. Ahmadian, F. Martinez, W. E. Acree Jr., and A. Jouyban, *Fluid Phase Equilibria*, **330**, 36-43 (2012).
15 V. Gurumurthy, R. Deveswaran, S. Bharath, B. V. Basavaraj, and V. Madhavan, *Chemica Sinica*, **2**, 198-203 (2011).
16 A. K. Nayak, and P. P. Panigrahi, *ISRN Phys. Chem*., **820653**, 5 (2012).
17 R. K. Maheshwari, R. Rajagopalan, *Pharmacia Lett.*, **4**, 170-174 (2012).
18 M. Kharwade, K. Mahitha, C. V. S. Subrahmanyam, and P. R. S. Babu, *J. Pharm. Res.*, **5**, 4204-4206 (2012).

19 K. Ban, R. Sonohara, M. Yoshida, K. Sako, S. Uchida, N. Namiki, *PDA J. Pharma. Sci. Technol*., **67**, 336-353 (2013).
20 S. Soltanpour, and A. Jouyban, *J. Molec. Liquids*, **180**, 1-6 (2013).
21 S. H. Yalkowsky, *J. Pharm. Sci.*, **101**, 3047 (2012).
22 S. C. Smolinske, **Handbook of Food, Drug, and Cosmetic Excipients**, *CRC Press*, Ann Arbor, MI, 1992.
23 C. S. Chen, and J. J. Delfino, *J. Environ. Eng.,* April, **354** (1997).
24 J. Molson, M. Mocanu, and J. Barker, *Water Resources Res*., **44**, (2008).
25 R. Gonzalez-Olmos, and M. Iglesias, *Separation Sci. Technol.*, **44**, 3615-3631 (2009).
26 F. Herzel, and A. S. Murty, *Bull. Environ. Toxicol.*, **32**, 53 (1984).
27 C. Munz, and P. Roberts, *Environ. Sci. Technol.*, **20**, 830 (1986).
28 K. R. Morris, R. Abramowitz, R. Pinal, P. Davis, and S. H. Yalkowsky, *Chemosphere*, **17**, 285 (1988).
29 F. R. Groves, Jr, *Environ. Sci. Technol*., **22**, 282 (1988).
30 R. M. Dickhut, A. W. Andren, and D. E. Armstrong, *J. Chem. Eng. Data*, **34**, 438 (1989)
31 R. Pinal, P. S. C. Rao, L. S. Lee, P. V. Cline, and S. H. Yalkowsky, *Environ. Sci. Technol.*, **24**, 639 (1990).
32 P. S. C. Rao, L. S. Lee, and A. L. Wood, *EPA*/600/M-91/009 (1991).
33 A. Li, W. J. Doucette, and A. W. Andren, *Chemosphere*, **24**, 1347 (1992).
34 A. Li, and A. W. Andren, *Environ. Sci. Technol*., **28**, 47 (1994).
35 A. Li, A. W. Andren, and S. H. Yalkowsky, *Environ. Toxicol. Chem.,* **15**, 2233 (1996).
36 H-C. Kwon, H-H. Kwon, *Environ. Sci. Technol*., **46**, 12550-12556 (2012).
37 X. Chen, C. J. Clark II, Clayton, *Environ. Forensics*, **11**, 193-200 (2010).
38 C. L. Yap, S. Gan, H. K. Ng, *J. Environ. Sci.*, **24**, 1064-1075 (2012).
39 E. Ruckenstein, I. Shulgin, *Environ. Sci. Technol*., **39**, 1623-1631 (2005).
40 Q. Huang and C-S. Hong, *Water Res.,* **36**, 3543-3552 (2002).
41 P. Nkedi-Kizza, P. S. C. Rao, and A. G. Hornsby, *Environ. Sci. Technol.*, **19**, 975 (1985).
42 J. K. Fu, and R. G. Luthy, *J. Environ. Eng.*, **112**, 346 (1986).
43 R. W. Walters, and A. Guiseppe-Elie, *Environ. Sci. Technol.*, **22**, 819 (1988).
44 P. Nkedi-Kizza, M. L. Brusseau, P. S. C. Rao, and A. G. Hornsby, *Environ. Sci. Technol*., **23**, 814 (1989)
45 A. L. Wood, D. C. Bouchard, M. L. Brusseau, and P. S. C. Rao, *Chemosphere*, **21**, 575 (1990).
46 P. S. C. Rao, L. S. Lee, and R. Pinal, *Environ. Sci. Technol.*, **24**, 647 (1990).
47 F. C. Spurlock, and J. W. Biggar, *Environ. Sci. Technol*., **28**, 1003 (1994).
48 W. J. M. Hegeman, C. H. Van der Weijden, and J. P. G. Loch, *Environ. Sci. Technol.*, **29**, 363 (1995).
49 L. S. Lee, and P. S. C. Rao, *Environ. Sci. Technol*., **30**, 1533 (1996).
50 V. A. Nzengung, E. A. Voudrias, P. Nkedi-Kizza, J. M. Wampler, and C. E. Weaver, *Environ. Sci. Technol*., **30**, 89 (1996).
51 R. P. Singh, *Colloids and Surfaces A*., **122**, 63 (1997).
52 V. A. Nzengung, P. Nkedi-Kizza, R. E. Jessup, and E. A. Voudrias, *Environ. Sci. Technol*., **31**, 1470 (1997).
53 T. C. Harmon, T. J. Kim, B. K. D. Barre, and C. V. Chrysikopoulos, *J. Environ. Eng.*, January, 87 (1999).
54 S. Hyun, and L. S. Lee, *Chemosphere*, **70**, 503-510 (2008).
55 M. Kim, and S. Hyun, *Chemosphere* (2014).
56 H. Peng, H. Li, C. Wang, D. Zhang, B. Pan, and B. Xing, *Chemosphere* (2014),
57 S. Hyun, M. Kim, K. Baek, and L. S. Lee, *Chemosphere*, **78**, 423-429 (2010).
58 M. Kim, J. Kim, and S. Hyun, *Chemosphere*, **89**, 262-268 (2012).
59 M. Kim, J. Han, and S. Hyun, *Chemosphere*, **93**, 133-139 (2013).
60 F. Xiao, K. J. Davidsavor, S. Park, M. Nakayama, and B. R. Phillips, *J. Colloid Interface Sci.*, **368**(1), 505-511 (2012).
61 M. A. Ei-Zoobi, G. E. Ruch, and F. R. Groves Jr., *Environ. Sci. Technol.*, **24**, 1332 (1990).
62 W. F. Lane, and R. C. Loehr, *Environ. Sci. Technol*., **26**, 983 (1992).
63 X. Chen, and C. J. Clark, *J. Hazard. Materials*, **164**(2-3), 565-570 (2009).
64 S. E. Heermann, S. E. Powers, *J. Contam. Hydrol*., **34**, 315-341 (1998).
65 H. X. Corseuil, B. I. A. Kaipper, and M. Fernandes, *Water Res*., **38**, 1449-1456 (2004).
66 S. Yu, J. G. Freitas, A. J. A. Unger, J. F. Barker, and J. Chatzis, *J. Contam. Hydrol*., **105**, 1-17 (2009).
67 J. G. Freitas, and J. F. Barker, *J. Contam. Hydrol*., **148**, 79-91 (2013).
68 G. R. Jones, *Environ. Prog.,* **11**, 223 (1992).
69 J. A. Tokarz III, M-Y. Ahn, J. Leng, T. R. Filley, and L. Nies. *Environ. Sci. Technol.*, **42**, 1157-1164 (2008).
70 K. Yu, C. Gu, S. A. Boyd, C. Liu, C. Sun, B. J. Teppen, and H. Li, *Environ. Sci. Technol.*, **46**, 8969-8975 (2012).
71 USEPA, **Assessment and Remediation of contaminated Sediments (ARCS) Program: Remediation Guidance Document**. *EPA* 905-R94-003, (1994) p.180.

72 **USEPA, In situ remediation-Technological innovations.** *EPA* 542-K-94-006 (1995).
73 C. T. Jafvert, **Ground-Water Remediation Technologies Analysis Center**, *Echnology Evaluation Report*, TE-96-02 (1996).
74 R. W. Falta, *GWMR*, Summer, 94 (1998).
75 D. C. M. Augustijin, R. E. Jessup, P. S. Rao, and A. L. Wood, *J. Environ. Eng.*, **120**, 42 (1994).
76 L. Strbak, **In Situ Flushing with Surfactants and Cosolvents**. *National Network of Environmental Management Studies Fellow*, 36 pp, 2000.
77 P. J. Dugan, R.L. Siegrist, and M.L. *Crimi. Remediation J*., **20**, 27-49 (2010).
78 R. K. Sillan, M. D. Annable, P. S. C. Rao, D. Dai, K. Hatfield, W. D. Graham, A. L. Wood, and C. G. Enfield, *Water Resources Res*., **34**, 2191 (1998).
79 P. S. C. Rao, M. D. Annable, R. K. Sillan, D. Dai, K. Hatfield, and W. D. Graham, *Water Resources Res.*, **33**, 2673 (1997).
80 J. W. Jawitz, M. D. Annable, P. S. C. Rao, and R. D. Rhue, *Environ. Sci. Technol*., **32**, 523 (1998).
81 A. T. Kan, M. B. Tomson, and T. A. McRae, Proceedings of the 203rd American Chemical Society National Meeting, San Francisco, CA (1992).
82 D. Brandes, and K. J. Farley, *J. Water Environ. Res*., **65**, 869 (1993).
83 A. Li, K. A. Cheung, and K. Reddy, *J. Environ. Eng*. **126**, 527-533 (2000).
84 A. Li, and S. H. Yalksowsky, *J. Pharm. Sci.,* **83**, 1735 (1994).
85 S. H. Yalkowsky, and T. J. Roseman, in **Techniques of solubilization of drugs**; S. H. Yalkowsky, Ed.; *Dekker*, New York, 1984, Chapter 3.
86 J. T. Rubino, and S. H. Yalkowsky, *J. Pharm. Sci.*, **74**, 416 (1985).
87 P. J. Leinonen, and D. Mackay, *Can. J. Chem. Eng*., **51**, 230 (1973).
88 R. P. Eganhouse, and J. A. Calder, *Geochimca et Cosmochimica Acta*, **40**, 555 (1976).
89 Y. B. Tewari, D. E. Martire, S. P.; Wasik, and M. M. Miller, *J. Solution Chem*., **11**, 435 (1982).
90 S. Banerjee, *Environ. Sci. Technol.*, **18**, 587 (1984).
91 D. R. Burris, and W. G. MacIntyre, *Environ. Toxicol. Chem.*, **4**, 371 (1985).
92 H. H. Hooper, S. Michel, and J. M. Prausnitz, *J. Chem. Eng. Data*, **33**, 502 (1988).
93 D. Mackay, *J. Contam. Hydrol*., **8**, 23 (1991).
94 A. Li, and W. J. Doucette, *Environ. Toxicol. Chem*., **12**, 2031 (1993).
95 S. Lesage, and S. Brown, *J. Contam. Hydrol.*, **15**, 57 (1994).
96 K. Brololm, and S. Feenstra, *Environ. Toxicol. Chem.*, **14**, 9 (1995).
97 G. T. Coyle, T. C. Harmon, and I. H. Suffet, *Environ. Sci. Technol*., **31**, 384 (1997).
98 P. S. C. Rao, L. S. Lee, P. Nkedi-Kizza, and S. H. Yalkowsky, in **Toxic Organic Chemicals in Porous Media**, Z. Gerstl, Eds. *Springer-Verlag*, New York, 1989, Chapter 8.
99 R. Pinal, L. S. Lee, and P. S. C. Rao, *Chemosphere*, **22**, 939 (1991).
100 IUPAC-NIST **Solubility Database**. http://srdata.nist.gov/solubility/
101 S. H. Yalkowsky, Y. He, and P. Jain. **Handbook of Aqueous Solubility Data**, Second Edition. *CRC Press* 2010.
102 A. Jouyban, *J. Pharm. Pharma. Sci*., **11**, 32-58 (2008).
103 A. Martin, J. Newburger, and A. Adjel, *J. Pharm. Sci*., **68**, 4 (1979).
104 A. Martin, J. Newburger, and A. Adjel, *J. Pharm. Sci*., **69**, 487 (1980).
105 A. Martin, A. N. Paruta, and A. Adjel, *J. Pharm. Sci.,* **70**, 1115 (1981).
106 P. Bustamante, B. Escalera, A. Martin, and E. Selles, *Pharm. Pharmacol.*, **45**, 253 (1993).
107 N. A. Williams, and G. L. Amidon, *J. Pharm. Sci.*, **73**, 9 (1984).
108 N. A. Williams, and G. L. Amidon, *J. Pharm. Sci*., **73**, 14 (1984).
109 N. A. Williams, and G. L. Amidon, *J. Pharm. Sci*., **73**, 18 (1984)
110 A. Jouyban, S. Romero, H. K. Chan, B. J. Clark, P. A. Bustamante, *Chem. Pharma. Bull.*, **50**, 594-599 (2002).
111 D. Khossrani, and K. A. Connors, *J. Pharm. Sci.,* **82**, 817 (1993).
112 D. Khossravi, and K. A. Connors, J. *Pharm. Sci.*, **81**, 371 (1992)
113 A. Jouyban-Gharamaleki, *Chem. Pharm. Bull.,* **46**, 1058 (1998).
114 W. E. Acree, Jr., J. W. McCargar, A. I. Zvaigzne, and I. L. Teng, *Phys. Chem. Liq.*, **23**, 27 (1991)
115 W. E. Acree, Jr. and A. I. Zvaigzne, *Thermochimica. Acta*, **178**, 151 (1991).
116 A. B., Ochsner, R. J. Belloto Jr., and T. D. Sololoski, *J. Pharm. Sci*., **74**, 132 (1985).
117 M. Barzegar-Jalali, and J. Hanaee, *Int. J. Pharm*., **109**, 291 (1994).
118 A. Li, and A. W. Andren, *Environ. Sci. Technol.*, **29**, 3001 (1995).
119 J. K. Fu, and R. G. Luthy, *J. Environ. Eng.,* **112**, 328 (1986)
120 M. Barzegar-Jalali, and A. Jouyban-Gharamaleki, *Int. J. Pharm.*, **140**, 237 (1996).

121 R. M. Dickhut, D. E. Armstrong, and A. W. Andren, *Environ. Toxicol. Chem*., **10**, 881 (1991).
122 A. Jouyban-Gharamaleki, L. Valaee, M. Barzegar-Jalali, B. J. Clark, and W. E. Acree, Jr., *Intern. J. Pharm*., **177**, 93 (1999)
123 S. H. Yalkowsky, and J. T. Rubino, *J. Pharm. Sci*., **74**, 416 (1985).
124 J. T. Rubino, and S. H. Yalkowsky, *J. Parent. Sci. Technol*., **41**, 172 (1984).
125 W. J. Lyman, W. f. Reehl, and D. H. Rosenblatt, **Handbook of Chemical Property Estimation Methods: Environmental Behavior of Organic Compounds**. *ACS Publications*, Washington, DC, 1990.
126 C. Hansch, and A. J. Leo, **Substituent constants for Correlation Analysis in Chemistry and Biology**. *John Wiley*, New York, 1979.
127 A. Li, and S. H. Yalkowsky, *Ind. Eng. Chem. Res*., **37**, 4470 (1998).
128 J. T. Rubino, and S. H. Yalkowsky, *Pharm. Res*., **4**, 220 (1987).
129 A. Li, and S. H. Yalkowsky, *Ind. Eng. Chem. Res.*, **37**, 4476 (1998).
130 R. Abramowitz, **Ph.D. Dissertation**, *University of Arizona*, 1986.
131 A. Li, and S. H. Yalkowsky, unpublished data.
132 J. T. Rubino, **Ph.D**. **Dissertation**, *University of Arizona*, 1984.
133 S. H. Yalkowsky, unpublished data.
134 J. T. Rubino, and S. H. Yalkowsky, *Pharm. Res.*, **4**, 231 (1987).
135 A. Fredenslund, R. L. Jones, and J. M. Prausnitz, *A.I.Ch.E. J*., **21**, 1086 (1975).
136 J. Gmehling, P. Rasmussen, and A. Fredenslund, *Ind. Eng. Chem. Process Des. Dev*., **21**, 118 (1982).
137 E. A. Macedo, U. Weidlich, J. Gmehling, and P. Rasmussen, *Ind. Eng. Chem. Process Des. Dev*., **22**, 678 (1983).
138 J. T. Rubino, and E. K. Obeng, *J. Pharm. Sci.*, **80**, 479 (1991).
139 L. S. Lee, C. A. Bellin, R. Pinal, and P. S. C. Rao, *Environ. Sci. Technol*., **27**, 165 (1997).
140 O. Exner, *Coll. Czech. Chem. Comm*., **26**, 1094-1113 (1964)
141 R. R. Krug, W. G. Hunter, and R. A. Grieger, *J. Phys. Chem*., **80**, 2335 (1976)
142 A. Cornish-Bowden, *J. Biosci.*, **27**, 121 (2002)
143 Y. J. Manrique, D. P. Pacheco, F. Martinez, *J. Solution Chem*., **37**, 165-181 (2008).
144 D. P. Pacheco, and F. Martinez, *Phys. Chem. Liquid*, **45**, 581- 595 (2007).
145 M. A. Peña, B. Escalera, A. Reíllo, A. B. Sánchez, and P. Bustamante, *J. Pharm. Sci*., **98**, 1129 (2009).
146 C. Bustamante, and P. Bustamante, *J. Pharm. Sci*., **85**:1109-1111 (1996).
147 P. Bustamante, J. Navarro J, S. Romero, and B. Escalera, *J. Pharm. Sci.*, **91**:874-883 (2002).
148 P. Bustamante, S. Romero, M. A. Peña, B. Escalera, and A. Reillo, *J. Pharm. Sci.,* **87**,1590-1596 (1998).
149 C. S. Chen, and S-J. Tseng, *Soil Sediment Contam*., **16**, 507-521 (2007).
150 R. Gonzalez-Olmos, and M. Iglesias, *Separation Sci. Technol*., **44**, 3615-3631 (2009).
151 A. Li, and G. M. Butler. (manuscript in preparation)

13.21 POLYMERS AND MAN-MADE FIBERS

George Wypych
ChemTec Laboratories, Toronto, Canada

The resin production industry in the USA was 48 billion kg in 2012. The resin production industry had 34,000 nonsupervisory employees. The man-made fiber industry employs in the USA about 27,000 people, produces 2.7 billion kg of fibers, and has sales of $8 billion/year.

In the polymer manufacture industry, production processes are diverse both in technology and equipment design. They have common steps which include preparation of reactants, polymerization, polymer recovery, polymer extrusion (if in pelletized form), and supporting operations. In some preparation operations, solvents are used to dissolve or dilute monomer and reactants. Solvents are also used to facilitate the transportation of the reaction mixture throughout the plant, to improve heat dissipation during the reaction, and to promote uniform mixing. Solvent selection is optimized to increase monomer ratio and to reduce polymerization costs and emissions. The final polymer may or may not be soluble in a solvent. These combinations of polymers and solvents are commonly used: HDPE – iso-butane and hexane, LDPE – hydrocarbons, LLDPE – octene, butene, or hexene, polypropylene – hexane, heptane or liquid propylene, polystyrene – styrene or ethylbenzene, acrylic-dimethylacetamide or aqueous inorganic salt solutions. These examples show that there are options available. The excess monomer may replace solvent or water can be used as the solvent. During polymer recovery, unreacted monomer and solvents are separated from polymer (monomers and solvents are flashed off by lowering the pressure and sometimes degassing under vacuum), liquids and solids are separated (the polymer may be washed to remove solvent), and residual water and solvent are purged during polymer drying. Residual solvents are removed by further drying and extrusion. Solvents are also used in equipment cleaning. Solvents are often stored under a nitrogen blanket to minimize oxidation and contamination. When these systems are vented solvent losses occur. Figure 13.21.1 shows a schematic diagram of potential emissions during polymer manufacture.

Manufacture of man-made fibers involves polymerization (usually the core part of the process), preparation of the solution, spinning, washing and coagulation, and drying and other operations. Fibers are formed by forcing the viscous liquid through small-bore orifices. A suitable viscosity can be achieved either by heating or dissolution. The rheological properties of the solution are governed to a large degree by the solvents selected. Wastes generated during the spinning operation include evaporated solvent and wastewater contaminated by the solvent. The typical solvents used in the production of fibers are dimethylacetamide (acrylic), acetone or chlorinated hydrocarbons (cellulose acetate), and carbon disulfide (rayon). In the dry spinning process, a solution of polymer is first prepared. The solution is then heated above the boiling temperature of the solvent and the solution is extruded through the spinneret. The solvent evaporates into the gas stream. With wet spinning, the fiber is directly extruded into a coagulation bath where solvent dif-

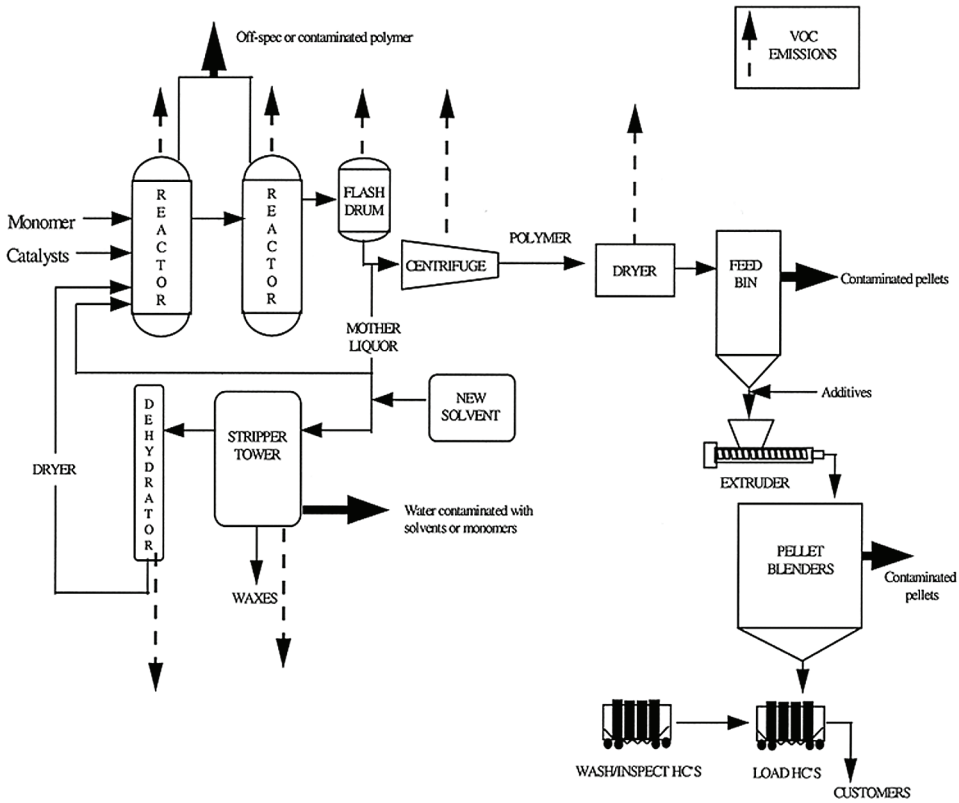


Figure 13.21.1. Schematic diagram of emissions from the polymer manufacturing industry. [Reproduced from EPA Office of Compliance Sector Notebook Project. Profile of the Petroleum Refining Industry. US Environmental Protection Agency, 1995.]

fuses into the bath liquid and the coagulant diffuses into the fiber. The fiber is washed free of the solvent by passing it through an additional bath. This process step generates emissions or wastewater. Solvents used in production are normally recovered by distillation. Figure 13.21.2 is a schematic diagram of fiber production showing that almost all stages of production generate emissions.

Tables 13.21.1 and 13.21.2 provide data on releases and transfers from both polymer manufacturing and man-made fiber production in the USA. Carbon disulfide, methanol, xylene, and ethylene glycol are used in the largest quantities. Carbon disulfide is used in the manufacture of regenerated cellulose and rayon. Ethylene glycol is used in the manufacture of poly(ethylene terephthalate), the manufacture of alkyd resins, and as a cosolvent for cellulose ethers and esters. Methanol is used in several processes, the largest being the production of polyester. This industry is the 10th largest contributor of VOC and 7th largest in releases and transfers.

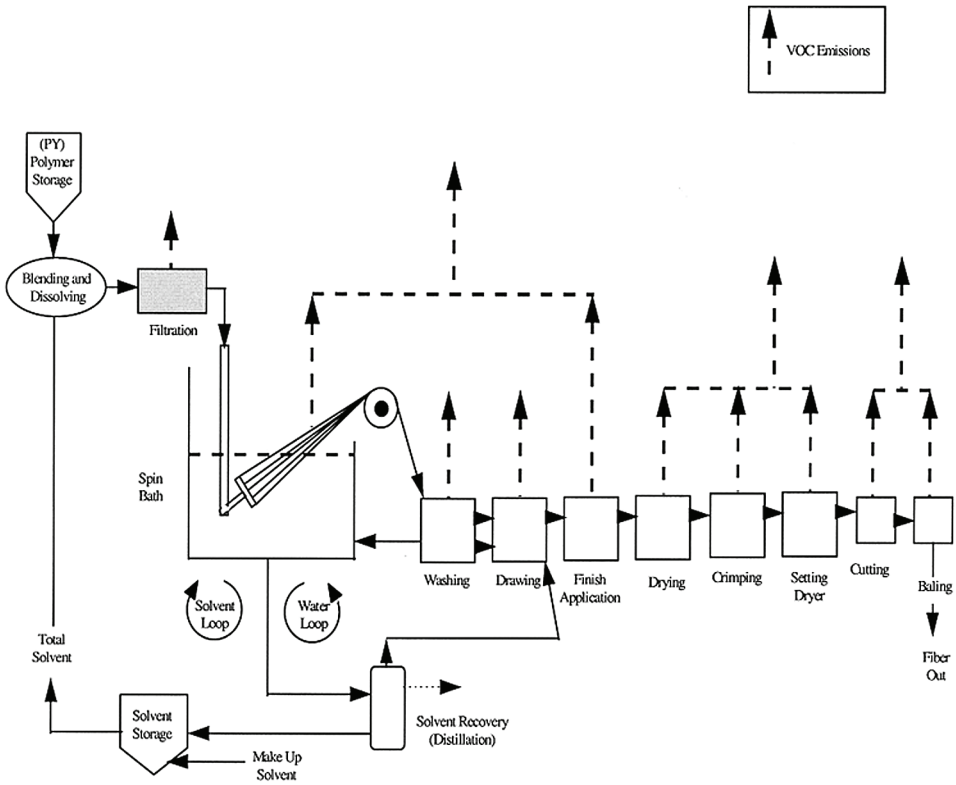


Figure 13.21.2. Schematic diagram of emissions from the man-made fiber manufacturing industry. [Reproduced from EPA Office of Compliance Sector Notebook Project. Profile of the Petroleum Refining Industry. US Environmental Protection Agency, 1995.]

There have been many initiatives to reduce emissions and use of solvents. Man-made fiber manufacturing no longer uses benzene. DuPont eliminated o-xylene and reduced methanol and ethylene glycol used in its Wilmington operation. This change resulted in annual savings of $1 million. Process modification in a polymer processing plant resulted in a decrease in total emissions of 74% and a reduction in the release of cyclohexane by 96%. Monitoring of thousands of valves in Eastman Texas plant resulted in a program of valve replacement which eliminated 99% of the emissions. Plant in Florida eliminated solvents from cleaning and degreasing. These examples show that in many cases pollution can be reduced by better equipment, organization, and care.

Table 13.21.1 Reported solvent releases from the polymer and man-made fiber industry in 1995 [Data from Ref. 1]

Solvent	Amount, kg/year	Solvent	Amount, kg/year
allyl alcohol	29,000	1,4-dioxane	10,000

Table 13.21.1 Reported solvent releases from the polymer and man-made fiber industry in 1995 [Data from Ref. 1]

Solvent	Amount, kg/year	Solvent	Amount, kg/year
benzene	60,000	ethylbenzene	130,000
n-butyl alcohol	480,000	ethylene glycol	1,400,000
sec-butyl alcohol	25,000	hexane	880,000
tert-butyl alcohol	16,000	methanol	3,600,000
carbon disulfide	27,500,000	methyl ethyl ketone	260,000
carbon tetrachloride	100	methyl isobutyl ketone	98,000
chlorobenzene	19,000	pyridine	67,000
chloroform	14,000	tetrachloroethylene	4,000
cresol	4,000	1,1,1-trichloroethane	120,000
cyclohexane	98,000	trichloroethylene	39,000
1,2-dichloroethane	98,000	1,2,4-trimethylbenzene	12,000
dichloromethane	1,300,000	toluene	900,000
N,N-dimethylformamide	19,000	xylene	460,000

Table 13.21.2. Reported solvent transfers from the polymer and man-made fiber industry in 1995 [Data from Ref. 1]

Solvent	Amount, kg/year	Solvent	Amount, kg/year
allyl alcohol	120,000	ethylbenzene	880,000
benzene	160,000	ethylene glycol	49,000,000
n-butyl alcohol	330,000	hexane	8,000,000
sec-butyl alcohol	12,000	methanol	5,600,000
tert-butyl alcohol	160,000	methyl ethyl ketone	460,000
carbon disulfide	14,000	methyl isobutyl ketone	43,000
carbon tetrachloride	200,000	N-methyl-2-pyrrolidone	780,000
chlorobenzene	570,000	pyridine	70,000
chloroform	59,000	tetrachloroethylene	330,000
cresol	20,000	1,1,1-trichloroethane	21,000
cyclohexane	420,000	trichloroethylene	76,000
dichloromethane	250,000	1,2,4-trimethylbenzene	98,000
N,N-dimethylformamide	300,000	toluene	2,800,000
1,4-dioxane	11,000	xylene	7,800,000

Technology is emerging to reduce solvent use. Inventions disclose that, in addition to reducing solvents, the stability of ethylene polymers can be improved with the developed process.[3] A proper selection of solvent improved a stripping operation and contributed to the better quality of cyclic esters used as monomers.[4] Solvent was used for the recovery of fine particles of polymer which were contaminating water.[5] A process for producing fiber for cigarette filters reduced the amount of solvent.[6] Optical fibers are manufactured by radiation curing which eliminates solvents.[7] An electrospinning process has been developed which produces unique fibers by the dry spinning method, providing a simpler separation and regeneration of the solvent.[8]

Polymer-containing solution can be purified and the solvent reused by subjecting the solution to microfiltration using tubular filters having an average pore diameter of less than 1 μm and a filtration pressure of at least 0.35 MPa.[9]

A polymer capable of selective extraction of solvent from the inorganic or organic solution has been patented.[10] Introduction of the polymer into the solvent solution created the formation of a polymer-rich phase and a solute-rich phase.[10] The recovered solvent may be separated from the polymer-rich phase by heating the polymer-rich phase.[10]

Chemical modification of cellulose was conducted by *in situ* reactive extrusion.[11] Environmentally friendly solvent – ionic liquid, namely, 1-N-butyl-3-methylimidazolium chloride was used as a reaction medium.[11] The high solid content resulted in high efficiency, a lower energy consumption in fiber production, and a solvent recycling.[11]

REFERENCES

1 **EPA Office of Compliance Sector Notebook Project. Profile of the Petroleum Refining Industry**. *US Environmental Protection Agency*, 1995.
2 **EPA Office of Compliance Sector Notebook Project. Sector Notebook Data Refresh - 1997**. *US Environmental Protection Agency*, 1998.
3 M M Hughes, M E Rowland. C A Strait, **US Patent 5,756,659**, *The Dow Chemical Company*, 1998.
4 D W Verser, A Cheung, T J Eggeman, W A Evanko, K H Schilling, M Meiser, A E Allen, M E Hillman, G E Cremeans, E S Lipinsky, **US Patent 5,750,732**, *Chronopol, Inc*., 1998.
5 H Dallmeyer, **US Patent 5,407,974**, *Polysar Rubber Corporation*, 1995.
6 J N Cannon, **US Patent 5,512,230**, *Eastman Chemical Company*, 1996.
7 P J Shustack, **US Patent 5,527,835**, *Borden, Inc.*, 1996.
8 A E Zachariades, R S Porter, J Doshi, G Srinivasan, D H Reneker, *Polym. New*s, **20**, No.7, 206-7 (1995).
9 M Z Ali, D C Bradford, **EP2401061**, *Eastman Kodak Company*, 4 Jan. 2012.
10 N Rajagopalan, V A Patel, **WO2010088170**, *Board of Trustees of University of Illinois*, 18 Nov. 2010.
11 Y. Zhang, H. Li, X. Li, M. E. Gibril, M. Yu, *Carbohydrate Polym*., **99**, 126-31, 2014.

13.22 PRINTING INDUSTRY

George Wypych
ChemTec Laboratories, Toronto, Canada

The number of printing and publishing operations in the US is estimated at over 30,000. 0.44 million people are employed. The value of shipments was over $898 billion in 2015 with 83% print orders placed online. 97% of printing was done by lithography, gravure, flexography, letterpress, and screen printing on substrates such as paper, plastic metal, and ceramic. Although these processes differ, the common feature is the use of cleaning solvents in imaging, platemaking, printing, and finishing operation. Most inks contain solvents and many of the adhesives used in finishing operations also contain solvents. Many processes use the so-called fountain solutions which are applied to enable the non-image area of the printing plate to repel ink. These solutions contain primarily isopropyl alcohol. But the printing operation is, by itself, the largest contributor of VOCs. Each printing process requires inks which differ drastically in rheology. For example, gravure printing requires low viscosity inks which contain higher solvent concentrations.

Tables 13.22.1 and 13.22.2 provide data on the reported releases and transfers of solvents by the US printing industry. These data show that there are fewer solvents and relatively low releases and transfers compared with other industries. In terms of VOC contribution, the printing industry was 5th and 10th in the total emissions and transfers.

Table 13.22.1. Reported solvent releases from the printing and publishing industry in 1995 [Data from Ref. 2].

Solvent	Amount, kg/year	Solvent	Amount, kg/year
n-butyl alcohol	43,000		170,000
dichloromethane	59,000		31,000
1,4-dioxane	8,000		34,000
ethylene glycol	46,000		180,000
ethylbenzene	23,000		13,000
hexane	50,000		36,000
isopropyl alcohol	27,000		12,200,000
methanol	170,000		700,000
methyl ethyl ketone	960,000		

Table 13.22.2. Reported solvent transfers from the printing and publishing industry in 1995 [Data from Ref. 2].

Solvent	Amount, kg/year	Solvent	Amount, kg/year
n-butyl alcohol	7,000	methyl isobutyl ketone	63,000
dichloromethane	43,000	N-methyl-2-pyrrolidone	28,000
1,4-dioxane	340	tetrachloroethylene	27,000
ethylene glycol	16,000	1,1,1-trichloroethane	39,000
ethylbenzene	9,200	trichloroethylene	4,000
hexane	12,000	1,2,4-trimethylbenzene	33,000
isopropyl alcohol	12,000	toluene	2,800,000
methanol	17,000	xylene	240,000
methyl ethyl ketone	700,000		

Literature shows that there is extensive activity within and outside the industry to limit VOCs and reduce emissions. Cleaning operations are the major influence on emissions. Shell has developed cleaning formulations containing no aromatic or chlorinated hydrocarbons.[3] An additional requirement was to optimize the solvent mixture to prevent swelling of the rubber in blanket cylinders and rollers. It is predicted that the European industry will increase the rate of the introduction of radiation-cured inks and eliminate isopropanol from fountain solutions.[4] It is also expected that the radiation-cured flexographic inks will grow by 30%/year in the next five years.[5] In Germany, 70-80% of emissions or 47,000 ton/year have been eliminated by the year 2007.[6] Beginning in 1999, the UK industry kept VOC concentration below 5 tonnes/year per plant.[7] VOC concentration in the outside atmosphere was not allowed to exceed 150 mg/m^3 (50 mg/m^3 if there was more than 5% aromatic solvents). Reactive hot melts are popular in bookbinding.[8] This eliminates emissions from solvent adhesives.

Solvent replacements are not the only solution at hand. Solvent-containing systems often give better quality than replacement systems, therefore, the methods have been developed to make the solvent based materials more acceptable. A soil bed biofiltration system was tested in California with excellent results.[9] This biofilter is a bed of soil impregnated with microorganisms which use VOC as their food. Present California regulations require that such a treatment system has a 67% capture and VOC destruction efficiency. The new method was proven to have 95.8% efficiency. In addition to the environmental issues with solvents, the printing industry has addressed the source of their raw materials. Present systems are based on petroleum products which are not renewable resources. Terpenes are natural products which are finding applications in the print industry.[10] In Denmark, 70% cleaning solvents are vegetable oil based. These and other such innovations will continue to be applied to reduce solvent use and emissions. It was also reported[10] that water-based system replaced fountain solutions.

Other factors are driving changes. Odors in packaging materials and the migration of solvent to foods are unacceptable. Most odors in packaging materials are associated with the process and coalescing solvents.[11] Foods which do not contain fat are more susceptible to the retaining the taste of solvents. Printing inks which may be acceptable for foods containing fat may not be suitable for fat-free applications (see more on this subject in Chapter 15.1).[12]

Many inventions have also been directed at solving the current environmental problems of printing industry.[13-21] The solvent in gravure printing inks not only contributed to pollution but also to the cost of solvent recovery and/or degradation. A technology was proposed in which a solvent-free ink with a low melting point can be processed in liquid state and then be solidified on cooling.[13] A non-volatile solvent for printing inks was developed based on a cyclic keto-enol tautomer and a drying oil.[14] An alcohol soluble polyamide for rotary letterpress printing inks was developed[15] and subsequently adapted to flexographic/gravure inks.[18] A polyamide was also used in a rotary letterpress ink which enabled low alcohols to be used as the solvent with some addition of an ester.[16] This ink was compatible with water-based primers and adhesives which could not be used with solvent-based inks. Inks for jet printers are water sensitive. One solvent-based technology was developed using esters and glycols[17] and the other using low alcohols.[20] Another recent invention describes aqueous ink containing some low alcohols.[19] UV- and electron beam-cured ink concentrates were also developed.[21]

Gravure printing requires inks containing fewer solvents.[22] Reduction of solvents in gravure printing inks was achieved by using a combination of alcohol-based and propyl acetate solvents.[22] Chlorine-free ink for printing on untreated polyolefin films has been invented.[23] The solvent is a combination of water and an organic solvent selected from among hydrocarbons, cyclic hydrocarbons, substituted hydrocarbons, aromatic compounds, alkyl acetates, alcohols and petroleum distillates.[23]

Printing processes are not restricted to the production of printed sheets of paper but they are used in many other industries, such as textile,[24] pharmaceutical (drug-printing for orodispersible films by flexographic printing),[25] polymer,[26] medical (water-based polyurethane 3D printed scaffolds with controlled-release function for customized cartilage tissue engineering),[27] electronics (inkjet-printed solar cells),[28] and many others. These industries also use and emit solvents as well as conduct research on elimination and restriction of solvents.

This information from open and patent literature clearly indicates that industry is actively working on the development of new technological processes to reduce emissions of solvents.

REFERENCES

1 **EPA Office of Compliance Sector Notebook Project. Profile of the Printing and Publishing Industry**. *US Environmental Protection Agency,* 1995.
2 **EPA Office of Compliance Sector Notebook Project. Sector Notebook Data Refresh - 1997**. *US Environmental Protection Agency*, 1998.
3 N C M Beers, M J Koppes, L A M Rupert, *Pigment & Resin Technol*., **27**, No.5, 289-97 (1998).
4 D Blanchard, *Surface Coatings International*, **80**, No.10, 476-8 (1997).
5 B Gain, *Chem. Week*, **160**, No.14, 28-30 (1998).
6 W Fleck, *Coating*, **31**(1), 23-25 (1998).

7 C H Williams, *Converter*, **34**, No.9, 11-2 (1997).
8 Hughes F, TAPPI 1997 Hot Melt Symposium. Conference Proceedings. TAPPI. Hilton Head, SC, 15th-18th June 1997, p.15-21.
9 A Mykytiuk, Paper, *Film & Foil Converter*, **72**, No.8, 120-3 (1998).
10 A Harris, Paper, *Film & Foil Converter*, **72**, No.5, 198-9 (1998).
11 R M Podhajny, *Paper, Film & Foil Converter*, **72**, No.12, 24 (1998).
12 T Clark, *Paper, Film & Foil Converter*, **70**, No.11, 48-50 (1996).
13 R Griebel, K A Kocherscheid, K Stammen, **US Patent 5,496,879**, *Siegwerk Druckfarben GmbH*, 1996.
14 D Westerhoff, **US Patent 5,506,294**, 1996.
15 P D Whyzmuzis, K Breindel, R A Lovald, **US Patent 5,523,335**, *Henkel Corporation*, 1996.
16 R J Catena, M C Mathew, S E Barreto, N Marinelli, **US Patent 5,658,968**, *Sun Chemical Corporation*, 1997.
17 J M Kruse, **US Patent 5,663,217**, *XAAR Ltd.*, 1997
18 P D Whymusis, **US Patent 5,714,526**, *Henkel Corporation*, 1998.
19 H Yanagi, S Wakabayashi, K Kaida, **US Patent 5,736,606**, *Kao Corporation*, 1998.
20 M Shinozuka, Y Miyazawa, M Fujino, T Ito, O Ishibashi, **US Patent 5,750,592**, *Seiko Epson Corporation*, 1998.
21 W R Likavec, C R Bradley, **US Patent 5,866,628**, *Day-Glo Color Corporation*, 1999.
22 T Inoue, T Ogawa, J Harada, **WO2013162003**, *Sakata Inx Corp*., 31 Oct. 2013.
23 Y Abe, H Wei, H Rallis, **EP2606096**, *Sun Chemical Corporation*, 26 Jun. 2013.
24 S. Jiang, Y. Wang, D. Sheng, W. Xu, G. Cao, *Carbohydrate Polym*., **153**, 364-70, 2016.
25 E. M. Janßen, R. Schliephacke, A. Breitenbach, J. Breitkreutz, *Int. J. Pharm*., **441**, 1-2, 2013.
26 J. Isdebska, **Flexographic Printing** in **Printing on Polymers**, *Elsevier*, 2016, pp. 179-97.
27 K.-C. Hung, C.-S. Tseng, L.-G. Dai, S.-h. Hsu, *Biomaterials*, **83**, 156-68, 2016.
28 A. Lange, W. Schindler, M. Wegener, K. Fostiropoulos, S. Janietz, *Solar Ener. Mater. Solar Cells,* **109**, 104-10, 2013.

13.23 PULP AND PAPER

George Wypych
ChemTec Laboratories, Toronto, Canada

The US pulp and paper industry operates over 250 facilities which employ over 100,000 people. Pulp and paper industry generated worldwide $564 billion in revenue during 2013. Several processes contribute to the emission of solvents. These include chemical pulping kraft process (terpenes, alcohols, methanol, acetone, chloroform), bleaching (acetone, dichloromethane, chloroform, methyl ethyl ketone, carbon disulfide, chloromethane, and trichloroethane), wastewater treatment (terpenes, alcohols, methanol, acetone, chloroform and methyl ethyl ketone), and evaporators in chemical recovery systems (alcohols and terpenes).

Tables 13.23.1 and 13.23.2 give the reported releases and transfers of solvent data for the US pulp and paper industry. If not for the emissions of methanol and chloroform the industry would be a much less serious polluter. It is 7th in VOC contributions and 8th in total releases and transfers.

Table 13.23.1. Reported solvent releases from the pulp and paper industry in 1995
[Data from Ref. 2]

Solvent	Amount, kg/year	Solvent	Amount, kg/year
benzene	320,000	methanol	63,000,000
n-butyl alcohol	46,000	methyl ethyl ketone	700,000
chloroform	4,500,000	methyl isobutyl ketone	10,000
chloromethane	260,000	1,2,4-trimethylbenzene	17,000
cresol	410,000	toluene	580,000
ethylbenzene	22,000	xylene	49,000
ethylene glycol	37,000	o-xylene	260
hexane	150,000		

Table 13.23.2. Reported solvent transfers from the pulp and paper industry in 1995
[Data from Ref. 2].

Solvent	Amount, kg/year	Solvent	Amount, kg/year
benzene	24,000	hexane	8,600
n-butyl alcohol	16,000	methanol	23,000,000
chloroform	150,000	methyl ethyl ketone	36,000
chloromethane	120	1,2,4-trimethylbenzene	1,400
cresol	3,600	toluene	23,000

Table 13.23.2. Reported solvent transfers from the pulp and paper industry in 1995
[Data from Ref. 2].

Solvent	Amount, kg/year	Solvent	Amount, kg/year
ethylene glycol	190,000	xylene	4,000

Fire retardant cigarette paper is produced by impregnation of a cigarette with a solution of fire retardant.[3] Solvents include water, ethanol, ethyl acetate, aqueous ammonia, or their mixture.[3] Isopropyl alcohol is used for paper deacidification.[4] Anode electrode paper is produced by application of titania-graphene dispersed in a solvent.

The combined effects of materials and solvents on the preparation, structural, and mechanical properties of the regenerated cellulose fibers have been studied.[6] The ionic liquids were the best solvents.[6]

REFERENCES

1 **EPA Office of Compliance Sector Notebook Project. Profile of the Pulp and Paper Industry**. *US Environmental Protection Agency*, 1995.
2 **EPA Office of Compliance Sector Notebook Project. Sector Notebook Data Refresh - 1997**. *US Environmental Protection Agency*, 1998.
3 Q Wang, **WO2012113357**, *Mudanjiang Hengfeng Paper Co., Ltd*., 10 May 2013.
4 R-M Ion, S M Doncea, **WO2012113357**, *Icechim*, 14 Aug. 2013.
5 W Bennett, D Choi, G L Graff, J Liu, Y Shin, **WO2012047372**, *Battelle Memorial Institute*, 12 Apr. 2012.
6 J. Chen, Y. Guan, K. Wang, X. Zhang, F. Xu, R. Sun, *Carbohydrate Polym*., **128**, 147-153, 2015.

13.24 RUBBER AND PLASTICS

George Wypych
ChemTec Laboratories, Toronto, Canada

The US rubber industry generated $18 billion sales in 2012. World rubber consumption in 2010 was 24,750,000 metric tonnes. Rubber and plastics industry employed in 2013 over 655,000 people in the USA in 13,024 plants. The industry produces a wide diversity of products some of which do not contain solvents but many of which require the use of process solvents. Solvents are contained in adhesives used in finishing operations. Large quantities of solvents are used for surface cleaning and cleaning of equipment.

Tables 13.24.1 and 13.24.2 provide data on the reported releases and transfers of solvents by the US rubber and plastics industry. These industries contribute small amounts of VOC which are in the range of 0.00001-0.00005 kg VOC/kg of processed rubber. It was the ninth largest contributor to releases and transfers of all US industries. Dichloromethane, toluene, carbon disulfide, methyl ethyl ketone, methanol, 1,1,1-trichloroethane, hexane, methyl isobutyl ketone, and xylene were emitted in very large quantities.

Table 13.24.1. Reported solvent releases from the rubber and plastics industry in 1995
[Data from Ref. 2].

Solvent	Amount, kg/year	Solvent	Amount, kg/year
benzene	5,800	ethylene glycol	120,000
n-butyl alcohol	380,000	hexane	1,700,000
sec-butyl alcohol	17,000	isopropyl alcohol	28,000
tert-butyl alcohol	240	methanol	4,000,000
carbon disulfide	5,500,000	methyl ethyl ketone	5,500,000
chlorobenzene	5,000	methyl isobutyl ketone	1,100,000
chloroform	46,000	N-methyl-2-pyrrolidone	32,000
chloromethane	47,000	tetrachloroethylene	160,000
cresol	9,000	1,1,1-trichloroethane	3,000,000
cyclohexane	480,000	trichloroethylene	660,000
dichloromethane	11,700,000	1,2,4-trimethylbenzene	260,000
N,N-dimethylformamide	350,000	toluene	7,600,000
1,4-dioxane	2,600	xylene	2,200,000
ethylbenzene	210,000	m-xylene	6,000

Table 13.24.2. Reported solvent transfers from the rubber and plastics industry in 1995 [Data from Ref. 2].

Solvent	Amount, kg/year	Solvent	Amount, kg/year
benzene	15,000	hexane	50,000
n-butyl alcohol	370,000	isopropyl alcohol	14,000
sec-butyl alcohol	1,100	methanol	1,400,000
tert-butyl alcohol	85,000	methyl ethyl ketone	3,500,000
carbon disulfide	150,000	methyl isobutyl ketone	450,000
chloroform	1,200	N-methyl-2-pyrrolidone	120,000
chloromethane	330	tetrachloroethylene	47,000
cresol	3,000	1,1,1-trichloroethane	160,000
cyclohexane	350,000	trichloroethylene	170,000
dichloromethane	900,000	1,2,4-trimethylbenzene	14,000
N,N-dimethylformamide	570,000	toluene	2,200,000
1,4-dioxane	49,000	xylene	940,000
ethylbenzene	350,000	m-xylene	5,700
ethylene glycol	15,300,000		

The common solvent is used for polymerization and bromination in the production of bromobutyl rubber.[3] The solvent is an aliphatic hydrocarbon.[3] The bromination process of butyl was accelerated by the dosage and polarity of the assistant solvent.[6] Hexane with 30 vol% dichloromethane was found as the most suitable solvent.[6]

Liquid, solventless ethylene propylene diene rubber can be produced according to the invention.[4] It is possible to produce water and solvent-free synthetic rubber products such as non-halogenated and halogenated butyl rubber products.[5]

A method of purifying a reclaimed polymer, such as a polymer reclaimed from post-consumer use or the post-industrial use, is disclosed.[7] The reclaimed polymer (e.g., polypropylene or polyethylene) is dissolved in a solvent (n-butane) at an elevated temperature (110-170°C) and pressure (7.6-38 MPa) to produce a polymer solution. A polymer is then separated from the polymer solution.[7]

REFERENCES

1 **EPA Office of Compliance Sector Notebook Project. Profile of the Rubber and Plastics Industry**. *US Environmental Protection Agency*, 1995.
2 **EPA Office of Compliance Sector Notebook Project. Sector Notebook Data Refresh - 1997**. *US Environmental Protection Agency*, 1998.
3 A Gronowski, **EP2526123**, *Lanxess International*, 28 Nov. 2012.
4 A J Fontenot, W Khan, W Summer, **US20120319331**, *Lion Copolymer, Llc*, 20 Dec. 2012.
5 J Kirchhoff, **CA2791615**, *Lanxess International*, 29 Sep. 2011.
6 W Wang, H Zou, G Chu, Y Xiang, H Peng, J Chen, *Chinese J. Chem. Eng*., **22**, 4, 398-404, 2014.
7 J M Layman, M Gunnerson, H Schonemann, K Williams, **US9695259B2**, *Phasex Procter and Gamble Co.,* Jul. 4, 2017.

13.25 USE OF SOLVENTS IN THE SHIPBUILDING AND SHIP REPAIR INDUSTRY

Mohamed Serageldin* and Dave Reeves**
***U.S. Environmental Protection Agency, Research Triangle Park, NC, USA**
****Midwest Research Institute, Cary, NC, USA**

13.25.1 INTRODUCTION

The focus of this chapter will be on the use of solvents in the shipbuilding and ship repair industry. This industrial sector is involved in building, repairing, repainting, converting, or alteration of marine and fresh water vessels. These vessels include self-propelled vessels, those propelled by other vessels (barges), military and Coast Guard vessels, commercial cargo and passenger vessels, patrol and pilot boats, and dredges. The industry sector is also involved in repairing and coating navigational aids such as buoys. This chapter begins with an overview of operations in a typical shipbuilding and/or ship repair facility (shipyard), to identify those operations that generate significant volatile organic compound (VOC) emissions and/or hazardous air pollutant (HAP) emissions from the use of organic solvents. Organic solvents that are VOCs contribute to the formation of ozone in the troposphere. Other organic solvents such as chlorinated fluorocarbons (CFCs) cause depletion of the ozone layer in the stratosphere. Therefore, VOCs and other air toxins, such as those compounds listed as HAPs, are both indirectly and directly detrimental to the general public's health. Because many solvents are VOCs and often contain large amounts of HAPs, many state agencies[1,2] and the United States Environmental Protection Agency (U.S. EPA) have issued regulations to limit their content in materials used for surface coating and cleaning operations at shipyards.[3-7]

13.25.2 SHIPBUILDING AND SHIP REPAIR OPERATIONS

Most facilities engaged in shipbuilding or ship repair activities (shipyards) have several manufacturing areas in common, each including one or more “unit operations”. These areas include: (a) surface preparation of primarily steel surfaces, which may include cleaning with multiple organic solvents; (b) assembly operations, which involve assembly of blocks that were constructed from sub-assembled parts (this step involves steel cutting and material movement using heavy equipment such as cranes); (c) cleaning operations (other than surface preparation) such as equipment and parts cleaning; and (d) coating operations.[8,9] There are secondary operations such as chrome plating, asbestos removal, fuel combustion, carpentry, and, to various degrees, polyester lay-up operations (composite materials construction activities). We will next discuss those operations that involve the use of organic cleaning solvents.

13.25.3 COATING OPERATIONS

Marine coatings can be applied by the use of spraying equipment, brushes, or rollers. Coating operations at shipyards are typically conducted at two primary locations: (1) outdoor work areas or (2) indoor spray booths. The outdoor work areas can include ship exte-

riors and interiors. Most shipyards report that typically only a small percentage (10%) of the coating operations are done indoors. However, in large construction yards, a larger proportion (up to 30%) of the coatings are applied indoors.[10] Coating and cleaning operations constitute the major source of VOC and HAP emissions from shipyards. If the metal surface is not well prepared before a coating is applied or if the coating is applied at the wrong ambient conditions, the coating system may fail and the work may have to be redone. The amount of cleaning necessary will depend on the type and extent of the problem and the coating system that is being used.

13.25.4 CLEANING OPERATIONS USING ORGANIC SOLVENTS

In most industrial applications involving metal substrates, organic cleaning solvents are used to remove contaminants or undesirable materials from surfaces, before a coating is applied, to clean equipment and parts, utilized to apply the coating, or soiled during that operation. Solvents are used for general maintenance of equipment parts. These surfaces are typically made of steel. However, vessels may also be made from natural materials such as wood and synthetic materials such as fiberglass. Therefore, a solvent must be selected that will not attack the substrate being cleaned.

For material accounting purposes, we can classify cleaning (unit) operations as follows:[11,12]

1. Surface preparation of large manufactured components (stage before a coating is applied).
2. Surface preparation of small manufactured components (stage before a coating is applied).
3. Line cleaning (includes piping network and any associated tanks).
4. Gun cleaning (manually or in a machine).
5. Spray booth cleaning (walls and floor).
6. Tank cleaning (mostly inner tank surfaces and any associated pipes).
7. Parts (machine) cleaning (simple dip tanks and large machines).
8. Cleaning of equipment and other items (e.g., bearings, buckets, brushes, contact switches).
9. Floor cleaning (organic solvents are no longer used).

These categories are similar to those found in other industries involved in the application of the surface coating. However, the number of cleaning categories varies from one industry to another. For example, the automotive manufacturing industry (SIC code 3711) and the furniture industry are involved to various degrees in all nine types of cleaning operations. On the other hand, the photographic supplies (chemicals) industry will not include the first three listed cleaning operations.[11]

13.25.4.1 Surface preparation and initial corrosion protection

Large manufactured ship components are often cleaned with an organic solvent as the first of a number of cleaning steps that are required before a coating is applied. The method of surface preparation is selected to work with a chosen coating system. Surface preparation may include the application of chemicals such as etching agents, organic solvents cleaners, and alkaline cleaners. Organic solvents such as mineral spirits, chlorinated solvents, and coal tar solvents are used to remove unwanted materials such as oil and grease.[13] If a ship is being repaired, existing coatings usually need to be removed. Solvents such as dichloromethane are commonly used for removing (stripping off) old or damaged coat-

ings. However, aqueous systems involving caustic compounds are now being used more frequently for such purposes.[14] Pressure washing and hydro-blasting are other cleaning techniques used. But, the predominant method is still particulate blasting (using abrasive media), which is used to remove mil scale, extra weld material, rust, and old coatings.

The angle at which the surface is blasted is chosen to generate the desired peaks and valleys on the substrate, that will accommodate the viscosity, chemistry (polar groups) of the primer coating. The surface profiling will also help the primer coating adhere mechanically to the substrate, contributing to the longevity of the coating system.[15] Pre-construction primers are sometimes used immediately following surface preparation (blasting) to prevent steel from oxidizing (rusting). This primer is removed by particulate blasting before the protective coating system (one or more coatings) is applied to the assembled parts or blocks. Removal of such primers (when they cannot be welded-through) can result in emissions of VOCs and HAPs.

13.25.4.2 Cleaning operations after coatings are applied

Surface coating operations at shipyards use predominantly solvent-based coatings. Hence, relatively large amounts of organic solvents are used for cleaning and thinning activities. Table 13.25.1 shows the most common organic solvents used for thinning and cleaning, based on 1992 data.[16] Table 13.25.2 gives examples of solvent products that can be used for both thinning coatings and for cleaning surfaces after coatings are applied and for maintenance cleaning. The solvent products are listed in decreasing order of evaporative rate. Acetone, a ketone solvent is commonly used for cleaning and thinning polyester resins and gel coats. However, it is also used in formulating low-VOC and low-HAP products. Methyl ethyl ketone (MEK) and methyl isobutyl ketone (MIBK) are fast evaporative solvents that are used for thinning and cleaning vinyl coatings, epoxy coatings, and many other high-performance coatings. Fast evaporative coatings that can improve application properties for a good finish may also be formulated by blending different solvents. Examples are shown in Table 13.25.2. The fast evaporative mix includes solvents varying in polarity and solubility parameters. They include an oxygenated solvent (MIBK), aromatic hydrocarbon solvents that contain less than 10 percent (by mass) HAPs, and aromatic hydrocarbons like xylene that are 100 percent HAPs as will be shown later. Together they produce the correct solvency for the polymer (resin).

Table 13.25.1. Predominant solvents used in marine coatings [from ref. 16] and EPA regulatory classifications.

Organic solvent	VOC	HAP, Sec. 112 (d)	Toxic chemicals, Sec. 313
ALCOHOLS			
Butyl alcohol	Y	Y	Y
Ethyl alcohol	Y	N	
Isopropyl alcohol	Y	N	Y[a]
AROMATICS			
Xylene	Y	Y	Y

Table 13.25.1. Predominant solvents used in marine coatings [from ref. 16] and EPA regulatory classifications.

Organic solvent	VOC	HAP, Sec. 112 (d)	Toxic chemicals, Sec. 313
Toluene	Y	Y	Y
Ethyl benzene	Y	Y	Y
ETHERS			
Ethylene glycol ethers	Y	Y	Y
Propylene glycol ethers	Y	N	N
KETONES			
Acetone		N	Y
Methyl ethyl ketone	Y	Y	Y
Methyl isobutyl ketone	Y	Y	Y
Methyl amyl ketone		N	N
PARAFFINIC			
Mineral spirits	Y	Y[b]	N
High-flash naphtha	Y	Y[b]	Y
n-Hexane	Y	Y	N

VOC = volatile organic compound; HAP = Hazardous air pollutant; Sec 313 of the Emergency Right-to-know Act (EPCRA), also known as Title III of the Superfund Amendments and Reauthorization Act of 1986 (40 CFR Part 372). Use of strong acid process, no supplier notification. Ligroine (light naphtha), VM&P naphtha, Stoddard solvent, and certain paint thinners are also commonly referred to as mineral spirits. These distillation fractions contain less than 10% by mass HAPs (see Table 13.25.4).

Table 13.25.2. Selected products that are used as both solvent thinners and solvent cleaners

Tcs	Tc	Compound, wt%	S	R	V	BP	ST	ASG	V
Acetone	Polyester	Acetone, 100% (approx.)	9.8	6.1	186	56	27.1	0.787	0.31
MEK*	Vinyl	MEK, 100% (approx.)	9.3	4.0	70	80	24.2	0.806	0.43
Spraying thinner & solvent cleaner (fast)[b]	Epoxy	MIBK**, 24%	8.58	1.7	28	116	23.3	0.796	0.54
		N-butyl alc., 24%	11.6	0.44	5.5	118	23.4	0.806	2.62
		Toluene, 52%	8.93	2.0	22	111	28.2	0.863	0.57
Brushing thinner & solvent cleaner (medium)[b]	Epoxy	MIBK, 23%	8.58	1.7	28	116	23.3	0.796	0.54
		EGBE***, 26%	10.2	0.072	0.6	>169	26.9	0.899	3.0
		AHC****, 30%	7.7	0.16	2.0	>160	23.4	0.775	0.88
		1,2,4-Trimethylbenzene, 16%	8.9	19	2.1	168	30.2	0.871	0.94
		Xylene (mixed), 2%	9.9	0.77	6.0	>135	27.6	0.856	0.63
Lacquer retarder (thinner) & cleaner (slow)[b]	Lacquer	EGBE, 51%	10.2	0.072	0.6	>169	26.9	0.899	3.0
		AHC, 30%	7.7	0.16	2.0	>160	23.4	0.775	0.88
		1,2,4-Trimethylbenzene, 16%	8.9	19	2.1	168	30.2	0.871	0.94
		Xylene (mixed), 1%	9.9	0.77	6.0	>135	27.6	0.856	0.63

Tcs – Thinner & cleaning solvents; Tc – Typical coating; S – Solubility parameter, $(cal/cm^3)^{1/2}$; R – Relative rate, nBUOAc =1.0; V – Vapor press., mmHg @20°C; BP – boiling point, °C @ 760 mmHg; ST – Surface tension, dynes/cm 20°C; ASG – Average specific gravity, @ 25°C; V – Viscosity, cP@25°C
*MEK=methyl ethyl ketone, **MIBK=methyl isobutyl ketone, ***EGBE=ethylene glycol monobutyl ether, ****AHC=aromatic hydrocarbon solvent; [a]Physical properties mainly from Industrial Solvents Handbook, 110 -114. [b]Material Safety Data Sheet (Mobile Paint Co. Alabama)

The lower specific gravity of ketones (see Table 13.25.2) than other materials such as glycol ethers helps reduce the total mass of VOCs (or HAPs) per volume of nonvolatiles (solids) in a container of the coating. Glycol ethers are good solvents for epoxies and acrylics. They also have good coupling abilities in blends of poorly miscible solvents[17] and have low evaporative rates. The properties of a solvent product are dependent on the chemical structure and distillation range of the solvent mix in the product. The latter will affect the evaporative rate from a coating or cleaner, affecting the solubility of the resin in the coating and viscosity of the coating and solvent cleaner. Therefore, the viscosity of the solvent product must be close to that of the resin in a coating.[18] The surface tension of a solvent provides a measure of the penetrability of a cleaning solvent. A low surface tension also means the solvent spreads more readily, which is an important property for a cleaning product. However, several properties in Table 13.25.2 come into play in determining the effectiveness of a cleaning solvent.

Most coating operations, due to the size and accessibility of ships, occur in open air in drydocks, graving docks, railway, or other locations throughout a facility. Because of the size of ships, the predominant application method is airless spray gun. The thickness of the coating will determine if the application equipment needs to be cleaned during application of the coating or after the job is completed. The lines from the supply tanks to the spray gun may in some instances exceed 46 m (150 ft) in length. The ensemble of equipment and items that have to do with the application of the coating or "unit operation system (UOS)" is shown schematically in Figure 13.25.1. The representation depicts a layout for outdoor application of coatings. It includes the container used to hold the coating, attached feed pump, line transferring the coating to the spray gun, the spray gun itself, and any other item soiled with a coating that will need to be cleaned with an organic solvent before it can be reused.

The need and frequency for cleaning will depend on the individual facility or company cleanliness standard (i.e., requirements) and the number of coating formulation or color changes. Cleaning of spray guns, internal transfer lines, and associated tanks account for a large part of organic solvent usage. At most shipyards, a small percentage of the coatings are applied indoors, in spray-booths. The walls and floors of these booths are cleaned by wiping with a solvent-laden cloth. The coating application equipment UOS for most facilities will look very similar to that shown in Figure 13.25.1, except that the coating transfer lines will be shorter if the coating storage tanks are positioned close to the spray booths. The transfer lines, that will need to be cleaned with solvent, will be longer if the coating tanks are located away from the application area. When this is the case, the transfer lines typically run underground at the facility and another representation than the one shown in Figure 13.25.1 will need to be used, to clearly identify the emission points and

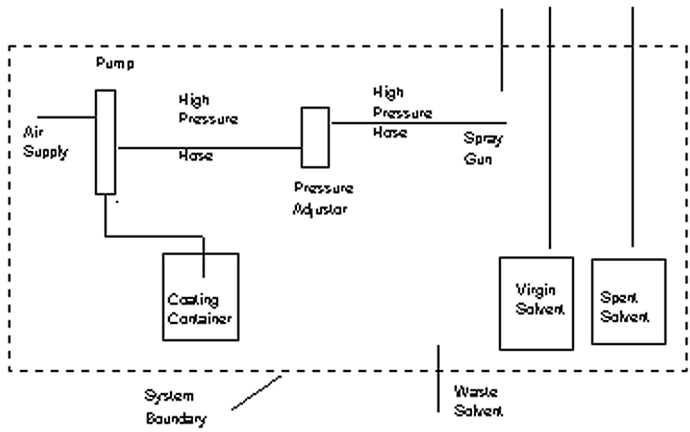


Figure 13.25.1 Schematic diagram of marine coating application equipment.

waste streams for properly quantifying solvent losses. The latter may include a unit for recycling or reclaiming solvents.

Spray gun cleaning procedures may be a once-through type with a collection of spent solvent in a container for disposal or reuse. Some facilities use commercial gun washers. Because gun washers are enclosed and recirculate solvent, they can reduce the amount of solvent lost by evaporation. In either case, the emissions are calculated as the difference between the amount used and the amount recovered.

To calculate the emissions associated with cleaning a spray gun it is recommended that a material balance around a "unit operation system" be considered. Several examples are provided in the Alternative Control Techniques (ACT) document on industrial cleaning solvents.[19]

Several types of part cleaners are used at shipbuilding and ship repair facilities. The types used in such facilities vary from the more simple sink and spray systems[20] to more elaborate parts (machine) cleaners of the cold or vapor types.[4] Most of the parts cleaners in shipyards are small – around 1.5 m x 1 m and 1 m deep – usually located in the machine shops, not the paint rooms. Most of the parts are small components being cleaned prior to being joined to other small parts into assemblies and sub-assemblies or being cleaned as part of some type of repair operation. Most of parts cleaners used were basket-type design with the parts loaded into a basket and dropped through the vapor zone several times to clean off the oils and dirt. Some shipyards use contractors to come in and change out the solvent on a routine schedule.

13.25.4.3 Maintenance cleaning of equipment items and components

Shipyards also undertake scheduled maintenance cleaning of many ship components such as contacts and switches and equipment items such as bearings and packaging machines. This is mostly done by hand-wiping the parts with organic solvents. These operations will generally consume a relatively small amount of the overall volume of organic solvents used for cleaning in shipyards. Solvents are also used in machine shop areas and thus contribute to the waste stream.

13.25.5 MARINE COATINGS

There are several categories of marine coatings that are used to protect the surface of a ship from the aggressive marine environment and for other performance requirements such as preventing corrosion and fouling; protecting cargoes from contamination; providing safety warnings and informational markings; providing cosmetic and camouflage colors; preventing slipping and sliding on walking surfaces; reducing fire hazards; and providing cathodic protection.[21] The coating systems of marine coatings are selected to meet:

- the type of marine environment to which a vessel will be exposed
- the time a vessel is to remain operational before it needs to be reworked.

General areas of a ship include (1) underwater hull, (2) superstructures and freeboard, (3) interior habitability areas, (4) exterior deck areas, and (5) fuel, water ballast and cargo tank.[22] The freeboard is the area above water hull. These areas have different characteristics and operational requirements. Table 13.25.3[23] shows the predominant resin and solvent types used on ships based on a 1991/1992 survey of the industry obtained as part of the shipbuilding and ship repair regulation was being developed. The summary table also gives average VOC and HAP content for the various coating category types. Epoxy coatings constitute a large percentage of the coatings used. The epoxy films are strongly resistant to most chemicals and are very good anti-corrosion coatings, and require little surface preparation.

Table 13.25.3. Summary of marine coating usage (by coating type)[23]

Coating type	Average usage in U.S. shipyards, %	Average VOC content, g/L (lb/gal)	Average HAP content, g/L (lb/gal)
General use types			
alkyd based	10	474 (3.95)	355 (2.98)
epoxy based	59	350 (2.92)	56 (0.47)
Speciality types			
antifouling (multiple resins)[1]	11	388 (3.23)	268 (2.25)
inorganic zinc based	10	545 (4.54)	274 (2.30)
other speciality categories	10	400 (3.33)	144 (1.20)
TOTAL	100		

resins: epoxy, polyurethane, vinyl, and chlorinated rubber

The coating system used will depend on service requirements. Maximum protection at an economical price can be achieved when the user understands the protection needed and the functions performed by the coatings. Coatings are designed for spray viscosity, drying time, potlife, and cure profile; all of these parameters affect shelf stability.[24] The physical parameters and properties of a coating are affected by the volatile constituents (mainly organic solvents) in a coating, some of which are VOCs, HAPs, ozone depleters, and SARA 313 toxic chemicals that need to be reported.[25]

13.25.6 THINNING OF MARINE COATINGS

The sprayability of a coating is determined by its viscosity at application. The viscosity is a measure of the ability of a material to resist flow and is an important formulation design parameter. Application viscosity is affected by the ambient conditions and by the degree of mixing that occurs within the applicator. The thinner is often the same material as the cleaner (as indicated in Table 13.25.2). The solvent material is often a blend of miscible materials. Together they will dissolve a dry resin that needs to be removed or give the coating certain needed properties such as reduced/increased viscosity or shorter drying times.

Standard spraying equipment will apply coatings up to some maximum viscosity. Above that maximum value, thinning solvents are required. Thinning solvent is sometimes added to enhance brushability or sprayability of a coating. The appropriate viscosity is provided by the coating manufacturer or supplier; it will depend on the solvent content of the coating and temperature at the point of application.[26] Since most coatings are applied outdoors, extreme weather conditions may require adding thinning solvents to the coating. Organic thinning solvents are added to coatings to alter their flowing properties. However, the flow properties of a coating may be altered by using special heaters or a combination of solvent and heat. The effect of a heater on the viscosity of a coating depends on the physical properties of the coating and on the flow rate in the inline heater. Under cold weather conditions, in-line heaters may provide good viscosity control, but may not be able to solve all application problems that are encountered in the field. Under extremely low temperatures, the substrate surface can act as a heat sink, which may inhibit the setting or curing of the coating. In-line heaters which are used for low volume coatings are not suitable for large volume coatings. As a result, thinning solvents are still needed to transfer the fluid from storage to pumps and hoses.

Under hot and humid weather conditions, certain coatings (e.g., lacquers) can rapidly lose organic solvent prior to and during application. Often under these situations, a facility will add solvent blends to make up for the reduction in viscosity and to overcome condensation on the surface (blushing).[27] Evaporative losses can be minimized by adopting good work practices and by using formulations that contain organic solvents with low vapor pressures.

13.25.7 SOLVENT EMISSIONS

Several states with their own rules regulating marine coatings have separate rules addressing solvent cleaning operations. While marine coating rules typically address VOC contents and types of application equipment, the cleaning solvent rules are more generic and address cleaning solvents used at any and all metal-related manufacturing operations.

Many types of solvents are used in marine coatings and in their associated cleaning materials as shown in Table 13.25.1. Almost all solvents used at shipyards are VOC and approximately one in three solvents are HAPs. Of the HAPs reported, several are included on the list of 17 high priority chemicals targeted by U.S. EPA for the 33/50 program.[28] These included xylene (commercial), toluene, and the ketones. Commercial grade xylene represents the major portion of the volatile HAPs reported.

Many of the commonly known solvents are actually petroleum distillation fractions and are composed of a number of compounds (e.g., mineral spirits and naphthas). There are two general types of solvents derived from petroleum, aliphatics or aromatics. Aromatics are stronger solvents than aliphatics since they dissolve a wider variety of resins. Most major solvent suppliers (chemical manufacturers) produce several types and variations of these solvents and the associated HAP contents can vary significantly from manufacturer to manufacturer and from batch to batch. These types of solvents are used extensively and are present in the majority of marine coatings. Table 13.25.4 provides a summary of common petroleum distillate solvents and solvent blends and their associated HAP content. For any solvent or solvent blend that is not listed as specified in Table 13.25.4, another table (Table 13.25.5) was developed to provide solvent groupings and associated HAP component/content values. The HAP values for Tables 13.25.4 and 13.25.5 were adapted from estimates provided in 1998 by the Chemical Manufacturer Association's Solvent's Council.

Table 13.25.4. HAP content of single solvents and solvent blends. [Adapted, by permission from Chemical Manufacturer Association's Solvent's Council].

Solvent/solvent blend	CAS #	HAP content range, wt%	Average HAP content, wt%	Typical HAP, wt%
Toluene	108-88-3	100	100	toluene
Xylene(s)	1330-20-7	100	100	xylenes, ethylbenzene
Hexane	110-54-3	49-55	50	n-hexane
Ethylbenzene	100-41-4	100	100	ethylbenzene
Aliphatic 140		0	0	none
Aromatic 100		<5	2	1% xylene, 1% cumene
Aromatic 150		<10	9	naphthalene
Aromatic naphtha	64742-95-6	<5	9	1% xylene, 1% cumene
Aromatic solvent	64742-94-5	<10	10	naphthalene
Exempt mineral spirits	8032-32-4	0	0	none
Ligroines (VM & P)	8032-32-4	0	0	none
VM&P	8032-32-4	0	0	none
Lactol spirits	64742-89-6	12-20	15	toluene
Low aromatic white spirit	64742-82-1	0	0	none
Mineral spirits	64742-88-7	<2	1	xylenes
Hydrotreated naphtha	64742-48-9	<0.01	0	none
Hydrotreated light distillate	64742-47-8	<0.1	0.1	toluene
Stoddard solvent	8052-41-3	1-2	1	xylenes
Super high-flash naphtha	64742-95-6	0-6	5	xylenes
Varsol® solvent 8052-49-3	8052-49-3	<1.1	1	0.5% xylenes, 0.5% ethylbenzene

Table 13.25.4. HAP content of single solvents and solvent blends. [Adapted, by permission from Chemical Manufacturer Association's Solvent's Council].

Solvent/solvent blend	CAS #	HAP content range, wt%	Average HAP content, wt%	Typical HAP, wt%
VM & P naphtha	64742-89-8	5-10	6	3% toluene, 3% xylene
Petroleum distillate mixture	68477-31-6	4-9	8	4% naphthalene, 4% biphenyl

Table 13.25.5. Petroleum solvent groups and associated HAP contents. [Adapted, by permission from Chemical Manufacturer Association's Solvent's Council].

Solvent Type	Solvent Name	HAP Component	HAP Concentration, wt%
Aliphatic	Mineral spirits 135 Mineral spirits 150 EC Naphtha Mixed hydrocarbon Aliphatic hydrocarbon Naphthol spirits Petroleum spirits Petroleum oil Petroleum naphtha Solvent naphtha Solvent blend	Xylene Toluene Ethylbenzene	1 1 1
Estimated total HAP for each solvent type			3
Aromatic	Medium-flash naphtha High-flash naphtha Aromatic naphtha Light aromatic naphtha Light aromatic hydrocarbons Aromatic hydrocarbons Light aromatic solvent	Xylene Toluene Ethylbenzene	4 1 1
Estimated total HAP for each solvent type			6

The percentage of solvent used that evaporates during cleaning operations will depend on the volatility of the solvent and on the type of cleaning operation. Any materials such as rags or sponges that come into contact with the solvent must also be considered part of the solvent cleaning system and disposed of properly.

Since marine coatings are mostly air dried, it is generally impractical to capture air emissions from coating operations and until recently, to duct air emissions into abatement devices such as incinerators or adsorbers. The use of a low solvent (VOC or HAP) containing coatings and high-performance coatings provide a suitable means of achieving lower volatile emissions from the coating of ships. Such coatings will lead to lower life-cycle costs and emissions since the ship will require less rework. EPA has recently

approved the use of technology for capturing and destroying air pollutant emissions from the application of coatings to the hull of a ship.[29]

13.25.8 SOLVENT WASTE

The waste cleaning solvent is handled differently by different shipyards. Facilities that use different type solvents for cleaning and thinning, or utilize multiple cleaners may select disposal rather than recycling for reuse. This decision is typically based on cost. Other facilities will first mix their waste solvents with the unused coating. Incineration is generally selected as the disposal method when it is determined to be less expensive than recycling.

The type of solvent waste generated from shipbuilding and ship repair facilities does not vary much. Surface preparation and cleaning operations following application of coatings do not represent the most significant part of the organic solvent waste. Certain coatings, such as antifouling coatings, contain toxic pigments (metals) such as chromium, lead, and tributyltin. The waste will likely be hazardous waste if the waste material contained coating residues or other materials that are toxic. Solvents used in cleaning are often mixed with other waste fuels such as hydraulic fluids, waste fuels, and other maintenance by-products. Some of the larger shipyards segregate the solvent waste or recycle it for reuse.

13.25.9 REDUCING SOLVENT USAGE, EMISSIONS, AND WASTE

The amount of organic solvent usage for cleaning operations makes up about 20 percent of the total solvent usage in cleaning operations and coating operations at shipyards. The waste from solvent cleaning represents a major portion of the waste in a plant that has surface coating operations. Line cleaning, gun cleaning, and tank cleaning are three operations that utilize most of the cleaning solvents. There are many steps that a facility can undertake to reduce the use of a solvent for cleaning. It can reuse some of the solvents, scrape off the paint left on the inside of a mix tank, or modify existing cleaning practices and procedures.[5,30] Some shipyards have modified their coating operations to use less solvent. For planning purposes, a facility needs to know where the major solvent usage, emissions, and waste occur in the facility. This may be achieved by:

- Developing a solvent accounting system for tracking the usage, fate, and costs of organic solvents in coating operations and cleaning operations;
- Identifying actions management will take to reduce solvent content in coatings and reduce usage of cleaning materials containing organic solvents.[5,31]

The steps are not mutually independent and require full management support and financial backing. Obtaining reliable data is one of the major problems that a manager or supervisor involved in pollution reduction faces. Any program adopted should be one that can identify accurate and specific material usage, emission data, and waste data that will be useful for evaluating pollution cost and risk.[32] The “unit operation system” (UOS) approach was used to categorize the universe of cleaning into nine main categories equivalent to those identified here in the section discussing cleaning operations. The concept of a UOS provides the foundation for a standardized material accounting method that provides transportable data, that a secondary user can understand, for setting up a material

balance, for comparing alternatives, or evaluating risk. The visual representation of a setup, as was done in Figure 13.25.1, is an essential component of this approach.

When facility managers and operators are able to identify with some confidence, at the source, final solvent disposition and cost of cleaning, they are in a better position to make informed decisions and take the necessary actions for reducing solvent usage. Facilities have the added incentive to reduce worker exposure to toxics contained in solvents because of OSHA requirements.[33] The facility owners and operators also have to abide by state, local, and federal regulations that limit the amount of VOCs and HAPs emitted to the air and water streams. Facilities that generate large amounts of solvent waste streams will have to deal with RCRA hazardous waste regulations.[34]

13.25.10 REGULATIONS AND GUIDELINES FOR CLEANING SOLVENTS

The U.S. EPA developed a guideline document to help state and local agencies reduce VOC emissions for the use of cleaning solvents. The document does not provide emission limits but instead recommends the use of a management system for tracking usage, emissions, and waste from the use of organic solvents and provides a list of definitions that should be used for that purpose.[35] Less than 20 states had regulated VOC emissions from the use of organic cleaning solvents by 1997.[36] Many states only had minimal record-keeping requirements. Some regulations are driving facilities to use solvents with lower vapor pressures. These low vapor pressure solvents evaporate more slowly at ambient temperatures. However, the emission benefits cannot be guaranteed to last forever. An organic solvent should eventually all evaporate unless it is reused, recycled, or sealed in a container.

Many of the cleaning solvents used, such as 1,1,1-trichloroethane, are not considered VOC in the United States. Those solvents are regulated as HAPs and are being phased out because of the Montreal Protocol which aims to reduce ozone depleters. Alternative cleaners are now being used and further developed. To meet regulatory requirements, a facility will often replace or substitute a cleaning product containing HAP material(s) with one or more products containing no HAP solvents (but may contain VOC solvents or *vice versa*). Acetone, once the preferred solvent for fiberglass boat manufacturers, was replaced starting in 1992 with other solvents such as diacetone alcohol.[37] The latter solvent is as effective as acetone, but has a much lower vapor pressure (0.80 mm Hg at 20°C) and flash point (52°C) to reduce the amount of VOC emitted and hazardous reportable releases. Acetone was recently determined not to have significant photochemical reactivity and is no longer considered a VOC in the United States. As a result, acetone is now making a comeback in cleaners and in some coatings. HCFCs are now being used instead of CFCs, but will soon need to be replaced because of the Montreal Protocol. There are many articles in the literature that discuss alternatives that will reduce VOC and HAP emissions.[38-42] The use of waterborne materials or other material(s) containing no HAPs or VOCs is the ideal solution when such coatings or cleaners will do the job. Software and internet sites also exist to help in the selection of the appropriate solvent cleaner or method of cleaning.

Different methods can be used to remove the primer before the welding: brushing, sand or ice blasting, waterjet, chemical solvent and laser cleaning.[43] Laser cleaning was

found a viable alternative which provided with a rapid process and helped to eliminate solvent pollution.[43]

Disclaimer

The views expressed in this chapter are those of the authors and do not necessarily reflect those of their affiliation. Mentioning the names of organizations does not constitute an endorsement.

REFERENCES

1 South Coast Air Quality Management District (SCAQMD), Rule 1106: Marine Coating Operations, 1995.
2 SCAQMD, Rule 1171: Solvent Cleaning Operations, (1996) and Rule 1122: Solvent Degreasers, (1996).
3 40 CFR Part 63, Subpart II, (1995), U.S. Government Printing Office, Washington, DC.
4 40 CFR, Part 63, Subpart T, (1996), U.S. Government Printing Office, Washington, DC.
5 U.S. Environmental Protection Agency (EPA), Control Techniques Guideline Shipbuilding and Ship Repair Operations (Surface Coating), Office of Air Quality Planning and Standards, North Carolina, EPA-453/R-94-015, (NTIS no. PB94-156791).
6 U.S. EPA, Federal Register, August 27, 1996 (vol. 61, no. 167), pp. 44050-44057.
7 M. A. Serageldin in Electrochemical Society Proceedings, Volume 95-16, *Electrochemical Society Inc.*, Chicago, Illinois 1997, pp. 1-16.
8 T. J. Snider, An Analysis of Air Pollution Control Technologies for Shipyard Emitted Volatile Organic Compounds (VOCs), National Shipbuilding Research Program, Report No. 0376. March 1993, pp. 3-5.
9 U.S. EPA, EPA Office of Compliance Sector Notebook: Profile of The Shipbuilding and Repairing Industry, EPA Office of Compliance, Washington, D.C, EPA/310-R-97-008, 1997, pp. 75-78.
10 U.S. EPA, Surface Coating Operations at Shipbuilding and Ship Repair Facilities-Background Information for Proposed Standards, OAQPS, North Carolina, EPA-453/D-94-011a, (NTIS no. PB95-197471), 1994, pp. 6-7 to 6-9.
11 U.S. EPA, Alternative Control Techniques Document-Industrial Cleaning Solvents, Office of Air Quality Planning and Standards, North Carolina, EPA-453/R-94-015, 1994, pp. 3-17 to 3-28.
12 M. A. Serageldin in Emission.Inventory Living in a Global Environment, Proc.Special. Conf., December 8-10, 1998, New Orleans, LA, Air and Waste Management Association, Pittsburgh, PA, VIP-88, vol.1, 1999, pp. 341-48.
13 **Metals Handbook**, 9th edition, v.5 Surface Cleaning, Finishing, and Coating, Table 21, *American Society for Metals*, Metal Park, Ohio, W.G. Wood, Ed., 1990, p. 506.
14 U.S. EPA, Guide to Pollution Prevention: The Marine Maintenance and Repair Industry, Office of Research and Development, Washington D.C., EPA/625/7-91/015, 1991, pp. 5-10.
15 **Metals Handbook**, 9th edition, v.5 Surface Cleaning, Finishing, and Coating, *American Society for Metals*, Metal Park, Ohio, W.G. Wood, Ed., 1990, pp. 504 - 505.
16 U.S. EPA, Surface Coating Operations at Shipbuilding and Ship Repair Facilities-Background Information for Proposed Standards, Office of Air Quality Planning and Standards, North Carolina, EPA-453/D-94-011a, (NTIS no. PB95-197471), 1994, p. 318.
17 C. H. Hare, **Protective Coatings Fundamentals of Chemistry and Composition**, 26. Solvent Families, *Technology Publishing Company*, Pittsburgh, PA, 1994, pp. 371-383.
18 H. Burrell, 1995 *Official Digest of the Federation of Society for Paint Technology*, vol. **27**, no. 369, 1955, p. 726.
19 U.S. EPA, Alternative Control Techniques Document-Industrial Cleaning Solvents, Office of Air Quality Planning and Standards, North Carolina, EPA-453/R-94-015, 1994, pp. H-1 to H-6.
20 U.S. EPA, Alternative Control Techniques Document-Industrial Cleaning Solvents, Office of Air Quality Planning and Standards, North Carolina, EPA-453/R-94-015, 1994, pp. C-1 to C-18.
21 H. Bleile and S. Rodgers, Marine Coatings. Federation Series on Coatings Technology. 1989. pp. 8.
22 U.S. EPA, Surface Coating Operations at Shipbuilding and Ship Repair Facilities-Background Information for Proposed Standards, OAQPS, North Carolina, EPA-453/D-94-011a, (NTIS no. PB95-197471), 1994, pp. 3-6 to 3-11.
23 U.S. EPA, Surface Coating Operations at Shipbuilding and Ship Repair Facilities-Background Information for Proposed Standards, Office of Air Quality Planning and Standards, North Carolina, EPA-453/D-94-011a, (NTIS no. PB95-197471), 1994, pp 3-18.
24 C. H. Hare in Protective Coatings Fundamentals of Chemistry and Composition, 1. The Basic Composition

of Paint, *Technology Publishing Company*, Pittsburgh, PA, 1994, pp.1-13.
25 40 CFR 372.65 (1986), U.S. Government Printing Office, Washington, D.C.
26 A. T. Chen and R. T. Wojcik in Metal Finishing, 97' Organic Finishing Guidebook and Directory Issue, Metal Finishing, Pittsfield, MA, 1997, pp. 167-179.
27 G. L. Muir in Metal Finishing, 97' Organic Finishing Guidebook and Directory Issue, Metal Finishing, Pittsfield, MA, 1997, pp.391-398.
28 U.S. EPA 33/50 Program: The Final Record, Office of Pollution Prevention and Toxics, EPA-745-R-99-004, Washington, D.C., March 1999.
29 U. S. EPA, Evaluation of Application for Approval of an Alternative Methodology for Compliance with the NESHAP for Shipbuilding and Recommended Requirements for Compliance, Research Triangle Park, N.C., EPA-453/R-99-005, 1999.
30 P.M. Randall in Proc: Poll. Prevent. Conf. Low- and No VOC Coating Technol., Air and Engineering Research Lab, RTP, NC, EPA-600/R-94-022, 1994, pp.489-499.
31 M. A. Serageldin, in Waste Minimization Through Process Design, A. P. Rossiter, Ed., *McGraw-Hill*, New York, April 1995, pp. 289-303.
32 M.A. Serageldin, The Unit Operation System for Measuring Plant Environmental Performance (with selected examples), NTIS PB98-124399INZ, November 1996.
33 Occupational Safety and Health Administration, Shipyard Industry, U.S. Department of labor. Document No. 2268, [Online]. URL: Available from http://www.osha-slc.gov/OshDoc/Additional.html#OSHG-HAZ, (revised 1998).
34 42 U.S.C. s/s 321 et seq. (1976)
35 U.S. EPA, Alternative Control Techniques Document-Industrial Cleaning Solvents, OAQPS, North Carolina, EPA-453/R-94-015, 1994, pp. A1- A7.
36 Emission Inventory Improvement Program: Volume III - Area Sources: Chapter 6- Solvent Cleaning, 1997 [Online]. Available from URL: http://www.epa.gov/ttn/chief/eiip/iii06fin.pdf.
37 M. Melody, **Boatmakers find solvent substitute cuts emission, costs**, *Hazmat World*, February 1992, pp36-39.
38 1991 UNEP Solvents, Coatings, and Adhesives Technical Options Report, *UNEP*, Paris, December 1991, pp.58-69 and pp. 153-178.
39 P. Milner in **The Coating Agenda America 1955/1996**, *Campden Publishing Limited* (in association with National Paint and Coating Association, U.S.A), London, U.K. pp. 125 and 127.
40 F. Hussey in Advanced Coating Technology, Proc. 3rd, Ann. ESD Adv. Coating. Conf., Dearborn, MI, 9-11 November 1993, ESD, The Engineering Society, Ann Arbor, Michigan, pp. 250 -261.
41 L. Clark, S. Kaldon, E. Reid, and D. Ellicks, **Putting Solvent Back in Paint Legally,** *Metal Finishing*, 1998, pp 24-28.
42 C. Mouche, **Army Tests Enviro-Friendly Solvents Alternative**, *Pollution Engineering*, September 1999, p. 35.
43 D.M. D'Addona, S. Genna, A. Giordano, C. Leone, D. Matarazzo, L. Nele, *Procedia CIRP*, **33**, 464-9, 2015.

13.26 STONE, CLAY, GLASS, AND CONCRETE

George Wypych
ChemTec Laboratories, Toronto, Canada

This is a very diverse industry segment which manufactures glass, glassware, cement, concrete, clay products, pottery, gypsum, and plaster products. In the USA, the industry operated over 31,000 facilities. There is a broad range of processes involved which use a wide variety of chemicals. Solvents are used for cleaning and are components of product decoration materials.

Tables 13.26.1 and 13.26.2 give data on the reported releases and transfers of solvents by the US stone, clay, glass, and concrete industry. Numerous solvents are used but most are used in small quantities the only high volume ones being toluene, xylene, methanol, 1,1,1-trichloroethane, and methyl ethyl ketone. Although the industry does not release large quantities of solvents, their total VOC contribution puts them second among the US industries. Total releases and transfers are one of the smallest of all industries.

Table 13.26.1. Reported solvent releases from the stone, clay, glass, and concrete industry in 1995 [Data from Ref. 2].

Solvent	Amount. kg/year	Solvent	Amount. kg/year
benzene	4,000	ethylene glycol	42,000
n-butyl alcohol	74,000	hexane	12,000
sec-butyl alcohol	1,700	isopropyl alcohol	300
tert-butyl alcohol	4,000	methanol	560,000
carbon disulfide	5	methyl ethyl ketone	700,000
carbon tetrachloride	14	methyl isobutyl ketone	25,000
chlorobenzene	14	tetrachloroethylene	44,000
chloroform	14,000	1,2,4-trichlorobenzene	46,000
cresol	610	1,1,1-trichloroethane	330,000
cyclohexane	77,000	trichloroethylene	110,000
1,4-dichlorobenzene	14,000	toluene	890,000
1,2-dichloroethane	17	xylene	500,000
dichloromethane	120,000	m-xylene	450
1,4-dioxane	230	o-xylene	540
ethylbenzene	60,000	p-xylene	110

Table 13.26.2. Reported solvent transfers from the stone, clay, glass, and concrete industry in 1995 [Data from Ref. 2]

Solvent	Amount. kg/year	Solvent	Amount. kg/year
benzene	6,000	ethylene glycol	29,000
n-butyl alcohol	44,000	hexane	15,000
sec-butyl alcohol	600	isopropyl alcohol	2,500
tert-butyl alcohol	2,000	methanol	300,000
carbon disulfide	5	methyl ethyl ketone	760,000
carbon tetrachloride	5,000	methyl isobutyl ketone	92,000
chlorobenzene	4,000	tetrachloroethylene	26,000
chloroform	20,000	1,2,4-trichlorobenzene	10,000
cresol	7,000	1,1,1-trichloroethane	60,000
cyclohexane	12,000	trichloroethylene	54,000
1,4-dichlorobenzene	3,000	toluene	800,000
1,2-dichloroethane	3,000	xylene	470,000
dichloromethane	20,000	m-xylene	600
N,N-dimethylformamide	5,000	o-xylene	1,200
ethylbenzene	67,000	p-xylene	340

Polar organic solvents, such as dimethylformamide, dimethyl acetamide, or 1-methyl-2-pyrrolidone are used in clay dispersion used in the manufacture of clay thin film usable for solar cells or display devices, due to the excellent gas barrier property and heat resistance.[3]

A method of making a glass article with an anti-smudge surface includes providing a coating solution consisting of a fluorosilane compound and a solvent that is miscible with the fluorosilane compound.[4] Solvent used in this process is composed of fluorocarbon, such as nonafluorobutylether.[4]

The solvent compositions of a degreaser and/or cleaner in both cold cleaning and hot rinsing systems for cleaning glass articles contains n-propyl bromide from 55 to 99% and a small amount of surfactant.[5]

A polar washing solvent is employed to effectively remove the sizing agent from a woven glass cloth while retaining its tensile strength.[6] Loss of tensile strength of the woven glass cloth due to the removal of a sizing agent from the woven glass cloth is compensated by simultaneous or subsequent deposition of a coupling agent on surfaces from which the sizing agent is removed.[6] The solvent is a polar solvent that includes at least one of the listed solvents, including acetone, tetrahydrofuran, ethyl acetate, ethanol, and methanol.[6]

Sunlight-polymerizable and solvent-free organically modified bohemite nanocomposite coatings were applied to the porous stone substrates.[7] Hydrophobicity and durabil-

ity characteristics were enhanced.[7] Trimethylolpropane trimethacrylate was selected as the main component for the coating.[7]

A solvent gel containing dimethyl sulfoxide (used to clean paintings) was applied on colonized marble artifacts at the monumental cemetery of Bonaria (Cagliari – Italy) to remove biological patinas.[8] The results demonstrate that DMSO gel is efficient at removing patinas on stone and has a low environmental impact.[8] It can be considered a more practical alternative to biocide treatments.[8]

Permeable epoxy-based coating with a reactive solvent for anticorrosion of concrete has good wettability and permeability, can permeate into the pores or defects and form composite with the concrete, improve mechanical properties of concrete, and resist the permeation of chloride ion.[9] The reactive solvent contained neopentyl glycol diglycidyl ether and MIK.[9]

The above few out of many available examples show that modern applications of glass, clay, stone and concrete products require the use of various solvents.

REFERENCES

1 **EPA Office of Compliance Sector Notebook Project. Profile of the Stone, Clay, Glass, and Concrete Products Industry**. *US Environmental Protection Agency*, 1995.
2 **EPA Office of Compliance Sector Notebook Project. Sector Notebook Data Refresh - 1997**. *US Environmental Protection Agency*, 1998.
3 T Inoue, K Motegi, H Tsuda, **US20130253214**, *Tomoegawa Co., Ltd*., 26 Sep. 2013.
4 J W Botelho, J J Domey, L F Reynolds-Heffer, L Zhang, **EP2507185**, *Corning Incorporated*, 10 Oct. 2012.
5 K Ando, H Miwa, **WO2012082591**, *Albemarle Corporation*, 21 Jun. 2012.
6 D J Boday, **US20130061401**, *Park Electrochemical Corp., IBM*, 14 Mar. 2013.
7 C. Esposito Corcione, R. Manno, M. Frigione, *Prog. Org. Coat*., **97**, 222-32, 2016.
8 G Toreno, D Isola, P Meloni, G Carcangiu, L Selbmann, S Onofri, G Caneva, L Zucconi, *J. Cultural Heritage*, in press, 2018.
9 G Zhang, Q Xie, C Ma, G Zhang, *Prog. Org. Coat*., **117**, 29-34, 2018.

13.27 TEXTILE INDUSTRY

George Wypych
ChemTec Laboratories, Toronto, Canada

The USA textile industry operated over 2,500 plants, employed over 565,000 people and had shipments exceeding $74.4 billion in 2016. In addition to conventional methods of processing and finishing, this industry also produces coated fabrics, tire cord and fabrics, and cordage and twine. Numerous operations are employed by the textile manufacturing and finishing but only a few of these operations involve the use of solvents. These include printing (volatile solvents and xylenes), finishing (e.g., methanol), scouring (glycol ethers and mineral spirits), cleaning knit goods, desizing (glycol ethers and methanol in PVA desizing), and coating (methyl ethyl ketone and toluene).

Tables 13.27.1 and 13.27.2 provide data on the reported releases and transfers of solvents by the US textile industry. Methyl ethyl ketone, toluene, and methanol are emitted in the greatest quantities. The total number of solvents used is low. The textile industry is among the lowest contributors to VOC and is the second smallest (after shipbuilding industry) in the amount of emitted and transferred solvents.

Table 13.27.1. Reported solvent releases from the textile industry in 1995 [Data from Ref. 1].

Solvent	Amount, kg/year	Solvent	Amount, kg/year
n-butyl alcohol	900	methyl isobutyl ketone	190,000
1,4-dichlorobenzene	700	N-methyl-2-pyrrolidone	180,000
1,2-dichloroethane	4,000	tetrachloroethylene	29,000
dichloromethane	230,000	1,2,4-trichlorobenzene	21,000
N,N-dimethylformamide	53,000	1,1,1-trichloroethane	150,000
ethylene glycol	66,000	trichloroethylene	130,000
hexane	59,000	1,2,4-trimethylbenzene	24,000
isopropyl alcohol	11,000	toluene	1,600,000
methanol	1,300,000	xylene	380,000
methyl ethyl ketone	2,200,000		

Table 13.27.2. Reported solvent transfers from the textile industry in 1995 [Data from Ref. 1]

Solvent	Amount, kg/year	Solvent	Amount, kg/year
1,2-dichloroethane	3,500	tetrachloroethylene	26,000
dichloromethane	9,000	1,2,4-trichlorobenzene	51,000
N,N-dimethylformamide	52,000	1,1,1-trichloroethane	2,000

Table 13.27.2. Reported solvent transfers from the textile industry in 1995 [Data from Ref. 1]

Solvent	Amount, kg/year	Solvent	Amount, kg/year
ethylene glycol	210,000	trichloroethylene	170,000
methanol	120,000	1,2,4-trimethylbenzene	20,000
methyl ethyl ketone	640,000	toluene	330,000
methyl isobutyl ketone	61,000	xylene	67,000
N-methyl-2-pyrrolidone	83,000		

Kreussler patented use of diether compounds, which are considered to have low toxicity, for drycleaning of textiles, leather, and furs.[3] Impregnation of textiles is used before printing to prevent bleeding of the inkjet ink. The solvent used for impregnating solution is water or alcohol capable to dissolve organic acid.[4]

Solvent-borne polyurethane is used for coating garment for production of textile glove liner. The solvent used is one of the following 2-methoxyethyl acetate, diethylene glycol monomethyl ether, butyrolactone, 2-methoxy-l,3-dioxolane, dipropylene glycol methyl ether, propylene glycol n-propyl ether, dipropylene glycol dimethyl ether, tripropylene glycol methyl ether, propyl cellosolve including ethylene glycol propyl ether, butyl triglycol including ethylene glycol n-butyl ether, or dimethylacetamide, unlike in other popular products were dimethylformamide is used.[5]

Adhesion of rubber to textile material is improved by impregnation with resorcinol compound dissolved in mineral spirit.[6] The textile sheet-like structure is impregnated with an antimicrobial active ingredient solution. The solvent is selected from aliphatic alcohols, aromatic alcohols, glycols, and water.[7]

An anti-mites and allergic asthma preventing textile is sprayed with an anti-mite solution and other required ingredients.[8] Textile fabric has stain and liquid resistance because it was coated with stain-resistant polyurethane coating, containing solvent such as methylethylketone, methylisobutylketone, acetone; an alcohol-based solvent such as isopropyl alcohol, n-hexanol; 1,2-dichlorobenzene, N-methylpyrrolidone, or N,N-dimethylformamide.[9]

In a process of dyeing textile fibers, a plurality of textile fibers are contacted with a polymer dispersed in a non-aqueous carrier liquid so as to deposit the polymer and the carrier on the fibers. Such polymer-treated fibers are then contacted with a disperse dye material under conditions effective to bond the disperse dye material to the polymer coating. The solvent used in the first stage is toluene/IPA.[10]

A tuneable green process of textile cleaning is achieved with supercritical carbon dioxide and an aqueous suspension as cosolvent.[11] The disinfection mechanism involves different stages, such as exposure to calcium hydroxide, exposure to $scCO_2$ and $CaCO_3$ that permits the simultaneous treatment of different microorganisms, and results in the disinfection of the textile.[11]

The above selection of papers shows that solvents are necessary for many processes involving textile materials, such as coating, impregnation to change their properties or increase adhesion, enhance dyeing, induce some new required properties which will not

be possible without application of such preparation, drycleaning of textile materials or removal of various preparations which prevent their proper processing.

REFERENCES

1 **EPA Office of Compliance Sector Notebook Project. Profile of the Textile Industry**. *US Environmental Protection Agency*, 1997.
2 **EPA Office of Compliance Sector Notebook Project. Sector Notebook Data Refresh - 1997**. *US Environmental Protection Agency*, 1998.
3 M Seiter, C Meyer, H Eigen, CA2763392, Chemische Fabric Kreussler & Co. GmbH, 29 Dec. 2010.
4 T Kobayashi, A Minemura, R Yamada, **EP2500463**, *Mimaki Eng. Co., Ltd.*, 19 Sep. 2012.
5 L Zhao, Y Abel, C Hansen, **WO2013107033**, *Honeywell International Inc.*, 25 Jul. 2013.
6 H M Brown, J H Creech, **EP2548902**, *Milliken & Company*, 23 Jan 2013.
7 A Dettmann, T Spuida, S Behrends, M Wolff, **EP2443924**, *L'Air Liquide Société Anonyme pour l'Etude et l'Exploitation des Procédés*, 25 Apr. 2012.
8 Y Jin, **WO2013097259**, *Jiangsu Tevel Co., Ltd.*, 4 Jul. 2013.
9 S K Jung, **WO2013018975**, 7 Feb. 2013.
10 D Lunsford, R Farwaha, H Schoots, **WO2013148295**, *Celanese International Corporation*, 3 Oct. 2013.
11 D Aslanidou, I Karapanagiotis, C Panayiotou, *J. Supercrit. Fluids*, **118**, 128-39, 2016.

13.28 TRANSPORTATION EQUIPMENT CLEANING

George Wypych
ChemTec Laboratories, Toronto, Canada

Transportation equipment cleaning includes cleaning of the interior of trucks, rail cars, barges, intermodal tank containers, intermediate tank containers, tank interiors, and the exterior of aircraft. These operations rarely involve solvents. Transportation equipment is also cleaned before refurbishing which includes old paint removal, surface cleaning, and painting. These processes usually do require solvents. Aircraft deicing is done using a mixture containing ethylene glycol (if the temperature is very low, a final spray of propylene glycol is applied, which lowers ice formation temperature to −58ºC). 2-Ethoxyethanol is a glycol alkyl ether used as a commercial deicing agent.[4] There is no data available on the amount of solvents used and emitted from these processes.

EPA issued effluent limitations guidelines and standards for the Transportation Equipment Cleaning.[2] This guidance includes information on trucks, containers, barges, and ocean/sea tankers. Code of Federal Regulation in Part 442 includes regulations specifically regarding transportation equipment cleaning.[3]

REFERENCES

1 **EPA Office of Compliance Sector Notebook Project. Profile of the Transportation Cleaning Industry.** *US Environmental Protection Agency*, 1995.
2 **EPA. Permit Guidance Document. Transportation Equipment Cleaning Point Source Category** (40 CFR § 442). March 2001.
3 **Code of Federal Regulations**. Part 442 - Transportation Equipment Cleaning Point Source Category. July 1, 2017.
4 B Standard, **2-Ethoxyethanol** in **Reference Module in Biomedical Sciences, from Encyclopedia of Toxicology**, 3rd Edition, Elsevier 2014, pp. 503-5.

13.29 WATER TRANSPORTATION

George Wypych
ChemTec Laboratories, Toronto, Canada

Water transportation equipment is divided into self-propelled vessels and barges. The US water transportation industry employed in 2017 65,400 people. In 2017, 2,074 companies were in operation in the US.A[2] Solvents were used for paint removal (paint strippers), painting (antifouling paints, thinners, degreasers, solvents, and gel coats), degreasing engines, and cleaning carburetors. There is no information available regarding solvent use by the industry.

REFERENCES

1 *EPA Office of Compliance Sector Notebook Project. Profile of the Water Transportation Industry*. *US Environmental Protection Agency*, 1997.
2 US Department of Transportation. Maritime Administration. **2011 U.S. Water Transportation Statistical Snapshot**. November 2013.

13.30 WOOD FURNITURE

George Wypych
ChemTec Laboratories, Toronto, Canada

The US wood furniture industry employed over 137,000 people in 2005. In 2012, US furniture industry operated over 20,000 plants. Total sales of US produced furnitures were over $85 billion in 2005 and $60 billion in 2012. In 2015, 63,900 individuals were employed in the furniture manufacturing sector and the Canadian furniture industry consisted of 3,907 establishments.[17] Global furniture manufacturing had estimated output of $400 billion in 2012. Several operations use solvents, including veneer application (adhesives), derosination (certain types of wood contain rosin which may interfere with the effectiveness of certain finishes; rosin is removed by application of a mixture of acetone and ammonia), pretreatment (coating contains coalescing solvent (slow evaporating) and diluent (fast evaporating), a UNICARB® technology uses carbon dioxide in the mixture with a coalescing solvent which eliminates the need for a diluent), several finishing operations (stains, paints, fillers, inks used to print simulated wood grain on plywood, topcoat, and cleaning liquids). Nitrocellulose lacquers are commonly used in the USA; polyurethane and unsaturated polyester finishes are still rarities. Solvents and thinners used in paints include toluene and xylene. Adhesives usually contain solvents such as methyl isobutyl ketone, methyl ethyl ketone, xylene, toluene, and 1,1,1-trichloroethane. Table 13.30.1 shows the relative amounts of VOC emissions from different finishing components depending on furniture type and type of process used. The long process consists of applications of 3 or more coats of stain, a washcoat, a filler, a sealer, a highlight, and two to three topcoat applications. In the short-sequence process, two stain coats are applied, followed by a washcoat, a sealer, and two topcoat applications. Office furniture uses only one application of a stain, a sealer, and a topcoat.

Table 13.30.1. Relative VOC emissions. [Reproduced from EPA draft Guidelines for the Control of Volatile Compound Emissions from Wood Furniture Coating Operations]

Operation	Percentage of total emissions		
	Long process	Short process	Office furniture
Stain	26	28	32
Washcoat	4	4	–
Filler	3	–	–
Wiping stain/glaze	8	–	–
Sealer	18	32	32
Highlight	1	–	–
Topcoat	40	36	36

Tables 13.30.2 and 13.30.3 provide data on the reported releases and transfers of solvents by the US furniture and fixtures industry. Toluene, xylene, methanol, and methyl ethyl ketone are released in the largest quantities. The furniture and fixtures industry is one of lesser contributors of VOCs releases and transfers among the US manufacturing industries.

Table 13.30.2. Reported solvent releases from the furniture and fixtures industry in 1995 [Data from Ref. 2].

Solvent	Amount, kg/year	Solvent	Amount, kg/year
n-butyl alcohol	940,000	methyl isobutyl ketone	590,000
cyclohexane	10	tetrachloroethylene	7,300
dichloromethane	180,000	1,2,4-trichlorobenzene	90
ethylbenzene	360,000	1,1,1-trichloroethane	160,000
ethylene glycol	30	trichloroethylene	29,000
hexane	25,000	1,2,4-trimethylbenzene	140,000
isopropanol	105,000	toluene	5,300,000
methanol	3,600,000	xylene	3,300,000
methyl ethyl ketone	1,900,000		

Table 13.30.3. Reported solvent transfers from the furniture and fixtures industry in 1995 [Data from Ref. 2]

Solvent	Amount, kg/year	Solvent	Amount, kg/year
n-butyl alcohol	53,000	methyl isobutyl ketone	145,000
cyclohexane	110	1,2,4-trichlorobenzene	110
dichloromethane	28,000	1,1,1-trichloroethane	5,700
ethylbenzene	340,000	trichloroethylene	300
hexane	16,000	1,2,4-trimethylbenzene	160,000
isopropanol	11,000	toluene	1,030,000
methanol	570,000	xylene	1,700,000
methyl ethyl ketone	380,000		

Several alternative technologies are available.[3-12] Waterborne clear varnishes are being used increasingly but the market is still dominated by solvent-based varnishes. One reason may be that waterborne varnishes are 2-3 times more expensive than solvent-based products.[3] It is also not clear if waterborne varnishes have a lower odor and can be applied at the same rate as solvent-based products. Waterborne varnishes have one important advantage in clear coatings for they have no color, therefore, the natural wood color is

more vivid. Two-component, water-based polyurethane coatings have been introduced.[4] They have a very low VOC content and very good drying speed, gloss, and potlife. The drying rate and potlife are controlled by the ratio of isocyanate and hydroxyl components. Increasing this ratio increases drying speed but decreases potlife. However, at 4 hours, potlife is acceptable. Polyurethane dispersions are used in furniture adhesive applications and are especially useful in the lamination of kitchen tables.[5]

One problem related to all water-based coatings is the degree to which they penetrate into the wood grain. Waterborne coatings are composed of relatively large emulsified particles which are frequently the size of the pit openings. After the emulsion droplets dry out, they become very viscous and penetration becomes even more difficult. The penetration of alkyd waterborne coatings was tested by microautoradiography.[6] The results indicate that the penetration rate is controlled by the viscosity and form of the material (solution vs. emulsion) is less important.

UV curable coatings have also problems in application to wood finishing. These finishes need to have low viscosity but it is difficult to formulate 100% solids curable coatings which have a sufficiently low application viscosity.[7] It possible to formulate waterborne UV curable coatings but their performance is still an issue.

Dunlop developed a two-part water-based adhesive which performed well in the lamination of wood and foam.[8] Also, a new reactive hot-melt system for attaching moldings in furniture assembly is in use.[9] A water-reducible coating for wood finishing has been developed based on copolymer which can be cured by crosslinking.[11] Another solvent-free material was developed to cover scratches and other damage to finished wood articles.[12] Replacement of solvent-based adhesives is essential if this industry, which uses 12% of all adhesives, is determined to significantly reduce its solvent usage.[10]

Wood stain composition contains hydrocarbon as its main solvent and glycol ether as compatibilizing solvent.[13] Isopropanol and n-hexyl ether are used as solvents in an antibacterial cleaning composition for furniture.[14] Butanol, glycol, glycol ethers, and propanols are used in penetrating UV-protecting composition which protects wood and lignins.[15]

National Institute of Standard and Technology issued guide to furniture compliance requirements.[16]

The influence of N,N-dimethylformamide on one-component moisture-cured polyurethane used for bonding wooden specimens was investigated.[18] DMF partially dissolves lignin and mobilizes moisture bound in the wood cell walls, which becomes available for the 1C-PUR conversion.[18]

REFERENCES

1 **EPA Office of Compliance Sector Notebook Project. Profile of the Wood Furniture and Fixtures Industry.** *US Environmental Protection Agency*, 1995.
2 **EPA Office of Compliance Sector Notebook Project. Sector Notebook Data Refresh - 1997**. *US Environmental Protection Agency*, 1998.
3 P B Bell, J J Bilancieri, *Paint & Ink International*, **9**, No.5, 6-10 (1996).
4 M J Dvorchak, *J. Coat. Technol*., **69**, No.866, 47-52 (1997).
5 M Moss, *Pigment Resin Technol*., **26**, No.5, 296-9 (1997).
6 R M Nussbaum, E J Sutcliffe, A C Hellgrn, *J. Coat. Technol.*, **70**, No.5, 49-57 (1998)
7 S Peeters, J P Bleus, Z J Wang, J A Arceneaux, J Hall, *Paint & Ink International,* **11**, No.1, 6-9 (1998).

8 Plast. Rubber Weekly, No.1691, 1997.
9 Hughes F, TAPPI 1997 Hot Melt Symposium. Conference Proceedings. TAPPI. Hilton Head, SC, 15th-18th June 1997, p.15-21.
10 L White, *Eur. Rubber J.*, **179**, No.4, 24-5 (1997).
11 S-H Guo, **US Patent 5.646,225**, *ARCO Chemical Technology*, 1997.
12 I J Barlow, **US Patent 5,849,838**, *SC Johnson & Sons, Inc*., 1998.
13 I J Shapiro, T A Pierce, **WO2009108348**, *The Sherwin-Williams Company*, 3 Sep. 2009.
14 T E Polzin, L M Werkowski, **WO2011159348**, *SC Johnson & Son, Inc.,* 22 Dec. 2011.
15 D Karoly, M Hansruedi, G Otto, **WO2010114728**, *Isp Investments Inc*., 7 Oct. 2010.
16 A Guide to the United States Furniture Compliance Requirements. GCR 12-957. NIST. Aug. 2013.
17 Government Canada. Furniture manufacturing industry profile.
18 O Kläusler, W Bergmeier, A Karbach, W Meckel, E Mayer, S Clauß, P Niemz, *Int. J. Adh. Adh.*, **55**, 69-76, 2014.

13.31 SUMMARY

George Wypych
ChemTec Laboratories, Toronto, Canada

The data from the US industry given in the various sections of this chapter allow analysis of releases and transfers of the various solvents and helps us to understand the patterns of solvent use. Also, industries can be ranked based on the amounts of solvents released. This information is provided in Tables 13.31.1, 13.31.2, 13.31.3, 13.31.4, 13.31.5, and 13.31.6 which contain total release of solvents from all reporting industries, the total transfers of solvents from all reporting industries, the sum of releases and transfers from these industries and the total release of solvents by each industry, the total transfers of solvents by each industry, and the total release and transfer of solvents by each industry, respectively. The three highest entries in the tables (either amount, release, or transfer) are marked by bold (first), italic (second), or underlining (third).

Table 13.31.1. Reported solvent releases from all industries in 1995 [Data from EPA Office of Compliance Sector Notebooks]

Solvent	Amount, ton/year	Solvent	Amount, ton/year
acetone	870	2-ethoxyethanol	19
allyl alcohol	60	ethylbenzene	3,810
benzene	3,378	ethylene glycol	8,122
n-butyl alcohol	5,640	hexachloroethane	16
sec-butyl alcohol	216	hexane	6,571
tert-butyl alcohol	482	isopropyl alcohol	205
carbon disulfide	33,085	methanol	**93,965**
carbon tetrachloride	30	2-methoxyethanol	23
chlorobenzene	181	methyl ethyl ketone	23,315
chloroform	458	methyl isobutyl ketone	6,876
chloromethane	310	N-methyl-2-pyrrolidone	1,111
cresol	800	methyl tert-butyl ether	1,477
m-cresol	320	pyridine	187
o-cresol	270	tetrachloroethylene	1,692
p-cresol	162	toluene	*41,015*
cyclohexane	3,001	1,2,4-trichlorobenzene	1,245
cyclohexanone	303	1,1,1-trichloroethane	8,631
cyclohexanol	1,100	trichloroethylene	6,611
1,2-dichlorobenzene	15	trichlorofluoromethane	84
1,4-dichlorobenzene	15	1,2,4-trimethylbenzene	2,308
1,2-dichloroethane	222	xylene	26,544

Table 13.31.1. Reported solvent releases from all industries in 1995 [Data from EPA Office of Compliance Sector Notebooks]

Solvent	Amount, ton/year	Solvent	Amount, ton/year
dichloromethane	16,332	m-xylene	269
N,N-dimethylformamide	447	o-xylene	82
1,4-dioxane	33	p-xylene	1,660

Table 13.31.2. Reported solvent transfers from all industries in 1995 [Data from EPA Office of Compliance Sector Notebooks]

Solvent	Amount, ton/year	Solvent	Amount, ton/year
acetone	767	2-ethoxyethanol	2
allyl alcohol	330	ethylbenzene	4,691
benzene	792	ethylene glycol	**72,549**
n-butyl alcohol	3,636	hexane	8,910
sec-butyl alcohol	1,723	isopropyl alcohol	168
tert-butyl alcohol	12,749	methanol	*55,287*
carbon disulfide	260	2-methoxyethanol	8
carbon tetrachloride	224	methyl ethyl ketone	15,119
chlorobenzene	704	methyl isobutyl ketone	6,811
chloroform	322	N-methyl-2-pyrrolidone	1,497
chloromethane	0.5	methyl tert-butyl ether	246
cresol	594	pyridine	103
m-cresol	720	tetrachloroethylene	1,189
o-cresol	57	toluene	18,717
p-cresol	870	1,2,4-trichlorobenzene	69
cyclohexane	1,711	1,1,1-trichloroethane	1,778
cyclohexanone	1	trichloroethylene	1,967
cyclohexanol	4	trichlorofluoromethane	4
1,2-dichlorobenzene	4	1,2,4-trimethylbenzene	729
1,4-dichlorobenzene	3	xylene	27,000
1,2-dichloroethane	3	m-xylene	98
dichloromethane	2,895	o-xylene	491
N,N-dimethylformamide	1,298	p-xylene	9
1,4-dioxane	60		

Methanol, ethylene glycol, toluene, xylene, and carbon disulfide occupy the highest places in Tables 13.31.1-13.31.3, followed by methyl ethyl ketone, dichloromethane, 1,1,1-trichloroethane, tert-butyl alcohol, hexane, and methyl isobutyl ketone. These eleven solvents constitute 86% of all 550,738 tons of solvents released and transferred per year. Methanol alone constitutes over a quarter (27.1%) of the released and transferred solvents.

Table 13.31.3. Reported solvent releases and transfers from all industries in 1995 [Data from EPA Office of Compliance Sector Notebooks].

Solvent	Amount, ton/year	Solvent	Amount, ton/year
acetone	1,637	2-ethoxyethanol	21
allyl alcohol	390	ethylbenzene	8,501
benzene	4,170	ethylene glycol	*80,671*
n-butyl alcohol	9,276	hexachloroethane	16
sec-butyl alcohol	1,939	hexane	15,481
tert-butyl alcohol	13,231	isopropyl alcohol	373
carbon disulfide	33,345	methanol	**149,252**
carbon tetrachloride	254	2-methoxyethanol	31
chlorobenzene	885	methyl ethyl ketone	38,434
chloroform	780	methyl isobutyl ketone	13,687
chloromethane	311	N-methyl-2-pyrrolidone	2,608
cresol	1,394	methyl tert-butyl ether	1,723
m-cresol	1,040	pyridine	290
o-cresol	327	tetrachloroethylene	2,881
p-cresol	1,032	toluene	59,732
cyclohexane	4,712	1,2,4-trichlorobenzene	1,314
cyclohexanone	304	1,1,1-trichloroethane	10,409
cyclohexanol	1,104	trichloroethylene	8,578
1,2-dichlorobenzene	19	trichlorofluoromethane	88
1,4-dichlorobenzene	18	1,2,4-trimethylbenzene	3,037
1,2-dichloroethane	225	xylene	53,544
dichloromethane	19,227	m-xylene	367
N,N-dimethylformamide	1,745	o-xylene	573
1,4-dioxane	93	p-xylene	1,669

Methanol + xylene + toluene constitute over half (52.6%) of all released and transferred solvents by the analyzed industries. This is, in fact, good news because neither of the five most frequently released and transferred solvents are considered to have a carcinogenic effect. But four (methanol, xylene, ethylene glycol, and toluene) contribute to the pollution of lower atmosphere and xylene and toluene cause formation of ozone in the

lower atmosphere by which it may affect the respiratory system. Carbon disulfide causes the formation of hydroxyl radicals which have a relatively long half-life (a few days) and thus participate in a variety of photochemical processes. All five solvents are relatively easy to biodegrade.

Table 13.31.4. Total releases from different industries in the USA in 1995. [Data from EPA Office of Compliance Sector Notebooks].

Industry	Release ton/year	Percent total %	Release/employee kg/year	Release/$1000 of shipment, g
Aerospace	3,483	1.1	4.3	48
Metal fabrication	24,310	7.9	221	2455
Inorganic chemicals	643	0.2	5.8	21
Iron and steel	2,434	0.8	6.1	24
Metal casting	7,051	2.3	28	237
Motor vehicle	30,675	10.0	77	153
Organic chemicals	24,678	8.0	197	380
Petroleum	19,419	6.3	259	139
Polymer & fiber	37,646	12.3	**358**	**818**
Printing	14,750	4.8	9.8	109
Pulp & paper	70,101	**22.8**	*351*	*876*
Rubber & plastics	45,119	*14*.7	56	501
Stone, clay,...	3,630	1.2	7.3	–
Textile	6,629	2.2	11	95
Wood furniture	16,636	5.4	67	756
Total	**307,204**	**100**	**Average = 111**	**Average = 472**

The largest releases and transfers of methanol are from the pulp and paper (57.7%), organic chemical (21.3%), and the polymer and man-made fibers industry (6.2%) which contribute 85.2% of the total methanol releases and transfers. Ethylene glycol releases and transfers are mostly from the polymer and fiber industry (62.5%), the rubber and plastics (19.1%), and the organic chemical industry (15.9%). These three industries contribute 97.5% of all releases and transfers of ethylene glycol from the reporting industries. Toluene and xylene are typical paint, ink, cleaning and process solvents. The largest source of these is from the motor vehicle assembly industry (20%), the printing industry (13.7%), the rubber and plastics industry (11.4%), and the metal fabrication industry (10.7%). In total, these industries contribute over half of all releases and transfers of toluene and xylene (55.8%). The majority of carbon disulfide (82.5%) is contributed by the man-made fiber industry from rayon production.

The solvents ranked below the top five in the releases and transfers are mostly used in the paint and surface cleaning. The majority of emitted methyl ethyl ketone comes from

the metal fabricating industry (25.2%), the rubber and plastics industry (23.4%), and the vehicle assembly industry (11.5%) which jointly contribute 60.1% of the total releases and transfers. 1,1,1-trichloroethane is released and transferred from the metal fabricating industry (36.6%), the rubber and plastics industry (30.4%), and the motor vehicle assembly industry (8.4%), totals 75.4% of all releases and transfers of this solvent. Tert-butyl alcohol is almost solely contributed by the organic chemical industry (94.6%). Hexane comes from polymer and fiber (57.4%), petroleum (19.5%), and rubber and plastics industry (11.3%) which together give 88.2% of all releases and transfers. Methyl isobutyl ketone is mostly contributed by the motor vehicle industry (56.7%) but metal fabricating (13%) and rubber and plastics industry (11.3%) also release and transfer large amounts of this solvent. Together all three industries account for 81% of its total release and transfer. Dichloromethane comes from rubber and plastics (65.5%), metal fabricating (24.8%), and polymer and fibers industry (8.1%) totals 98.4% of dichloromethane.

Table 13.31.5. Total transfers from different industries in the USA in 1995. [Data from EPA Office of Compliance Sector Notebooks].

Industry	Release ton/year	Percent total %	Release/employee kg/year	Release/$1000 of shipment, g
Aerospace	1,080	0.4	1.3	15
Metal fabrication	13,164	5.3	120	*1*,330
Inorganic chemicals	324	0.1	2.9	11
Iron and steel	4,328	1.7	10.8	43
Metal casting	178	0.1	0.7	6
Motor vehicle	23,980	9.6	60	60
Organic chemicals	63,680	25.3	*509*	980
Petroleum	1,382	0.6	18	10
Polymer & fiber	78,584	**31.4**	**748**	**1,708**
Printing	4,051	1.6	2.7	30
Pulp & paper	23,457	9.4	117	293
Rubber & plastics	27,215	10.9	34	302
Stone, clay,...	2,736	1.1	5.5	–
Textile	1,845	0.7	3.1	26
Wood furniture	4,439	1.8	18	202
Total	**250,443**	**100**	**Average = 110**	**Average = 358**

The second tier solvents are more harmful to health and environment than the first five most frequently released and transferred solvents. Ketones are suspected carcinogens by some sources. Dichloromethane is a probable human carcinogen. 1,1,1-trichloroethane is an ozone depleter. Because of their volatility, these solvents reside mostly in the lower atmosphere causing pollution and participating in radical processes.

Five industries are the largest contributors to the second tier solvents: rubber and plastics (23.8%), metal fabricating (18.1%), motor vehicle assembly (11.8%), organic chemicals (11.7%), and polymer and fiber (9.4%). Their joint contribution accounts for 74.8% of the releases and transfers of these solvents.

Two pertinent observations can be concluded from the above data

- tight controls and applications of new technology in the top three industries using a particular solvent can make a big difference
- most releases and transfers stem from the use of paints and coatings.

Tables 13.31.4-13.31.6 analyze releases from different industries. The polymer & fiber, pulp & paper, organic chemicals, rubber & plastics industries pollute the most from the point of view of releases and transfers of solvents.

Table 13.31.6. Total releases and transfers from different industries in the USA in 1995. [Data from EPA Office of Compliance Sector Notebooks]

Industry	Release ton/year	Percent total %	Release/employee kg/year	Release/$1000 of shipment, g
Aerospace	4,563	0.8	5.7	63
Metal fabrication	37,474	6.7	341	**3,785**
Inorganic chemicals	967	0.2	8.8	32
Iron and steel	6,762	1.2	16.9	68
Metal casting	7,229	1.3	28.9	243
Motor vehicle	54,355	9.8	136	271
Organic chemicals	88,358	15.8	*707*	1,359
Petroleum	20,801	3.7	277	158
Polymer & fiber	116,230	**20.9**	**1,107**	*2,527*
Printing	18,801	3.4	12.5	139
Pulp & paper	93,558	*16.8*	467	1,169
Rubber & plastics	72,334	13.0	90	803
Stone, clay,...	6,366	1.1	12.7	-
Textile	8,474	1.5	14.1	121
Wood furniture	21,075	3.8	84	958
Total	**557,347**	**100**	**Average = 230**	**Average = 835**

It can be speculated from the release data per employee that workers in pulp & paper, rubber & plastics, and polymer & fiber are the most exposed to solvents. Some technologies cost taxpayers more than others. Metal fabrication is one example. In order to produce goods valued at $1,000, the industry releases and transfers almost 3.8 kg of solvents. The cost of health and cleanup may exceed the value of goods manufactured.

It is characteristic that traditional industries which maintain older plants (metal fabrications, polymer & fiber, rubber & plastics, wood furniture, organic chemicals) contribute

more to releases and transfers of solvents (as measured by releases plus transfers per $1,000 sales), than industries which invest capital in the improvement of equipment, safety, and research and development (e.g., printing, motor vehicle assembly). This suggests that the avoidance of cost of the required investment is one reason for pollution. This reason was illustrated in the discussion of the petroleum industry where one manufacturer almost eliminated pollution by fixing leaking valves.

Industries consisting of smaller individual companies have fewer resources to develop new, non-polluting technologies (or even enforce safe practices). For example, the metal fabrication industry is composed of smaller plants using older technology which do not have the resources to make environmental improvements and remain competitive.

The traditional chemical industries (pulp & paper, rubber & plastics, and polymer & fiber) will hopefully apply their knowledge and chemical know-how to eliminate most of their contribution to pollution. In the future, this will become an increasingly important requirement in competing by decreasing the social cost of applied technology. Perhaps more plastics could replace metals if the polymer, rubber, and plastics industries could demonstrate that their cost of pollution per dollar of output is much smaller than that of the metal industry.

U.S. Environmental Protection Agency modified the hazardous waste management regulations under the Resource Conservation and Recovery Act (RCRA) to conditionally exclude solvent-contaminated wipes from hazardous waste regulations provided that businesses clean or dispose of them properly. The rule is based on EPA's final risk analysis, which was peer reviewed in 2008 and published for public comment in 2009, that concluded wipes contaminated with certain hazardous solvents do not pose a significant risk to human health and the environment when managed properly. EPA estimates that the final rule will result in a net savings of between $21.7 million and $27.8 million per year.[1]

Industrial cleaning in the United States has changed dramatically over the past 20 to 25 years. Ozone-depleting substances, Class I were eliminated on 1 Jan. 1996 and Class II on 1 Jan. 2003.[2]

REFERENCES

1 EPA. News release, 23 Jun. 2013.
2 The U.S. Solvent Cleaning Industry and the Transition to non-Ozone Depleting Substances. EPA. Sep. 2004.

14

Methods of Solvent Detection and Testing

14.1 STANDARD METHODS OF SOLVENT ANALYSIS

George Wypych
ChemTec Laboratories, Toronto, Canada

This section includes information on solvent analysis based on methods included in national and international standards. ASTM standard methods are emphasized because they contain more methods on solvent testing than any other set of methods available. ISO standards are also covered in full detail because they are used in practical applications and are a basis for preparation of national standards. References to other national standards are also given, including Australian (AS), Australian/New Zealand (AS/NZS), (British (BS), Canadian (CAN/CGSB), German (DIN), Japanese (JIS), and Finish (SFS). The same number is given in references to all national and international standards for the same solvent property to facilitate searching and referencing. Methods of analysis are grouped by subject in alphabetical order.

14.1.1 ALKALINITY AND ACIDITY

Amine acid acceptance by halogenated solvents is the degree to which an amine is capable of absorbing or neutralizing acid present from an external source or generated by the solvent.[1] This method is useful for comparing the effect of an amine with other acid-accepting compounds. The test is performed by the titration of an alkaline water extract from the solvent with 0.2 N hydrochloric acid to pH = 3.9 as detected by pH electrode.

The alkalinity of acetone is determined by a titration with 0.05 N H_2SO_4 in the presence of methyl red indicator.[2] The test method provides a measure of acetone alkalinity calculated as ammonia.

The acidity of halogenated solvents can be determined by titration with 0.01 N sodium hydroxide in the presence of a 0.1% solution of bromophenyl blue indicator.[3] Similar to the determination of alkalinity,[1] acidity is determined in water extract. The determination can also be done directly in solvent but the solution of sodium hydroxide should be prepared in methanol. A third option is to determine acidity by a pH-metric titration of a water extract. Prior to determination, the pH of solvent is measured. If the pH is above 7, then an alkalinity measurement is done by the above method.[1] If the pH is below 7, acidity

is determined by this method.[3] The method is used to establish purchasing and manufacturing specifications and control the quality of solvents.

The acidity of benzene, toluene, xylenes, naphthas, and other aromatic hydrocarbons is determined by the titration of a water extract with 0.01 N sodium hydroxide in the presence of 0.5% phenolphthalein indicator solution.[4] The method is suitable for setting specifications, internal quality control, and development of solvents. The result indicates the potential corrosivity of solvent.

The acidity of solvents used in paint, varnish, and lacquer is determined by the titration of solvent diluted with water (for water soluble solvents) or isopropyl alcohol or ethanol (for water insoluble solvents) in proportion of 1:1. A water solution of 0.05 N sodium hydroxide in the presence of 0.5% phenolphthalein indicator dissolved in ethanol or isopropanol is used for titration.[5] The method is useful for determination of acidity below 0.05%. Acidity is a result of contamination or decomposition during storage, transportation or manufacture. The method is used to assess compliance with specification.

Solvents which are depleted of stabilizers (amine or alpha epoxide) may become acidic. The following method determines the combined effect of both alkaline (amine) and neutral (usually epoxy) stabilizers.[6] The determination is done in two steps. First solvent is mixed with hydrochlorination reagent (0.1 N HCl), then the excess is titrated with 0.1 N sodium hydroxide in the presence of 0.1% bromophenyl blue as an indicator.

The total acidity of trichlorotrifluoroethane and other halocarbons is determined by titration of a sample diluted with isopropanol with 0.01 N sodium hydroxide in isopropanol in the presence of a 0.05% isopropanol solution of phenolphthalein as an indicator.[7] The method is used for setting specifications and quality control.

14.1.2 AUTOIGNITION TEMPERATURE

The autoignition temperature can be determined by the hot and cold flame method.[8] Cool flames occur in vapor-rich mixtures of hydrocarbons and oxygenated hydrocarbons in air. The autoignition temperature is the spontaneous (self-ignition) temperature at which a substance will produce a hot flame without an external ignition source. Autoignition occurs when a hot flame inside a test flask suddenly appears accompanied by a sharp rise in temperature. With cold flame ignition the temperature rise is gradual.

The test equipment shown in a schematic drawing in the method[8] consists of a test flask, a furnace, a temperature controller, a syringe, a thermocouple and other auxiliary parts. The measurement is performed in a dark room for optimum visual detection of cool flames. The results are reported as ignition temperature, time lags (delay between sample insertion and material ignition), and reaction threshold temperature (the lowest flask temperature at which nonluminous pre-flame reactions (e.g., temperature rise) occur).

The results depend on the apparatus employed. The volume of vessel is especially critical. A larger flask will tend to produce lower temperature results. The method is not designed for materials which are solid at the measurement temperature or which undergo exothermic decomposition.

14.1.3 BIODEGRADATION POTENTIAL

The method covers a screening procedure which assesses the anaerobic biodegradation of organic materials.[9] The procedure converts organic substances into methane and carbon dioxide which are measured by a gas volumetric pipette – part of the standard apparatus. Other parts include, a biodegradation flask, a magnetic stirrer, a pressure transducer, a syringe, and a water seal. The apparatus may be interfaced with a gas chromatograph to determine quantities of the two gases.

The biodegradation process is conducted in a specially prepared medium inoculated with sludge inoculum. The process occurs under the flow of a mixture of 70% nitrogen and 30% carbon dioxide to provide anaerobic conditions.

The method was developed to screen organic substances for their potential to biodegrade. If a high degree of biodegradability is determined, it provides a strong evidence that the test substance will be biodegradable in the anaerobic digestors of a waste treatment plant and in many natural environments. The references[9] give methods of determining of biological and chemical oxygen demand.

14.1.4 BOILING POINT

The boiling point of solvent, its specific heat capacity, and its enthalpy of vaporization determine the energy required for solvent separation in a distillation column. They also determine numerous other properties of solvents (see Chapter 2).

Several methods of determination can be used, but two: distillation and gas chromatography are the most popular. Industrial aromatic hydrocarbons are determined by distillation. The temperature is recorded for the initial boiling point, for the sample which has been distilled at 5%, 10%, then at 10% increments up to 90%, then finally at 95%. The temperature should be recorded with precision of 0.1°C.[10] A general test method to determine the distillation range of volatile liquids[11] outlines a similar method of measurement. In addition to the measurements at the intervals given above, the temperature of the dry point (distillation temperature of residual quantities) is also recorded. Results must be reported as specified in the method.

A vacuum distillation procedure is used to determine the amount of solvents in solvent-based paints.[12] The paint sample is diluted with tricresyl phosphate, distilled for a while under normal pressure to evaporate the more volatile solvents, followed by vacuum distillation at 2 mm Hg.

Capillary gas chromatography is used to determine the boiling point of hydrocarbon solvents.[13] The initial boiling point is defined as the point at which the cumulative area of chromatogram equals 0.5% of its final total surface area. The final boiling point is at cumulative area of 95% of the total surface area of chromatogram. The method reports boiling point distribution in 1% intervals over the 1-99% range of the total cumulative surface area of chromatogram as well as the initial and final boiling points. A flame ionization detector is used in the determination and a standard solvent containing 16 known components is used for calibration.

14.1.5 BROMINE INDEX

Two methods are used to determine bromine index of aromatic hydrocarbons which contain trace amounts of olefins and are substantially free of materials lighter than isobutane and have distillation end-point lower than 288ºC. The methods measure trace amounts of unsaturations in materials which have a bromine index below 500.

The bromine index can be measured by electrometric[14] and coulometric[15] titration. In the electrometric titration method, a sample is titrated with bromide-bromate solution (0.1 N solution of mixture of potassium bromide and potassium bromate) until the end-point increase in potential remains steady for 30 s.[14] In coulometric titration, a potassium bromide solution is used to titrate the solvent until the bromine concentration increases because it is no longer being consumed by the unsaturation of the solvent.[15]

Both methods can be used for setting specification, quality control, and testing of development solvents to find olefinic content. The methods do not differentiate between the types of unsaturations.

14.1.6 CALORIFIC VALUE

The heat of combustion of liquid hydrocarbon fuels can be determined with bomb calorimeter.[16] Two definitions are used in result reporting: gross heat of combustion (the quantity of energy released from fuel burned in constant volume with all products gaseous except water which is in liquid state) and net heat of combustion (the same but water is also in a gaseous state). These determinations are useful in assessing the thermal efficiency of equipment used for generation of power or heat. The results are used to estimate the range of an aircraft between refueling stops which is a direct function of heat of combustion. The calorimeter bomb is standardized against benzoic acid standard. Net and gross heats of combustion are reported. A specific method is used for aviation fuels.[17] This method reports results in SI units and the measurements are made under constant pressure. The method is applicable for aviation gasolines or aircraft turbine and jet engine fuels. The method is used when heat of combustion data are not available. An empirical equation was developed which gives net heat of combustion based on the determined values of aniline point (ASTM D 611) and API gravity (ASTM D 287). If the fuel contains sulfur, a correction is applied for sulfur determined according to ASTM D129, D 1266, D 2622, or D 3120 (the method selected depends on the volatility of the sample).

Gross calorific value and ash content of waste materials can be determined by a calorimetric method.[19] After a calorimetric analysis, the bomb washing can be used to determine of mineral content by elemental analysis. The sample is burned under controlled conditions in oxygen. The calorimeter is standardized by burning known amount of benzoic acid. The formation of acids can additionally be determined by titration.

14.1.7 CLEANING SOLVENTS

Several standard procedures are available for evaluation of cleaning solvents. The stability of aircraft cleaning compounds is determined after 12 months storage at controlled conditions which may include moderate temperatures, cold storage, and hot storage.[20] Solvent vapor degreasing operations which use halogenated solvents follow standardized procedure.[21] The standard contains information on the location and design of a degreasing

installation and operation during startup, degreasing, shutdown, and solvent reclamation. The purpose of the standard is to reduce the probability of accidents and exposure to personnel. A separate standard practice[22] gives reasons for and methods of preventing acid formation in degreasing solvents. The formation of acid is generally related to excessive heat, contaminations, the presence of chlorinated and sulfonated oils, admixture of acids, and solvent mixtures.

14.1.8 COLOR

Impurities in benzene, toluene, xylene, naphthas, and industrial aromatic hydrocarbons are determined by a simple colorimetric analysis of an acid wash.[23] A solvent is washed with sulfuric acid and the color of the acid layer is determined by a visual comparison with color standards prepared from solutions of cobalt chloride and ferric chloride.

Aromatic hydrocarbons which melt below 150°C can be subjected to color analysis in the liquid (molten) state using a visual comparison with platinum-cobalt standards.[24] Standards are prepared from a stock solution of K_2PtCl_2 to form a scale varying in color intensity. Similar procedure was developed to evaluate color of halogenated organic solvents and their admixtures.[25]

Objective color measurement is based on tristimulus colorimetry.[26] This instrumental method measures tristimulus values of light transmitted by a sample and compares the results to the values transmitted by distilled water. The results can be recalculated to the platinum-cobalt scale referred to in the previous standards.[24,25] The results can also be interpreted by normal methods of color measurement to yellowness index, color, color depth, etc.

14.1.9 CORROSION (EFFECT OF SOLVENTS)

The corrosiveness of perchloroethylene to copper is determined using Soxhlet apparatus.[27] Three pre-weighed strips of copper are used, one placed in the bottom flask, the second in the bottom of the Soxhlet attachment, and the third below the condenser. The specimens are exposed to refluxing solvent for 72 h after which the entire apparatus is flushed with distilled water to wash all acidic substances back to the flask. The water layer is titrated with 0.01 N NaOH to determine its acidity and the strips are weighed to determine weight loss. The results indicate quality of solvent. A different method is used to test copper corrosion by aromatic hydrocarbons.[28] Here, a copper strip is immersed in a flask containing solvent and the flask is placed in boiling water for 30 min. Next, the copper strip is compared with ASTM standard corroded copper strips.

If 1,1,1-trichloroethane is not properly stabilized, it forms hydrochloric acid in the presence of aluminum. HCl corrodes aluminum. The presence of free water invalidates the result of this test.[29] An aluminum coupon is scratched beneath the surface of a solvent. The coupon is observed for 10 min and 1 h and the degree of corrosion is recorded in form of pass (no reaction) or fail (gas bubbles, color formation, or metal corrosion). The test is important to cleaning operations because aluminum should not be used for parts of machines (pumps, tanks, valves, spray equipment) in contact with corrosive solvent.

14.1.10 DENSITY

Density and specific gravity of solvents are discussed together. The difference in their definitions is that specific gravity is the density of material relative to the density of water whereas the density is the weight in vacuo of a unit volume. The density of liquids (including solvents) can be measured by a Bingham pycnometer.[30] The determination includes introduction of the liquid to the tared pycnometer, equilibration of temperature, then weighing. Other standardized method[31] determines the specific density of liquid industrial chemicals by two methods: hydrometer and pycnometer. The pycnometric method is essentially similar to the previously described. It differs in that the water and then solvent are weighed. Thus the density determination error may only be due to an imprecise weighing (the pycnometer calibrated volume does not enter calculations). In the hydrometer method, the calibrated hydrometer is immersed in controlled temperature liquid and direct readings are obtained.

The standard method for determining the specific gravity of halogenated organic solvents[32] involves the use of both a pycnometer and a hydrometer as described above but, in addition, an electronic densitometer is also used. Here, a liquid is placed in U-shaped tube and subjected to electronic excitations. The density changes the mass of tube and frequency of oscillations which is the basis for measurement and display of specific gravity readings.

Two standard tables[33,34] (American and metric system of units) are used to calculate weight and volume of benzene, toluene, xylenes mixture and isomers, styrene, cumene, and ethylbenzene as well as aromatic hydrocarbons and cyclohexane. Tables provide volume corrections for these solvents in a temperature range from -5 to 109ºF (-20.5 to 43ºC).

14.1.11 DILUTION RATIO

The dilution ratio is the maximum number of units of diluent that can be added to unit volume of solvent before precipitation occurs. Cellulose nitrate dissolved in an oxygenated solvent (8 wt% resin) is the most classical method to determine dilution ratio used to evaluate toluene as a standard diluent and to compare different diluents and solvents with a standard solvent (n-butyl acetate). The standard dilution ratio of toluene by n-butyl acetate solution is 2.73-2.83. Two end points are determined. The first occurs when a known amount of diluent forms precipitate after 2 min of vigorous swirling. The second is determined by redissolving the precipitate, adding a known volume of solvent (dependent on dilution ratio) and precipitating it again with diluent.[35]

Similar method can be used for any resin, solvent, or diluent.[36] A solution of resin is prepared by the method described in ASTM D 1725 or by dispersing in blender (results may differ). Precipitation with diluent is determined at 25ºC. The diluent is added dropwise from burette or weight is controlled throughout the experiment. The resin dilutability is recorded. If more than 100 g of diluent is required for 10 g of solution then diluent is regarded as being infinitely soluble.

Heptane miscibility in lacquer solvents is determined by mixing equal amounts of the specimen (lacquer) and heptane.[37] If a clear solution results after mixing, it indicates good miscibility. If a turbid solution results, either the heptane is immiscible with the tested specimen or water is present in either component.

Water-insoluble admixtures in solvents may affect many uses of solvent. The specimen solvent (primarily acetone, isopropanol, methanol, and many other) is diluted to 10 volumes with water and the resulting turbidity or cloudiness is recorded.[38]

14.1.12 DISSOLVING AND EXTRACTION

A standard practice for preparing polymer solution contains information on solvents, their concentration, temperature, pressure, mixing time, and heating.[39] The annex contains information on the best solvents for 75 typical polymers with different degrees of substitution or modification. Frequently, temperature and concentration of solution is also given.

Solvent extraction is used on textile materials to determine naturally occurring oily and waxy materials that have not been completely removed from the fibers.[40] The percentage of extracted material is given in relationship to the dry mass of fiber. Solvents used for extraction including 1,1,2-trichloro-1,2,3-trifluoroethane and dichloromethane but these may be replaced by other solvents by mutual agreement. The Soxhlet extraction and gravimetric determination are used.

14.1.13 ELECTRIC PROPERTIES

Specific resistivity is numerically equivalent to the volume resistance between opposite faces of one centimeter cube. The specific resistivity of electronic grade solvents is measured by a low-voltage a-c bridge operating at 1000 Hz providing the specific resistance does not exceed 10^9 Ω-cm.[41] If the specific resistance is higher than 10^9 Ω-cm, d-c equipment is used. D-c equipment is capable of measuring up to at least 10^{12} Ω-cm.

The electrical conductivity of liquid hydrocarbons can be measured by a precision meter.[42] The method is used to evaluate aviation fuels and other low-conductivity hydrocarbons. The generation and dissipation of electrostatic charges in liquids during handling depends on ionic species which may be characterized by electrical conductivity at rest. The dissipation time of the charges is inversely proportional to the conductivity. The measurement is done by a conductivity meter.

Two standard methods[43,44] were designed to determine the electric breakdown voltage of insulating oils of petroleum origin. These are VDE electrodes method[43] and the method under impulse conditions.[44] The dielectric breakdown voltage measurement allows to estimate the ability of an insulating liquid to withstand electric stress without failure. In the presence of contaminations such as water, dirt, or cellulosic fibers low breakdown voltages are obtained. VDE stands for Verband Deutscher Electrotechniker, an organization which designed brass electrodes used for measurement. The equipment uses a transformer, voltage control equipment, and a voltmeter. The impulse method[44] uses highly divergent field under impulse conditions. The breakdown voltage of fresh oil decreases as the concentration of aromatic hydrocarbons increases. The method can be used for quality control of fresh oil, and determining the effect of service aging, and effect of impurities. The material is placed in test cell containing electrodes which are supplied from an impulse generator controlled by voltage control equipment.

14.1.14 ENVIRONMENTAL STRESS CRACKING

Crazing is a group of surface fissures which appear as small cracks after the material has been exposed to solvent and stress. Crazes are usually oriented perpendicular to stress and

their appearance depends on the index of refraction and on the angle of viewing. A suitable light source must be used. Transparent plastic materials can be directly tested for crazing.[45] Two variations of method are used to determine stress crazing of transparent plastics: determination of stress required to cause cracking or determination of craze development along the time of stress application. In the first method specimens are exposed to solvent by the direct contact of specimen surface with filter paper wetted with solvent. By selecting different values of stress (using each time new specimen) the range of two stress forces is searched for the largest stress under which specimen does not craze and the smallest stress under which it does craze. In the second variation of the method, sample is tested first without solvent to assure that it does not craze under the selected load. Solvent is then applied and specimen inspected in 15 min time intervals taking note of location of craze front as crazing progresses. If the sample does not craze higher load is selected and *vice versa*. Similar to the first variation the range is determined within which specimen crazes and does not craze.

The crazing effect can be indirectly determined by testing chip impact resistance of specimens which crack either because of weathering or environmental stress cracking.[46]

14.1.15 EVAPORATION RATE

The evaporation rate of a solvent is determined to obtain relative value to some standard, selected solvent. The solvent selection depends on reasons for solvent use and the type of solvent and it is usually agreed upon between interested parties. In Europe, diethyl ether is the most frequently used reference solvent and in the US butyl acetate. The evaporation rate of other solvents is determined under identical conditions and the resultant values are used to rank solvents. The most obvious requirement is that the determination is done without excessive drafts and air currents. The evaporation rate is the ratio of the time required to evaporate a test solvent to the time required to evaporate the reference solvent under identical conditions. The results can be expressed either as the percentage evaporated within certain time frame, the time to evaporate a specified amount, or a relative rate. Relative rate is the most common.

For halogenated solvents used in cleaning applications, the relative evaporation rate is compared either to xylene or perchloroethylene.[47] The determination is done on a test panel using 10 ml of solvent. The relative evaporation rate is calculated.

14.1.16 FLAMMABILITY LIMITS

These tests cover the methods of determination of the minimum temperature at which vapors in equilibrium with liquid solvent are sufficiently concentrated to form flammable mixtures with air at atmospheric pressure and concentration limits of chemicals. Flammable (explosive) limits are the percent levels, volume by volume, of a flammable vapor or gas mixed in air between which the propagation of a flame or an explosion will occur upon the presence of ignition. The leanest mixture at which this will occur is called the lower flammable limit. The richest mixture at which it will occur is the upper flammable limit. The percent of vapor mixture between the lower and upper limits is known as the flammable range.

The temperature limits of flammability can be determined in an air/vapor mixture above a flammable liquid in a closed vessel.[48] The temperature in vessel is varied until a minimum temperature is reached at which the flame will propagate away from the ignition source. A glass vessel is equipped with an ignition device, a magnetic stirrer, a clamping devices, and a safety glass window. The initial temperature of determination is estimated from closed-cup flash point measurement. If the flash point is below 38°C, the initial temperature should be 8°C below flash point temperature. If the flash point is between 38 and 96°C, the starting temperature should be at least 14°C below the flash point. If the flash point temperature is above 96°C then the initial temperature should be 22 to 44°C below the flash point temperature. Selecting higher initial temperature may result in explosion. The lower temperature limit of flammability is obtained from the test which can be used to determine guidelines for the safe handling of solvents in closed process and storage vessels.

The concentration limits of flammability are determined using another method.[49] The method is limited to atmospheric pressure and temperature of 150°C. Equipment is similar to that used in the previous method. A uniform mixture of vapor and air is ignited and flame propagation from ignition source is noted. The concentration of flammable components is varied until a composition is found which is capable to propagate flame.

14.1.17 FLASH POINT

A variety of apparatus such as the small scale closed tester,[50] the tag open cup,[51] the tag closed tester,[52] the Cleveland open cup,[53] the Pensky-Martens closed cup,[54] and the equilibrium method[55] are used to determine the flash point. The selection of method is based suggestions included in separate standard.[56]

The small scale closed tester[50] is a metal cup with a thermometer fitted below the bottom of the internal chamber with a hinge mounted cover having filling orifice. The sample is introduced to the cup and the cup is maintained at a constant temperature by means of temperature controller. After a specific time, a test flame is applied for 2.5 s and an observation is made whether or not flash has occurred. If flash did not occur the cup is cleaned, a new sample is introduced and the temperature is increased by 5°C. The measurements are repeated until the flash point is determined with accuracy of 1°C.

The tag open cup[51] is a larger unit equipped with water-glycol bath for temperature control or a solid carbon dioxide-acetone bath for lower flash points. A much larger sample is used with this equipment and the temperature is gradually increased at a rate of 1°C/min. A taper flame is passed for 1 s in 1 min intervals until the flash point is detected. The tag closed tester[52] can use either a manual or an automated procedure. A sample volume of 50 ml is used. Either a gas flame or an electric ignitor is used. In the automated mode, the equipment is programmed to perform the standard procedure.

The Cleveland open cup[53] is placed on a heated plate which increases temperature at a rate of 5-6°C/min. This method can also be automated. The method is designed for testing petroleum products which are viscous and have flash point above 79°C. The Pensky-Martens[54] closed cup tester was also designed for petroleum products but for those with flash points from 40 to 360°C. This apparatus has its own heating source, stirrer, and cover by which it differs from Cleveland cup. It can be either manual or automated. The equilib-

rium method[55] uses either a modified tag close cup or the Pensky-Martens apparatus. The modification intended to keep the vapor/air temperature in equilibrium with the liquid temperature. The method is limited to the temperature range from 0 to 110°C.

Depending on the viscosity of liquid and its expected flash point range, one of the above methods is chosen as described in detail elsewhere.[56] It should be additionally noted that if the flash point method uses continuous heating, it is not suitable for testing mixtures of flammable substances because their vapor concentrations are not representative of equilibrium conditions. One of the weaknesses of flash point analysis is that the flame is well above the liquid surface therefore full vapor concentration is not attained. Many cases exist where a flash point cannot be detected but the material does form flammable mixtures. Before a method is chosen and a data interpretation made full information on the test procedure should be studied in detail and the proper authorities should be consulted to define safe practices for a particular material.

14.1.18 FREEZING POINT

Freezing point apparatus consists of freezing tube, Dewar flasks to act as cooling and warming baths, stirring mechanisms, absorption tubes, clamps and other auxiliary parts.[57] Freezing point can be obtained precisely from interpretation of time-temperature freezing and melting curves. The determination is made by measuring the electrical resistance of liquid which decreases on cooling and becomes constant when it freezes. This method in conjunction with the testing details described in a separate standard[58] can be used to determine the purity of many hydrocarbon solvents. The data given in the last standard[58] allow for a precise determination of the purity of solvent in percent of pure compound. A simple method was designed to determine solidification point of benzene based on visual observation of formation of solid phase.[59]

14.1.19 FREE HALOGEN IN HALOGENATED SOLVENTS

This simple qualitative test involves the extraction by water of free halogen, followed by the reaction of the halogens with potassium iodide in the presence of a starch indicator.[60] The solution color changes to blue in the presence of free halogen.

14.1.20 GAS CHROMATOGRAPHY

Gas chromatography provides many tools for the analysis of solvents. In section 14.1.4, a method was discussed which determines the distribution of boiling points of hydrocarbon mixtures. Many uses of gas chromatography for the determination of purity of different solvents are discussed in Section 14.1.25. In this section, some examples of gas chromatography are included to show its usefulness in the qualitative determination of solvents mixtures[61] the analysis of solvent impurities,[62-64] the determination of solvents in a product by direct injection,[65] and the generation of data to evaluate waste materials to determine their hazardous content.[66]

The relative distribution of aromatic hydrocarbons in xylene products can be quantitatively determined by gas chromatography.[61] A flame ionization or thermal conductivity detector is used with a capillary or packed column containing crosslinked polyethylene glycol as the stationary phase. The peak area of each component is measured and the

weight percentage concentration is calculated by dividing the peak area of the component by the sum of the areas of all peaks.

Ortho-xylene concentration and the concentrations of its admixtures and impurities are measured using a flame ionization detector and a polar fused-silica capillary column.[62] An internal standard (isooctane) is used to increase precision and a standard mixture is used for calibration. A similar method is used with p-xylene but either n-undecane or n-octane are used as the internal standards.[63] In both methods, peak areas are interpreted relative to the peak area of internal standard. The main impurities in benzene are non-aromatics with less than 10 carbons, toluene, 1,4-dioxane and aromatics containing 8 carbon atoms. The method of determination of benzene impurities[64] is similar to two methods described above.[62,63] Normal-nonane is used as an internal standard. In all three methods the internal standards must be at least 99% pure.

A gas chromatograph equipped with a thermal conductivity or a flame ionization detector and capillary or packed columns is used for direct determination of solvents in paints.[65] Columns are usually packed with either polyethylene glycol (molecular weight 20,000) or a diisodecyl phthalate as liquid phase on diatomaceous earth (60-80 mesh) used as a solid support. Low viscosity paints are drawn into a syringe and injected through the injection port. High viscosity paints are diluted with solvent that does not interfere with the analysis, usually ethyl ether or dichloromethane. A standardized gas chromatographic technique[66] is capable of determining the 67 solvents most frequently found in hazardous wastes. Several detectors are suggested for analysis such as flame ionization, electron capture, thermal conductivity, photoionization, or mass selective. Each waste mixture may contain a large number of solvents. Their detection is facilitated by the use of gas chromatograph interfaced with mass spectrometer. The method is designed to facilitate site assessment, recycling operations, plant control, and pollution programs.

14.1.21 LABELING

Warnings, first aid measures and operating instructions are standardized for vapor degreasers.[67] Placards containing this information should be placed close to the degreaser in an area accessible to employees. The placards should contain the information required by applicable federal and local laws and regulations. The placard should include name of the solvent used, and warnings indicating that the vapor is harmful, that breathing the vapor should be avoided, that the machine should only be used with proper ventilation, that swallowing and contact with the skin should be avoided, that cutting or welding should not be performed close to the machine, and that the tank should not be entered unless a proper procedure is followed. In addition, startup and operation procedures should be available.

Minimum labeling requirements for several halogenated solvents should also follow a standard practice.[68] The label should state the company name, its logo and address, emergency telephone numbers, lot number, the net weight, solvent name, its CAS number, OSHA PEL and ACGIH TLV values, and quantity. In addition, health and safety information, precautions, first aid, and handling and storage information should be provided.

14.1.22 ODOR

Strips of rapid qualitative paper are dipped in a standard liquid and in the liquid under the test. Their odor is compared to establish if the odor of sample is more or less acceptable than the standard to the purchaser and the manufacturer.[69] In a similar method, papers dipped in a standard and specimens are allowed to dry at room temperature and tested for residual odor at specified time intervals.

Odor testing may be performed by a selected group of panelist to either determine the effect of various additives on the odor or taste of a medium or to determine the odor or taste sensitivity of a particular group of people.[70] For this purpose, a series of samples is prepared in concentration scale which increases in geometric increments. At each concentration step two samples containing the medium alone are given to a panelist. The panelist should determine which sample is different from the other two samples. The panelist should begin with the lowest concentration selected to be two or three concentration steps below estimated threshold. The method description contains information on sample selection and preparation, result, and precision determination.

A method of evaluation of denatured and undenatured alcohols to assess their acceptability is used.[71] This method is developed specifically to compare methanol, ethanol, isopropanol, and n-propanol. The group of panelist is asked to compare the characteristic and residual odors of evaporation, its intensity by dilution, and its concentration. A similar method was developed for a series of glycols.[72] Here, odor character and intensity are evaluated.

The residual odor of a drycleaning grade of perchloroethylene is determined by comparing treated and untreated samples of bleached cotton fabric. The treated fabric is soaked for 5 min in perchloroethylene and dried for 4 hours at room temperature.[73] Good quality perchloroethylene should leave no odor.

14.1.23 PAINTS – STANDARDS RELATED TO SOLVENTS

The paint industry, a major user of solvents, has developed numerous standards. Some are included in Sections 14.1.25, 14.1.31, and 14.1.35. The paint industry also uses many general standards and some specific standards, which have not been included in any other section of this chapter. Details of these are given below.

Sampling and testing requirements for solvents used in the paint industry are summarized in a special standard.[74] This comprehensive list of standards used by paint industry also includes a brief discussion of each method of testing, including sampling, specific gravity, color, distillation range, nonvolatile matter, odor, water, acidity, alkalinity, ester value, copper corrosion test, sulfur, permanganate time test for acetone and methanol, flash point, purity of ketones, solvent power evaluation, water miscibility, analysis of methanol, analysis of ethylene and propylene glycols, acid wash color of aromatic hydrocarbons, paraffins and other nonaromatic hydrocarbons in aromatics, and aromatics in mineral spirits.

The nonvolatile matter in paints is determined by a gravimetric method after drying a 100 ml sample in oven at 105°C.[75] The transfer efficiency of paints is a volume or weight ratio of paint solids deposited to the volume/weight of the paint solids sprayed, expressed in percent. This method[76] can be used to optimize the paint application process. The mea-

surement is done by weighing or measuring the volume of paint used on a certain sprayed surface area and comparing this value with known or predetermined by the above method weight of solids in the paint used for spraying.

In order to determine an ester value for solvents or thinners, the specimen is reacted with aqueous potassium hydroxide, using isopropanol as the mutual solvent.[77] The hydrolysis is conducted at 98°C and the excess potassium hydroxide is determined by titration. From the amount of potassium hydroxide consumed, the ester value is calculated.

14.1.24 pH

A method developed for halogenated solvents is applicable for determining the pH of water extracts of solvents.[78] The solvent sample is shaken with distilled or deionized water and the pH is determined either by comparing color upon the addition of Gramercy universal indicator or by using a glass electrode pH meter.

14.1.25 PURITY

Several techniques are used to determine purity of solvents. Gas chromatography is the most common and this and other methods are discussed first followed by other analytical methods which include instrumental and simple methods. The aim of these tests is to determine the concentration of the main component but more frequently qualitative and quantitative determination of admixtures. Some methods have already been discussed in Sections 14.1.1, 14.1.5, 14.1.8, 14.1.9, 14.1.18, 14.1.20 and 14.1.23.

Alcohol content and purity of an acetate ester is determined by gas chromatography.[79] The method was applied to ethyl, n-propyl, isopropyl, n-butyl, isobutyl, and 2-ethylhexyl acetates. Water and acetic acid cannot be measured by this method and other methods are used. A thermal conductivity or flame ionization detector is used. A stainless steel column with 80-100 mesh Chromosorb G-HP is used with 9.05% Dow Corning QF-1 and 0.45% Igepal CO-990. The concentration of the main component and the amount of free alcohol are measured by the method.

Traces of benzene in hydrocarbon solvents are measured by capillary gas chromatography.[80] Because of the hazardous nature of benzene, the method was introduced to ensure compliance with the stringent regulations. A flame ionization detector is used with 0.53 mm fused silica capillary columns with bound methyl silicone or polyethylene glycol. Similar method is used to determine benzene content in cyclic products (cyclohexane, toluene, cumene, styrene, etc.).[81] This method does not specify any particular column but the column used should be able to resolve benzene from other components. The method can determine benzene in concentrations of 5 to 300 mg/kg. Traces of thiophene in refined benzene are determined by a flame photometric detector.[82] Several column types given in standard are found satisfactory to overcome potential problem of quenching effects of hydrocarbons on the light emissions from thiophene. High purity benzene for cyclohexane feedstock is tested for several known impurities by capillary gas chromatography.[83] The gas chromatograph is equipped with a flame ionization detector and a splitter injector suitable for fused silica capillary column internally coated with crosslinked methyl silicone. The concentration of benzene and the concentrations of impurities can be adequately determined.

The purity of halogenated solvents is determined using a thermal conductivity or flame ionization detector, a column made from 3.2 mm stainless tubing packed with 30 wt% silicone fluid on 80-100 mesh diatomaceous earth or using capillary column.[84] Admixtures in 1,1,1-trichloroethane are determined using a thermal conductivity or hydrogen flame detector. Column from copper or stainless steel is packed with Chromosorb W HP with 20% polydimethylsiloxane.[85]

Various impurities, such as hydrocarbons, acetone, alcohols and other can be determined using a thermal conductivity or a flame detector.[86] Several columns are specified in the standard mostly using polyethylene glycol on diatomaceous earth. For determination of purity of methyl isobutyl ketone different method is used.[87] In both cases the amounts of determined impurities are subtracted from total mass to give purity of specimen.

The determination of aromatics in mineral spirits is another method that has been developed to ensure compliance with regulations restricting aromatic content.[88] Three methods are given, each capable to determine ethylbenzene and total aromatic content. The methods differ in column type and packing.

A spectrophotometric method[89] for determining thiophene in benzene is available as alternative to gas chromatography.[82] The spectrometer used is capable of detecting absorbance in the range from 400 to 700 nm with a repeatability of 0.005 absorbance units. Thiophene is reacted with isatin to form a colored compound. The quantitative determination is based on reading concentrations from master curve.

The presence of reducing substances in pyridine can be detected by a simple visual observation.[90] The sample of pyridine is mixed with 0.32% potassium permanganate solution and color is observed after 30 min. If color of the potassium permanganate is retained, the sample is free of reducing agents.

Oxidative microcoulometry is used to determine trace quantities of sulfur in aromatic hydrocarbons.[91] An oxidative pyrolysis converts sulfur to sulfur dioxide which is titrated in titration cell with the triiodide ion present in the electrolyte.

The total chloride (organic and inorganic) in aromatic hydrocarbons and cyclohexane can be determined by titration.[92] Bromides and iodides present are recorded as chlorides. The sample is mixed with toluene in a proportion which depends on the expected concentration of chloride. The reagent sodium biphenyl is added to convert organic halogens into in organic halides. After decomposing the excess reagent with water, the separated aqueous phase is titrated in presence of acetone with a silver nitrate solution. Organic chlorides present in aromatic hydrocarbons can also be determined by microcoulometry.[93] The presence of chlorine compounds may adversely affect equipment and/or reaction therefore their concentration is frequently controlled. A liquid specimen is injected into a combustion tube maintained at 900°C, converted to hydrogen halides, and carried by a carrier gas (50% oxygen, 50% argon) to a titration cell where it reacts with silver ions in the electrolyte.

The determination of peroxides has two goals: one is to monitor peroxide concentration used as initiator and catalysts and the other is to detect formation of hazardous peroxides formed as autoxidation products in ethers, acetals, dienes, and alkylaromatic hydrocarbons. A sample is dissolved in a mixture of acetic acid and chloroform. The solu-

tion is deaerated and potassium iodide reagent is added and let to react for 1 hour in darkness.[94] The iodine formed in reaction is measured by absorbance at 470 nm and result calculated to active oxygen in the sample. The method can determine hydroperoxides, peroxides, peresters, and ketone peroxides. Oxidizing and reducing agents interfere with the determination.

Mercaptans in motor fuels, kerosene and other petroleum products can be detected by shaking the liquid sample with sodium plumbite solution, adding powdered sulfur and shaking again.[95] If a mercaptan or hydrogen sulfide is present, discoloration of the floating sulfur or liquid phase occurs.

The nonvolatile content of a halogenated solvent is determined by drying the sample in a platinum evaporating dish at 105ºC.[96] Depending on boiling point and the concentration of nonvolatile matter three alternate procedures are proposed.

The Karl Fisher method is recommended for general use in solvents to determine the water content.[97] It is not suitable if mercaptans, peroxides, or appreciable quantities of aldehydes and amines are present. Water in halogenated solvents may cause corrosion, spotting, reduce shelf-life of aerosols, or inhibit chemical reactions, thus special method, also based on the Karl Fischer titration, was developed for halogenated solvents.[98]

The titration of ionizable chlorides with mercuric acetate solution in the presence of s-diphenylcarbazone as an indicator is used to determine chloride in trichlorotrifluoroethane.[99] A visual appearance test to detect admixtures in halogenated solvents is based on the observation of suspended particles, sediment, turbidity and free floating water.[100]

The aromatic content of hydrocarbon mixture is estimated from the determination of aniline point.[101] Aromatic hydrocarbons have the lowest and paraffins the highest aniline points. Cycloparaffins and olefins are between the two. Aniline point increases as the molecular weight increases. A mixture of specific aniline and solvent is heated at a controlled rate until it forms one phase. The mixture is then cooled and the temperature at which the miscible liquid separates into two phases is determined. Four methods are discussed in the standard[101] suitable for transparent, non-transparent, easily vaporizing, and measured in small quantities.

The presence of oxidizable materials in acetone and methanol that are associated with contaminations during manufacture and distribution can be evaluated by permanganate time.[102] Oxidizable contaminants may adversely affect catalysts or ligand complexes which are sensitive to oxidation. Oxidizable substances reduce potassium permanganate to manganese oxide which is yellow. The method is designed to measure the time required to change color to the color of a standard.

Small admixtures of acetone in methanol (more than 0.003 wt%) can be detected after a reaction with Nessler's reagent.[103] The reacted sample is compared with a standard, which contains 0.003 wt% acetone and the difference in turbidity is reported.

14.1.26 REFRACTIVE INDEX

Refractive index is measured by a standard method.[104] It covers transparent and light colored liquids having a refractive index in the range from 1.33 to 1.50. The refractive index is the ratio of light velocity of a specified wavelength in air to its velocity in the substance under evaluation. The refractive dispersion is the difference between refractive indices for

light of two different wavelengths. This value is usually multiplied by 10,000. The method uses a Bausch & Lomb refractometer equipped with a thermostat and with a circulating bath to control the sample temperature with a precision of 0.2°C. Several light sources can be used, including the sodium arc lamp, mercury light lamp, and hydrogen or helium discharge lamp. Light sources are equipped with filters which transmit a specific spectral line. Standardization of equipment is done using a solid reference standard or using liquids standards such as 2,2,4-trimethylpentane (1.39), methylcyclohexane (1.42), or toluene (1.49).

14.1.27 RESIDUAL SOLVENTS

Residual solvents may cause odor, off-taste, blocking, and an increased degradation rate in outdoor exposures. A single standard test method has been developed to determine residual solvent levels and it is primarily used for the evaluation of flexible barrier materials.[105] The method is based on gas chromatography. The specimen of the barrier material is enclosed in a container and heated to vaporize the retained solvents into the head space. The vapor from the head space is taken by a gas syringe and injected into a gas chromatograph. The recovery of solvents is compared by the means of response factor which is a peak intensity of the detector in response to a given volume of injected sample. Response factors of different solutions vaporized in the test containers are compared. Round robin tests have demonstrated that this method has a coefficient of variation between laboratories of ±15%. The method does not specify the detector or the columns. Before a flexible barrier material is analyzed, the optimum heating time to recover volatilized solvents is determined.

14.1.28 SOLUBILITY

Solvent power of a hydrocarbon solvents is determined by kauri-butanol value.[106] The method applies to solvents having a boiling point above 40°C and a dry point below 300°C. The method is most frequently used to evaluate solvents for applications in paints and lacquers. The kauri-butanol value is the volume of solvent required to produce a defined degree of turbidity when added to 20 g of a standard solution of kauri resin in n-butanol (400 g of resin in 2000 g of solvent). High kauri value indicates a relatively strong dissolving power. The method is standardized using 105±5 ml of toluene.

The solubility of common gases in hydrocarbon liquids is determined to meet requirements of aerospace industry.[107] This test method is based on the Clausius-Clapeyron equation, Henry's law, and the perfect gas law. The results are important in the lubrication of gas compressors where dissolved gas may cause erosion due to cavitation. In fuels, dissolved gases may cause interruption of fuel supply and foaming in tank. The liquid density is determined experimentally. Using this density, the Ostwald coefficient is taken from a chart and used for the calculation of the Bunsen coefficient (solubility of gas). The solubility of the gas or mixture of gases and Henry's law constant are also calculated.

14.1.29 SOLVENT PARTITIONING IN SOILS

A procedure is available to determine partitioning organic chemicals between water and soil or sediment.[108] By measuring sorption coefficients for specific solids, a single value is obtained which can be used to predict partitioning under a variety of conditions. The

underlining principle of the method is that organic chemicals bind with the surfaces of solids through chemical and physical interactions. However, the sorption coefficient is based on organic carbon content which does not apply to all solvents or all soils.

The sorption coefficient of a particular solvent is measured by equilibrating its aqueous solution, containing a realistic concentration similar to that found in the environment, with a known quantity of soil or sediment. After equilibrium is reached, the concentration of solvent in the water and the soil is measured by a suitable analytical technique. The sorption constants for all solids tested are averaged and reported as a single value. The standard does not define the actual method of determining the concentrations but strategy that should be followed. The data are useful in predicting the migration of chemicals in soil, in estimating their volatility from water and soil, determining their concentration in water, and their propensity to leach through the soil profile.

14.1.30 SOLVENT EXTRACTION

Often materials must be extracted from a compounded product to perform testing. Extracted material must then be recovered from solution without degradation to be subjected to testing. The method discussed here was developed as means of recovering asphalt from pavement samples.[109] The solution of extracted asphalt in solvent is distilled by rotating the distillation flask of a rotary evaporator in a heated oil bath. The distillation is carried out under partial pressure in the presence of nitrogen to prevent degradation. The asphalt recovered by this method can be tested in the same manner as were the original asphalt samples.

14.1.31 SPECIFICATIONS

Standard specifications are designed to set criteria for commercial solvents which can be used to determine the compliance of a solvent sample. Because applications of solvents differ very widely, the selected criteria are also different for different groups of solvents. Table 14.1.1 is a compiled list of parameters all of which can be found in solvent specifications. The most common parameters used to characterize solvent include acidity, appearance, color, concentration of main component, distillation range, dry point, initial boiling point, and specific gravity. The methods of determining these parameters are found in this chapter.

The list of references includes information on specifications for various solvents. Solvents in this list are arranged into groups: alcohols,[110-120] aromatic hydrocarbons,[121-128] other hydrocarbons,[129-132] ketones,[133-138] esters,[139-145] glycol,[146] and chlorine-containing solvents.[147-152]

14.1.32 SUSTAINED BURNING

The sustained burning test was originally developed for British Standard BS-3900 and adapted by ASTM.[153] The purpose of the test is to determine the sustained burning characteristics of solvents by direct experiment rather than by deducing characteristics from flash point data. Mixtures of some flammable liquids (e.g., alcohol and water) are classified as flammable based on the closed-cup flash point method. Some mixtures may be classed as flammable even though they do not sustain burning. The test is performed in a block of aluminum with a concave depression called a well. The liquid under test is heated

to a temperature of 49°C and a flame is passed over the well and held in position for 15 s. The specimen is observed to determine if it can sustain burning.

Table 14.1.1. Typical chemical and physical properties of solvents included in their specifications.

Acid acceptance	Distillation range
Acidity	Doctor test
Acid wash color	Dry point
Alkalinity	Flash point
Aluminum scratch	Free halogens
Aniline point	Initial boiling point
Appearance	Iron concentration
Bromine index	Kauri-butanol value
Color	Non-volatile matter
Concentration of admixtures	Permanganate time
Concentration of isomers	Residual odor
Concentration of main component (or purity)	Specific gravity
Concentration of sulfur	Water concentration
Copper corrosion	Water miscibility

14.1.33 VAPOR PRESSURE

The vapor pressure is the pressure of the vapor of a substance in equilibrium with the pure liquid at a given temperature. Two procedures are used: an isoteniscope procedure (standard) for measuring vapor pressures from $1x10^{-1}$ to 100 kPa and a gas-saturation pressure for measuring vapor pressures from $1x10^{-11}$ to 1 kPa.[154-155] In the isoteniscope method, a sample is deaerated by heating under reduced pressure. The vapor pressure is then determined by balancing the pressure of the vapor against a known pressure of an inert gas. The vapor pressure is determined at minimum three different temperatures.

In the gas-saturation method, an inert gas is passed through a sufficient amount of compound to maintain saturation. The vapor is then removed from the gas by a sorbent or a cold trap and quantitatively determined by gas chromatography or other suitable technique.

14.1.34 VISCOSITY

The viscosity of solvents can be determined by one of three methods: glass viscometer,[156] Saybolt viscometer,[157] and bubble time method.[158] Glass viscometry is applicable to Newtonian, transparent liquids which because of volatility cannot be measured in conventional capillary viscometers. The viscometer uses a purge gas which helps to transfer the measuring liquid from a lower reservoir to the sample bulb. The time of flow is measured for a fixed volume of liquid at a temperature controlled with a precision of 0.01°C. A set of liq-

uids is available as viscosity standards in order to select the standard having closest viscosity to the measured sample.

The Saybolt viscometer was developed for petroleum products. A sample of 60 ml flows through a calibrated orifice and the time of flow is measured at a controlled temperature. Measurements are made at a temperature selected from the range 21-99°C. The instrument is standardized by measuring the flow of a standard oil at both 37.8 and 50°C.

In the bubble method, a standard viscosity tube is filled with a specimen liquid, the temperature of liquid is equilibrated to 25°C in a bath, the level of the meniscus is adjusted to 100 mm line, cork is inserted to end on 108 mm line, sample is hold in thermostating bath for another 20 min. Then the tube is inverted and the time for the bubble to flow from a mark at 27 mm to 100 mm is measured.

14.1.35 VOLATILE ORGANIC COMPOUND CONTENT, VOC

Several terms are used in the paint industry to provide data on the VOC content of paints.[159] The percent of solids in paints is calculated either per unit weight or per unit volume. The weight solids content is the weight of non-volatile materials divided by the total weight of the coating. In practice, it is calculated by subtracting the total weight of volatile solvents from the total weight of the coating and dividing the result by the total weight of coating. The final result is multiplied by 100 to express it in percent. Percent of solids by weight is calculated in similar manner.

A solvent, as defined by paint standards, is a volatile liquid that is incorporated primarily for vehicle solvency and control of the application characteristics. The solvent content is the calculated weight of solvents in a specific volume of paint. This definition is not equivalent to the definition of VOC compound because it does include compounds which are excluded by EPA (see more on this subject in Section 17.1).

Volatile organic compound by EPA definition means any compound of carbon, excluding carbon monoxide, carbon dioxide, carbonic acid, metallic carbides or carbonates, and ammonium carbonate, which participates in atmospheric photochemical reactions. This includes any such organic compound other than the following, which have been determined to have negligible photochemical reactivity: methane; ethane; methylene chloride; 1,1,1-trichloroethane; 1,1,2-trichloro-1,2,2-trifluoroethane; trichlorofluoromethane; dichlorodifluoromethane; chlorodifluoromethane; trifluoromethane; dichlorotetrafluoro-ethane; chloropentafluoroethane; dichlorotrifluoroethane; tetrafluoroethane; dichlorofluoroethane; chlorodifluoroethane; 2-chloro-1,1,1,2-tetrafluoroethane; pentafluoroethane; 1,1,2,2-tetrafluoroethane; 1,1,1-trifluoroethane; 1,1-difluoroethane; perchloroethylene; acetone; parachlorobenzotrifluoride; cyclic, branched, or linear completely methylated siloxanes; and perfluorocarbon compounds which fall into these classes: cyclic, branched, or linear, completely fluorinated alkanes; cyclic, branched, or linear, completely fluorinated ethers with no unsaturations; cyclic, branched, or linear, completely fluorinated tertiary amines with no unsaturations; and sulfur containing perfluorocarbons with no unsaturations and with sulfur bonds only to carbon and fluorine. For purposes of determining compliance with emissions limits, VOC is measured by the test methods in the approved State implementation plan (SIP) or 40 CFR Part 60, Appendix A, as published in (7/1/91) edition, as applicable.

Based on the above definition of VOC, the VOC content is calculated from a formula by excluding from the total solvent content of the paint, the content of water and solvents excluded by the above regulation. The following formula can be used for VOC calculation:

$$VOC = \frac{W_{\text{total solvents}} - W_w - W_{\text{excluded solvents}}}{V_{\text{paint}} - V_w - V_{\text{excluded solvents}}} \quad [14.1.1]$$

where:

$W_{\text{total solvents}}$	total weight of solvents
W_w	weight of water present in formulation
$W_{\text{excluded solvents}}$	total weight of solvents excluded by EPA regulation
V_{paint}	total volume of paint
V_w	volume of water present in formulation
$V_{\text{excluded solvents}}$	total volume of solvents excluded by EPA regulation

The above definition may vary in various countries thus the proper definition should be obtained from the appropriate authorities. Examples of other definitions are included in Chapter 17.1.

The weight percent of the volatile content in waterborne aerosol paints is determined by releasing the propellant from can, testing the remaining paint for water content using the Karl Fischer method, and determining non-volatiles.[160] The VOC content in a solvent-borne automotive paints is determined by the simulation of VOC loss during baking using laboratory panels.[161]

REFERENCES

1 ASTM D 2106-07(2012). Standard test method for determination of amine acid acceptance (alkalinity) of halogenated organic solvent.

2 ASTM D 1614-09. Standard test method for alkalinity in acetone.
ISO 755-2-81. Butan-1-ol for industrial use - Methods of test - Part 2: Determination of acidity -Titrimetric method. Withdrawn 2002.
ISO 756-2-81. Propan-2-ol for industrial use - Methods of test - Part 2: Determination of acidity - Titrimetric method.
ISO 757-2-82. Acetone for industrial use - Methods of test - Part 2: Determination of acidity to phenolphthalein - Titrimetric method. Withdrawn 2002.

3 ASTM D 2989-01(2011). Standard test method for acidity-alkalinity of halogenated solvents and their admixtures.
ISO 1393-77. Liquid halogenated hydrocarbons for industrial use - Determination of acidity - Titrimetric method. Withdrawn 2002.
ISO 3363-76. Fluorochlorinated hydrocarbons for industrial use - Determination of acidity - Titrimetric method.

4 ASTM D 847-08. Standard test method for acidity of benzene, toluene, xylenes, solvent naphthas, and similar industrial aromatic hydrocarbons.

5 ASTM D 1613-06(2012). Standard test method for acidity in volatile solvents and chemical intermediates used in paint, varnish, lacquer, and related products.

6 ASTM D 2942-02(2013). Standard test method for total acid acceptance of halogenated organic solvents (nonreflux method).

7 ASTM D 3444-00(2010)e1. Standard test method for total acid number of trichlorotrifluoroethane.

8 ASTM E 659-13. Standard test method for autoignition temperature of liquid chemicals.
AS 1896-1976. Method of test for ignition temperature of gases and vapors.

9 ASTM E 6006-11. Standard guide for assessing biodegradability of hydraulic fluids.
BS 6068-2.34-88. Water quality. Physical, chemical and biochemical methods. Method for the determination of the chemical oxygen demand.

DIN 38409-41-80. German standard methods for examination of water, waste water and sludge. Summary action and material characteristic parameters (group H). Determination of the chemical oxygen demand (COD) in the range over 15 mg/l.
ISO 5815-2003. Water quality - Determination of biochemical oxygen demand after 5 days - Dilution and seeding method.
ISO 6060-89. Water quality - Determination of the chemical oxygen demand.
JIS K 0400-20-10-99. Water quality - Determination of the chemical oxygen demand.
JIS K 0400-21-10-99. Water quality - Determination of biochemical oxygen demand after 5 days. Dilution seeding method. Withdrawn.
JIS K 3602-90. Apparatus for the estimation of biochemical oxygen demand with microbial sensor.

10 ASTM D 850-11. Standard test method for distillation of industrial aromatic hydrocarbons and related materials.
BS 7392-90. Method for determination of distillation characteristics of petroleum products (ISO 3405).
918-83. Volatile organic liquids for industrial use - Determination of distillation characteristics.
ISO 3405-2011. Petroleum products - Determination of distillation characteristics.
ISO 4626-80. Volatile organic liquids - determination of boiling range of organic solvents used as raw materials.
JIS K 2254-98. Petroleum products - Determination of distillation characteristics.

11 ASTM D 1078-11. Standard test method for distillation range of volatile organic liquids.
BS 4591-90. Method of determination of distillation characteristics of organic liquids (other than petroleum products) (ISO 918).
JIS K 0066-92. Test methods for distillation of chemical products.

12 ASTM D 3272-76(2003). Standard practice for vacuum distillation of solvents from solvent-reducible paints for analysis. Withdrawn 2008.

13 ASTM D 5399-09. Standard test method for boiling point distribution of hydrocarbon solvents by gas chromatography.
ISO 3924-2010. Petroleum products - Determination of boiling range distribution - Gas chromatography method.

14 ASTM D 5776-13. Standard method for bromine index of aromatic hydrocarbons by electrometric titration.
ISO 3839-96. Petroleum products - Determination of bromine number of distillates and aliphatic olefins - Electrometric method.
JIS K 2605-96. Petroleum distillates and commercial aliphatic olefins - Determination of bromine number - Electrometric method.

15 ASTM D 1492-96. Standard test method for bromine index of aromatic hydrocarbons by coulometric titration.

16 ASTM D 240-97. Standard test method for heat of combustion of liquid hydrocarbon fuels by bomb calorimeter.
BS 7420-91. Guide for determination of calorific values of solid, liquid and gaseous fuels (including definitions).
DIN 5499-72. Gross and net Calorific values. Terms.
DIN 51900-1-00. Determination of gross calorific value of solid and liquid fuels by the bomb calorimeter and calculation of net calorific value. Part 1: Principles, apparatus, methods.
DIN 51900-2-03. Testing of solid and liquid fuels. Determination of gross calorific value by bomb calorimeter and calculation of net calorific value. Method of using isothermal water jacket.
DIN 51900-3-05. Testing of solid and liquid fuels. Determination of gross calorific value by bomb calorimeter and calculation of net calorific value. Method of using adiabatic jacket.
JIS K 2279-03. Crude petroleum and petroleum products - Determination and estimation of heat of combustion.

17 ASTM D 1405M-08(2013). Standard test method for estimation of net heat of combustion of aviation fuels.

18 ASTM D 5468-02(2007). Standard test method for gross calorific value of waste materials.

19 ASTM D 5468-02(2007). Standard test method for gross calorific and ash value of waste materials.

20 ASTM F 1105-09. Standard test method for preparing aircraft cleaning compounds, liquid-type, temperature sensitive, or solvent-based, for storage stability testing.

21 ASTM D 3698-04(2010). Standard practices for solvent vapor degreasing operations.

22 ASTM D 4579-00(2012). Standard practice for handling an acid degreaser or still.

23 ASTM D 848-09. Standard test method for acid wash color of industrial aromatic hydrocarbons.
ISO 5274-79. Aromatic hydrocarbons - Acid wash test. Withdrawn 2002.
ISO 755-3-81. Butan-1-ol for industrial use - Methods of test - Part 3: Sulfuric acid color test. Withdrawn

2002.
JIS K 0072-98. Testing method of color after treatment with sulfuric acid.

24 ASTM D 1686-10. Standard test method for color of solid aromatic hydrocarbons and related materials in the molten state (platinum-cobalt scale).
BS 5339-76. Method of measurement of color in Hazen units (platinum-cobalt scale) of liquid chemical products (ISO 2211).
ISO 2211-73. Liquid chemical products - Measurement of color in Hazen units (platinum-cobalt scale).
ISO 6271-2004. Clear liquids - Estimation of color by the platinum-cobalt scale.
JIS K 0071-98. Testing methods for color of chemical products - Part 1. Estimation of color in Hazen units (platinum-cobalt scale).

25 ASTM D 2108-10. Standard test method for color of halogenated organic solvents and their admixtures (platinum-cobalt scale).

26 ASTM D 5386-10. Standard test method for color of liquids using tristimulus colorimetry.

27 ASTM D 3316-06(2011). Standard test method for stability of perchloroethylene with copper.

28 ASTM D 849-11. Standard test method for copper strip corrosion by industrial aromatic hydrocarbons.
ISO 2160-98. Petroleum products - Corrosiveness of copper - Copper strip test.
JIS K 2513-00. Petroleum products - Corrosiveness to copper - Copper strip test. SFS-EN ISO 2160. Petroleum products. Corrosiveness to copper. Copper strip test.

29 ASTM D 2943-02(2012). Standard test method for aluminum scratch of 1,1,1-trichloroethane to determine stability.

30 ASTM D 1217-12. Standard test method for density and relative density (specific gravity) of liquids by Bingham pycnometer.

31 ASTM D 891-09. Standard test method for specific gravity, apparent, of liquid industrial chemicals.
BS 4522-88. Method for determination of absolute density at 20ºC of liquid chemical products for industrial use (ISO 758).
JIS K 0061-01. Test methods for density and relative density of chemical products.

32 ASTM D 2111-10. Standard test methods for specific gravity of halogenated organic solvents and their admixtures.

33 ASTM D 1555-09. Standard test method for calculation of volume and weight of industrial aromatic hydrocarbons.

34 ASTM D 1555M-08e1. Standard test method for calculation of volume and weight of industrial aromatic hydrocarbons (metric).
ISO 5281-80. Aromatic hydrocarbons - Benzene, xylene and toluene - Determination of density at 20ºC. Withdrawn 2002.
SFS 3772-76. Determination of density of liquids at 20ºC.

35 ASTM D 1720-03(2012). Standard test method for dilution ratio of active solvents in cellulose nitrate solutions.

36 ASTM D 5062-09. Standard test method for resin solution dilutability by volumetric/gravimetric determination.

37 ASTM D 1476-02(2012). Standard test method for heptane miscibility of lacquer solvents

38 ASTM D 1722-09. Standard test method for water miscibility of water-soluble solvents.

39 ASTM D 5226-98(2010)e1. Standard practice for dissolving polymer materials.

40 ASTM D 2257-98(2012). Standard test method for extractable mater in textiles.

41 ASTM D 1169-11. Standard test method for specific resistance (resistivity) of electrical insulating liquids.
JIS C 0052-95. Environmental testing procedure of electronic and electrical resistance to solvents.

42 ASTM D 4308-13. Standard test method for electrical conductivity of liquid hydrocarbons by precision meter.

43 ASTM D 1816-12. Standard test method for dielectric breakdown voltage of insulating oils of petroleum origin using VDE electrodes.

44 ASTM D 3300-12. Standard test method for dielectric breakdown voltage of insulating oils of petroleum origin under impulse conditions.

45 ASTM F 791-96(2008). Standard test method for stress crazing of transparent plastics.
ISO 22088-1-06. Plastics -- Determination of resistance to environmental stress cracking (ESC) -- Part 1: General guidance.
ISO 22088-2-06. Plastics -- Determination of resistance to environmental stress cracking (ESC) -- Part 2: Constant tensile load method.
ISO 22088-3-06. Plastics -- Determination of resistance to environmental stress cracking (ESC) -- Part 3: Bent strip method.

ISO 22088-4-06. Plastics -- Determination of resistance to environmental stress cracking (ESC) -- Part 4: Ball or pin impression method.
ISO 22088-5-06. Plastics -- Determination of resistance to environmental stress cracking (ESC) -- Part 5: Constant tensile deformation method.
ISO 22088-6-06. Plastics -- Determination of resistance to environmental stress cracking (ESC) -- Part 6: Slow strain rate method.
46 ASTM D 4508-10. Standard test method for chip impact strength of plastics.
47 ASTM D 1901-10. Standard test method for relative evaporation time of halogenated organic solvents and their admixtures.
48 ASTM E 1232-07(2013). Standard test method for temperature limit of flammability of chemicals.
49 ASTM E 681-09. Test method for concentration limits of flammability of chemicals.
BS 6713-3-86. Explosion protection systems. Method for determination of explosion indices of fuel/air mixtures other than dust/air and gas/air mixtures (ISO 6184-3).
50 ASTM D 3828-12a. Standard test method for flash point by small scale closed tester.
AS 2106.0-05. Methods for determination of flash point of flammable liquids (closed cup) -General.
AS/NZS 2106.1-99. Methods for the determination of the flash point of flammable liquids (closed cup) - Abel closed cup method.
ISO 13736-13. Determination of flash point -- Abel closed-cup method
51 ASTM D 1310-01(2007). Standard test method for flash point and fire point of liquids by tag open-cup apparatus.
52 ASTM D 56-05(2010). Standard test method for flash point by tag closed tester.
53 ASTM D 92-12b. Standard test method for flash and fire points by Cleveland open cup.
ISO 2592-2000. Petroleum product - Determination of flash and fire points - Cleveland open cup method.
SFS-EN 22592. Petroleum products. Determination of flash and fire points. Cleveland open cup method (ISO 2592). Withdrawn.
54 ASTM D 93-13. Standard test methods for flash-point by Pensky-Martens closed cup tester.
AS/NZS 2106.2-99. Methods for determination of the flash point of flammable liquids (closed cup) - Pensky-Martens closed cup method.
ISO 2719-02. Petroleum products and lubricants - Determination of flash point - Pensky-Martens closed cup method.
SFS-EN 22719. Petroleum products and lubricants. Determination of flash point. Pensky-Martens closed cup method (ISO 2719). Withdrawn.
55 ASTM D 3941-90(2007). Standard test method for flash point by the equilibrium method with a closed-cup apparatus.
AS/NZS 2106.3-99. Methods for the determination of the flash point of flammable liquids (closed cup) - Flash/no flash test - Rapid equilibrium method.
AS/NZS 2106.4-99. Methods for the determination of the flash point of flammable liquids (closed cup) - Determination of flash point - Rapid equilibrium method.
AS/NZS 2106.5-99. Methods for the determination of the flash point of flammable liquids (closed cup) - Flash/no flash test - Closed cup equilibrium method.
AS/NZS 2106.6-99. Methods for the determination of the flash point of flammable liquids (closed cup) - Determination of flash point - Closed cup equilibrium method.
ISO 1516-02. Paints, varnishes, petroleum and related products - Flash/no flash test - Closed cup equilibrium method.
ISO 1523-02. Paints, varnishes, petroleum and related products - Determination of flash point - Closed cup equilibrium method.
ISO 3679-04. Paints, varnishes, petroleum and related products - Determination of flash point - Rapid equilibrium method.
ISO 3680-04. Paints, varnishes, petroleum and related products - Flash/no flash test - Rapid equilibrium method.
SFS-EN 456-93. Paints, varnishes, and related products. Determination of flash point. Rapid equilibrium method (ISO 3679).
56 ASTM E 502-07(2013). Standard test method for selection and use of ASTM standards for the determination of flash point of chemicals by closed cup methods.
57 ASTM D 1015-05(2010). Standard test method for freezing points of high-purity hydrocarbons.
JIS K 0065-92. Test method for freezing point of chemical products.
58 ASTM D 1016-05(2010). Standard test method for purity of hydrocarbons from freezing points.
59 ASTM D 852-13. Standard test method for solidification point of benzene.

ISO 5278-80. Benzene - Determination of crystallizing point. Withdrawn 2002.
60 ASTM D 4755-95(2010). Standard test method for free halogenated organic solvents and their admixtures.
61 ASTM D 2306-96. Standard test method for C8 hydrocarbon analysis by gas chromatography.
DIN 51437-04. Testing of benzene and benzene homologues. Determination of the content of non-aromatics, toluene and C8-aromatics in benzene. Gas chromatography.
62 ASTM D 3797-05. Standard test method for analysis of o-xylene by gas chromatography.
63 ASTM D 3798-03. Standard test method for analysis of p-xylene by gas chromatography. Withdrawn 2009.
64 ASTM D 4492-10. Standard test method for analysis of benzene by gas chromatography.
65 ASTM D 3271-87(2012). Standard test method for direct injection of solvent reducible paints into a gas chromatograph for solvent analysis.
66 ASTM D 5830-95(2006). Standard test method for solvent analysis in hazardous waste using gas chromatography.
67 ASTM D 4757-98. Standard practice for placarding solvent vapor degreasers. Withdrawn 2004.
68 ASTM D 3844-02(2008). Standard guide for labeling halogenated hydrocarbon solvent containers.
69 ASTM D 1296-01(2012). Standard test method for odor of volatile solvents and diluents.
ISO 2498-74. Methyl ethyl ketone for industrial use - Examination for residual odor. Withdrawn 2002.
70 ASTM E 679-04(2011). Standard practice for determination of odor and taste thresholds by forced-choice ascending concentration series method.
71 ASTM E-769-85(2004). Standard test methods for odor of methanol, ethanol, n-propanol, and isopropanol.
72 ASTM E 1075-85(2004). Standard test methods for odor of ethylene glycol, diethylene glycol, triethylene glycol, propylene, glycol, and dipropylene glycol and taste of propylene glycol.
73 ASTM D 4494-95(2010)e1. Standard test method for detecting residual odor of drycleaning grade perchloroethylene.
74 ASTM D 268-01(2012). Standard guide for sampling and testing volatile solvents and chemical intermediates for use in paint and related coatings and material.
75 ASTM D 1353-13. Standard test method for nonvolatile matter in volatile solvents for use in paint, varnish, lacquer, and related products.
76 ASTM D 5286-01(2011). Standard test methods for determination of transfer efficiency under general conditions for spray application of paints.
77 ASTM D 1617-07(2012). Standard test method for ester value of solvents and thinners.
78 ASTM D 2110-00(2012). Standard test method for pH of water extractions of halogenated organic solvents and their admixtures.
79 ASTM D 3545-06(2012). Standard test method for alcohol content and purity of acetate esters by gas chromatography.
80 ASTM D 6229-06(2010). Standard test method for trace benzene in hydrocarbon solvents by capillary gas chromatography.
81 ASTM D 4534-99. Standard test method for benzene content of cyclic products by gas chromatography. Withdrawn 2006.
82 ASTM D 7011-10a. Standard test method for determination of trace thiophene in refined benzene by gas chromatography and sulfur selective detection.
DIN 51438-05. Testing of benzene and benzene homologues. Determination of the content of thiophene in benzene. Gas chromatography.
83 ASTM D 5713-09. Standard test method for analysis of high purity benzene for cyclohexane feedstock by capillary gas chromatography.
84 ASTM D 3447-01. Standard test method for purity of halogenated organic solvents. Withdrawn 2004.
CAN/CGSB 1-GP-71 No. 73-96. Methods of testing paints and pigments. Beilstein test for chlorinated solvents. Withdrawn.
85 ASTM D 3742-98. Standard test method for 1,1,1-trichloroethane content. Withdrawn 2003.
86 ASTM D 2804-02(2012). Standard test method for purity of methyl ethyl ketone by gas chromatography.
87 ASTM D 3329-03(2009). Standard test method for purity of methyl isobutyl ketone by gas chromatography.
88 ASTM D 3257-06(2012). Standard test methods for aromatics in mineral spirits by gas chromatography.
89 ASTM D 1685-05. Standard test method for traces of thiophene in benzene by spectrophotometry. Withdrawn 2009.
90 ASTM D 2031-97. Standard test method for reducing substances in refined pyridine. Withdrawn 2003.
91 ASTM D 3961-98. Standard test method for trace quantities of sulfur in liquid aromatic hydrocarbons by oxidative microcoulometry. Withdrawn 2004.
ISO 5282-82. Determination of sulfur content - Pitt-Ruprecht reduction and spectrophotometric

determination method.
ISO 8754-03. Petroleum products - Determination of sulfur content - Energy-dispersive X-ray fluorescence method.
SFS-EN ISO 8754. Petroleum products. Determination of sulfur content. Energy-dispersive X-ray fluorescence method.
ISO 14596-07. Petroleum products - Determination of sulfur content - Wavelength-dispersive X-ray fluorescence method.

92 ASTM D5194-13. Standard test method for trace chloride in liquid aromatic hydrocarbons.

93 ASTM D 5808-09a. Standard test method for determining organic chloride in aromatic hydrocarbons and related chemicals by microcoulometry.

94 ASTM E 299-08. Standard test method for trace amounts of peroxides in organic solvents.

95 ASTM D 4952-12. Standard test method for qualitative analysis for active sulfur species in fuels and solvents (Doctor Test).
ISO 5275-03. Petroleum products and hydrocarbon solvents - Detection of thiols and other sulfur species - Doctor test.

96 ASTM D 2109-01(2011). Standard test methods for nonvolatile matter in halogenated organic solvents and their admixtures.
BS 5598-3-79. Methods of sampling and test for halogenated hydrocarbons. Determination of residue on evaporation (ISO 2210). Withdrawn.
ISO 759-81. Volatile organic liquids for industrial use - Determination of dry residue after evaporation on water bath - General method.
ISO 2210-72. Liquid halogenated hydrocarbons for industrial use - Determination of residue on evaporation. Withdrawn 2002.
ISO 5277-81. Aromatic hydrocarbons - Determination of residue on evaporation of products having boiling points up to 150ºC. Withdrawn 2002.
JIS K 0067-92. Test methods for loss and residue of chemical products.
SFS 3773-77. Determination of residue on evaporation.

97 ASTM D 1364-02(2012). Standard test method for water in volatile solvents (Karl Fischer reagent titration method).
BS 2511-70. Methods for determination of water (Karl Fischer method).
ISO 6191-81. Light olefins for industrial use - Determination of traces of water - Karl Fischer method. Withdrawn 2002.
ISO 8917-88. Light olefins for industrial use - Determination of water - Guidelines for use of in-line analyzers. Withdrawn 2002.
SFS 3774-76. Determination of water by the Karl Fischer method.

98 ASTM D 3401-97(2012). Standard test methods for water in halogenated organic solvents and their admixtures.

99 ASTM D 3443-00(2010)e1. Standard test method for chloride in trichlorotrifluoroethane.

100 ASTM D 3741-00(2010). Standard test methods for appearance of admixtures containing halogenated organic solvents.

101 ASTM D 611-12. Standard test methods for aniline point and mixed aniline point of petroleum products and hydrocarbon solvents.
ISO 2977-97. Petroleum products and hydrocarbon solvents - Determination of aniline point and mixed aniline point.

102 ASTM D 1363-06(2011). Standard test method for permanganate time of acetone and methanol.
ISO 757-4-83. Acetone for industrial use - Methods of test - Part 4: Determination of permanganate time. Withdrawn 2002.

103 ASTM D 1612-05. Standard test method for acetone in methanol. Withdrawn 2011.

104 ASTM D 1218-12. Standard test method for refractive index and refractive dispersion of hydrocarbon liquids.
ISO 5661-83. Petroleum products - Hydrocarbon liquids - Determination of refractive index.
JIS K 0062-92. Test methods for refractive index of chemical products.

105 ASTM F 151-97. Standard test method for residual solvents in flexible barrier materials. Withdrawn 2004.
ISO 17052-07. Rubber, raw -- Determination of residual monomers and other volatile low-molecular-mass compounds by capillary gas chromatography -- Thermal desorption (dynamic headspace) method.

106 ASTM D 1133-13. Standard test method for Kauri-butanol value of hydrocarbon solvents.

107 ASTM D 2779-92(2012). Standard test method for estimation of solubility of gases in petroleum liquids.

108 ASTM E 1195-01(2008). Standard test method for determining a sorption constant, K_{oc}, for an organic

chemical in soil and sediments. Withdrawn 2013.
109 ASTM D 5404-12. Standard practice for recovery of asphalt from solution using the rotary evaporator.
110 ASTM D 304-11. Standard specification for n-butyl alcohol (butanol).
BS 508-1-86. Butan-1-ol for industrial use. Specification for butan-1-ol.
BS 508-2-84. Butan-1-ol for industrial use. Methods of test.
JIS K 1504-93. Butanol. Withdrawn.
JIS K 8810-07. 1-butanol.
111 ASTM D 319-04. Standard specification for amyl alcohol (synthetic). Withdrawn 2010.
112 ASTM D 331-11. Standard specification for 2-ethoxyethanol.
113 ASTM D 770-11. Standard specification for isopropyl alcohol.
BS 1595-1-86. Propan-2-ol (isopropyl alcohol) for industrial use. Specification for propan-2-ol (isopropyl alcohol).
BS 1595-2-84. Propan-2-ol (isopropyl alcohol) for industrial use. Methods of test.
ISO 756-1-81. Propan-2-ol for industrial use - Methods of test - Part 1: General.
JIS K 1522-12. Isopropyl alcohol.
114 ASTM D 1007-11. Standard specification for sec-butyl alcohol.
ISO 2496-73. sec-butyl alcohol for industrial use - List of methods of test. Withdrawn 2002.
JIS K 1523-78. 2-butanol. Withdrawn.
115 ASTM D 1152-06(2012). Standard specification for methanol (methyl alcohol).
BS 506-1-87. Methanol for industrial use. Specification for methanol.
BS 506-2.84. Methanol for industrial use Methods of test.
CAN/CGSB-3-GP-531M. Methanol, technical.
ISO 1387-82. Methanol for industrial use - Methods of test. Withdrawn 2002.
JIS K 1501-05. Methanol.
116 ASTM D 1719-95. Standard specification for isobutyl alcohol.
117 ASTM D 1969-96. Standard specification for 2-ethylhexanol (synthetic).
BS 1835-91. Specification for 2-ethylhexan-1-ol for industrial use.
118 ASTM D 2627-08(2012). Standard specification for diacetone alcohol.
BS 549-70. Specification for diacetone alcohol.
ISO 2517-74. Diacetone alcohol for industrial use - List of methods of test. Withdrawn 2002.
119 ASTM D 3128-07(2013). Standard specification for 2-methoxyethanol.
120 ASTM D 3622-11. Standard specification for 1-propanol (n-propyl alcohol).
JIS K 8838-95. 1-propanol.
121 ASTM D 841-13. Standard specification for nitration grade toluene.
AS 3529-1988. Solvent - Toluene.
ISO 5272-79. Toluene for industrial use - Specification.
JIS K 8680-06. Toluene.
122 ASTM D 843-06(2011)e1. Standard specification for nitration grade xylene.
ISO 5280-79. Xylene for industrial use - specification.
JIS K 8271-07. Xylene.
123 ASTM D 4734-12. Standard specification for refined benzene-545.
124 ASTM D 5136-09(2013). Standard specification for high purity p-xylene.
125 ASTM 5211-12. Standard specification for xylenes for p-xylene feedstock.
126 ASTM D 5471-10. Standard specification for o-xylene 980.
127 ASTM D 5871-12. Standard specification for benzene for cyclohexane feedstock.
ISO 5721-79. Benzene for industrial use - Specification. Withdrawn 2002.
128 ASTM D 3734-05(2010). Standard specification for high-flash aromatic naphthas.
129 ASTM D 5309-08(2013)e1. Standard specification for cyclohexane.
130 ASTM D 235-02(2012). Standard specification for mineral spirits (petroleum spirits) (hydrocarbon dry cleaning solvent).
AS 3530-2009. Solvents - Mineral turpentine and white spirit.
BS 245-76. Specification for mineral solvents (white spirit and related hydrocarbon solvents) for paints and other purposes.
131 ASTM D 1836-07(2013). Standard specification for commercial hexanes.
132 ASTM D 3735-07(2012). Standard specification for VM&P naphthas.
133 ASTM D 740-11. Standard specification for methyl ethyl ketone.
134 ASTM D 4360-11. Standard specification for n-amyl ketone.
135 ASTM D 329-07(2013). Standard specification for acetone.

BS 509-1-87. Acetone for industrial use. Specification for acetone.
BS 509-2-84. Acetone for industrial use. Methods of test.
CAN/CGSB-15.50-92. Technical grade acetone.
ISO 757-1-82. Acetone for industrial use - Methods of test - Part 1: General. Withdrawn 2002.
JIS K 1503-09. Acetone.
SFS 3775 ISO/R 757. Acetone for industrial use. Methods of test. Withdrawn.
136 ASTM D 740-11. Standard specification for methyl ethyl ketone.
CAN/CGSB-15.52-92. Technical grade methyl ethyl ketone.
ISO 2597-73. Methyl ethyl ketone for industrial use - List of methods of test. Withdrawn 2002.
JIS K 1524-12. Methyl ethyl ketone.
137 ASTM D 1153-12. Standard specification for methyl isobutyl ketone.
ISO 2499-74. Methyl isobutyl ketone for industrial use - List of methods of test. Withdrawn 2002.
138 ASTM D 2917-07(2013). Standard specification for methyl isoamyl ketone.
ISO 2500-74. Ethyl isoamyl ketone for industrial use - List of methods of test. Withdrawn 2002.
139 ASTM D 5137-07(2013). Standard specification for hexyl acetate.
140 ASTM D 1718-09. Standard specification for isobutyl acetate (95% grade).
BS 551-90. Specification for butyl acetate for industrial use.
141 ASTM D 2634-07(2013). Standard specification for methyl amyl acetate (95% grade).
142 ASTM D 3130-11. Standard specification for n-propyl acetate (96% grade).
143 ASTM D 3131-07(2013). Standard specification for isopropyl acetate (99% grade).
BS 1834-68. Specification for isopropyl acetate.
144 ASTM D 3540-12. Standard specification for primary amyl acetate, synthetic (98% grade).
145 ASTM D 3728-08(2012). Standard specification for 2-ethoxyethyl acetate (99% grade).
146 ASTM D 5164-05(2011). Standard specification for propylene glycol and dipropylene glycol.
JIS K 1530-78. Propylene glycol. Withdrawn
147 ASTM D 4701-00(2011). Standard specification for technical grade methylene chloride.
ISO 1869-77. Methylene chloride for industrial use - List of methods of test. Withdrawn 2002.
JIS K 1516-84. Methyl chloride. Withdrawn.
148 ASTM D 4079-00(2011). Standard specification for vapor-degreasing grade methylene chloride.
149 ASTM D 4080-00(2011). Standard specification for trichloroethylene, technical and vapor-degreasing grade.
ISO 2212-72. Trichloroethylene for industrial use - Methods of test. Withdrawn 2002.
JIS K 1508-82. Trichloroethylene. Withdrawn.
150 ASTM D 4081-00(2011). Standard specification for drycleaning-grade perchloroethylene.
ISO 2213-72. Perchloroethylene for industrial use - Methods of test. Withdrawn 2002.
JIS K 1521-82. Perchloroethylene. Withdrawn.
151 ASTM D 4126-02(2012). Standard specification for vapor-degreasing grade and general solvent grade 1,1,1-trichloroethane.
AS 2871-1988. Solvents. 1,1,1-trichloroethane (inhibited).
ISO 2755-73. 1,1,1-trichloroethane for industrial use - List of methods of test. Withdrawn 2002.
JIS K 1600-81. 1,1,1-trichloroethane. Withdrawn.
152 ASTM D 4376-02(2012). Standard specification for vapor-degreasing grade perchloroethylene.
153 ASTM D 4206-96(2013). Standard test method for sustained burning of liquid mixtures using small scale open-cup apparatus.
ISO 9038-13. Determination of sustained combustibility of liquids.
154 ASTM E 1194-07. Standard test method for vapor pressure. Withdrawn 2013.
ISO 3007-99. Petroleum products and crude petroleum - Determination of vapor pressure - Reid method.
155 ASTM D 2879-10. Standard test method for vapor pressure-temperature relationship and initial decomposition temperature of liquids by isoteniscope.
156 ASTM D 4486-10. Standard test method for kinematic viscosity of volatile and reactive liquids.
DIN EN ISO 3104. Petroleum products. Transparent and opaque liquids. Determination of kinematic viscosity and calculation of dynamic viscosity.
ISO 3104-94. Petroleum products - Transparent and opaque liquids - Determination of kinematic viscosity and calculation of dynamic viscosity.
SFS-EN ISO 3104. Petroleum products. Transparent and opaque liquids. Determination of kinematic viscosity and calculation of dynamic viscosity. Withdrawn
157 ASTM D 88-07(2013). Standard test method for Saybolt viscosity.
158 ASTM D 1545-13. Standard test method for viscosity of transparent liquids by bubble time method.

159 ASTM D 5201-05a(2010). Standard practice for calculating formulation physical constants of paints and coatings.
ISO 11890-1-07. Paints and varnishes - Determination of volatile organic compound content (VOC) - Part 1: Difference method.
ISO 11890-2-13. Paints and varnishes - Determination of volatile organic compound (VOC) content - Part 2: Gas-chromatographic method.
160 ASTM D 5325-03(2008)e1. Standard test method for determination of weight percent volatile content of water-borne aerosol paints.
161 ASTM D 5087-02(2008). Standard test method for determining amount of volatile organic compound (VOC) released from solventborne automotive coatings and available for removal in a VOC control device (Abatement)

14.2 SPECIAL METHODS OF SOLVENT ANALYSIS

14.2.1 USE OF BREATH MONITORING TO ASSESS EXPOSURES TO VOLATILE ORGANIC SOLVENTS

Myrto Petreas
Hazardous Materials Laboratory, Department of Toxic Substances Control, California Environmental Protection Agency, Berkeley, CA, USA

14.2.1.1 Principles of breath monitoring

Exposure to organic solvents may occur as a result of occupation, diet, lifestyles, hobbies, etc., in a variety of environments (occupational, residential, ambient). Solvents reach the organism through inhalation, ingestion and dermal exposure. The magnitude of exposures, however, may be modulated by factors such as the use of protective equipment (decrease) or physical exertion (increase). All sources and routes of exposure are integrated in the resulting internal dose. The dose at the target organ may trigger mechanisms that eventually may result in irreversible biological changes and disease. Cellular repair mechanisms and individual susceptibility have a significant effect on the onset of disease, resulting in a broad distribution of outcomes. This continuum between exposure to organic solvents and disease can be depicted, in a simplified way, in Figure 14.2.1.1. Biological monitoring focuses on the elucidation of the first step of this process; i.e., the relationship between environmental exposure and internal dose. Whereas the dose at the target organ is the biologically important, concentrations of the solvent (or its metabolites) may be more easily measured in other fluid or tissue samples, such as blood, breath, urine, etc.

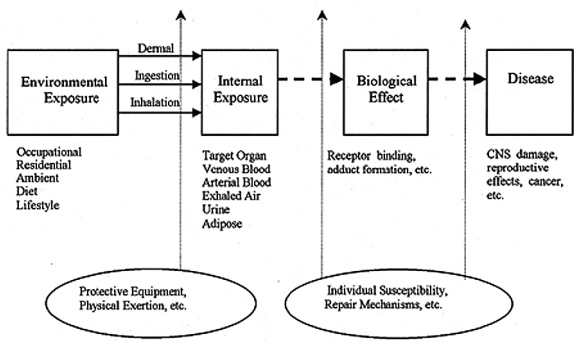


Figure 14.2.1.1. Relationship between exposure to volatile organic solvents and potential outcomes.

Traditional workplace monitoring relied on measurements of airborne contaminant concentrations at the breathing zone, and comparisons to reference values or regulatory benchmarks, such as the Threshold Limit Values (TLVs) and the Permissible Exposure Limits (PELs) in the USA, and similar values promulgated by the European Union and other organizations. Air measurements, however, may not always represent actual personal exposures since workers may be exposed dermally and orally, or they may be using protective equipment. Over the last decade, workplace monitoring programs have expanded to include biological monitoring. Biological monitoring gives an estimate of the dose inside the body (or specific target organ) rather than the concentration of the solvent

in the external environment. Internal dose is defined as the amount of the solvent taken up by the whole organism (or a body compartment) over a specified period of time.[1] Depending on the chemical, the time of sampling and the tissue analyzed, the dose may reflect the amount of the chemical recently absorbed, the amount of the chemical stored (body burden), or the amount of the chemical bound to the active sites of a receptor. It is the dose at the receptor or sensitive tissue (the biologically effective dose) that is related to toxicity and/or damage. In general, the dose at the receptor cannot be measured because, at this time, available methodology is unacceptably invasive to be employed. On the other hand, biological monitoring allows measurements to be made on body fluids or tissues that would serve as surrogate measurements of the dose at the receptor. Certain conditions, however, are required for meaningful interpretation of the analytical results.

1. There should be adequate information on the absorption, distribution, biotransformation, metabolism, and elimination of the chemical in the body. This type of information will indicate what tissues to sample, for what compound (parent chemical or a metabolite) and at what time. The latter issue is very important with chemicals that are eliminated rapidly (i.e., those with short half-lives).
2. The concentration of the chemical (or its metabolite) to be measured in the selected medium (breath, blood, urine) must be in equilibrium with the concentration of the chemical at the target organ.
3. The assay has to be sensitive, in order to detect low levels of the compound before any adverse effects take place; specific, in order to link exposure to dose; and accurate and precise, in order to be reliable.

Very few chemicals have been adequately studied to allow biological monitoring according to the above criteria. This is, however, an expanding area, as indicated by the number of substances for which Biological Exposure Indices (BEIs) have been proposed by the American Conference of Governmental Industrial Hygienists (ACGIH). In the 1984-85 Threshold Limit Value (TLV) booklet there were BEIs for 10 chemicals; in the 1998 booklet there were 37 compounds with adopted BEIs.[2] BEIs are considered reference values intended as guidelines and do not determine whether the worker is at risk of disease. They are supplementary to TLVs in evaluating workers' exposures to workplace hazardous agents. The recommended values of BEIs are based on data correlating exposure intensity and biological effects from field studies and/or on pharmacokinetic treatment of data obtained from controlled human exposures. The BEIs developed by the ACGIH, assume 8-hour exposures for 5 days, followed by 2 days of non-exposure, and they strictly specify the time of sample collection.

A clear advantage of biological monitoring over environmental or personal monitoring is that the estimate of the internal dose takes into account all possible routes of entry (inhalation, ingestion and dermal exposure). In addition, exposures other than occupational, such as through diet, hobbies or residential air, all contribute to the internal dose, which is related to adverse effects. When the effect of occupational exposure alone needs to be evaluated, non-occupational exposures need to be assessed and controlled to allow interpretation of biological monitoring results. A special case is the evaluation of protective equipment in reducing workplace exposures.

Biological monitoring is limited by parameters that can affect the exposure and dose relationship. Such parameters include the following: biological conditions (age, sex, obe-

sity, pregnancy, disease), physical workload, or exposure to other agents (other chemicals, tobacco smoking, dietary components) that in some way interfere with the uptake, distribution, metabolism or elimination of the chemical in the body.[3-6] Such parameters may introduce large inter-individual variation in the resulting dose. When simulation techniques were used to evaluate the influence of these parameters, it was shown[6] that up to 100% bias may result from inter-individual variation in the metabolism of aromatic compounds. If these differences occur randomly, they will widen the confidence limits of the biological monitoring results, decreasing the statistical power of a study. This is just one example illustrating the care that must be taken when interpreting biological monitoring results.

In short, biological monitoring should be used with specific objectives, such as to evaluate exceedance of a reference or regulatory value; dermal or oral exposure not assessed by personal monitoring; efficacy of protective equipment; etc. Accordingly, current, recent or cumulative exposure may need to be assessed and, therefore, the appropriate chemical (parent or metabolite) should be monitored in the appropriate specimen, collected at the appropriate time, from the appropriate worker(s).

14.2.1.2 Types of samples used for biological monitoring

Of the various tissues/fluids that can be used for biological monitoring, the most common are blood, urine, and exhaled air because they are relatively easy to obtain.

Blood collection is the most invasive of the three and the chemical analysis may be subject to interferences because of the complex matrix. Additionally, concern over hepatitis and HIV infection, and confidentiality issues, make blood sampling less attractive for routine collection. Nevertheless, concentrations of a compound of interest in blood are easier to relate to concentrations at the target organ.

Analysis of urine samples allows elimination rates of the chemical or its metabolite(s) to be ascertained. However, measurements in urine require specimen collection under a schedule (first morning urine, or 24-hour sample) that can create logistical difficulties. The concentration of the contaminant, or its metabolite(s), is usually corrected for the dilution of the urine (specific gravity or, more commonly, creatinine correction) to be used as a measure of dose.

Collection of breath samples is the easiest of the three methods. It is noninvasive; it can take place almost anywhere; and the analytical matrix is usually very simple. The basic assumption underlying breath monitoring is the existence of gaseous equilibrium between the concentration of the vapor of interest in the alveolar air and in the arterial blood. This relationship must be established for every solvent for which biological monitoring by exhaled air analysis is considered. The apparent simplicity of breath sampling should not be overstated, however, and the limitations and pitfalls should be identified before any large scale, routine applications of breath monitoring can be envisioned. Since breath is a non-homogeneous mixture of air coming from different regions of the lung with varying ventilation, perfusion, and diffusion characteristics, some portion of the breath should be consistently identified and tested for its relationship to the blood concentration.

The ACGIH only recommends measurements in exhaled air when:[7]

- The chemical is poorly metabolized and, therefore, exhalation is the primary route of elimination;
- Sampling can occur when the effect of time and other circumstantial factors can be controlled
- The sampling method is well defined.

14.2.1.3 Fundamentals of respiratory physiology

In order for any inhaled solvent vapors to enter the blood circulation, they need to reach the alveoli, cross the gas-blood interface and dissolve in the blood. Gas is carried to the gas-blood interface by airways, while blood is carried by blood vessels. Since these functions take place in the lung, the essentials of respiratory physiology will be briefly reviewed.

The primary function of the lungs is to allow oxygen to move from the inhaled air into the arterial blood and to allow carbon dioxide to move from the venous blood to the exhaled air. Both oxygen and carbon dioxide move between air and blood by simple diffusion from an area of high partial pressure to an area of low partial pressure. The barrier between air and blood is less than 0.5 μm in thickness and has an area of between 50 to 100 m^2.[8] This barrier is very efficient for gas exchange by molecular diffusion, according to Fick's 2nd law.

The airways consist of a series of tubes that become narrower and shorter as they extend deeper into the lung. The first segment, the trachea, divides into two main bronchi, which in turn divide into lobar and segmental bronchi, which turn into terminal bronchioles. All these segments collectively constitute the anatomical dead space with a volume of about 150 mL for an adult male. The function of this conducting portion of the lung is to transport the inspired air into the gas exchange regions. The terminal bronchioles divide within a distance of 5 mm into respiratory bronchioles and alveolar ducts, which are completely lined with alveoli. This region of the lung is the respiratory zone where the gas exchange takes place. The volume of this zone (about 2,500 mL) makes up most of the lung volume.

14.2.1.3.1 Ventilation

Air is drawn into the lungs by contractions of the diaphragm and the intercostal muscles, which raise the rib cage, and flows to the terminal bronchioles by bulk flow. After that point, the velocity of the inspired air diminishes as the cross-sectional area of the airways increases dramatically. Thereafter, ventilation is carried out by molecular diffusion, which results in rapid exchange of gases.

Similarly to the airways, the pulmonary blood vessels form a series of branching tubes from the pulmonary artery to the capillaries and back to the pulmonary veins. The diameter of a capillary segment is about 10 μm, just large enough for a red blood cell. The capillaries form a dense network in the walls of the alveoli, with the individual capillary segments so short that the blood forms an almost continuous sheet around the alveoli, providing ideal conditions for gas exchange. In about one second, each red blood cell transverses two or three alveoli in the capillary network, achieving complete equilibration of oxygen and carbon dioxide between alveolar gas and capillary blood.

For an adult male at rest, a typical breathing frequency is 15 breaths per minute and a typical exhaled air volume (tidal volume), at rest, is about 500 mL. The total volume of air exhaled in 1 min is, therefore, about 7,500 mL. This is the minute volume total ventilation. The inhaled volume during the same time is slightly greater, since more oxygen is taken up than carbon dioxide released. Not all the inhaled air reaches the alveoli; the anatomical dead space (volume of conducting airways where no gas exchange takes place) contains approximately 150 mL of each breath. Therefore, the volume of fresh inhaled air that reaches the alveoli in 1 min is 5,250 mL [(500-150) mL/breath * 15 breaths/min = 5,250 mL/min].[8] This is the alveolar ventilation and it represents the volume of fresh air available for gas exchange in 1 min. The alveolar ventilation cannot be measured directly, but it can be calculated by measuring the minute volume and subtracting the anatomical dead space. The former is easily measured by collecting all the expired air in a bag. The volume of the anatomical dead space can be assumed to be 150 mL, with minimal variation for all adults, and the dead space ventilation can be calculated given a respiratory frequency. Subtraction of the dead space ventilation from the total ventilation (or minute volume) results in the alveolar ventilation. Pulmonary ventilation may be affected by chronic diseases such as asthma or pulmonary fibrosis, or even by transient hyperventilation or hypoventilation.

14.2.1.3.2 Partition coefficients

Whereas the rate of transfer of a solvent vapor between alveolar air and capillary blood is determined by its diffusivity, the equilibrium between these matrices is determined by the blood/air partition coefficient (λ). This is the ratio of the concentration of the vapor in blood and air at 37°C, at equilibrium. Partition coefficients are commonly determined *in vitro*, and occasionally *in vivo*.[2,9,10] Although considered constant at a particular temperature, partition coefficients may be affected by the composition of the blood. The blood/air partition coefficients of some industrial solvents were shown to increase by up to 60% after meals,[4] presumably due to an increase in lipid content of the blood.

Depending on the affinity of a gas or vapor for blood, the transfer from the alveoli to the capillaries may be diffusion-limited or perfusion-limited. The difference can be illustrated by examining two solvents, styrene and methyl chloroform. Because of the high solubility of styrene ($\lambda = 52$)[11] large amounts of it can be taken up by the blood, and the transfer is only diffusion-limited. On the other hand, methyl chloroform is not very soluble ($\lambda = 1.4$)[12] and its partial pressure rises rapidly to that of the alveolar air, at which point no net transfer takes place. The amount of methyl chloroform taken up by the blood will depend exclusively on the amount of available blood flow and not on the diffusion properties of the gas-blood interface. This kind of transfer is perfusion-limited.

It is the concentration in the mixed venous blood, however, that better reflects the concentration at the target organ. It has been shown that:[13]

$$P/Pv = \frac{\lambda}{\lambda + V/Q}$$

where:

P partial pressure in the alveoli and in the arterial blood leaving that region of the lung
Pv partial pressure in the venous blood coming to the lung

λ blood/air partition coefficient
V alveolar ventilation
Q blood flow of the lung region under consideration

The greater the blood/air partition coefficient, the closer the arterial concentration will be to the venous concentration.

The concentration in the alveolar air will reflect both arterial and venous blood if the blood/air partition coefficient of the vapor is greater than 5,[14] a criterion that applies to most industrial solvents. In a normal subject at rest, the ventilation-to-perfusion ratio (V/Q) ranges from 0.7 to 1.0, with an average of about 0.9.[15] Variations in the V/Q ratio exist in various parts of the lung because not all alveoli are ventilated and perfused in ideal proportions. The V/Q ratio may vary from 0.5 at the lung base to 3.0 at the apex,[16] and it becomes more homogeneous with physical exertion.[17] When the partition coefficient exceeds 10, however, even large degrees of ventilation/perfusion imbalance have very little effect on the relationship between alveolar and mixed venous solvent partial pressures.[14]

14.2.1.3.3 Gas exchange

When a person is exposed to a volatile organic solvent through inhalation, the solvent vapor diffuses very rapidly through the alveolar membranes, the connective tissues and the capillary endothelium and into the red blood cells or plasma. With respiratory gases the whole process takes less than 0.3 seconds.[15] This results in almost instantaneous equilibration between the concentration in alveolar air and in blood and, therefore, the ratio of the solvent concentration in pulmonary blood to that in alveolar air should be approximately equal to the partition coefficient. As the exposure continues, the solvent concentration in the arterial blood exceeds that in the mixed venous blood.[18] The partial pressures in alveolar air, arterial blood, venous blood and body tissues reach equilibrium at steady state. When the exposure stops, any unmetabolized solvent vapors are removed from the systemic circulation through pulmonary clearance. During that period the concentration in the arterial blood is lower than in the mixed venous blood[18] and the solvent concentration in alveolar air will depend on the pulmonary ventilation, the blood flow, the solubility in blood and the concentration in the mixed venous blood. These are the prevailing conditions when breath monitoring takes place after the end of the exposure[17] and therefore, samples of alveolar air after exposure should reflect concentrations in mixed venous blood. During exposure, however, alveolar air should reflect concentrations in arterial blood. Solvent concentrations in arterial and venous blood diverge even more with physical exertion.

To summarize, the uptake of solvent vapors through inhalation will depend on the following factors:[3]

1. Pulmonary ventilation, i.e., the rate at which fresh air (and solvent vapor) enters the lungs. This is determined by the metabolic rate and therefore depends on physical exertion. The concentration in alveolar air approaches that in inhaled air when the physical exertion is great. When exertion is low, the alveolar air concentration approaches the concentration in mixed venous blood.
2. Diffusion of the solvent vapor through the gas-blood interface. According to Fick's 2nd law, the rate of diffusion through the interface depends on the concentration gradient across the tissue membrane. Therefore, the concentration of the vapor leaving

the lungs depends on the amount of vapor entering the alveoli, on the solubility in blood (blood/gas partition coefficient) and on the flow rate of the blood through the lungs. For lipophilic chemicals, such as organic solvents that readily cross cellular membranes, diffusion is not the rate-limiting factor.[18]

3. The solubility of the vapor in the blood. The higher the blood/gas partition coefficient, the more rapidly the vapor will diffuse into the blood, until equilibrium is achieved. At equilibrium, the net diffusion between blood and air ceases, but the concentrations in air and blood may still be different. A highly soluble vapor will therefore demonstrate a lower alveolar air concentration relative to the inhaled air concentration during exposure, and a higher alveolar concentration relative to the inhaled air concentration after exposure.
4. The circulation of the blood through the lungs and tissues. This depends on the cardiac output and therefore, on physical exertion. For a soluble vapor, high exertion moves blood faster, increasing uptake.
5. The diffusion of the vapor through the tissue membranes, which depends on membrane permeability and is governed by Fick's law, as discussed in #2 above.
6. The solubility of the solvent vapor in the tissue. This reflects the tissue/blood partition coefficient of the solvent vapor and depends largely on the lipid composition of the particular tissue. Lipophilic vapors will exhibit high solubility in tissues with high fat content, freeing blood of vapors and increasing uptake.

Substances that are not well metabolized are eliminated primarily through the lungs[3] and to a lesser extent through the kidneys. During elimination through the lungs the same physiological principles apply in a reverse sequence.

14.2.1.4 Types of exhaled air samples

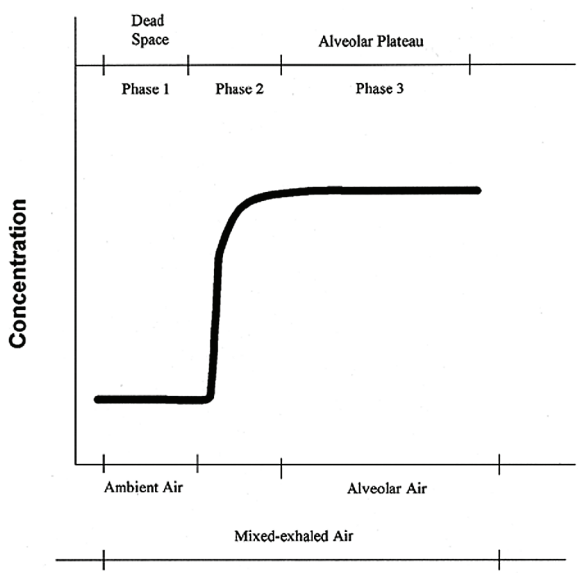


Figure 14.2.1.2. Solvent concentration in breath during exhalation.

Samples obtained from even a single breath may contain different concentrations of the solvent vapor of interest depending on the way the sample was collected. This is a result of the non-homogeneity of the exhaled air discussed previously. Figure 14.2.1.2 depicts a concentration curve of a solvent in exhaled air. When measurement takes place in an environment free of that solvent, the first part of the exhalation, corresponding to air in the anatomical dead space, will be solvent-free (Phase 1). Then the solvent concentration curve rises sharply reflecting exhalation of air from the respiratory zone of the lungs (Phase 2). This phase is followed by a slowly increasing plateau, indicating an alveolar steady state (Phase 3). The level of this plateau depends on the preceding ventilatory state of the subject, being higher for a hypoventilating subject and lower for a hyperventilating subject.[6] Sample collection at the

alveolar plateau constitutes end-exhaled air. When the total expiration is collected (combination of all three phases), the sample is considered mixed-exhaled air. Simultaneous monitoring of CO_2[6,19-21] or oxygen and nitrogen[22] has been suggested to normalize the measured solvent vapor concentrations in breath samples in order to facilitate data interpretation and comparisons.

The various sampling techniques must be evaluated and the one most applicable to the purpose of sampling chosen. The most commonly used sampling techniques based on physiological principles include mixed-exhaled air and end-exhaled air:

Mixed-exhaled air. This technique involves the collection of the entire volume of exhaled air. It corresponds to a mixture of the alveolar air with air from the dead space. The collection apparatus may also contribute to the dead space. Total dead space should be considered and the concentration adjusted, either by subtraction, or by regression against some other technique unaffected by the dead space. Timing of the breath collection is important here since the concentration of the air in the dead space may equal that of the air in the workroom if the sample is taken during exposure, or it may equal zero if taken after the end of exposure.

End-exhaled air. This technique excludes air from the dead space and collects only the last part of the breath, in order to estimate the concentration in the alveolar air which is in equilibrium with the arterial blood. Use of a Haldane-Priestley tube,[23] or simultaneous monitoring of the peaking of the temperature of the breath,[19] or its CO_2 concentration,[6,19,24] will assure a valid alveolar air sample.[6,25,26]

Two less frequently used techniques include breath holding or rebreathing to homogenize the breath sample:

Breath holding. For compounds that achieve equilibrium slowly, some researchers have used the breath holding technique, which involves holding the breath for 5-30 seconds prior to exhaling into the collection device. This results in a more constant concentration in the exhaled breath. The extent to which the lungs are filled with air (as with a deep inhalation) will affect the results. Kelman[14] showed, however, that breath holding is not necessary for solvents with blood/gas partition coefficients greater than 10.

Rebreathing. With this technique the subject rebreathes his/her exhaled air to provide a more homogenized breath sample. This technique is applicable to solvents that reach steady state very slowly. For prolonged rebreathing, removal of CO_2 to avoid pH changes and/or supply of oxygen may be necessary.[27]

14.2.1.5 Breath sampling methodology

The theoretical principles discussed above lead to two choices for collecting breath samples: Should a mixed-exhaled air or an end-exhaled air sample be collected?

End-exhaled air is becoming the standard for breath monitoring. Of the 36 chemicals with established BEIs,[7] end-exhaled air is recommended for 6, while earlier BEIs recommending mixed-exhaled air have been withdrawn. Beyond the regulatory arena, however, mixed-exhaled air continues to be used with satisfactory results.

Methodologically, the difference between these two types of samples is the control over which portion of the breath is collected. Many techniques[28-32] make use of the Haldane-Prestley tube to collect the last portion of the expiration. Earlier work[6,19] used the

simultaneous monitoring of CO_2 or temperature in the exhaled breath to identify the moment (CO_2 or temperature reaching a maximum) when air from the anatomical dead space has been purged and alveolar air can be sampled.

A variety of sampling techniques has been tried for measuring organic vapors in exhaled air. Table 14.2.1.1 shows a classification of these techniques. The main distinction is between direct reading instruments and transportable samples that require analysis in the laboratory. The former group covers the widest range, from simple detector tubes to High Resolution Mass Spectrometry.

Table 14.2.1.1. Techniques for sampling organic vapors in exhaled air.

Technique	References
A. SAMPLE COLLECTION	
A.1 END-EXHALED AIR	
Use of Haldane-Prestley tube	23, 25-26, 28-29, 31
Simultaneous CO_2 monitoring	6, 20-21, 24
Simultaneous temperature monitoring	19
B. SAMPLE ANALYSIS	
B.1 DIRECT READING INSTRUMENTS	
B.1.1 DETECTOR TUBES	
Colorimetric	33
B.1.2 GAS CHROMATOGRAPHS with various detectors and modified injector/inlet with mouthpiece	
GC/FID	52
GC/PID	25-26
GC/MS	24, 41-43
B.2 TRANSPORTABLE SAMPLE COLLECTORS	
B.2.1 CONTAINERS	
B.2.1.1 Rigid containers	
Stainless steel tubes	24
Glass tubes	9, 53-55, 61, 64
Aluminum tubes	28-29, 47
B.2.1.2 Flexible containers	
Tedlar bags	6, 49
Saran bags	54-55, 60
Mylar bags	
B.2.2 ADSORBENTS	
B.2.2.1 Tubes/cartridges containing:	
Charcoal	25-26, 28-29, 40
Tenax	31, 49
Silica gel	6
B.2.2.2 Felt/cloth	48

Specifically, detector tubes operating on colorimetric reaction principles have been used to determine the concentration of alcohol in breath for traffic safety.[33] Alcohol measurements in breath have been thoroughly studied and scrutinized because of the forensic and legal repercussions associated with the results. Portable devices have been developed for field use with on-site analysis of alcohol.[34-36] These portable devices could be adapted for use with other organic solvents of interest in industrial hygiene and occupational health.

Gas chromatographs (GCs) equipped with suitable detectors allow analysis of more than one solvent vapor at a time. The subject exhales through a valve system and the exhaled volume of air, or a fraction of it, is drawn into the GC.[21,26,37-39] Depending on the detector used, one or more cylinders containing appropriate gases under pressure are required to operate the instrument, limiting its field use. An Electron Capture Detector (ECD), which is the most sensitive for polyhalogenated solvents, requires helium and/or nitrogen. A Flame Ionization Detector (FID), which is a universal detector for aliphatic and aromatic hydrocarbons, requires nitrogen, air and hydrogen. The advent of the Photoionization Detector (PID) offered a compromise, in that it can detect all the above classes of organic solvents (with varying sensitivity) requiring only one gas (nitrogen, air or helium) for its operation. A simple system employed a portable GC/PID modified to sample 1 mL of air from a Haldane-Priestley tube into which the subject would exhale.[25,40] The latter assured collection of end-exhaled air and this device was successfully used to assess exposures to styrene[26] and PERC.[40]

Mass spectrometry (MS) offers the advantages of high sensitivity and specificity at the cost of portability and the need of highly trained operators. Direct exhalation into the MS is not possible because the ion source of the detector operates under high vacuum. Two approaches have been taken to overcome this limitation. In the first, an inlet system was designed where the high pressure breath sample was directed over a methyl silicone membrane, permeable to organic molecules but not to air, that served as the entry port to the ion source operating under high vacuum.[41] With the second approach, the inlet system was attached to the source of an Atmospheric Pressure Ionization mass spectrometer (API/MS), that operates under atmospheric pressure.[42,43]

In summary, the basic advantage of the direct reading/analyzing instruments is that there is no sample collection, transportation, storage, handling and analysis where the sample integrity may be compromised. The disadvantages are the need for expensive, specialized equipment, usually requiring highly trained operators and the difficulty, or some times impossibility, of field use.

The other category of breath sampling methodology involves sample collection in the field with subsequent analysis in the laboratory. There are two groups of devices in this category:

1. Sample containers that hold the total volume or part of the exhalation in a gaseous form.
2. Sample adsorbents that trap the chemicals of interest from the exhaled breath.

Rigid containers such as stainless steel, aluminum, or glass vials of various sizes, open at both ends belong to the first group. The subject exhales into the vial and then the two openings are closed, either with caps or with stopcocks. Vials of this kind have been

used extensively in experimental studies involving exposures to industrial chemicals.[24,28,29,44-47,53-55,61,64]

The advantages of these containers are inertness of the walls, low cost, reusability and simplicity of the technique. The disadvantages are the potential for contamination, photodegradation, or dilution of the collected breath sample with atmospheric air, sorption and/or reaction of the vapor with surfaces and breakage during transportation or storage. The problem of condensation of water vapor has been addressed by heating the tubes,[28,29,47] but this approach increases the complexity and counters the main advantages. Another limitation is that only a small volume of sample can be withdrawn for analysis from a rigid container, with ensuing restrictions on the analytical sensitivity.

The last limitation is overcome when collapsible bags are used for sample collection. The bags are commonly made of Tedlar (clear) or Mylar (aluminized) material. The subject exhales directly into the bag through a valve and when an appropriate volume has been collected, the valve is closed. The bag is transported to the laboratory where an aliquot is withdrawn for analysis through a septum. The collapsibility of the bag allows any volume to be withdrawn without air infiltration. Disadvantages, however, include losses because of permeation through the walls, sorption and/or reaction of the vapor with the wall surfaces and photodegradation. The latter concern is eliminated with the aluminized Mylar bags, which also minimize sorption and permeation through the walls.

The second group of field sampling devices with subsequent analysis involves the use of adsorbents. Extensively used in personal monitoring in industrial hygiene surveys, these devices were naturally considered for exhaled breath sampling. Commercially available glass tubes containing granular adsorbent material such as activated charcoal, Tenax, molecular sieve, etc. could be used with selected organic vapors. However, because of the high pressure drop during exhalation through the adsorbent bed, and the condensation of water vapor, these materials have not been used much for direct sampling of exhaled breath. One device[48] is, basically, a respirator mask with two commercial charcoal inhalation canisters and an exhalation port fitted with a wafer of charcoal cloth. A Wright respirometer connected to the exhalation port records the volume of exhaled air. Another handheld device employed a custom-made glass tube containing charcoal to collect organic vapors in exhaled air, while the volume collected was measured with a Wright respirometer and adjusted for back-pressure measured with an attached pressure gauge.[25,40]

Commercial tubes or specially made cartridges containing the appropriate adsorbent have been used in conjunction with bag sampling for exhaled breath monitoring.[49] The subject exhales into the bag, the contents of which are subsequently pumped through the tube or canister containing the adsorbent. This combination offers the advantages of bag sampling (low cost, low resistance), while eliminating the disadvantages (losses, bulkiness). The organic vapors can be thermally desorbed from the adsorbent material and the concentrations measured with polymer-coated surface-acoustic-wave detector,[50] GC or GC/MS analysis.[31,49] Alternatively, solvent vapors can be extracted from the adsorbent with an appropriate solvent prior to conventional analysis.

14.2.1.6 When is breath monitoring appropriate?

Breath monitoring may be used to assess exposures to solvents either qualitatively or quantitatively. Qualitative information may be useful when exposure to a number of solvents is suspected. For qualitative purposes, either mixed-exhaled or end-exhaled air samples may be used. Provided that the sample collection and the analytical techniques are appropriate, a list of solvents may be thus identified and quantitative measurements planned.

Quantitative information is needed for regulatory enforcement situations, where appropriately collected breath samples are compared to BEIs to assess whether exposure limits have been exceeded. BEIs have been developed after thorough studies of pharmacokinetics for a limited number of occupational contaminants. Exhaled air is used as a surrogate for blood when the relationships between exhaled air, alveolar air and (arterial or mixed venous) blood have been established.

Besides regulatory purposes, breath monitoring can provide valid information on solvent exposures when:

- The pharmacokinetics (absorption, distribution, metabolism, elimination) of the solvent are well established.
- The solvent is not soluble in the conducting portion of the lung (anatomical dead space).
- The solvent is not metabolized to a great extent, and it is mainly eliminated *via* exhalation.
- Sample collection is conducted in a location unaffected by ambient levels of the solvent(s) of concern that may interfere and bias the measurements.
- The concentration in exhaled air is compatible with the analytical method allowing adequate sensitivity.
- Appropriate timing is strictly followed.

14.2.1.7 Examples of breath monitoring

Two solvents are used to illustrate the use of breath monitoring in assessing solvent exposure: A solvent with minimal metabolism, tetrachloroethylene (PERC) and a solvent with significant metabolism, styrene. Both solvents are used extensively in industry with a great number of workers potentially exposed. As shown in Table 14.2.1.2, styrene is only minimally excreted through the lungs, whereas exhaled air is the major elimination route for PERC. Accordingly, end-exhaled air is recommended as a BEI for PERC, but not for styrene. Nevertheless, end-exhaled and mixed-exhaled air techniques have been studied in experimental settings and in real-life occupational environments for both solvents. A compilation of such studies is presented below.

Table 14.2.1.2. Characteristics of styrene and tetrachloroethylene (PERC). [Information compiled from ACGIH, Documentation of Threshold Limit Values and Biological Limit Values, 1991][7]

	STYRENE	PERC
Eliminated *via* lungs	~5%	~80-100%
Eliminated in the urine	~90%	~2%
Urinary metabolite(s)	Mandelic acid (MA), Phenylglyoxylic acid (PA)	Trichloroacetic acid (TCA)
Blood/air partition coefficient (λ)	32-55	9-15
Pulmonary elimination half-lives ($T_{1/2}$)	13-52 min 4-20 hr 3 days	15 min 4 hrs 4 days
TLV (1998)	50 ppm	25 ppm
STEL (1998)	100 ppm	100 ppm
BEI (1998) End-exhaled air Blood Urine	 Not recommended 0.55 mg/L end-of-shift 0.02 mg/L prior-to-next-shift MA=800 mg/g creatinine, end-of-shift MA=300 mg/g creatinine, prior-to-next-shift PA=240 mg/g creatinine, end-of-shift PA=100 mg/g creatinine, prior-to-next-shift	 10 ppm end-of-shift, after at least 2 shifts 1 mg/L end-of-shift, after at least 2 shifts TCA=7 mg/L
Major Industry	Reinforced Plastics	Dry Cleaning

14.2.1.7.1 PERC

Tetrachloroethylene (PERC) is used extensively in the textile industry as a dry cleaning aid and in metal processing as a metal degreaser. The major concern is on occupational exposures, but elevated indoor air concentrations of PERC have also been documented.[49] As a result, the potentially exposed population is very large, with a wide range of exposures. The uptake of PERC by the lung is high[51,52] because of its high solubility in blood and adipose. Most of it is eliminated *via* the lung, with very small amounts metabolized to trichloroacetic acid (TCA) and eliminated in the urine.[51,52] Even smaller amounts of trichloroethanol in the urine have been reported.[52]

A number of field studies have been published with similar designs, in which breathing zone air, blood, breath and urine were measured in groups of workers. In addition,

chamber studies allowed measurements under predetermined consistent conditions. The emerging patterns formed the basis for recommendations for biological monitoring.

In a study of thirty two workers,[9] end-exhaled air was measured at the beginning of the first shift of the week, after 15-30 min after the end of the shift on the 3rd and 5th day of the same week, and at the beginning of the first shift of the subsequent week. The authors required the subjects to hold their breaths for 5 seconds and collected only the last part of the breath to obtain alveolar air. These measurements correlated with personal breathing zone samples collected each day. The highest correlation was found between PERC and TCA in blood at the end of the workweek and the average exposure for the entire week (R^2=0.953). Among the non-invasive techniques, PERC in exhaled air collected 15-30 min after the end of the shift at the end of the week had an R^2 of 0.931, and was followed by TCA in urine (R^2=0.909).

In a field study of workers employed in dry cleaning,[53] twenty-four female and two male subjects were monitored. End-exhaled air and blood samples were collected at the beginning and at 30 minutes after the end of the 3rd workday of the week. On that same day, personal, shift-long, breathing zone samples were also collected from each worker. Urine samples were collected before and after the shift on a daily basis and analyzed for TCA. With a mean exposure of 20.8 ppm, no TCA was detected in any of the urine samples (no detection limit was reported). Among the three exposure parameters (breathing zone air, blood and end-exhaled air) only the correlation between the PERC concentration in the blood and in the breath was reported as statistically significant by the authors (R^2=0.77). The authors concluded that if the concentration of PERC in blood, 16 hours after the end of exposure, was below 1000 µg/L, the average exposure was likely to have been below 50 ppm.

A group of thirteen male dry cleaners[40] was followed for a week with daily shift-long personal (badge) monitoring; mixed-exhaled air collected daily before- and after-shift; and mixed-exhaled air, blood and urine measurements on the morning after the last shift. Results indicated strong correlations between PERC concentrations in mixed-exhaled air and blood (R^2=0.944), as well as mixed-exhaled air and personal air samples collected either after the shift (R^2=0.885), or on the following morning (R^2=0.770). Mixed-exhaled air measurements collected either at the end of the last shift of the week (R^2=0.814) or in the morning following the last shift (R^2=0.764) were better indicators of exposure over the entire week than either blood (R^2=0.697) or urine (R^2=0.678). The authors recommended consideration of mixed-exhaled air as a potential BEI.

In addition to field studies, controlled human exposures to PERC have been reported. In this type of studies, subjects were exposed to various constant levels of PERC for different lengths of time with or without exercise. Samples of blood, exhaled air and urine were collected according to a variety of schedules both during exposure and for varying lengths of time after exposure. One study involved single exposures, whereas in others at least some of the subjects participated more than once.

In one of the first chamber studies, nine male volunteers were exposed to 100-200 ppm of PERC for 80 to 180 minutes. Concentrations of PERC in exhaled air were measured over time.[54] The authors demonstrated that exposures of similar duration resulted in

similar decay curves of PERC concentrations in breath after exposure. In addition, the data showed that the length of time that PERC was measurable in exhaled air was proportional to both the concentration and the duration of the exposure.

The same group[55] exposed sixteen males to single and repeated concentrations of 100 ppm PERC for periods of 7 hrs/day over a 5-day workweek. Alveolar air samples were collected over a period of up to 300 hours post-exposure. The authors observed higher alveolar air concentration in subjects with greater body mass. They recommended measurement of PERC in alveolar air 2-16 hours post-exposure to assess the average exposure.

Six healthy males were exposed to 72 and 144 ppm, as well as 142 ppm with 2 half hours of 100 W of exercise.[51] Uptake of PERC was calculated from the minute volume and the concentration of PERC in breath. PERC was measured in breath and blood and TCA was measured in blood and urine. During the first hour of exposure the uptake was higher by 25% than during the last hour and retention decreased with time and with exercise. The mean ratio of the concentration of PERC in venous blood and the concentration of PERC in mixed exhaled air was 23. Assuming a mix-exhaled air to end-exhaled air ratio of 0.71, they estimated a blood/air partition coefficient of 16. After 20 hours from the end of exposure the half-life was estimated to be 12-16 hours, after 50 hours the half-life was estimated to be 30-40 hours and after 100 hours it was estimated at approximately 55 hours. The authors estimated that 80-100% of PERC was excreted unchanged through the lung, and about 2% was excreted as TCA in the urine.

Simple and multiple linear regression analyses were applied to the data collected above to predict the best estimator of exposure to PERC.[56,57] PERC in blood was the best predictor followed by PERC in exhaled air. TCA per gram of creatinine in urine was the least reliable predictor.

Twenty four subjects were exposed to 100, 150 and 200 ppm of PERC for 1 to 8 hours.[52] The concentration of PERC in alveolar air decreased rapidly during the first hours of the post-exposure period, but 2 weeks were required for complete elimination following an exposure of 100 ppm for 8 hours. The authors were the first to demonstrate that the rate of rise and of decay of the alveolar concentration with respect to time was independent of the level of the inspired concentration during exposure.

The experimental data from the above study were used in a pharmacokinetic model[58] that divided the body into four tissue compartments: the Vessel Rich Group (VRG), the Muscle Group (MG), the Fat Group (FG) and the Vessel Poor Group (VPG). No metabolic pathway was considered. After 20 hours from the end of the exposure the concentration of PERC in alveolar air was related to release from the FG with an approximate half-life of 71.5 hours. The model predicted small differences in alveolar concentrations due to differences in body weight, height and fat tissue. The authors provided a nomogram to predict mean exposure given the exposure duration (0-8 hrs), time since end of exposure (0-8 hrs) and post-exposure measurement of the alveolar air concentration.

A perfusion-limited, four compartment model was used to simulate the effect of several confounding factors on the levels of several contaminants in the breath, including PERC.[6] The model, which considered metabolic clearance, consisted of a pulmonary com-

partment, a vessel-rich group, a group of low-perfused tissues containing muscles and skin, and a group of poorly perfused fatty tissues. The authors predicted that intra-day fluctuations in exposure would have a large effect on breath sampled just after the shift, but that the effect would be negligible the next morning. Breath samples collected the next morning would reflect exposure on preceding days and the measurements would be independent of level of physical exertion. Finally, individual differences in body build and metabolism would have the greatest effect on breath levels, with the largest variations expected for metabolized solvents.

Experimental data were used in a model,[59] which divided the body into four tissue compartments: vessel rich group, muscle group, fat group and liver. Metabolism was assumed to take place in the liver as a combination of a linear metabolic component and a Michaelis-Menten component. Metabolic parameters and partition coefficients determined for rats were scaled for body weight and were used in fitting results for humans. The model fit very well the data reported from other controlled human exposure studies.[51,52,54]

The BEI committee of the ACGIH recommends[2] three indices of PERC exposure:

1. PERC in end-exhaled air collected prior to the shift after at least 2 consecutive workdays.
2. PERC in blood collected prior to the shift after at least 2 consecutive workdays.
3. Trichloroacetic acid (TCA) in urine voided at the end of the workweek. This index is recommended only as a screening test because of the variability associated with urinary excretion of TCA and, as such, no creatinine correction is necessary.

14.2.1.7.2 Styrene

The highest exposures to styrene take place in plants manufacturing glass-reinforced plastics, particularly during lamination, where there is considerable evaporation of styrene. Most of the inhaled styrene is absorbed and retained in the body. The first step in the major metabolic pathway is the formation of styrene-7,8-oxide (phenyloxirane), a reaction catalyzed by Cytochrome P-450 in the liver. The oxide is then hydrated to styrene glycol (1-phenyl-1,2-ethanediol) by microsomal epoxide hydratase. The styrene glycol is conjugated with β-glucuronic acid, or is oxidized to mandelic acid and further to phenylglyoxylic acid. In humans, less than 5% of absorbed styrene is eliminated *via* the lung, whereas 90% is eliminated in the urine as mandelic and phenylglyoxylic acids.

A number of chamber and field studies have been reported, where blood, exhaled air and urine have been studied as possible biological indicators. Although conditions and study design differed among studies, certain consistent patterns emerged, which formed the basis for subsequent recommendations.

In an early series of chamber exposures,[60] nine healthy males were exposed to styrene concentrations of 50 to 370 ppm for periods ranging from 1 to 7 hours. Alveolar air samples were collected during and for 8 hours following exposure. The authors showed that the amounts of styrene present in the breath were directly related to the level and the duration of exposure.

In another study,[61] fourteen healthy males were exposed to 50 and 150 ppm of styrene in inspired air during rest and light (50 W) physical exercise. The duration of exposure for each styrene concentration was 30 minutes, with total pulmonary ventilation,

cardiac output, and styrene concentration in alveolar air, arterial blood and venous blood measured during and after exposure. During exposure at rest to either 50 or 150 ppm, the alveolar air concentrations were about 20% of the inspired air concentrations. When alveolar ventilation almost tripled with exercise at 50 W, the alveolar air concentrations increased slightly, whereas arterial blood concentrations almost tripled. Alveolar air concentrations reached a plateau within a minute or so, that persisted throughout the 30-minute period. Arterial blood concentrations, however, rose rapidly during each such period and even more with increasing exercise intensity (50, 100 and 150 W). Venous blood concentrations also rose sharply during the 30-minute exposure periods without ever reaching a plateau. No linear relationship was found between exposure duration and arterial and venous blood concentrations, even after log-log transformations. The decay of styrene concentrations in alveolar air and in venous and arterial blood was slower in the first 30 to 50 minutes than later on. The authors concluded that post-exposure alveolar air measurements were poor predictors of exposures to styrene, whereas arterial blood would be the best index of exposure. For practical reasons, they recommended capillary blood samples from fingertips as a surrogate for arterial blood.

In a follow-up study[62] using the same experimental set up as above, seven male subjects were exposed to 50 ppm (210 mg/m^3) of styrene in inspired air for 30 minutes at rest, followed by 30 minute exposure periods under exertion at intensities of 50, 100 and 150 W. The mean alveolar air concentration at the end of the first 30-minute period was 16% of the concentration in the inspired air and 23% at the end of the final period. Both the arterial and venous blood concentrations of styrene rose with increasing workload during exposure with no equilibrium achieved between alveolar air and arterial blood during 2 hours of total exposure. Weak correlations were found for the amount of styrene taken up per kg of body weight and the concentrations of styrene in alveolar air 0.5 and 2 hours after exposure. The elimination was faster during periods of exercise than during rest periods, leading to the authors' recommendation for leisure time physical activity for people exposed to solvents as a means to enhance elimination.

In another study,[63] four male volunteers were exposed to 80 ppm of styrene in a chamber for 6 hours. Venous blood samples were collected during exposure and a nearly simultaneous set of 10 blood and mixed exhaled air samples were collected following exposure for up to 40 hours. Blood levels during exposure rose rapidly and reached an almost constant level by the end of the 6 hours. Following exposure, the results showed that styrene was cleared from the blood according to a linear two-compartment pharmacokinetic model, with half-life values of 0.58 and 13 hours, for the rapid and slow elimination phases, respectively.

Retention of styrene was studied in a chamber setting where healthy males were exposed to either constant or fluctuating air concentrations of styrene.[26] A computer-controlled system was used to generate time-varying air concentrations over 4-5 hrs with a mean air concentration of 50 ppm. End-exhaled air measurements taken throughout the exposure period showed styrene retention of 93.5% during constant exposures, but higher retention (96-97%) during fluctuating exposures. The authors speculated that the differ-

ence in retention was related to non-steady-state behavior of styrene in the richly perfused tissues.

In summary, pulmonary retention during exposure is about 60-70%[62,64] with exhaled concentrations accounting for 25-35%.[60] Higher retention (96-97%) was observed when volunteers were exposed to fluctuating, rather than constant, air concentrations.[26] Following exposure, the desaturation curve shows two exponential decays with half-lives of 13 minutes[60] to 52 minutes[63] for the rapid elimination phase and 4 hours[60] to 20 hours[63] for the slower elimination phase. A third compartment can be defined to represent elimination from the adipose tissue with a half-life of 3 days.[62]

Measurements of styrene in venous blood at the end of the workshift and/or prior to the next shift have been recommended by the ACGIH.[2] Monitoring of urinary metabolites of styrene has also been recommended by the ACGIH[2] at the end of the week, even though they are not specific to styrene exposure. Styrene in exhaled air after the end of exposure was not recommended as a BEI because the levels would be too low to detect, leading to uncertainties.

Terminology

ACGIH	American Conference of Governmental Industrial Hygienists
Alveolar air	Gas in the alveoli
Alveolar ventilation	Inhaled air available for gas exchange in 1 min
Anatomical dead space	Volume (~150 mL) of conducting airways where no gas exchange occurs
BEI	Biological Exposure Index. Reference value developed by ACGIH
Blood/air partition coefficient	Ratio of the vapor concentration in blood and in air at 37°C
Breathing frequency	15 breaths per minute at rest, increases with physical exertion
Conductive zone of lungs	First segment of the airways, which includes the trachea, bronchi, terminal bronchioles
End-exhaled air	Operationally defined as the last portion of an exhalation to simulate alveolar air
Exhaled air volume	Approx. 500 mL at rest, increases with workload
GC-MS	Gas Chromatography Mass Spectrometry
Minute volume	Ventilation The volume of air exhaled in 1 min, approx. 7,500 mL
Mixed-exhaled air	Entire volume of exhaled air collected from alveolar space and anatomically dead space
Respiratory zone	Consists of respiratory bronchioles and alveolar ducts where gas exchange takes place. Approx. 2,500 mL
STEL	Short-Term Exposure Limit. The concentration to which most workers may be exposed continuously for a short period of time without adverse effects. Issued by ACGIH
Tidal volume	Volume of exhaled air; ~500 mL at rest
TLV	Threshold Limit Value. Airborne concentration of a substance to which most workers may be exposed without adverse health effects. Established by ACGIH and intended as guideline.

REFERENCES

1 R Lauwerys, **Industrial chemical exposure: Guidelines for biological monitoring**. *Biomedical Publications. Davis*, California, 1983.

2 **ACGIH, American Conference of Governmental Industrial Hygienists: TLV, Threshold Limit Values and Biological Limit Values**. Cincinnati, Ohio, 1998.

3 I Astrand, *Scand. J. Work Environ. Health*. **1**, 199-218, 1975.

4 V Fiserova-Bergerova, J Vlach, JC Cassady, *Br. J. Ind.Med*., **37**, 42-49, 1980.

5 PJA Borm and B de Barbanson, *J. Occup. Med.,* **30**, 214-223, 1988.

6 PO Droz and MP Guillemin, *J. Occup. Med*., **28**, 593-602, 1986.

7 **ACGIH, American Conference of Governmental Industrial Hygienists, Documentation of Threshold Limit Values and Biological Limit Values**. Cincinnati, Ohio, 1991.

8 JB West, **Respiratory Physiology - The essentials**, *The Williams & Wilkins Co*., Baltimore, 1981.
9 AC Monster, W Regouin-Peeters, A van Schijndel, J van der Tuin, *Scand. J. Work Environ. Health*, **9**, 273-281, 1983.
10 V Fiserova-Bergerova, **Modeling of inhalation exposure to vapors, Uptake, distribution and elimination**, *CRC Press Inc*., Boca Raton, Florida, 1983.
11 A Sato and T Nakajima, *Brit. J. Ind. Med*., **36**, 231-234, 1979.
12 A Morgan, A Black, DR, Belcher, *Ann. Occup. Hyg.*, **13**, 219-233, 1970.
13 LE Farhi, *Respir. Physiol.*, **3**, 1-11, 1967.
14 GR Kelman, *Br. J. Ind. Med.*, **39**, 259-264, 1982.
15 JE Cotes, **Lung function, Assessment and application in medicine**, *Blackwell Scientific Publications*, Oxford, 1979.
16 J Widdicombe and A Davies, **Respiratory physiology**, *Edward Arnold*, London, 1983.
17 HK Wilson, Breath analysis, *Scand. J. Work Environ. Health,* **12**, 174-192, 1986.
18 V Fiserova-Bergerova, M Tichy, and FJ DiCarlo, *Drug metabolism rev.*, **15**, 1033-1070, 1984.
19 KM Dubowski, *Clin. Chem*., **20**, 966-972, 1974.
20 HC Niu, DA Schoeller, PD Klein, *J. Lab. Clin. Med.*, **91**, 755-763, 1979.
21 M Guillemin and E Guberan, *Br. J. Ind. Med.*, **39**, 161-168, 1982.
22 TA Robb TA and GP Davidson, *Clinica Chim. Acta*, **111**, 281-285, 1981.
23 JS Haldane, and JG Priestley, *J. Physiol*., **32**, 225-266. 1905.
24 JH Raymer, KW Thomas, SD Cooper, DA Whitaker, ED Pellizzari, *J. Anal. Toxicol.*, **14**, 337-344, 1990.
25 SM Rappaport, E Kure, MX Petreas, D Ting, J Woodlee, *Scand. J. Work Envir. Health*, **17**, 195-204, 1991.
26 M Petreas, J Woodlee, CE Becker, SM Rappaport, *Int. Arch. Occup. Environ. Health*, **67**, 27-34, 1995.
27 RH Hill, M Guillemin, PO Droz, in **Methods for Biological Monitoring**, TJ Kneip and JV Crable Eds., *American Public Health Association*, Washington DC, 1988.
28 JF Periago, A Luna, A Morente, A Zambudio, *J. Appl. Toxicol.*, **12**, 91-96, 1992.
29 JF Periago, A Cardona, D Marhuenda, J Roel, *et al., Int. Arch. Occup. Environ. Health*, **65**, 275-278, 1993.
30 L Campbell, AH Jones, HK Wilson, *Am. J. Ind. Med*., **8**, 143-153, 1985.
31 D Dyne, J Cocker, HK Wilson, *Sci. Total Envir*., **199**, 83-89, 1997.
32 L Drummond, R Luck, AS Afacan, HK Wilson, Br. *J. Ind. Med*., **45**, 256-261, 1988.
33 Dragerwerk AG, **Detector tube handbook**, *Lubeck*, Germany, 1976.
34 NC Jaim, *J. Chromatogr. Sci*., **12**, 214-218, 1974.
35 MF Mason and KM Dubowski, *J. Forensic Sci.*, **4**, 9-41, 1975.
36 D Clasing, U Brackmeyer and G Bohn, *Blutalcohol*, **18**, 98-102, 1981.
37 CG Hunter and D Blair, *Am. Occ. Hyg.*, **15**, 193-199, 1972.
38 R Teraniski, TR Mon, AB Robinson, P Cary, L Pauling, *Anal. Chem*., **44**, 18-20, 1972.
39 PO Droz and JG Fernandez, *Br. J. Ind. Med.*, **35**, 35-42, 1978.
40 MX Petreas, SM Rappaport, B Materna, D Rempel, *J. Exp. Analysis & Env. Epidem., Supplm*. **1**, 25-39, 1992
41 HK Wilson and TW Ottley, *Biomed. Mass Spectrom*., **8**, 606-610, 1981.
42 FM Benoit, WR Davidson, AM Lovett, S Nacson, and A Ngo, *Anal. Chem*., **55**, 805-807, 1983.
43 FM Benoit, WR Davidson, AM Lovett, S Nacson, and A Ngo, *Int. Arch. Occup. Environ. Health*, **55**, 113-120, 1985.
44 RJ Sherwood, and FWG Carter, *Ann. Occup. Hyg*., **13**, 125-146, 1970.
45 DA Pasquini, *Am. Ind. Hyg. Assoc. J*., **39**, 55-62, 1978.
46 F Brugnone, L Perbellini, GL Faccini, F Pasini, L Romeo, M Gobbi, A Zedde, *Int. Arch. Occup. Environ. Health*, **61**, 303-311, 1989.
47 M Imbriani, S Ghittori, G Pezzagno, E Capodaglio, *G. Ital. Med. Lav.*, **4**, 271-278, 1982.
48 RA Glaser, and JE Arnold, *Am. Ind. Hyg. Assoc. J*., **50**, 112-121, 1989.
49 L Wallace, R Zweidinger, M Erickson, S Cooper, D Whitaker, E Pellizzari, *Environ. Inter.*, **8**, 269-282, 1982.
50 WA Groves and ET Zellers, *Am. Ind. Hyg. Assoc*. J., **57**, 1103-1108, 1996.
51 AC Monster, G Boersma, H Steenweg, *Int. Arch. Occup. Environ. Health*, **42**, 303-309, 1979.
52 J Fernandez, E Guberan, J Caperos, *Am. Ind. Hyg. Assoc. J*., **37**, 143-150, 1976.
53 R Lauwerys, J Ferbrand, JP Buchet, A Bernard, J Gaussin, *Int. Arch. Occup. Environ. Health*, **52**, 69-77, 1983.
54 RD Stewart, HH Gay, DS Erley, CL Hake, AW Scaffer, *Arch. Environ. Health*, **2**, 40-46, 1961.
55 RD Stewart, ED Baretta, HC Dodd, TR Torkelson, *Arch. Environ. Health*, **20**, 224-229, 1970.
56 AC Monster, *Int. Arch. Occup. Environ. Health*, **42**, 311-317, 1979.

57 AC Monster, JM Houtkooper, *Int. Arch. Occup. Environ. Health*, **42**, 319-323, 1979.
58 E Guberan and J Fernandez, *Br. J. Ind. Med.*, **31**, 159-167, 1974.
59 RC Ward, CC Travis, DM Hetrick, ME Andersen, ML Gargas, *Tox. Appl. Pharmacol*., **93**, 108-117, 1988.
60 RD Stewart, HC Dodd, ED Baretta, *et al*., *Arch. Environ. Health*, **16**, 656-662, 1968.
61 I Astrand, A Kilbom, P Ovrum, I Wahlberg, O Vesterberg, *Work-Environm. Health*, **11**, 69-85, 1974.
62 J Engstrom, R Bjurstrom, I Astrand P Ovrum, *Scand. J. Work Environ. Health*, **4**, 315-323, 1978.
63 JC Ramsey, JD Young, RJ Karbowski, MB Chenoweth, LP McCarty, WH Braun, *Toxicol. Appl. Pharmacol*., **53**, 54-63, 1980.
64 E Wigaeus, A Lof, R Bjustrom, MB Nordqvist, Scand. *J. Work. Environ. Health*, **9**, 479-488. 1983.

15

Residual Solvents in Products

15.1 RESIDUAL SOLVENTS IN VARIOUS PRODUCTS

George Wypych
ChemTec Laboratories, Toronto, Canada

There are physical and chemical barriers that control solvent removal from solid-solvent systems. The most basic relation is given by the following equation:

$$W = \frac{P_1}{K_w} \qquad [15.1.1]$$

where:

W	equilibrium fraction of residual solvent
P_1	partial pressure of solvent in vapor phase
K_w	Henry's law constant

Both the partial pressure and Henry's law constant depend on temperature, pressure, and solvent properties. This relationship does not consider interaction between solute and solvent. In the case of polymers, the Flory-Huggins theory gives a simplified relationship for low concentrations of solvent:

$$\ln\frac{P_1}{P_1^0} = \ln\phi_1 + 1 + \chi \qquad [15.1.2]$$

where:

P_1^0	vapor pressure of pure solvent
ϕ_1	volume fraction of solvent
χ	Flory-Huggins interaction parameter

Vapor pressures of some solvents can be found in the referenced monograph.[1]

The weight fraction of residual solvent at equilibrium can be calculated from the following equation, which accounts for polymer-solvent interaction:

$$W = \frac{P_1\rho_1}{P_1^0\rho_2}\exp-(1+\chi) \qquad [15.1.3]$$

where:

ρ_1	density of solvent
ρ_2	density of polymer

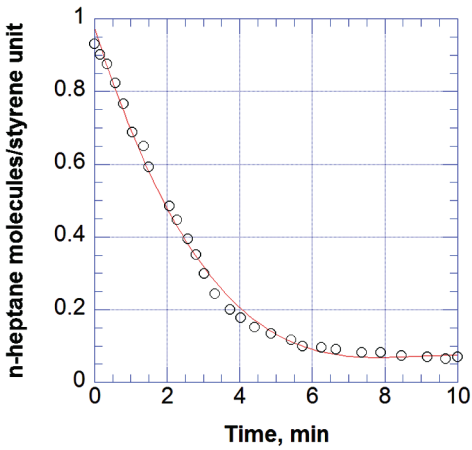


Figure 15.1.1. Number of n-heptane molecules per one mer of polystyrene vs. drying time. [Data from L A Errede, P J Henrich, J N Schrolpfer, *J. Appl. Polym. Sci*., **54**, 649 (1994).]

The last equation does not give the real values of residual solvents because equilibrium is not attained in real drying processes and the prediction of different interactions by the interaction parameter is too simplistic. The real values are substantially higher and the real barriers of solvent removal more complex. These are discussed below.

In real systems, several phenomena take place. These include chemical interaction between the functional groups of polymer and the solvent. These are mostly related to hydrogen bond formation. The crystalline structure of polymer is responsible for the modification of the diffusion process. Solvent properties determine diffusion. Polymer properties are responsible for the macromechanism of solvent removal from a highly viscous polymer. In addition, some real systems make use of stripping solvents which are designed to help in removal of trace quantities of solvents by use of stripping solvent displacing process solvent. These various factors interplay and determine the result. Figure 15.1.1 shows the number of residual solvent molecules per one mer of polystyrene. It is evident that solvent removal has zero-kinetics until its concentration is decreased to about 0.2 molecules of solvent per mer. It is also true that some solvent remains after drying. Even after 24 h drying, 0.06% solvent remains.

These data indicate that there is a different mechanism of removing residual solvent. It is not clear if this is because of interactions, a change in the glass transition temperature, or a change in crystallinity. So far the partial effects of these influences cannot be separated. It is confirmed by experiment that in the last stages of drying, glass transition temperature of polymer changes rapidly. Also, the degree of crystallinity of the polymer increases during drying.[3,4] From studies on polyaniline, it is known that its conductivity depends on the concentration of adsorbed molecules of water.[5] Water interacts by hydrogen bonding with the polymer chain. The activation energy of hydrogen bonding is very low at 3-5 kcal/mol. Drying at 120°C reduced the amount of water molecules from 0.75 to 0.3 molecules per aniline unit. This change in water concentration drastically alters electrical conductivity which decreases by three orders of magnitude. Drying for two hours at 120°C did not result in complete removal of water. Given that the activation energy of hydrogen bonding is very low, the process of interaction is probably not the main barrier to removal of residual moisture. Also the relationship between conductivity and number of molecules of water is linear in the range from 0.15 to 0.75 molecules of water per aniline unit which means that there is no drastic change in the mechanism by which water participates in increasing the conductivity of polyaniline. Its conductivity simply depends on the

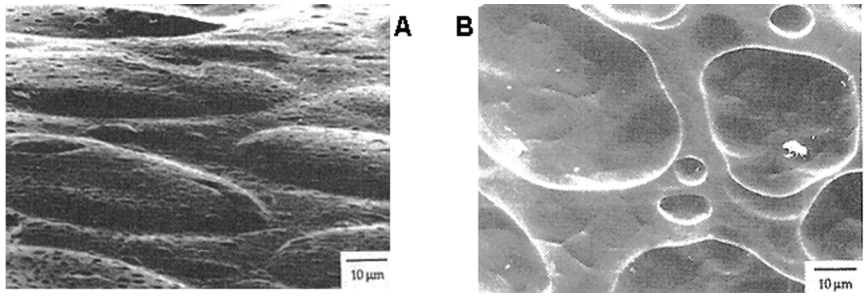


Figure 15.1.2. Blister formation in polyethylene containing originally 4000 ppm hexane. a – lateral surface 2.2 s after extrusion, b – cross-section after 28 s. [Adapted, by permission from R J Albalak, Z Tadmor, Y Talmon, *AIChE J*., **36**, 1313 (1990).]

distance between neighboring adsorbed molecules of water which apparently participate in the charge migration.

SEM studies contribute to an understanding of a major obstacle to residual solvent removal. Figure 15.1.2 shows two photographs of polyethylene strands extruded from a melt which initially contained 4000 ppm hexane. After a short period of time following the extrusion, blisters form which remain in the material and become enlarged until they break and release solvent. This blistering mechanism, determines the rate of residual solvent removal from the material. The rate of removal depends on bubble nucleation, temperature, and polymer rheological properties.[6]

Observing such mechanisms makes it easy to understand the principle involved in stripping solvents which became popular in some inventions.[7-9] Stripping solvents were used to improve the taste and odor properties and the oxidative thermal stability of thermoplastic ethylene polymers.[7] Volatile components, such as products of degradation, solvent and monomer contribute to taste problems and odor formation. Striping solvents used include highly volatile hydrocarbons (ethylene, propylene, isobutane), inert gases, and supercritical fluids. An addition of at least 0.1% stripping solvent reduces volatiles from the typical levels of between 300-950 ppm to 45 ppm with even as low as 10 ppm possible. A stripping solvent helps in the generation of bubbles and their subsequent breaking by which both the stripping and the residual solvent are removed. In cosmetics and pharmaceutical formulations traces of solvents such as benzene or dichloromethane, used in the synthesis of acrylic acid polymer, disqualify the material. It is not unusual for this polymer to contain up to 1000 ppm of dichloromethane or up to 100 ppm of benzene. The use of mixed ester solvents helps to reduce residual solvent to below 5 ppm.[8] Polycarbonate pellets from normal production may contain up to 500 ppm solvent. This makes processing polycarbonate to optical products very difficult because of bubble formation. Elimination of volatiles renders the product suitable for optical grade articles.[9] These inventions not only demonstrate how to eliminate solvents but also confirm that the mechanism discussed in Figure 15.1.2 operates in industrial processes. The examples also show that large quantities of residual solvents are retained by products in their normal synthesis.

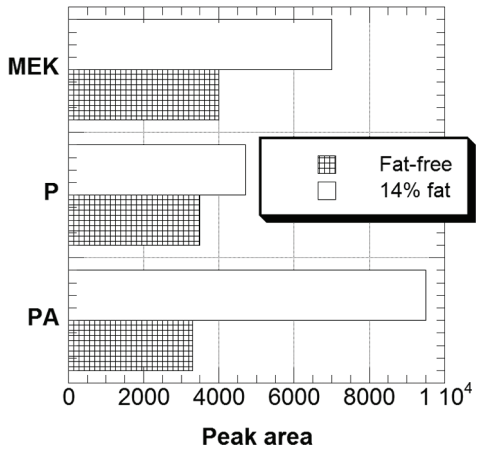


Figure 15.1.3. Volatility of three printing solvents (PA – propyl acetate, P – n-propanol, MEK - methyl ethyl ketone) from fat-free and fat-containing cookies. 20 mg solvent added to 2.5 g cookies. [Data from T Clark, *Paper Film Foil Converter*, **70**, 11, 48 (1996).]

Many standard methods are used to devolatilize materials. Flash devolatilizer or falling strand devolatilizer are synonyms of equipment in which the falling melt is kept below the saturation pressure of volatiles. Styrene-acrylonitrile copolymers devolatilized in flash devolatilizer had a final concentration of ethylbenzene of 0.04-0.06.[1] Devolatilization of LLDPE in a single-screw extruder leaves 100 ppm of hydrocarbon solvent. 500 ppm chlorobenzene remains in similarly extruded polycarbonate.[1] It is estimated that if the polymer contains initially 1-2% solvent, 50-70% of that solvent will be removed through the vacuum port of an extruder.[1] These data seem to corroborate the information included in the above discussed patents. The data show that considerable amounts of residual solvents can be found in polymers and plastic materials.

In the food industry, residual solvents associated with packaging odors enter food products from two sources: packing materials and printing inks.[10] It is estimated that concentrations of residual solvents have recently decreased (from 2000 mg/ream in past to 1000 mg/ream).[10] However, a new problem has become apparent in introduction of low fat or no fat food.[11] It was discovered[11] that more customer complaints about odor were received for these low fat baked goods products. Analysis shows that fat was a good solvent for volatiles (solvents) and consequently solvent odor was not detected because flavor perception is developed relative to the concentration of gaseous flavor compounds. Figure 15.1.3 shows the concentrations of three solvents as detected by gas chromatography. Substantially higher concentrations are detected in solvent-spiked fat-free cookies than in fat-containing cookies.[11] In this experiment solvents were added to the cookies. In another experiment, packaged cookies were exposed to a solvent vapor atmosphere and different trends were recorded for cookies packaged in two different films. If the film had good barrier properties, no difference was noticeable between both types of cookies and the adsorbed quantities of solvents were minimal. If the cookies were packaged in a coextruded film having lower barrier properties, no-fat cookies absorbed 42% more solvent than full fat cookies.

In the construction industry, residual solvent evaporation becomes an increasingly more critical issue, especially in the case of products used for indoor applications. Sealants, adhesives, and paints are now a major focus of this concern since they contribute to indoor pollution. Similar trends are observed in the automotive industry where both solvents and plasticizers are suspected of contributing to a “plastics” odor in car interiors.

In contrast, changes in the solvent evaporation rate may also contribute to product improvement in paints. Small quantities of properly selected solvents can improve physical properties and the appearance of paints. Other applications of residual solvents include time-controlled release of fertilizers and production of materials with controlled morphology.

Pharmaceutical industry is most concerned about residual solvents in their products because they do not provide therapeutic benefits but may endanger life of those who are using preparations containing high concentrations of residual solvents.[12] Pharmaceutical industry divided residual solvent into 3 classes: Class 1 comprises solvents which should not have been used in manufacture of pharmaceutical products, Class 2 solvents that are safer than Class 1 solvents, and Class 3 solvents which can be safely consumed at doses of at least 50 mg per day.[12] Class 1 includes benzene, carbon tetrachloride, 1,2,-dichloroethane, and 1,1-dichloroethene and 1,1, 1-trichloroethane.[12] Acetonitrile and hexane belong to Class 2 and ethanol to Class 3.[12]

The problem with residual solvents is magnified with counterfeit tablets and capsules, which are manufactured under less stringent conditions.[13] This subject is the focus of attention in the next section of this chapter.

The better analyze the problem and control production and products, many analytical techniques were perfected, most are based on headspace gas chromatography,[14] but proton transfer reaction mass spectrometry have also been used.[15]

More effective methods of residual solvent removal include: microwave-assisted drying,[16] use of eutectic solvents,[17] and freeze drying.[18]

REFERENCES

1 R J Albalak, Ed., **Polymer Devolatilization**, *Marcel Dekker, Inc*., New York, 1996.
2 L A Errede, P J Henrich, J N Schrolpfer, *J. Appl. Polym. Sci*., **54**, 649 (1994).
3 M O Ngui, S K Mallapragada, *J. Polym. Sci., Polym. Phys.*, **36**, 2771 (1998).
4 H-T Kim, S-K Kim, J-K Park, *Polym. J*., **31**, 154 (1999).
5 E S Matveeva, *Synthetic Metals,* **79**, 127 (1996).
6 R J Albalak, Z Tadmor, Y Talmon, *AIChE J*., **36**, 1313 (1990).
7 M M Hughes, M E Rowland, C A Strait, **US Patent 5,756,659**, *The Dow Chemical Company*, 1998.
8 A Bresciani, **US Patent 5,342,911**, 1994.
9 T Hosomi, T Umemura, T Takata, Y Mori, **US Patent 5,717,055**, *Mitsubishi Gas Chemical, Ltd*., 1998.
10 R M Podhajny, *Paper Film Foil Converter*, **72**, 12, 24 (1998).
11 T Clark, *Paper Film Foil Converter*, **70**, 11, 48 (1996).
12 J V McArdle, **Residual Solvents** in **Specification of Drug Substance and Products**, *Elsevier*, 2014.
13 E Deconinck, M Canfyn, P-Y Sacre, P Courselle, J O De Beer, *J Pharm. Biomed. Anal.*, **81-82**, 80-88 (2013).
14 E Deconinck, M Canfyn, P-Y Sacre, S Baudewyns, P Courselle, J O De Beer, *J Pharm. Biomed. Anal.*, **70**, 64-70 (2012).
15 Y Wang, C Shen, J Li, H Wang, H Wang, H Jiang, Y Chu, *J Pharm. Biomed. Anal.*, **55**, 5, 1213-17, (2011).
16 J-Y Lee, J-H Kim, *Process Biochem*., **48**, 3, 545-50 (2013).
17 K Shahbaz, F S Mjalli, M A Hashim, I M AlNashef, *Separation Purification Technol*., **81**, 2, 216-22 (2011).
18 W Zheng, S L Simon, *Polymer*, **47**, 10, 3520-27, (2006).

15.2 RESIDUAL SOLVENTS IN PHARMACEUTICAL SUBSTANCES AND PRODUCTS

ERIC DECONINCK AND BART DESMEDT
Section of Medicines & Health Care Products,
Scientific Direction Chemical & Physical Health Risks,
Sciensano, Juliette Wytmanstraat 14, 1050 Brussels, Belgium

15.2.1 INTRODUCTION

The need to test for residual solvents (RS) in pharmaceutical substances was recognized in the late 70's when some pharmacopoeias, such as USA (USP XX) or Great Britain (BP 80 + add 82) introduced specific tests for RS in some monographs. But we had to wait until the early 80's to see a rational approach for establishing specifications from toxicological data. This strategy was developed by a working group of the Italian Pharmacopoeia[1] starting from the threshold limit values for Chemical Substances and Physical Agents in the Work Environment published by the American Congress of Governmental Experts for Industrial Hygiene.[2] In the late 80's, RS were definitively classified as impurities per se. Methods and specifications appeared in different issues of the Pharmacopoeial Forum and were submitted for discussion and finally integrated into the USP. At the same time, only a few such monographs could be found in the European Pharmacopoeia (Eur. Ph.) or British Pharmacopoeia (BP). Interestingly, the notion of a content limit for residual solvents concerning the daily intake of the drug was introduced (see Eur. Ph. 2nd edition), a concept which was taken up later in the ICH Guideline. Numerous publications have been devoted to this subject.[3-9] Some more recent articles show that the subject continues to be of interest.[10-16]

The number of papers on RS is immense, but they are very often limited to specialized areas such as regulatory aspects or methodology aspects. In this chapter, various topics will be considered, starting with the fundamental question: why look for RS in pharmaceutical products? It is worth noting that Witschi and Doelker[17] published in 1997 a very detailed and up-to-date review stressing the importance of this subject in the pharmaceutical field. Grodowska and Parczewski[18] reviewed in 2010 the importance of the use of organic solvents in the pharmaceutical industry and the importance of purification processes to eliminate these solvents from the final products. This was more recently confirmed by Anders and Lee.[16]

It also has to be mentioned that several research groups and pharmaceutical companies are developing techniques to avoid the use of organic solvents in the production processes of pharmaceuticals. An example of this is the use of solventless coating processes.[19] At the same time, the use of organic solvents is still necessary to produce the majority of the drug products.

15.2.2 WHY SHOULD WE LOOK FOR RS?

RS could have various effects on the drug substances, excipients and drug products.

15.2.2.1 Modifying the Acceptability of the Drug Product

The presence of RS could seriously impair customer compliance because of the odor or the taste they can cause in the final pharmaceutical preparation. Rabiant[3,4] quotes the case of a drug substance having undergone, for technical reasons, a washing with isopropanol not planned in the manufacturing protocol. The oral solution prepared from this batch contained 100 ppm of this solvent and consequently had an odor that the majority of the patients accepted only with reluctance; the batch concerned was finally removed from the market.

15.2.2.2 Modifying the Physico-chemical Properties of Drug Substances (DS) and Drug Products (DP)

The role of the quality of the solvents on the stability of the raw materials, DS and DP (see chapter 13.21.1) has already been discussed. It must be remembered that RS (including water) can show different kinds of interactions with solid substances:[20]

- Solvents adsorbed on the crystal surfaces, which generally are easily removed because of the existence of weak physical interactions.
- Occluded solvents and clathrates which are more difficult to extract without impairing the quality of the drug by, for example, excessive drying.
- Solvents bound to drug molecules in the crystal lattice. These solvents present as solvates (hydrates) are lost at a characteristic temperature and may be stable only over a limited range of relative humidity. The solvates, while being two different chemical entities, can retain the same crystalline structure (similarity of x-ray diffraction pattern) but show different physicochemical properties.[21-23]

One of the most critical effects of organic solvents absorbed on crystal surfaces is the ability to reduce the wettability of the crystals, especially if the solvent concerned is hydrophobic.[24]

Another interesting aspect, particularly in case of residual water, is their role as an agent of recrystallization of poorly crystalline substances. It is well known that amorphous or partially amorphous products can undergo a recrystallization[25,26] process over time in the presence of water. If amorphous phases are an interesting way to promote the dissolution rate of poorly soluble drugs, their main drawback is their physical instability triggering the possible crystallization of the drug and leading to a decrease in dissolution rate and possibly of bioavailability, over a period of time.

Furthermore, the residual adsorbed water may have an impact on the flowability of a powder, which is linked to the solubility of the substance and the hydrophilicity of the crystal faces.[24] Other physicochemical parameters are influenced by RS, like particle size and dissolution properties. For more information, we refer to the publications of Witschi and Doelker[17] and Guyot-Hermann[24] and references quoted therein. Nevertheless, one example deserves to be mentioned here.[17,25] Residual isopropyl alcohol enhanced the water permeability of Eudragit® L films used as tablet coating for protecting water-sensitive drugs as demonstrated by List and Laun.[25] This implies particular conditions for the

storage of coated tablets during the film-drying process. The atmosphere should be as dry as possible.

In general, it can be stated that residual solvent or water in the coating of tablets can result in unstable coatings, affecting permeability, the stability of the drug product and disintegration and release. These phenomena were described for tablet coatings based on methacrylate copolymers (the Eudragit® family).[27]

The need to keep the RS level as low as possible can lead to some problems. It has been reported[24,26] that a drug substance displaying a strong odor of residual solvent was submitted to reprocessing, consisting of displacement of the residual solvent by a stream of water vapor. During this process, which slightly modified the surface crystallinity of the particles, a small amount of impurity was produced. The consequence was an increase of the surface solubility of this drug substance. During the preparation of the DP using an aqueous wet granulation, a liquefaction of the granulate was observed making the manufacture impossible. After having removed the impurity by purifying the DS successful manufacture of the DP was achieved.

There are other aspects linked to the manufacturing process and drying conditions, which impact on the final RS content. Another example of the relationship between the manufacturing process and RS is worth mentioning here. It relates to the formation of volatile compounds produced by radiolysis, which can induce odor. Barbarin *et al.*[28] have investigated this subject in different antibiotics belonging to the cephalosporin group (Cefotaxime, Cefuroxime and Ceftazidine). Using GC-MS and GC-IR they were able to identify carbon monoxide, nitric oxide, carbon disulfide, methanol, acetaldehyde, ethyl formate, methyl acetate, and acetaldehyde O-methyloxime. In a subsequent publication[29] on cefotaxime, they demonstrated that some of the radio-induced compounds (such as carbon monoxide sulfide (COS) and carbon disulfide) came from the degradation of the drug itself whereas the formation of others required the RS, present before the irradiation. For instance, acetaldehyde arises from the irradiation of methanol. Incidentally, this is an excellent way to differentiate between radiosterilized and non-radiosterilized products.

It is worth remarking that residual humidity can favor[24] microbiological growth especially in some natural products used as excipients (starch, gelatine, etc.). From a physicochemical point of view, residual moisture may have an impact on the hardness of the tablets as shown by Chowhan[30] and Down and McMullen.[31]

15.2.2.3 Implication in Possible Drug/container Interactions

It is possible that the RS contained in powder may migrate up to the interface between the contents and the container facilitating the extraction and migration into the drug of additives used during the container manufacture. On the contrary, solvents may be used during the packaging of a drug. An example of this situation is described by Letavernier *et al.*[32] Cyclohexanone was used for sealing PVC blisters containing suppositories. After 42 months storage at ambient temperature up to 0.2 mg to 0.3 mg of cyclohexanone was found per gram of suppository.

15.2.2.4 As a Tool for Forensic Applications

Forensic laboratories are interested in identifying and assessing trace impurities in bulk pharmaceutical products with the idea of using the impurity profile as a "fingerprint" of the manufacturer. Indeed, RS can be an essential aid in this process.[33,34] Such fingerprints do not only allow to detect counterfeit, as is discussed later but also patent fraud and origin. The impurity profile and especially the profile of the residual solvents in a bulk product or even in the finished product can often be related to the synthesis pathway of the active ingredients.[35] Similar profiles indicate similar synthesis pathways and so possible patent fraud if the pathway is patented by a specific company. The more, similar impurity profiles of residual solvents in illegal medicines can be related to the same bulk pharmaceutical ingredient used and so to the same origin/producer. This approach is also applied by the API-working group of the European Official Medicine Control Laboratory (OMCL) network.[36,37] This workgroup performs projects in the domain of API surveillance, and next to it conducts fingerprint projects to identify counterfeit and substandard API's on the European market. The projects are a close collaboration between the different OMCLs represented in the workgroup, and therefore samples are taken from the different national markets and analyzed together, following identical protocols.

The same "fingerprint" principle can also be used in the domain of illicit drugs and narcotics. It was for instance demonstrated[38] that static headspace (GC) coupled with mass spectrometry (MS) was able to detect and identify volatile impurities, making possible the characterization of illicit heroin or cocaine samples.

15.2.2.5 As Detection and Characterization Method for Counterfeit Medicines

Counterfeit medicines are a growing problem in both developing as industrialized countries. The presence of counterfeited medicines on the regular market cannot only represent a risk for public health but also endanger the social security system. This is due to the fact that adverse effects originating from counterfeit products decrease the confidence of the public in the health care practitioners, the health care system, and the pharmaceutical industry.[39]

The risks for public health can be due to the absence of the active principle, the presence of a wrong dosage of the active principles or the presence of non-authorised active components, but also to the presence of toxic impurities.[39] The residual solvents form a group of important impurities. Recognized pharmaceutical companies follow the Good Manufacturing Practices (GMP) to limit the concentrations of residual solvents in their products according to the ICH guidelines[40] (see further). This, however, cannot be expected from companies producing counterfeit medicines. The majority of these products are produced in street laboratories, without any respect of quality and safety regulations.

The detection of counterfeit medicines represents a challenge for the analytical scientist. Several techniques can be used for this purpose. One of them is the use of static headspace GC coupled with MS to detect and identify volatile impurities, with residual solvents as the major group.

In 2013, a study was conducted comparing the residual solvent content of a group of counterfeit medicines to that of the genuine products.[35] For this purpose, a validated GC-MS method, using static headspace injection, adapted from the GC-FID method described

in the European Pharmacopoeia (see below), was used. The method was validated for the quantification of the encountered solvents according to the ICH guidelines, using accuracy profiles.[41]

The study was conducted for Viagra® (sildenafil citrate) and Cialis® (tadalafil) and a group of their respective counterfeit products. The results showed a significantly higher amount of residual solvents in the counterfeit products compared to the genuine ones, both in concentrations and in the number of solvents detected. As an example: for Viagra® 2-butanone, ethylacetate, and toluene were detected in amounts far beneath the limits set by the ICH. However, in the counterfeit products also ethanol, 2-propanol, acetone, carbon tetrachloride, and dichloromethane were detected. In general, solvents were present at higher concentrations than in the genuine product, e.g., in some samples 10 times more ethylacetate was found, but for most solvents below the limits set by the ICH. However, some samples were found in which the concentrations of dichlormethane and carbon tetrachloride were above the ICH limits, even for one sample a concentration of carbon tetrachloride was found to be 10 times the maximal limit (4 ppm).[35]

These results showed that it is possible to detect counterfeit medicines using static headspace-GC-MS with a minimal effort in sample preparation. Most results also point out that the determination of the residual solvent content in counterfeit medicines is an important factor in the risk evaluation for public health.

The profile of residual solvents present in a counterfeit product may also be helpful from a forensic point of view. Indeed this profile reflects partly the synthetic route of the active principle, which makes it possible to group samples using an active principle of the same origin and possibly link them to the same producer.[35]

15.2.2.6 As a Source of Toxicity

15.2.2.6.1 General points

Toxicity is obviously the main reasons for testing for RS. Besides the toxicity of the drug itself, the related impurities,[42] degradants, and the RS can each bring their own contribution. A drug could be prescribed to a patient either for a short period of time or a long one. To minimise either acute toxicity or chronic toxicity resulting from some accumulation process, RS has to be kept at the lowest achievable level. When developing new chemical entities, the presence of RS could bias toxicity studies including mutagenicity and carcinogenicity and cause a risk of wrongly ascribing to the drug substance or the formulation, side effects which are actually due to volatile impurities. Knowing the cost of such studies, it is preferable to have the RS under control.

The long-term exposure to solvents has been recognized for a long time as a possible cause of serious adverse effects in human. Tables of maximally tolerated solvent concentrations in air for defined exposures have been published and used to set limits for residual organic solvents in pharmaceuticals.[1-9,17] In the late 90's, a set of articles appeared in the pharmacopeial forum proposing RS limits from toxicological data,[43-47] including carcinogenicity, mutagenicity, teratogenicity, and neurotoxicity.

In the early 90's, the “International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use” (ICH) was created. Among the different topics deserving to be harmonized, the need to have an agreement

amongst Europe, Japan and the USA on the way to limit the RS in pharmaceuticals was clearly identified and the topic adopted in June 1994. The final guide was finally adopted in 1998 by the Health Authorities of the three zones and is now in force. This Guideline will be examined in detail in the last paragraph of this section.

15.2.2.6.2 Brief overview of the toxicology of solvents[48,49]

15.2.2.6.2.1 Aspects concerning metabolism

There are four main routes by which solvents can interact with the human body:

- ear, nose, throat (ENT)
- transdermal (including the ocular area)
- oral
- injection

A special situation regards implants, such as stents. Stents are metallic scaffolds that are implanted after balloon angioplasty, which is the main therapy used in case of cardiovascular diseases caused by atherosclerosis. Atherosclerosis is a process of vessel wall degradation and calcification. In this case, balloon angioplasty is used to reopen the affected blood vessel, followed by the implantation of the stent in order to prevent elastic recoil of the vascular wall. Even though this therapy is very effective it was observed that the injury caused by the implantation of the stent resulted in neointimal proliferation and in stent restenosis, resulting in a new blockage of the blood vessel. In order to prevent the latter drug-eluting stents were developed. These stents are coated with a polymer or lipophilic layer, in which medicines are embedded, that prevent restenosis. Once the stent is implanted the medicine is released in a controlled way in order to reduce the risk of necrosis and restenosis and this in the first period until the injury of the vascular wall is healed.[50]

During the fabrication process of such drug-eluting stents the coating and the drug is dissolved in a solvent (e.g., dichloromethane) and sprayed onto the metallic scaffold. Since these matrices act as carriers for controlled drug release, they are considered as pharmaceutical excipients and thus should meet the quality requirements of pharmaceuticals. This means that the residual solvent content should also be limited as described in the ICH guidelines. Intuitively it can be said that the limits should even be lowered for these kind of products, since the stent is in close contact with the injured vascular wall. Local high concentrations of residual solvents can cause necrosis and restenosis, eliminating the beneficial effects of the drugs released by the coating matrix and causing a new cardiovascular incident.[12,50]

15.2.2.6.2.2 Aspects concerning metabolism

Once in the organism, solvents may undergo biotransformation which essentially takes place in the liver. This metabolism very often leads to more water-soluble products than the parent compound[51,52] and, as such, more easily excreted by the kidneys. This detoxification process is beneficial for the individual but varies greatly from one subject to another. Unfortunately, this metabolic detoxification can be complicated by the appearance of reactive intermediates which, if not rapidly inactivated, will destroy the essential constituents of the cells (proteins, nucleic acids, unsaturated lipids) and cause intoxication.

The latter ranges from a simple allergic reaction to tissue necrosis or, at worst, to cancer. Figure 15.2.1 summarizes the different events which can occur in the organism.

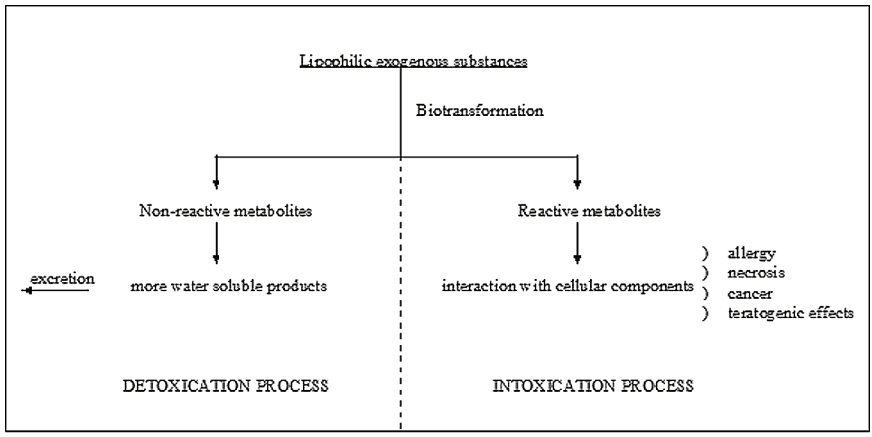


Figure 15.2.1. Events which may occur in the organism. [Data from A Picot, **Information Toxicologique n° 3, Unité de prévention du risque chimique**. *CNRS* (France) (1995).]

15.2.2.6.2.3 Solvent-related pathology

15.2.2.6.2.3.1 Acute toxicity

It is especially the affinity of the solvents for lipid-rich organs, which triggers problems of acute toxicity and this concerns primarily the nervous system, the heart, the liver, and kidneys. In this acute toxicological process, the molecules act *per se* without any previous biotransformation. The acute toxicity encompasses:

- nervous toxicity (headache, somnolence, coma, which can extend to death)
- cardiac toxicity[53]
- action on skin and mucous membranes generating irritation (including ocular area)[54]

Another acute local toxicity is the occurrence of necrosis and restenosis at the implant site of drug-eluting stents, as discussed before.

15.2.2.6.2.3.2 Long-term toxicity

A prolonged exposure, even at low doses to several lipo-soluble solvents leads sooner or later to irreversible effects on different organs:

- central nervous system (e.g., toluene could lead to degeneration of the brain)
- peripheral nervous system (e.g., methanol shows a peculiar affinity to the optic nerve leading eventually to blindness)
- liver and kidneys; as solvents are metabolized in the liver and excreted by kidneys, these two organs are, of course, particular targets for these products
- skin and mucous membranes (e.g., dermatitis)
- blood (cyanosis, anaemia, chromosomal abnormality)

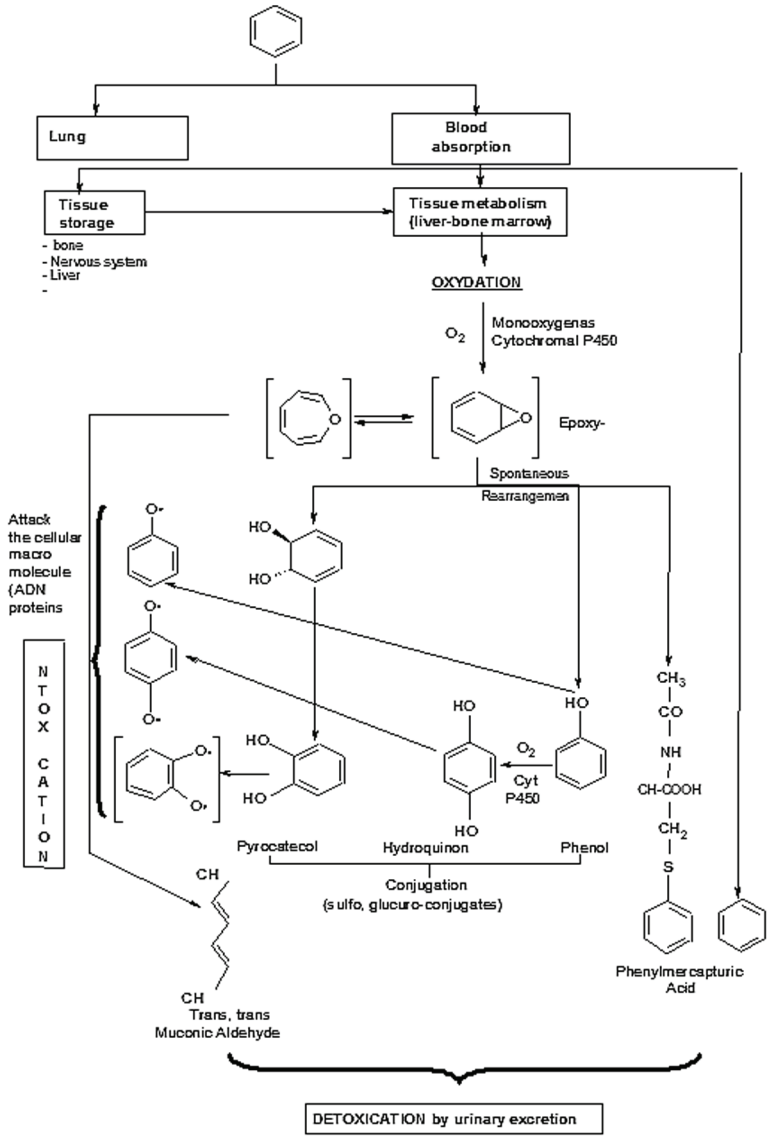


Figure 15.2.2. Overview of benzene metabolism. [Adapted, by permission, from Le Goff. Les risques physico-chimiques et toxiques des solvants. *Communication personnelle*.]

With regard to carcinogenicity, benzene has long been recognized as carcinogen in man. It is the reason why its use is strictly limited and not recommended (ICH class 1/ specification 2 ppm). Carbon tetrachloride and 1,2-dichloroethane have been demonstrated to be carcinogenic in animals and potentially carcinogenic in man. Also, the

embryotoxicity of solvents must be taken into account. As solvents can cross the placenta, pregnant women should be especially protected.

15.2.2.6.2.3.3 Metabolism of benzene

By the way of illustration, Figure 15.2.2 summarizes the metabolic pathway of benzene.[55] Numerous publications dealing with the metabolism of benzene are given in reference.[44]

15.2.3 HOW TO IDENTIFY AND CONTROL RS IN PHARMACEUTICAL SUBSTANCES?

15.2.3.1 Loss on drying

Historically this is the first method which appeared in the pharmacopoeias, performed either at normal pressure or under vacuum. This is, of course, an easy method, particularly for routine control but there are several drawbacks:

- lack of specificity
- it is product demanding (sample size 1 – 2 g)
- the limit of detection (LOD) is currently about 0.1%
- the atmospheric humidity can significantly modify the results

Due to these limits, this test is not generally recommended anymore for the determination of residual solvents by the pharmacopoeias. The exception to this is the determination of water content and the use of loss on drying when only class 3 solvents (see further) are present.

The determination of residual solvents can also be done using thermogravimetric analysis (TGA) which makes the method more sensitive (possible LOD 100 ppm) and less product demanding (5-20 mg). It can also be used as a hyphenated method linking TGA to a mass spectrometer, allowing the identification of the desorbed solvents (specificity).

15.2.3.2 Differential Thermal Analysis (DTA) and Differential Scanning Calorimetry (DSC)

Next to TGA also DTA and DSC found applications in the field of the determination of the residual solvent content of pure drug substances and end products. Examples of their use is the determination of loss of methylene chloride,[56] chloroform[57] and isopropanol.[58] Due to the lack of specificity only the general content of solvents can be determined in case that more than one solvent is present.

15.2.3.3 Miscellaneous Methods

Fourier-transform IR[59] and ^{1}H-NMR[60] have been used occasionally to identify and quantify residual solvents, but their sensitivity is rather limited as compared to GC. In general it can be stated that the detection limits for these techniques are above 100 ppm, which makes these techniques inadequate for the levels presented in the international guidelines. The more interferences of matrix and analyte peaks cannot be excluded. However, when a specific class 2 or 3 solvent is the only solvent present in a product, these methods can be useful.[61,62]

15.2.3.4 Gas Chromatography (GC)

15.2.3.4.1 General points

This is, of course, still the method of choice which has long been used to determine RS whatever the area of application (pharmaceuticals, polymers, water analysis, etc.).[63-65]

From the late 70's to the beginning of the 80's, there was a large number of publications dealing with different possible GC techniques which could be applied for detecting or analyzing residual solvents especially in pharmaceuticals (intermediates of synthesis, drug substances, excipients, and drug products). So much has been written that it is difficult to be original. Methodological aspects will be briefly covered in the next paragraph. The paper of Witschi and Doelker[17] is particularly recommended. With 171 references, it represents a worthwhile review of the different GC techniques available. That the subject is still of actual interest is proven by two more recent reviews written by B'Hymer[61] and Grodowska and Parczewski[62] and some recent scientific publications.[10-16] The last part of this chapter concerns pharmacopoeial methods.

15.2.3.4.2 Review of methods

Regarding GC methodology, four aspects must be examined:

- injection systems
- columns
- detectors
- method validation

15.2.3.4.2.1 Injection systems

For the injection systems three main procedures can be distinguished: direct injection, headspace injection, and Solid Phase Micro-Extraction (SPME). Each procedure will be discussed in detail in the following sections.

15.2.3.4.2.1.1 Direct injection

After having dissolved the substance containing the RS to be looked for in an appropriate solvent, it is possible to directly inject into the system 100% aliquot of the solution (if packed columns are used) or partially through a split system (if capillary, narrow-bore and wide-bore columns are used). It is simple, accurate, and repeatable (with an internal standard). The main drawback is that samples very often contain non-volatile substances which are retained by the column, leading rapidly to a loss of efficiency and a dramatic decrease in sensitivity.[67] Also drug matrix effects cannot be excluded. In the current literature dealing with the RS, the direct injection process is less frequently used. Nevertheless, different publications exist.[68,69]

Split injection is used for volatile to semi-volatile compounds, and is one of the easiest injection techniques. With this technique, the flow of carrier gas is split between the capillary column and the atmosphere. This split does not occur in case of splitless injection. Splitless injection is used in case residual solvents remain in the sample at low concentrations, due to increased sensitivity compared to split injection. Other possibilities of direct injection are on-column injection and Programmed Temperature Vaporisation (PTV) injection. Both techniques allow detection limits to achieve put levels but are large volume injection techniques. In on-column injection systems, the sample is injected on a pre-column and then the solvent is vented, leaving only the analytes to be injected on the column. In PTV, after the sample injection, the solvent is evaporated at a low temperature in a packed chamber and then removed. This leaves the solutes on the packing. When the injection port is heated the analytes are transferred to the analytical column.[61,62]

15.2.3.4.2.1.2 Static headspace injector

In general this is the most widely used technique for RS determination in pharmaceuticals. The solubilized or suspended sample in an appropriate vehicle is heated at a defined temperature in a tightly closed vial until thermodynamic equilibrium is reached between the liquid phase and the gas phase. A known aliquot is then transferred either with the aid of a syringe or by an automatic transfer system onto the column. The main advantage is that only volatile products including solvents are injected onto the column greatly improving its lifetime and avoiding interfering peaks originating from volatiles during degradation, extraction and pre-concentration. The sensitivity is sufficient for the levels required by the ICH guidelines and last but not least, the system is easily automated.

The main drawback is the existence of matrix effects and the possible non-ideality of the solvents mixture.[70] This imply that ideally, one should determine the calibration curve by adding standard solutions of the solvents of interest to the sample matrix, free of solvents. Because it is very challenging to obtain such a sample matrix, the classical standard addition method is recommended. It consists of adding to the sample matrix to be analyzed a known amount of the solvents to be determined. This method requires two analyses for the final calculation, but the main advantage is that the matrix effect is overcome. The linearity of the response has, of course, to be demonstrated before the use of the simplified version mentioned above. Nevertheless, if based on a sound validation, external calibration can be used.[67,71]

The nature of the solvent used to prepare the solution (e.g., water, dimethylformamide, dimethylacetamide, 1,3-dimethyl-2-imidazolidinone (DMI)), equilibration temperature, the ratio between the gas phase and the liquid phase and the possible need to promote a salting out effect by adding mineral salts are the parameters, amongst others, which should be investigated and optimized to improve the sensitivity (LOD, LOQ) of the method.[72,73]

Another version of this static headspace chromatography is what has been called by Kolb[74] multiple headspace extraction (MHE) chromatography. This is a multi-step injection technique which was alluded to in the Suzuki publication[65] and more openly developed by McAuliffe.[75] The principle of this method is the following.[76,77] After the first extraction has been made and the aliquot injected, the gas phase is removed by ventilating the vial and re-establishing the thermodynamic equilibrium. The equilibrium between the analyte in the solid or liquid phase and the gas phase will be displaced each time. After n extractions the analyte content in the liquid or solid phase becomes negligible. It is then sufficient to sum the peak areas obtained for each extraction (which decrease exponentially) and, from an external calibration curve, determine the amount of RS in the substance.

This method is particularly useful for insoluble products or in cases where the partition coefficient of the RS is too favorable, relative to the liquid phase. As an example the method proved successful for the determination of RS in transdermal drug delivery systems.[77]

15.2.3.4.2.1.3 Dynamic headspace injection

In the dynamic headspace method, the sample is put in a thermal desorption unit in order to desorb the RS; a continuous flow of a carrier gas pushes the RS into a trapping system which is refrigerated and where it is accumulated prior to analysis. Then the RS are rapidly desorbed by rapid heating and carried onto the column *via* the carrier gas. There are different ways to apply this technique.[17,78] The arrangement when purge gas passes through the sample is often called the purge and trap technique (some other equipment uses the acronym DCI (desorption, concentration, injection)). This method is particularly useful for very low concentrations of RS. Because the "total" amount of volatile substance is extracted, trapped and analyzed at one time, much lower detection limits can be obtained. The more the techniques can be applied directly to powders without having to dissolve them. Dynamic headspace also has the advantage of avoiding an equilibrium between the gas and sample matrix, as is required with static headspace and SPME. Another advantage is that a dissolution solvent peak can be avoided in the chromatogram. Drawbacks of the technique are the problem of artifact volatiles collecting in the trap and the fact that the dynamic headspace methods are not readily automated.[67]

15.2.3.4.2.1.4 Solid Phase Micro Extraction (SPME)

Even though SPME is not yet accepted as sample preparation technique by the pharmacopoeia's it is considered as a valuable alternative to headspace injection for the determination of residual solvents in pharmaceuticals.[79] As in dynamic headspace injection SPME concentrates the analytes and so it is able to lower the detection limits. A small amount of the extraction phase is coated on a support, commonly a fused silica fiber which is then placed in contact with the sample for a predefined amount of time. When the contact time is sufficient a concentration equilibrium of the volatile analyte(s) is reached between the sample matrix and the extraction phase. The fiber with the extraction phase is generally attached to a sampling device, which is essentially a syringe. The fiber is extended into the inlet of the GC, where the volatile analytes are thermally desorbed and swept towards the chromatographic column.[61,62]

The main advantages of SPME is its solventless character as well as its improved sensitivity compared to static headspace injection. The main disadvantage of the technique is the time consuming optimization of the analytical conditions. Other drawbacks are the facts that the SPME fiber efficiency might change as a function of the number of injections and that these fibers show sometimes low inter-batch reproducibility and sensitivity.[61,62,80]

Another injection technique, showing high similarity to SPME is called single drop microextraction (SDME). It this technique a drop of solvent is suspended at the end of a microsyringe needle in the headspace phase over the sample solution. A drop has a higher surface than the fiber in SPME, but instability of the drop is a factor that should be taken into account, to ensure reproducibility of the results. The main advantage of this technique is that it is less expensive than SPME. The main drawback is the higher detection limit for RS compared to SPME.[81]

15.2.3.4.2.2 Columns

The wealth of publications dealing with RS determination by GC is so impressive that it is difficult to provide an exhaustive review. The interested reader will find plenty of information in the references quoted in this chapter. Packed columns,[82] wide or narrow bore columns, capillary columns, etc. have been used for RS determination. It is true to say that currently capillary columns and narrow bore columns are the most often mentioned techniques. Today, it is almost certain that any user could find in the literature[17] the stationary phase and the relevant conditions to resolve his RS problem, at least in terms of selectivity. By the way of example, it has been shown by Brinkmann and Ebel[83,84] how it was possible to screen 65 of the 69 solvents mentioned in the ICH Guideline (discussed in paragraph 15.2.4) using capillary columns filled with two stationary phases (DB 624 and Stabilwax) which basically constitute the strategy proposed by the European Pharmacopoeia.

15.2.3.4.2.3 Detectors

The almost universally used detector is obviously the flame ionization detector (FID) which works with all organic solvents and is used in the official method proposed by the pharmacopoeias, but which is not selective. The mass spectrometer detector (MSD) is nowadays at least equally used for RS determination as the FID[34,79,85-87] and is also recognized as detector by the USP and the European Pharmacopoeia. It can be either universal in its electron ionisation (EI) mode or selective in its selective ion monitoring mode (SIM). Other detectors, selective and/or universal, can be used.[17,88] Among them the electron capture detector deserve special attention when looking for chlorinated solvents, but also photoionization and thermal conductivity detection are possible in this domain.

15.2.3.4.2.4 Method validation

Whatever the technique used for determining the RS content in pharmaceuticals, a thorough validation of the complete analytical process has to be conducted according to the ICH Guidelines[89] and/or the ISO17025 guidelines.[90] For testing impurities in a quantitative manner the following items have to be included:

- specificity and selectivity
- accuracy
- precision
- repeatability
- intermediate precision (first part of reproducibility)
- limit of detection (LOD), limit of quantification (LOQ)
- linearity of the response
- the range which is the interval between the upper and lower concentrations (amounts) of analyte in the sample (including these concentrations) for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy and linearity.

In the publications mentioned above,[34,67-69,77-79,83,85,91,92] it is possible to find experimental procedures required to conduct the validation efficiently. Attention is drawn to the fact that, when using the static headspace technique, in particular, some other parameters have to be investigated, such as[34,77]

- ratio gas phase/solid or liquid phase
- the temperature of equilibrium between the two phases and time to reach it
- the temperature of the transfer line
- pressurization time and sampling time when using a fully automated headspace injector

Finally, some additional comments are worth making:

- As regards reproducibility, it is true that the best way to assess it is to set up an interlaboratory study. It is, of course, burdensome, but this is probably the only way to infer reasonable suitability parameters for the routine quality control monograph (resolution, plate number, tailing factor, repeatability, LOD, LOQ) and specifications. It is worth noting that the latter should take the performance of the analytical method into account. But for those who cannot follow this approach, sound ruggedness testing has to be performed. Wynia *et al*. have designed a method[93] for evaluating the ruggedness of a gas chromatographic method for residual solvents in pharmaceutical substances. A more general overview on how to conduct ruggedness tests is given in reference.[94]
- When using the static headspace injector, the possible matrix effect should be studied and can be evaluated by a statistical method.[95,96]
- One of the most critical suitability parameters in case of RS determination is, of course, the LOQ (and LOD). To avoid an unrealistic value in the QC monograph, it is highly recommended to use a working limit of quantification WLOQ (and WLOD), which consists of determining a reasonable upper limit for LOQ (and LOD). In fact, the LOQ derived from the validation package is obtained in what we can call an ideal or optimized environment.

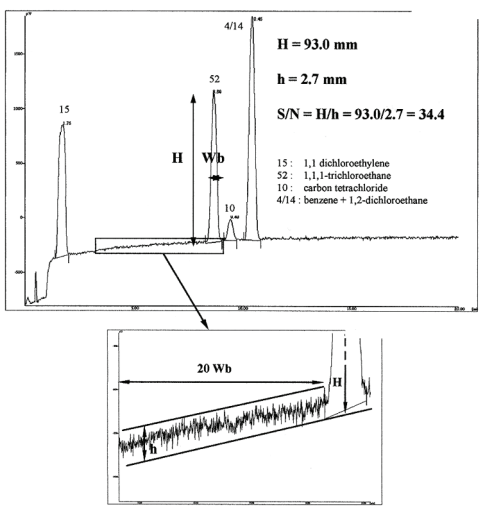


Figure 15.2.3. Head-space injection of the gaseous sample onto the chromatographic system. Typical chromatogram of class 1 solvents using the conditions described for System A (European Pharmacopoeia method). Flame-ionisation detector: calculation of H/h for 1,1,1-trichloroethane.

A way of determining α (> 1) in the relationship:

$$WLOQ = \alpha \times LOQ$$

is to calculate the LOQ according to the signal to noise ratio S/N method[89-93,95-97] and to repeat this determination independently several times (e.g., n = 6) during the intermediate precision determination (Figure 15.2.3). If LOQ_m is the mean value and σ the standard deviation, a possible definition of WLOQ could be the upper limit of the one side confidence limit at a specified risk α (e.g., 0.05).

$$WLOQ = LOQ_m + t_{n-1,\alpha}\sigma$$

where:

t is Student's coefficient

Validation of analytical methods can be performed using integrated approaches. One of these approaches which is often used for validations according to the ICH and ISO17025 guidelines is the total error approach. This approach estimates the "total error" by combining the bias (trueness) and the random error (intermediate precision) to know the difference between the observed result and the true value. In other words, the highest error of an analytical method can be estimated. For more information about this approach, readers are referred to references.[98-100]

15.2.3.4.3 Official GC methods for RS determination

Current official GC methods are described in USP 36 under chapter 467 "Residual Solvents".[101] This chapter describes three procedure (A, B and C) and this for both water-soluble articles and water-insoluble articles. Procedures A and B are used for the identification of class 1 and class 2 solvents, where procedure C is used for quantification. When it is known which specific solvents are present, only procedure C has to be carried out for the quantification of the residual solvents present. The identifications are performed using external standardization while the quantification with procedure C is performed using standard addition.

All three procedures make use of a FID detector and a static headspace injection system. The differences are in the choice of columns:

Procedure A: a 0.32 mm x 30 m fused silica column coated with a 1.8 µm layer of a 6% cyanopropylphenyl-94% dimethylpolysiloxane phase or a 0.53 mm x 30 m wide bore column coated with a 3.0 µm layer of the same phase. For water-insoluble products only the second type of column is used.

Procedure B: a 0.32 mm x 30 m fused silica column coated with a 0.25 µm layer of polyethylene glycol (average molecular weight ~ 15,000) phase or a 0.53 mm x 30 m wide bore column coated with the same layer.

Procedure C: In general the chromatographic system of procedure A is used, but it can be substituted by the one of procedure B if the quality of chromatography of the first system is found to be inferior.

For water-soluble articles water is used as a solvent for preparation of standard and test solutions while for water insoluble articles dimethylformamide is used. The latter may be substituted with dimethylsulfoxide.

The European Pharmacopoeia[102] suggests use of a two-tiered process based on two different columns:

System A

Fused silica capillary or wide bore column (0.32 mm x 30 m (ID) or 0.53 mm x 30 m (ID)) coated with a layer of 1.8 µm or 3 µm of the phase (6 percent polycyanopropylphenyl-94 percent dimethylpolysiloxane) which is identical to the columns used in procedure A of the USP.

System B

Fused silica capillary or wide bore column (0.32 mm x 30m (ID) or 0.53 mm x 30 m (ID)) coated with a 0.25 µm layer of Macrogol 20000R.

The static headspace injector has been selected, and the method uses water as dissolution medium for water-soluble products and N,N-dimethylformamide for water-insolu-

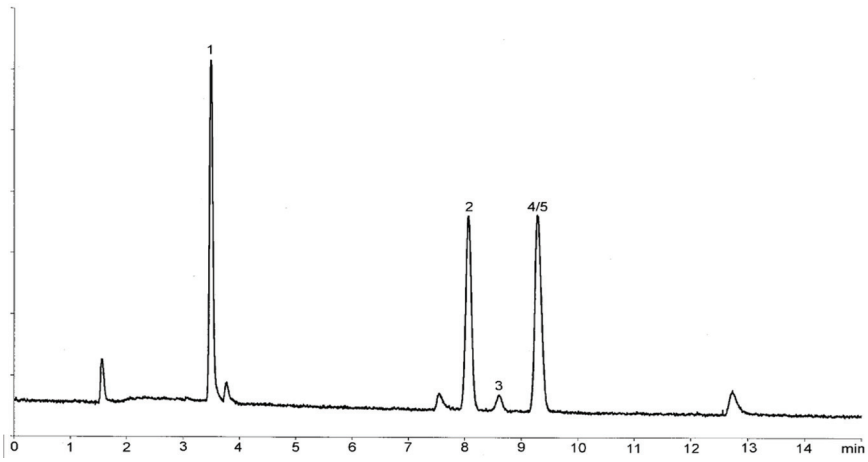


Fig. 15.2.4. Typical chromatogram of class 1 solvents using the conditions described for system A and procedure 1. Flame-ionisation detector. 1. 1,1-dichloroethane; 2. 1,1,1-trichloroethane; 3. Carbon tetrachloride; 4. benzene; 5. 1,2-dichloroethane. [Reprinted, with permission, from **European Pharmacopoeia** 7.0 (2018), *Council of Europe*, Strasbourg, France.]

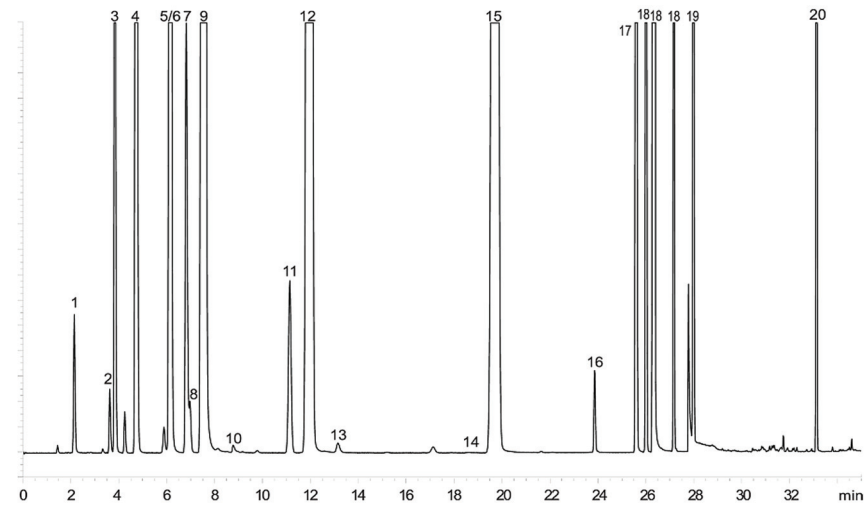


Figure 15.2.5. Chromatogram of class 2 solvents using the conditions described for system A and procedure 1. Flame-ionisation detector. 1. methanol; 2. acetonitrile; 3. dichloromethane; 4. hexane; 5. cis-1,2-dichloroethene; 6. nitromethane; 7. Tetrahydrofuran; 8.chloroform; 9. cyclohexane; 10. 1,2-dimethoxyethane; 11. 1,1,2-trichloroethene; 12. methylcyclohexane; 13. 1,4-dioxan; 14. Pyridine (t_r = 18.7 min); 15. toluene; 16. methylbutylketone; 17. chlorobenzene; 18. xylene o-, m-, p-; 19. Cumene; 20. tetralin; [Reprinted, with permission, from **European Pharmacopoeia** 9.0 (2018), *Council of Europe*, Strasbourg, France.]

ble products. If N,N dimethylacetamide and/or N,N-dimethylformamide are suspected in the drug under investigation 1,3-dimethyl 2-imidazolinone (DMI) is used as dissolving medium.

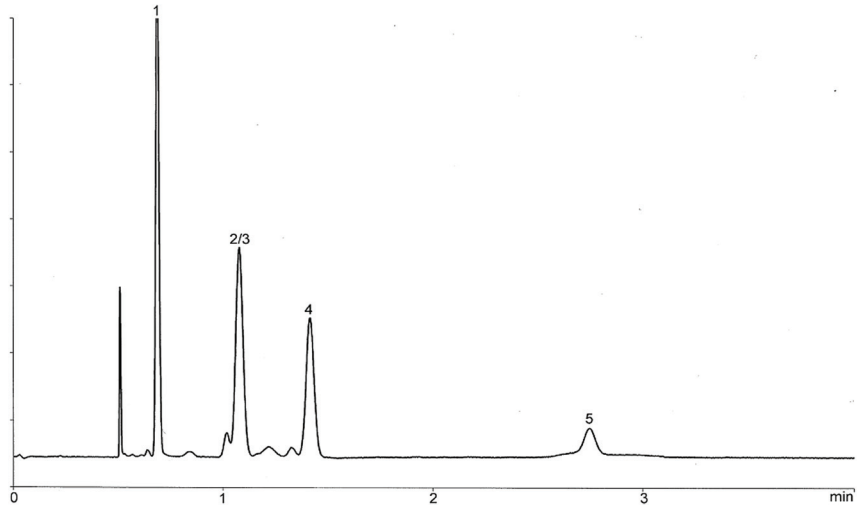


Figure 15.2.6. Chromatogram of class 1 residual solvents using the conditions described for system B and procedure 1. Flame-ionisation detector. 1. 1,1-dichloroethane; 2. 1,1,1-trichloroethane; 3. carbon tetrachloride; 4. benzene; 5. 1,2-dichloroethane. [Reprinted, with permission, from **European Pharmacopoeia** 9.0 (2018), *Council of Europe*, Strasbourg, France.].

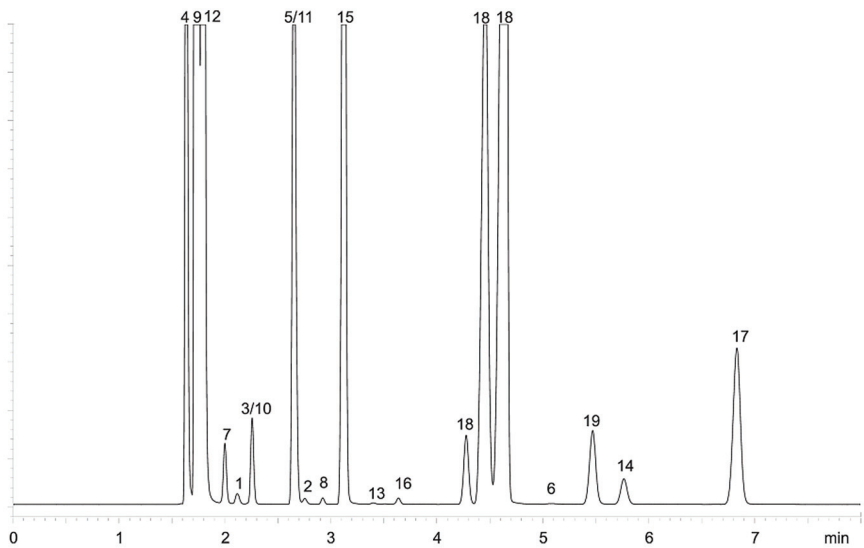


Figure 15.2.7. Typical chromatogram of class 2 residual solvents using the conditions described for system B and procedure 1. Flame ionisation detector. 1. methanol; 2. acetonitrile; 3. dichloromethane; 4. hexane; 5. 1,2-dichloroethene; 6. nitromethane; 7. tetrahydrofuran; 8. chloroform; 9. cyclohexane; 10. 1,2-dimethoxyethane; 11. 1,1,2-trichlo-roethene; 12. methylcyclohexane; 13. 1,4-dioxane; 14. pyridine; 15. toluene; 16. methylbutylketone; 17. chlorobenzene; 18. xylene o-, m-, p-; 19. cumene; 20. Tetralin (t_r = 27 min.). [Reprinted, with permission, from **European Pharmacopoeia** 9.0 (2018), *Council of Europe*, Strasbourg, France.]

The method has been designed:

- in order to identify most class 1 and class 2 RS potentially present in drug substances, excipients or drug products.
- as a limit test for class 1 and class 2 RS present in drug substances, excipients and drug products.
- to quantify class 2 RS where the content is higher than 1000 ppm or class 3 RS if the need arises.

Figures 15.2.4, 15.2.5, 15.2.6 and 15.2.7 illustrate the separation obtained for the two systems for solvents belonging to class 1 and class 2 solvents.

It should be stressed that the use of a general pharmacopeial method is not a reason not to validate the latter when analyzing a particular substance. The matrix effect, in particular, has to be investigated when using the static headspace mode of injection.

15.2.4 HOW TO SET SPECIFICATIONS? EXAMINATION OF THE ICH GUIDELINE ON RESIDUAL SOLVENTS

The introduction briefly summarizes the strategies dealing with the setting of specifications in pharmaceuticals.

From the early 90's onwards, the International Conference on Harmonization was initiated by three important pharmaceutical areas (Europe, Japan, USA) to define a common way of preparing a registration file acceptable in the three zones. The topics included in this harmonization process are:

- Quality
- Safety
- Efficacy

Regarding Quality, a set of Guidelines have been already adopted. Three of them are particularly relevant with regard to this chapter:

- Guideline Q3A: Impurities in new active substances
- Guideline Q3B: Impurities in new medicinal products
- Guideline Q3C: Note for guidance on impurities: residual solvents

Comments on the latter are given below. The full text can be found in the US Pharmacopoeia,[101] in the European Pharmacopoeia[102] and in the ICH guideline.[40]

15.2.4.1 Introduction

The Guideline[40] recommends acceptable amounts of RS in pharmaceuticals which are safe for a patient. Residual solvents in pharmaceuticals are defined as volatile organic chemicals that are used or produced in the manufacturing of active substances or excipients, or in the preparation of medicinal products. It is stated that medicinal products should contain no higher levels of residual solvents than can be supported by safety data. Three classes of solvents have been defined based on risk assessment.

15.2.4.2 Classification of residual solvents by risk assessment

Class 1 solvents: solvents to be avoided, known as human carcinogens or strongly suspected carcinogens and environmental hazards.

Class 2 solvents: solvents to be limited. Non-genotoxic animal carcinogens or possible causative agents of other irreversible toxicities such as neurotoxicity or teratogenicity. Solvents suspected of other significant but reversible toxicities.
Class 3 solvents: Solvents with the low toxic potential to man: no health-based exposure limit is needed. Class 3 solvents have permitted daily exposures (PDE) of 50 mg or more per day.

15.2.4.3 Definition of "permitted daily exposure" (PDE)/method for establishing exposure limits

The PDE is defined as a pharmaceutically acceptable intake of RS. The method used to establish PDEs for RS is described in the references.[40,43-47]

15.2.4.4 Limits of residual solvents

15.2.4.4.1 Solvents of class 1 (see Table 15.2.1) should not be employed.
However, if their use is unavoidable to produce a significant therapeutic advance, then their levels should be restricted as shown in Table 15.2.1 unless otherwise justified. 1,1,1-trichloroethane was classified as class 1 for reason of its environmental hazard.

Table 15.2.1. Class 1. Solvents in pharmaceutical products (solvents that should be avoided)

Solvent	Concentration limit (ppm)	Concern
Benzene	2	Carcinogen
Carbon tetrachloride	4	Toxic and environmental hazard
1.2-Dichloroethane	5	Toxic
1.1-Dichloroethene	8	Toxic
1.1.1-Trichloroethane	1500	Environmental hazard

15.2.4.4.2 Solvents of class 2 (see Table 15.2.2) should be limited because of their inherent toxicity.
Two options are available when setting limits for class 2 solvents.

Option 1

The concentration limits in ppm stated in Table 15.2.2 can be used. They were calculated using the following equation by assuming a product mass of 10 g administered daily.

$$\text{concentration (ppm)} = \frac{1000 \times \text{PDE}}{\text{dose}}$$

where:

PDE given in terms of mg/day and dose given in g/day.

Table 15.2.2. Class 2 solvents in pharmaceutical products.

Solvent	PDE (mg/day)	Concentration limit (ppm)
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cumene	0.7	70
Cyclohexane	38.8	3880
1,2-Dichloroethene	18.7	1870
Dichloromethane	6.0	600
1,2-Dimethoxyethane	1.0	100
N,N-Dimethylacetamide	10.9	1090
N,N-Dimethylformamide	8.8	880
1,4-Dioxane	3.8	380
2-Ethoxyethanol	1.6	160
Ethylene glycol	6.2	620
Formamide	2.2	220
Hexane	2.9	290
Methanol	30.0	3000
2-Methoxyethanol	0.5	50
Methylbutylketone	0.5	50
Methylcyclohexane	11.8	1180
Methylisobutylketone	45	4500
N-Methylpyrrolidone	5.3	530
Nitromethane	0.5	50
Pyridine	2.0	200
Sulfolane	1.6	160
Tetrahydrofuran	7.2	720
Tetralin	1.0	100
Toluene	8.9	890
1,1,2-Trichloroethene	0.8	80
Xylene	21.7	2170

*usually 60% m-xylene, 14% p-xylene, 9% o-xylene with 17% ethyl benzene

Option 2

It is not considered necessary for each component of the medicinal product to comply with the limits given in option 1. The PDE in terms of mg/day as indicated in Table 15.2.2 can be used with the known maximum daily dose and the above equation to determine the concentration of residual solvent allowed in the medicinal product. Option 2 may be applied by adding the amounts of RS present in each of the components of the pharmaceu-

tical formulation. The sum of the amounts of solvent per day should be less than that given by the PDE.

15.2.4.4.3 Solvents with low toxic potential solvents of class 3 (see Table 15.2.3) may be regarded as less toxic and of lower risk to human health. It is considered that amounts of RS of 50 mg per day or less (corresponding to 5000 ppm or 0.5% under option 1) would be acceptable without justification. Higher amounts may be acceptable provided they are realistic concerning manufacturing processes and good manufacturing practice.

Table 15.2.3. Class 3. Solvents which should be limited by GMP or other quality-based requirements

Acetic acid	Heptane
Acetone	Isobutyl acetate
Anisole	Isopropyl acetate
1-Butanol	Methyl acetate
2-Butanol	3-Methyl-1-butanol
Butyl acetate	Methylethyl ketone
tert-Butylmethyl ether	2-Methyl-1-propanol
Dimethylsulfoxide	Pentane
Ethanol	1-Pentanol
Ethyl acetate	1-Propanol
Ethyl ether	2-Propanol
Ethyl formate	Propyl acetate
Formic acid	Trimethylamine

15.2.4.4.4 *Solvents for which no adequate toxicological data was found* (Table 15.2.4) These solvents can be used in the manufacture of drug substances, excipients and drug products, but the manufacturer should supply justification for residual levels of these solvents in pharmaceutical products.

Table 15.2.4. Solvents for which no adequate toxicological data was found.

1,1-Diethoxypropane	Methylisopropyl ketone
1,1-Dimethoxymethane	Methyltetrahydrofuran
2,2-Dimethoxypropane	Petroleum ether
Isooctane	Trichloroacetic acid
Isopropyl ether	Trifluoroacetic acid

15.2.4.5 Analytical procedures

If only class 3 solvents are present, a non-specific method such as loss of drying may be used. In the other cases, a selective method (e.g., GC) is required. Especially if solvents of class 2 and class 3 are present at greater levels than their option 1 limits or 0.5%, respectively, they should be identified and quantified. If Class 1 solvents are likely to be present, they should be identified and quantified.

15.2.4.6 Conclusions regarding the ICH Guideline

The lists are not exhaustive, and other solvents can be used and added later to the lists. Solvents can change class based on new data, as was the case of cumene and methylisobutylketone, which became a class 2 solvents (before class 3) with the updated guideline in 2017. Recommended limits of class 1 and class 2 solvents or classification of solvents may change as new safety data become available.

Nevertheless, this Guideline is of great interest for those involved in the pharmaceutical development to prepare successfully a pharmaceutical dossier acceptable everywhere in the world.

15.2.5 GENERAL CONCLUSIONS

Those who have worked for many years in pharmaceuticals will have observed continuous progress in standards of Quality and Control in manufacturing.

Solvents including water are still used in almost every step of the processing of a drug product. Their residues could be detrimental to the processability and stability of the pharmaceutical products and the safety of patients. It can be said that the testing and control of RS has been thoroughly assessed and is based on robust and sensitive techniques, for which the limitations are known, resulting in a sound strategy accepted almost everywhere in the world. The legislation concerning residual solvents in drug products is clear and well documented. The legislation should be followed closely since it is continuously evolving based on new toxicological data.

ACKNOWLEDGMENT

We acknowledge the original authors of this chapter, Dr. M. Bauer and Dr. C. Barthélémy, for their work, which was updated by the authors for the Second Edition of the Handbook of Solvents.

REFERENCES

1 *Societa Italiana di Scienze Farmaceutiche*, *Cronache Farmaceutiche*, **6**, 227-229 (1980).
2 **Threshold limit values for chemical substances and physical agents in the work environment**, *AGGIH* 6500 GLENWAY.
3 J. Rabiant, *Ann. Pharm. Fr*., **42**, 503 (1984).
4 J. Rabiant, *S.T.P. Pharma Pratiques*, **1**, 278 (1991).
5 M. Gachon, *S.T.P. Pharma Pratiques*, **1**, 531 (1991).
6 Procedures for setting limits for organic volatile solvents with methylene chloride as an example of the process, *Pharm For.*, **15**, 5748 (1989).
7 Survey: residual solvents, *Pharmeuropa*, **2**, 142 (1990).
8 H. Stumpf, E. Spiess and M. Habs, *Dtsch. Apoth. Ztg*, **132**, 508 (1992).
9 A. Eichhorn, T. Gabrio and S. Plagge, *Zent. Bl. Pharm. Pharmakother. Lab. Diagn*.; **128**, 675 (1989).
10 W. D'Autry, C. Zheng, K. Wolfs, S. Yarramraju, J. Hoogmartens, A. Van Schepdael, E. Adams, *J. Sep Sci*.; **34**, 1299 (2011).
11 W. D'Autry, C. Zheng, J. Bugalama, K. Wolfs, J. Hoogmartens, E. Adams, B. Wang, A. Van Schepdael, *J. Pharm. Biomed. Anal*.; **55**, 1017 (2011).
12 W. D'Autry, K. Wolfs, J. Hoogmartens, E. Adams, A. Van Schepdael, *J. Chromatogr. A*; **18**, 4034 (2011).
13 K. Grodowska, A. Parczewski, *Acta Pol. Pharm.*; **70**, 191 (2013).
14 K. Grodowska, A. Parczewski, *Acta Pol. Pharm*.; **70**, 181-189 (2013).
15 C. D. Medley, J. Kay, Y. Li, J. Gruenhagen, P. Yehl, N.P. Chetwyn, *Anal Chim Acta*; **19**, 92 (2014).
16 K. Anders, G. Lee, *Int J Pharm*.; **491**, 42 (2015).
17 C. Witschi and E. Doelker, *Eur. J. Pharm. Biopharm*.; **43**, 215 (1997).
18 K. Grodowska, A. Parczewski, *Acta Pol. Pharm*.; **67**, 3 (2010).
19 S. Bose, R. H. Bogner, *Pharm Dev Technol.*; **12**, 115 (2007).

20 E. Ettabia, C. Barthelemy, M. Jbilou and A. M. Guyot-Hermann, *Pharmazie*; **53**, 8 (1998).
21 G. A. Stephenson, E. G. Groleau, R. L. Kleemann, W. Xu and D. R. Rigsbee, *J. Pharm. Sci*.; **87**, 536 (1998).
22 S. R. Byrn, C. T. Lin, P. Perrier, G. G. Clay and P. A. Sutton, *J. Org. Chem.*; **47**, 2978 (1982).
23 J. Bauer, J. Quick, R. Oheim, *J. Pharm. Sci*.; **74**, 899 (1985).
24 A. M. Guyot-Hermann, *S.T.P. Pharma Pratiques*; **1**, 258 (1991).
25 P. H. List and G. Laun, *Pharm. Ind*.; **42**, 399 (1980).
26 C. Lefebvre Ringard, A. M. Guyot-Hermann, R. Bouche et J. Ringard, *S.T.P. Pharma*; **6**, 228 (1990).
27 H. U. Petereit, W. Weisbrod, *Eur J Pharm Biopharm*.; **47**, 15 (1999).
28 N. Barbarin, A. S. Crucq and B. Tilquin, *Radiat. Phys. Chem.*; 48, 787 (1996).
29 N. Barbarin, B. Rollmann, B. Tilquin, *Int. J. Pharm.*; **178**, 203 (1999).
30 Z.T. Chowhan, *Drug Dev. Ind. Pharm*.; **5**, 41 (1979).
31 G. R. B. Down and J. N. McMullen, *Powder Technol*.; **42**, 169 (1985).
32 J. F. Letavernier, M. Aubert, G. Ripoche et F. Pellerin, *Ann. Pharm. Franc*.; **43**, 117, (1985).
33 K. J. Mulligan, T. W. Brueggemeyer, D. F. Crockett, J. B. Shepman, *J. Chrom*.; **686**, 85 (1996).
34 K. J. Mulligan and H. McCaulay, *J. Chrom. Sc*i.; **33**, 49 (1995).
35 E. Deconinck, M. Canfyn, P.-Y. Sacré, P. Courselle, J. O. De Beer, *J. Pharm. Biomed. Anal*.; **81**-82, 80 (2013).
36 European Directorate of Quality of Medicines (EDQM), Strasbourg, France https://www.edqm.eu/en/testing-active-pharmaceutical-ingredients-apis
37 API position paper for OMCL PA/PH/OMCL (12) 51 3R (2012), OMCL network of the Council of Europe, European Directorate of Quality of Medicines (EDQM), Strasbourg, France https://www.edqm.eu/medias/fichiers/api_pp.pdf
38 D. R. Morello and R.P. Meyers, *J. Forensic Sci., JFSCA*, **40**, 957 (1995).
39 E. Deconinck, P.-Y. Sacré, P. Courselle, J. O. De Beer, *J. Chrom. Sci*.; **51**, 791 (2013).
40 International Conference on Harmonization (ICH) of Technical Requirements for the Registration of Pharmaceuticals for Human Use, Q3C: impurities: Guidelines for Residual Solvents, Step 5 (2017).
41 E. Deconinck, M. Canfyn, P.-Y. Sacré, S. Baudewyns, P. Courselle, J. O. De Beer, *J. Pharm. Biomed. Anal.*; **70**, 64 (2012).
42 A. C. Cartwright, *Int. Pharm. J*.; **4**, 146 (1990).
43 Procedure for setting limits for organic volatile solvents with methylene chloride as an example of the process, *Pharm. For*.; **15**, 5748 (1989).
44 D. Galer, R. H. Ku, C. S. Schwartz, *Pharm. For*.; **17**, 1443 (1991).
45 L. Brooks, J. S. Mehring, *Pharm. For.*; **16**, 550 (1990).
46 B. D. Naumann, E. V. Sargent, *Pharm. For.*; **16**, 573 (1990).
47 G. L. Sprague, S. Beecham-K., D. L. Conine, *Pharm. For.*; **16**, 543 (1990).
48 A. Picot, **Information Toxicologique n° 3**, Unité de prévention du risque chimique - *CNRS* (France) (1995).
49 J. Belegaud, *Communication personnelle* (1997).
50 E. Deconinck E, J. Sohier, I. De Scheerder, G. Van den Mooter, *J Pharm Sci*.; **97**, 5047 (2008).
51 H. H. Cornish, B. P. Ling and M. L. Barth, *Amer. Ind. Hyg. Ass. J*.; **34**, 487 (1973).
52 K. Morpoth, U. Witting and M. Springorum, *Int. Arch. Arveits Med*.; **33**, 315 (1974).
53 J. W. Hayden and E. G. Comstock, *Clinical Toxicology*; **9**, 164 (1976).
54 M. J. Archieri, H. Janiaut, A. Picot, *L'Actualité Chimique*, Mai-Juin, 241 (1992).
55 Le Goff – Les risques physicochimiques et toxiques des solvants – Communication personnelle.
56 J. P. Benoit, F. Courteille, *C. Thies, Int. J. Pharm*.; **29**, 95 (1986).
57 C. Dubernet, J. C. Rouland, J. P. Benoit, *Int. J.Pharm*.; **64**, 99 (1990).
58 P. H. List, G. Laun, *Pharm. Ind*., **42**, 399 (1980).
59 M. G. Vachon, J. G. Nain, *J. Microencapsul*.; **12**, 287 (1995).
60 H. W. Ardovich, M. J. Lebelle, C. Savard, W. L. Wilson, *Forensic. Sci. Int*.; **49**, 225 (1991).
61 C. B'Hymer, *Pharm. Res.*; **20**, 337 (2003).
62 K. Grodowska, A. Parczewski, *Acta. Pol. Pharm*.; **67**, 13 (2010).
63 J. Haslam and A. R. Jeffs, *Analyst*; **83**, 455 (1958).
64 J. A. Hudy, *J. Gas Chromatogr*.; **4**, 350 (1966).
65 M. Suzuki, S. Tsuge and T. Takeucni, *Anal. Chem*.; **42**, 1705 (1970).
66 K. Grob, *J. Chrom*.; **84**, 255 (1973).
67 T. K. Natishan and Y. Wu, *J. Chromatogr. A*; **800**, 275 (1998).
68 Q. Chanli, K. A. Cohen and G. Zhuang, *J. Chrom. Sci.*; **36**, 119 (1998).

69 T. K. Chen, J. G. Phillips and W. Durr, *J. Chromatogr*.; **A811**, 145 (1998).
70 T. Wenzl, E. P. Lankmayr, *Anal. Bioanal. Chem*.; **372**, 649 (2002).
71 J. P. Guimbard, M. Person and J.P. Vergnaud, *J. Chromatogr*.; **403**, 109 (1987).
72 Progress report of the working party on residual solvents (technical) of the European Pharmacopoeia Commission, *Pharmeuropa*, **8**, 586 (1996).
73 M. de Smet, K. Roels, L. Vanhoof and W. Lauwers, *Pharm. Forum*; **21**, 501 (1995).
74 B. Kolb, *Chromatographia*; **10**, 587 (1982).
75 C. McAullife, *Chem. Tech*.; **46**, 51 (1971).
76 J. P. Guimbard, J. Besson, S. Beaufort, J. Pittie et M. Gachon, *S.T.P. Pharma Pratiques*; **1**, 3, 272 (1991).
77 P. Klaffenbach, C. Brüse, C. Coors, D. Kronenfeld and H.G. Schulz, *LC-GC*; **15**, 1052 (1997).
78 P. Kuran and L. Sojak, *J. Chromatogr., A*; **773**, 119 (1996).
79 C. C. Camarasu, M. Mezei-Szüts, G. Bertok Varga, *J. Pharm. Biomed. Ana*l.; **18**, 623 (1998).
80 M. Lakatos, *J. Pharm. Biomed. Anal*.; **47**; 954 (2008).
81 M. Michulec, W. Wardencki, *Chromatographia*; **64**, 191 (2006).
82 G. Castello, S. Vezzani and T.C. Gerbino, *J. Chromatogr*.; **585**, 273 (1991).
83 K. Brinkmann and S. Ebel, *Pharm. Ind*.; **61**, 263 (1999).
84 K. Brinkmann and S. Ebel, *Pharm. Ind*.; **61**, 372 (1999).
85 F. J. Santos, M. T. Galceram and D. Fraisse, *J. Chromatogr*.; **742**, 181 (1996).
86 W. D. Bowers, M. L. Parsons, R. E. Clement, G. A. Eiceman and F. W. Karaseck, *J. Chromatogr*.; **206**, 279 (1981).
87 C. N. Kunigami, M. S. Sanctos, M. Helena, W. Morelli-Cardoro, *J. High Resol. Chromatog*r.; **22**, 477 (1999).
88 D. G. Westmorland, G. R. Rhodes, *Pure Appl. Chem*.; **61**, 1148 (1989).
89 International Conference on Harmonization (ICH) of Technical Requirements for the Registration of Pharmaceuticals for Human Use, Q2 R1: Validation of Analytical Procedures: Text and Methodology, Step 4 (2005).
90 EN ISO/IEC 17025 General requirements for the competence of testing and calibration laboratories (www.iso.org) (2005).
91 R. J. Bartelt, *Anal. Chem*.; **69**, 364 (1997).
92 R. B. George and P. D. Wright, *Anal. Chem*.; **69**, 2221 (1997).
93 G. Wynia, P. Post, J. Broersten and F. A. Maris, *Chromatographia*; **39**, 355 (1994).
94 B. Dejaegher, Y. Vanderheyden, *J. Chromatogr A*.; **1158**, 138-157 (2007)
95 R. J. Markovitch, S. Ong and J. Rosen, *J. Chromatogr. Sci*.; **35**, 584 (1997).
96 M. Desmet, K. Roels, L. Vanhoof and W. Lauwers, *Pharm. Forum*; **21**, 501 (1995).
97 C. M. Riley in **Development and Validation of Analytical Methods**, C.M. Riley and T.W. Rosanske, Ed. *Pergamon*, 1996, pp15-72.
98 M. Fienberg, *J. Chromatogr. A*; **1158**, 174 (2007).
99 M. Feinberg, M. Laurentie, *Accred. Qual. Assur*.; **11**, 3 (2011).
100 B. De Backer, B. Debrus, P. Lebrun, L. Theunis, N. Dubois, L. Decock, A. Verstraete, P. Hubert, C. Charlier, *J. Chromatogr. B*; **877**, 4115 (2009).
101 **United States Pharmacopoeia** 40 (2017), *United States Pharmacopeial Convention, Inc.*, Rockville, MD, USA.
103 **European Pharmacopoeia** 9.0 (2018), *Council of Europe*, Strasbourg, France.

16

Environmental Impact of Solvents

16.1 THE ENVIRONMENTAL CHEMISTRY OF ORGANIC SOLVENTS

William R. Roy
2404 Brookens Circle, Urbana, Illinois 61801-6621, USA

16.1.1 INTRODUCTION

Organic solvents are released into the environment by air emissions, industrial and waste-treatment effluents, accidental spillages, leaking tanks, and the land disposal of solvent-containing wastes. Once released, there are numerous physical and chemical mechanisms that will influence how a solvent will behave in the environment. As solvents are released into the environment, they may partition into air, water, and soil phases. While in these phases, solvents may be chemically transformed into other compounds that are less problematic to the environment. Understanding how organic solvents partition and behave in the environment has led to better management approaches to solvents and solvent-containing wastes. There are many published reference books written about the environmental fate of organic chemicals in air, water, and soil.[1-5] The purpose of this chapter is to summarize the most current information available about the environmental fate of five groups of commonly used solvents (Table 16.1.1) in air, water, and soil. Information about the likely pathways for the environmental fate of organic solvents can serve as the technical basis for the management of solvents and solvent-containing wastes.

16.1.2 RELEASES TO THE ENVIRONMENT

The U.S. Environmental Protection Agency (EPA) maintains the Toxic Chemical Release Inventory.[6] This database summarizes estimated chemical releases from industrial sources to air, water, land, and the subsurface by deep-well injection in the United States. Not all industrial sources are required to provide release data to the EPA, and nine of the solvents discussed in this chapter are not included in the database. The information provided, however, indicated that about 93,587,585 kg of solvents were released into the environment in 2016, and that the major solvents were hexane, methanol, and toluene (Table 16.1.2). On a weight basis, methanol accounted for more than half of the releases. With the exception of nitrobenzene and pyridine, the major on-site releases were made to the atmosphere. For

example, about 98% of the hexane released was to the atmosphere. In contrast, of the 234,983 kg of pyridine released, about 85% was done by deep-well injection.

Table 16.1.1. The five groups of solvents discussed in this chapter.

Alcohols	**Ketones**
n-Butyl alcohol	Acetone
Isobutyl alcohol	Cyclohexanone
Methanol	Methyl ethyl ketone
	Methyl isobutyl ketone
Benzene Derivatives	
Benzene	**Others**
Chlorobenzene	Carbon disulfide
o-Cresol	Diethyl ether
o-Dichlorobenzene	Ethyl acetate
Ethylbenzene	Hexane
Nitrobenzene	Decane
Toluene	Pyridine
o-Xylene	Tetrahydrofuran
Chlorinated Aliphatic Hydrocarbons	
Carbon tetrachloride	
Methylene chloride	
Tetrachloroethylene	
1,1,1-Trichloroethane	
Trichloroethylene	

Table 16.1.2. Estimated on-site releases (in kg) of the solvents in 2016 [Data from TRI].[6]

Solvent	Air	Land	Water	Underground injection	Total
Alcohols					
n-Butyl alcohol	3,901,132	19,561	3,214	26,732	4,191,309
Isobutyl alcohol	NR				
Methanol	45,731,441	1,145,220	1,416,175	5,304,418	53,597,260
Benzene derivatives					
Benzene	1,364,041	97,327	1,748	149,074	1,612,190
Chlorobenzene	183,009	41	29	54,431	237,510
o-Cresol	2,156	0.5	94	72,049	74,301

Table 16.1.2. Estimated on-site releases (in kg) of the solvents in 2016 [Data from TRI].[6]

Solvent	Air	Land	Water	Underground injection	Total
o-Dichlorobenzene	35,426	6,752	21	0	42,200
Ethylbenzene	1,125,413	62,268	1,411	334,222	1,523,313
Nitrobenzene	10,185	4	17	230,381	240,592
Toluene	8,774,319	717,227	3,411	144,895	9,039,852
o-Xylene	93,565	15	59	51	93,690
Chlorinated aliphatic hydrocarbons					
Carbon tetrachloride	168,584	10,209	2,153	3,169	184,114
Methylene chloride	1,182,737	1,883	115	2,074	1,192,809
Tetrachloroethylene	302,955	27,345	207	5	324,512
1,1,1-Trichloroethane	17,509	13,651	94	0	31,254
Trichlororethylene	966,272	18,805	59	58	985,193
Ketones					
Acetone	NR				
Cyclohexanone	NR				
Methyl ethyl ketone	NR				
Methyl isobutyl ketone	NR				
Others					
Carbon disulfide	3,970,699	6,755	2,078	9	3,979,541
Diethyl ether	NR				
Ethyl acetate	NR				
Hexane	15,660,603	330,045	1,923	10,786	16,003,362
Decane	NR				
Pyridine	22,343	1,340	460	198,593	234,983
Tetrahydrofuran	NR				

NR – No report

16.1.3 LEVELS IN THE ENVIRONMENT

Of the 27 organic solvents chosen for this chapter, there are data available that document the presence of almost all the solvents in the atmosphere at trace levels (Table 16.1.3). In compiling these data, an effort was made, when possible, to exclude data from confirmed or suspected point sources. Indoor air-quality studies were also excluded. The emphasis was given to reporting information from remote, rural or suburban environments when possible, or data that represented large geographic areas. The emphasis on such background data may serve as a first approximation of residual levels of organic solvents left

after the partitioning, transformation, and degradation reactions discussed in this chapter. Although highly dependent on many study-specific variables, the compilation suggests that relatively large concentrations of benzene, carbon tetrachloride, decane, and toluene have been detected in air samples in urban areas. The major source of toluene in air samples is from the combustion of gasoline.[8] However, such data must be interpreted cautiously. Although there are no known natural sources of carbon tetrachloride, benzene for example also occurs naturally from crude oil seeps, forest fires, and plant volatiles.[9]

Table 16.1.3. Summary of organic solvent concentrations detected in ambient air samples. Data from confirmed and suspected point sources, and indoor air samples were excluded. [Data from HSDB].[7]

Solvent	Concentration	Comments
Alcohols		
n-Butyl alcohol	11.2, 17.3 μg/m^3	Rural and urban air, Arizona
Isobutyl alcohol	No data located	
Methanol	0.10 to 2.21 ng/m^3 5.09 to 35.5 μg/m^3	Urban Japan Urban Sweden
Benzene derivatives		
Benzene	63.8 μg/m^3 4.47 μg/m^3 0.6 to 1.2 μg/m^3	Mean, U.S. urban Mean, U.S. rural Rural Canada
Chlorobenzene	< 0.09 to 9.1 μg/m^3 0 to 3.76 μg/m^3 < 0.09 μg/m^3	728 air samples, U.S. "Typical U.S. cities" Remote, U.S.
o-Cresol	9.81 μg/m^3 0.07 μg/m^3	Mean, U.S. Mean, Portland, Oregon
o-Dichlorobenzene	0.34 μg/m^3 0.14 μg/m^3 0.01 μg/m^3	Mean, suburban U.S. Mean, Minnesota, U.S. Mean, rural U.S.
Ethylbenzene	11.6 μg/m^3 2.17 to 9.55 μg/m^3 3.47 to 45.1 μg/m^3	Mean, cities, U.S. Rural, continental U.S. State forest, Texas
Nitrobenzene	0.86 μg/m^3 0.19 ng/m^3	Mean, urban/suburban U.S. Rural China
Toluene	0.23 to 113 μg/m^3 0 to 320 μg/m^3	Remote, U.S. Urban, U. S.
o-Xylene	0.41 μg/m^3 0.5 μg/m^3 1.6 to 6.9 μg/m^3	Median, remote U.S. Median, rural Minnesota City, Brazil

Table 16.1.3. Summary of organic solvent concentrations detected in ambient air samples. Data from confirmed and suspected point sources, and indoor air samples were excluded. [Data from HSDB].[7]

Solvent	Concentration	Comments
Chlorinated aliphatic hydrocarbons		
Carbon tetrachloride	0.82 μg/m^3 0 to 267 μg/m^3 0.70 to 0.89 μg/m^3	Mean, rural U.S. Urban, U.S. Northern hemisphere
Methylene chloride	No data located	
Tetrachloroethylene	0.022 μg/m^3 0.27 μg/m^3 0.38 to 0.87 μg/m^3	Mean, North America Mean, Northern hemisphere Alaska, U.S.
1,1,1-Trichloroethane	0.32 to 0.84 μg/m^3 0.71 ng/m^3	Rural U.S. Median, remote U.S.
Trichloroethylene	43.0 ng/m^3 80.6 to 85.9 ng/m^3 0.6 μg/m^3	Mean global concentration Northern hemisphere Mean, rural Illinois
Ketones		
Acetone	2.37 to 19.0 μg/m^3 0.93 to 5.37 μg/m^3 2.87 μg/m^3	Urban, Colorado Rural Ontario Mean, rural Alaska
Cyclohexanone	No data located	
Methyl ethyl ketone	1.87 μg/m^3 18 μg/m^3 4.40 μg/m^3	Mean, urban U.S. Mean, rural Canada Mean, urban Boston, Massachusetts
Methyl isobutyl ketone	0 to 6 μg/m^3 23 to 63 μg/m^3	Urban, U.S. Urban, Brazil
Others		
Carbon disulfide	47 ng/m^3 0.20 μg/m^3	"background global concentration" Mean, urban, Pennsylvania
Diethyl ether	No data located	
Ethyl acetate	0.83 μg/m^3	Mean, suburban, Sweden
Hexane	0.71 μg/m^3 14.5 μg/m^3 0.33 μg/m^3	Median, rural North Carolina Rural, Texas Rural, Germany
Decane	3.44 μg/m^3 2.29 to 159 μg/m^3 4.04 μg/m^3	Mean, urban South Africa Rural Texas Median, urban, Canada
Pyridine	4.41 μg/m^3	Mean, U.S.
Tetrahydrofuran	No data located	

There are also data available to document that most of the 27 solvents have been detected in surface and groundwater samples at trace levels (Table 16.1.4). In compiling these data, an effort was made to exclude data from confirmed or suspected point sources such as municipal landfills (see Roy),[11] industrial sites, leaking underground storage tanks, hazardous waste sites, and effluent from waste water treatment plants. Data for precipitation and sea water samples were also excluded. As above, the emphasis was given to samples that represented relatively large geographic areas, and as a consequence, the concentrations listed may give an idea of background or residual levels remaining after partitioning, transformation, and degradation reactions in the natural environment. As before, such data must be interpreted cautiously. For example, although trichloroethylene does not occur naturally, methyl ethyl ketone occurs in certain foods, and the major source of carbon disulfide is from the oceans.[7]

There are fewer data available to assess the residual concentrations of the 27 organic solvents in soil and sediment samples (Table 16.1.5). Although an effort was made to exclude data from point sources such as industrial sites or chemical spills, the influence of point sources cannot be ignored. Although some of solvents have been detected at trace levels, the median concentration of the chlorinated aliphatic hydrocarbons in sediments has often been less than the analytical ability to measure them accurately.

Table 16.1.4. Summary of organic solvent concentrations detected in ambient water samples. Data from confirmed and suspected point sources, precipitation, sea water, and wastewater treatment samples were excluded. [Data from HSDB].[7]

Solvent	Concentration	Comments
Alcohols		
n-Butyl alcohol	318 µg/L	Surface water, Japan
Isobutyl alcohol	No data located	
Methanol	No data located	
Benzene derivatives		
Benzene	5 to 15 ng/L 0 to 1 µg/L 0 to 7 µg/L 3 µg/L	Gulf of Mexico Lake Erie Lake Michigan Median (when detected), drinking water supplies, U.S.
Chlorobenzene	1.65 µg/L 0.26 µg/L 0.21 µg/L	Maximum, river, Taiwan Maximum, river, Spain Mean (?), river, Japan
o-Cresol	390 µg/L	Groundwater, Florida
o-Dichlorobenzene	0.21 µg/L 5 ng/L 23 ng/L	Mean, river, Japan Mean, Lake Ontario Mean, Niagara River
Ethylbenzene	4.0 µg/L 1.1 µg/L	River, Kentucky Maximum, groundwater, U.S.

Table 16.1.4. Summary of organic solvent concentrations detected in ambient water samples. Data from confirmed and suspected point sources, precipitation, sea water, and wastewater treatment samples were excluded. [Data from HSDB].[7]

Solvent	Concentration	Comments
Nitrobenzene	< 4 µg/L 0.42 µg/L	River, Virginia Mean, river, Germany
Toluene	3 to 376 ng/L 30 to 243 ng/L 2.9 µg/L	Gulf of Mexico River, Germany Maximum, groundwater, U.S.
o-Xylene	0.9 µg/L[1] 0.17 µg/L	Maximum, groundwater, U.S. Mean, river, Italy
Chlorinated aliphatic hydrocarbons		
Carbon tetrachloride	9 to 47 ng/L 0.2 to 20 µg/L	Great Lakes, U.S. Groundwater, U.S.
Methylene chloride	< 0.10 µg/L 6.1 µg/L	Groundwater, Japan Mean of detections, drinking water, five U.S. states
Tetrachloroethylene	0.6 µg/L 0.3 µg/L 9 ng/L 2 µg/L	Median, groundwater, U.S. Median, drinking water, U.S. Mean, Lake Ontario Median, surface water, U.S.
1,1,1-Trichloroethane	0.2 µg/L 1.1 µg/L 0.1 to 191 µg/L	Median, surface water, U.S. Median, groundwater, U.S. Drinking water samples, U.S.
Trichloroethylene	4.1 to 120 ng/L 0.1 to 1.0 µg/L 0.2 to 125 µg/L < 0.1 to 220 µg/L	Lake Superior Ohio River, U.S. Groundwater, 13 U.S. cities Groundwater, Japan
Ketones		
Acetone	1 to 4 µg/L	Lake Michigan, U.S.
Cyclohexanone	30 µg/L	Maximum, groundwater, Netherlands
Methyl ethyl ketone	< 40 µg/L	River, Maryland
Methyl isobutyl ketone	90 µg/L 2.8 to 332 µg/L	Maximum, groundwater, Florida River, Italy
Others		
Carbon disulfide	0.40 µg/L 0.1 to 4.5 µg/L	Median, Great Lakes, U.S. Surface water, Netherlands
Diethyl ether	1 to 10 µg/L	Surface water, U.S.

Table 16.1.4. Summary of organic solvent concentrations detected in ambient water samples. Data from confirmed and suspected point sources, precipitation, sea water, and wastewater treatment samples were excluded. [Data from HSDB].[7]

Solvent	Concentration	Comments
Ethyl acetate	No data located	
Hexane	1.5 to 7.8 ng/L	Gulf of Mexico
Decane	0.9 to 1.6 ng/L 1.6 µg/L 7.9 µg/L	Gulf of Mexico Mean, river, England Mean, river, England
Pyridine	< 0.5 µg/L	Groundwater, Wyoming, U.S.[2]
Tetrahydrofuran	0.2 to 0.8 µg/L 1.1 to 6.4 mg/L	River, New York, U.S. Surface water, Netherlands

[1]Combined isomers (ortho plus para).
[2]ATSDR[10]

Table 16.1.5. Summary of organic solvent concentrations detected in soil and sediment samples. Data from confirmed point sources were excluded.

Solvent	Concentration	Comments	Ref.
Alcohols			
n-Butyl alcohol, isobutyl alcohol, and methanol	No data located		
Benzene derivatives			
Benzene	0 to 20 µg/kg	Marine sediment, South Africa	7
Chlorobenzene	< 5 µg/kg	Median, sediment, U.S.	12
o-Cresol	0 to 8.8 µg/kg	Soil, Quebec, Canada	7
o-Dichlorobenzene	11 µg/kg 0.35 µg/kg 0 to 0.52 µg/kg 86 µg/kg	Mean, sediment, Lake Ontario Lake sediments, Netherlands Marine sediment, Japan Maximum, 20 river basins, U.S.	7
Ethylbenzene	5 µg/kg	Median, sediment, U.S.	12
Nitrobenzene	< 0.06 to 0.15 mg/kg < 500 µg/kg 1.9 µg/kg	Soil, Canada Median, sediment, U.S. Mean, soil, Japan	7 12 7
Toluene	3 to 250 µg/kg 5 µg/kg	River sediments, New Jersey Median, sediment, U.S.	7 12
o-Xylene	< 10 µg/kg	Sediment, Illinois	7
Chlorinated aliphatic hydrocarbons			
Carbon tetrachloride	< 5 µg/kg	Median, sediment, U.S.	12
Methylene chloride	1.5 µg/kg < 5 µg/kg	Lake sediment. Louisiana Median, sediment, U.S.	7 12

Table 16.1.5. Summary of organic solvent concentrations detected in soil and sediment samples. Data from confirmed point sources were excluded.

Solvent	Concentration	Comments	Ref.
Tetrachloroethylene	< 5 µg/kg 0.2 to 1.0 µg/kg	Median, sediment, U.S. Soil, rural Netherlands	12 7
1,1,1-Trichloroethane	< 5 µg/kg	Median, sediment, U.S.	12
Trichloroethylene	< 5 µg/kg 0.1 to 0.2 µg/kg < 0.01 to 0.06 µg/kg	Median, sediment, U.S. Sediment, Louisiana Soil, Netherlands	12 7 13
Ketones			
Acetone, cyclohexanone, methyl ethyl ketone, and methyl isobutyl ketone	No data located		
Others			
Carbon disulfide, diethyl ether, ethyl acetate, hexane, decane, pyridine, and tetrahydrofuran	No data located		

16.1.4 ORGANIC SOLVENTS IN WATER

16.1.4.1 Solubility

One of the most important properties of an organic solvent is its solubility in water. The greater a compound's solubility, the more likely that a solvent or a solvent-containing waste will dissolve into water and become part of the hydrologic cycle. Hence, water solubility can affect the extent of leaching of solvent wastes into groundwater, and the movement of dissolved solvent into rivers and lakes. Aqueous solubility also determines the efficacy of removal from the atmosphere through dissolution into precipitation. The solubility of solvents in water may be affected by temperature, salinity, dissolved organic matter, and the presence of other organic solvents.

The solubility of the solvents in Table 16.1.1 ranges from those that are miscible with water to those with solubilities that are less than 0.1 mg/L (Table 16.1.6). Acetone, methanol, pyridine and tetrahydrofuran will readily mix with water in any proportion. The solvents that have an aqueous solubility of greater than 10,000 mg/L are considered relatively hydrophilic. Most of the benzene derivatives and chlorinated fluorocarbons are relatively hydrophobic. Hexane and decane are the least soluble of the 27 solvents in Table 16.1.1. Most material safety data sheets for decane indicate that the n-alkane is "insoluble" and that the solubility of hexane is "negligible." How the solubility of each solvent affects its fate in soil, water, and air is illustrated in the following sections.

Table 16.1.6. The solubility of the solvents in water at 25°C.

	Solubility (mg/L)	Solvent (reference)
∞	Miscible	Acetone (14) Methanol (14) Pyridine (14) Tetrahydrofuran (14)
10^5 mg/L	223,000	Methyl ethyl ketone (14)
10,000 mg/L	63,200 85,000 80,000 60,000 25,950 23,000 19,000 13,030	n-Butyl alcohol (14) Isobutyl alcohol (14) Ethyl acetate (14) Diethyl ether (14) o-Cresol (15) Cyclohexanone (14) Methyl isobutyl ketone (14) Methylene chloride (14)
1,000 mg/L	2,160 2,090 1,790 1,290 1,280	Carbon disulfide (16) Nitrobenzene (17) Benzene (14) 1,1,1-Trichloroethane (18) Trichloroethylene (18)
100 mg/L	793 535 200 200 221 169 92	Carbon tetrachloride (14) Toluene (19) Chlorobenzene (14) Tetrachloroethylene (14) o-Xylene (14) Ethylbenzene (14) o-Dichlorobenzene (14)
10 mg/L	9.5	Hexane (20)
1 mg/L		
0.1 mg/L	0.05	Decane (14)

16.1.4.2 Volatilization from water

Solvents dissolved in water may volatilize into the atmosphere or soil gases. A Henry's Law constant (K_H) can be used to classify the behavior of dissolved solvents. Henry's Law describes the ratio of the partial pressure of the vapor phase of an ideal gas (VP_i) to its mole fraction (X_i) in a dilute solution, viz.,

$$K_{H(I)} = VP_i/X_i \qquad [16.1.1]$$

In the absence of measured data, a Henry's Law constant for a given solvent may be estimated by dividing the vapor pressure of the solvent by its solubility in water (S_i) at the same temperature;

$$K_{H(I)} = P_i \text{ (atm)}/S_i \text{ (mol/m}^3 \text{ solvent)} \quad [16.1.2]$$

If K_H is less than 3 x 10^{-7} atm-m^3/mole, the substance is less volatile than the water it is dissolved in, and its concentration will increase as the water evaporates.[22] The *rate* of volatilization is more complex, and depends on the rate of flow, depth, and turbulence of both the body of water and the atmosphere above it. In the absence of measured values, there are a number of estimation techniques to predict the rate of removal from water.[22]

Henry's Law constants were compiled for each of the solvents in Table 16.1.1. The numerical values ranged over seven orders of magnitude (Table 16.1.7). Based on these values, it can be expected that volatilization from water will be a significant fate mechanism for decane, hexane, carbon tetrachloride, tetrachloroethylene and trichloroethylene. Many of the solvents in Table 16.1.1 are characterized by K_H values of 10^{-3} to 10^{-2} atm-m^3/mole; volatilization from water can be an important pathway for these solvents, depending on the specific situation. Volatilization may be a relatively slow process for the remaining solvents. The actual *rate* of volatilization of some solvents from water has been experimentally measured.[2,15] However, experimental data are lacking for some compounds, and the diversity of experimental conditions makes generalizations difficult.

Table 16.1.7. Henry's Law constants (K_H) for the solvents at 25°C.

	K_H (atm-m^3/mole)	Solvent (reference)
10 atm-m^3/mole	6.98	Decane (21)
	1.69	Hexane (20)
1.0 atm-m^3/mole		
0.1 atm-m^3/mole	3.04 x 10^{-2}	Carbon tetrachloride (14)
	1.77 x 10^{-2}	Tetrachloroethylene (23)
	1.72 x 10^{-2}	1,1,1-Trichloroethane (14)
	1.44 x 10^{-2}	Carbon disulfide (24)
	1.03 x 10^{-2}	Trichloroethylene (14)
10^{-2} atm-m^3/mole	7.80 x 10^{-3}	Ethylbenzene (14)
	6.64 x 10^{-3}	Toluene (14)
	5.55 x 10^{-3}	Benzene (14)
	5.19 x 10^{-3}	o-Xylene (14)
	3.70 x 10^{-3}	Chlorobenzene (14)
	2.46 x 10^{-3}	Methylene chloride (14)
	1.50 x 10^{-3}	o-Dichlorobenzene (25)
10^{-3} atm-m^3/mole	7.48 x 10^{-4}	Diethyl ether (26)
	1.38 x 10^{-4}	Methyl isobutyl ketone (14)
	1.38 x 10^{-4}	Ethyl acetate (14)

Table 16.1.7. Henry's Law constants (K_H) for the solvents at 25°C.

	K_H (atm-m^3/mole)	Solvent (reference)
10^{-4} atm-m^3/mole	7.05 x 10^{-5}	Tetrahydrofuran (27)
	5.59 x 10^{-5}	Methyl ethyl ketone (14)
	5.11 x 10^{-5}	Cyclohexanone (14)
	4.26 x 10^{-5}	Acetone (28)
	2.44 x 10^{-5}	Nitrobenzene (29)
	1.18 x 10^{-5}	Isobutyl alcohol (14)
10^{-5} atm-m^3/mole	9.31 x 10^{-6}	Pyridine (14)
	8.81 x 10^{-6}	n-Butyl alcohol (14)
	4.55 x 10^{-6}	Methanol (30)
	1.71 x 10^{-6}	o-Cresol (14)

Thomas[22] described a two-layer model of the liquid-gas interface that is based on a Henry's Law constant and mass-transfer coefficients. To illustrate the relative volatilities of the solvents in water, the half-lives of each solvent in a shallow stream were compiled (Table 16.1.8). The stream was assumed to be 1.0 meter deep and flowing at a rate of 1.0 meter per second. It was also assumed that there was a breeze blowing across the stream at a rate of 3.0 meters per second. Under these conditions, the predicted half-lives of many of the solvents in Table 16.1.1 are less than 10 hours, indicating that volatilization into the atmosphere can be a relatively rapid pathway for solvents that have been released to surface water. The volatilization of nitrobenzene, isobutyl alcohol, n-butyl alcohol, cyclohexanone, and, in particular, o-cresol may be a slow process, and other fate processes may be more important in water.

Table 16.1.8. Estimated half-lives for the solvents in a flowing stream [Data from HSDB).[7]

	Half-life (hours)	Solvent
1 hour	1.0	Benzene, methylene chloride, 1,1,1-trichloroethane, toluene
	1.1	Ethylbenzene
	1.3	Carbon tetrachloride
	2.6	Carbon disulfide
	2.7	Hexane
	3.0	Trichloroethylene, pyridine
	3.1	Diethyl ether
	3.2	o-Xylene
	3.4	Chlorobenzene
	4.0	Tetrachloroethylene, o-Dichlorobenzene
	4.6	Methanol
	8.9	Ethyl acetate
	9.0	Methyl isobutyl ketone

Table 16.1.8. Estimated half-lives for the solvents in a flowing stream [Data from HSDB).[7]

	Half-life (hours)	Solvent
10 hours	13	Tetrahydrofuran
	16	Methyl ethyl ketone
	38	Acetone
	44	Nitrobenzene
	48	n-Butyl alcohol, isobutyl alcohol
	98	Cyclohexanone
100 hours	504	o-Cresol

16.1.4.3 Degradation in water

The disappearance of a solvent from solution can also be the result of a number of abiotic and biotic processes that transform or degrade the compound into daughter compounds that may have different physico-chemical properties from the parent solvent. Hydrolysis, a chemical reaction where an organic solvent reacts with water, is not one reaction, but a family of reactions that can be the most important processes that determine the fate of many organic compounds.[31] Photodegradation is another family of chemical reactions where the solvent in solution may react directly under solar radiation, or with dissolved constituents that have been made reactive by solar radiation. For example, the photolysis of water yields a hydroxyl radical:

$$H_2O + h\nu \rightarrow H\dot{O} + H \qquad [16.1.3]$$

Other oxidants such as peroxyl radicals ($R\dot{O}_2$) and ozone can react with solvents in water. The subject of photodegradation is treated in more detail under atmospheric processes (16.1.6).

Biodegradation is a family of biologically mediated (typically by microorganisms) conversions or transformations of a parent compound. The ultimate end-products of biodegradation are the conversion of organic compounds to inorganic compounds associated with normal metabolic processes.[32] Howard *et al.*[33] estimated ranges of half-lives for solvents in water without regard to the specific degradation mechanism(s) involved. If a "rapid" half-life is defined as in the range of 1 to 10 days, then about 12 of the solvents in Table 16.1.1 may degrade rapidly in surface water by biodegradation (Figures 16.1.1 and 16.1.2). Abiotic mechanisms such as photooxidation, photolysis, and hydrolysis appear to be either slow or not significant. If "slow degradation" is defined as that taking longer than 100 days, then it appears that most of the chlorinated hydrocarbons may be relatively persistent in surface water. The available data suggest that the half-life of nitrobenzene and isobutyl alcohol may be variable. Note that data were not available for all of the solvents listed in Table 16.1.1. In groundwater, the half-life values proposed by Howard *et al.*[33] appear to be more variable than those for surface water. For example, the half-life of benzene ranges from 10 days in aerobic groundwater to two years in anaerobic groundwater.[9] Such ranges in half-lives make meaningful generalizations difficult. However, it appears that methanol, n-butyl alcohol, and other solvents (see Figures 16.1.1 and 16.1.2) may bio-

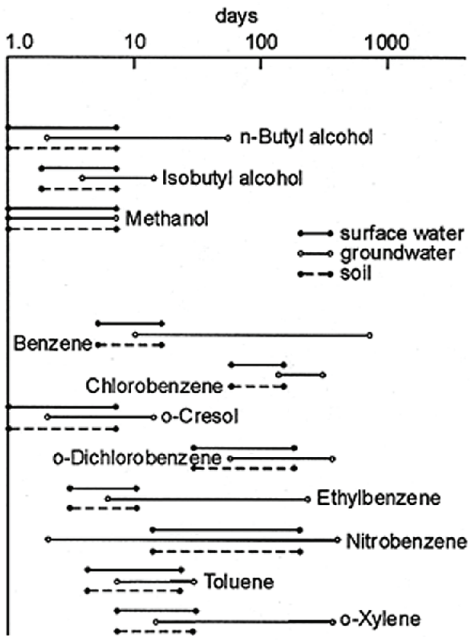


Figure 16.1.1. The ranges in degradation half-lives for the alcohols and benzene derivatives in surface water, groundwater, and soil [Data from Howard P H, **Handbook of Environmental Fate and Exposure Data for Organic Chemicals**. Vol. I. Large Production and Priority Pollutants. *Lewis Publishers*, Chelsea, Michigan, 1989.]

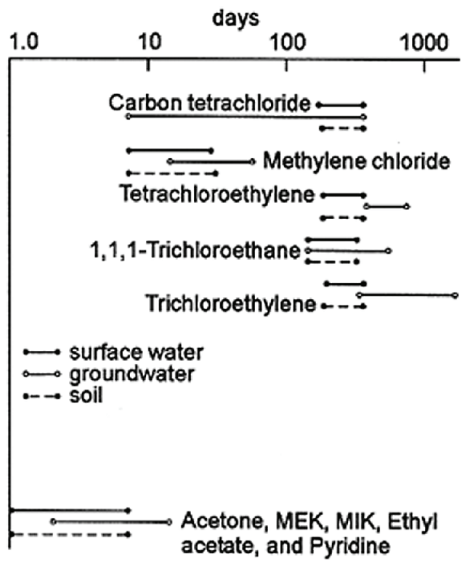


Figure 16.1.2. The ranges in degradation half-lives for the chlorinated aliphatic hydrocarbons, and ketones in surface water, groundwater, and soil [Data from Howard P H, **Handbook of Environmental Fate and Exposure Data for Organic Chemicals**. Vol. I. Large Production and Priority Pollutants. *Lewis Publishers*, Chelsea, Michigan, 1989.]

degrade in groundwater with a half-life that is less than 60 days. As with surface water, the chlorinated hydrocarbons may be relatively persistent in groundwater. Howard *et al*.[33] cautioned that some of their proposed half-life generalizations were based on limited data or from screening studies that were extrapolated to surface and groundwater. There are no procedures for estimating the rate of biodegradation of chemicals because of the complexity of the biochemical reactions, and the diverse experimental conditions imposed in individual investigations.[32] Hence, Figures 16.1.1 and 16.1.2 should be viewed as a summary of the potential for each solvent to degrade, pending more site-specific information.

16.1.4.4 Adsorption from water

Adsorption is a physico-chemical process whereby a dissolved solvent may be concentrated at solid-liquid interfaces such as water in contact with soil or sediment. In general, the extent of adsorption is inversely proportional to solubility; sparingly soluble solvents have a greater tendency to adsorb or partition to the organic matter in soil or sediment (see 16.1.5.2).

16.1.5 ORGANIC SOLVENTS IN SOIL

16.1.5.1 Volatilization from soil

Volatilization from soil may be an important mechanism for the movement of solvents from spills or from the disposal of solvent-containing wastes. The efficacy and rate of volatilization from soil depends on the solvent's vapor pressure, water solubility, and the properties of the soil such as soil-water content, airflow rate, humidity, temperature and the adsorption and diffusion characteristics of the soil.

Organic-solvent vapors move through the unsaturated zone (the interval between the ground surface and the water-saturated zone) in response to two different mechanisms; convection and diffusion. The driving force for convective movement is the gradient of total gas pressure. In the case of diffusion, the driving force is the partial-pressure gradient of each gaseous component in the soil air. The rate of diffusion of a solvent in bulk air can be described by Fick's Law, viz.,

$$Q = -D_f \nabla_a \qquad [16.1.4]$$

where:

Q diffusive flux (mass/area-time)
D_f diffusion coefficient (area/time)
∇_a concentration gradient (mass/volume/distance)

Compared with the relatively unobstructed path for the diffusion of solvents in the atmosphere, diffusion coefficients for solvents in soil air will be less because of the tortuosity of the soil matrix pathways. Several functional relationships have been developed that relate the soil diffusion coefficient (D_s) to various soil properties (see Roy and Griffin),[26] such as the Millington equation[34]

$$D_s = D_f \eta_a^{3.3} / \eta_t^2 \qquad [16.1.5]$$

where:

η_a the air-filled porosity, and
η_t total soil porosity

Soil diffusion coefficients were estimated for most of the solvents in Table 16.1.1. Using the Millington equation, the resulting coefficients (Table 16.1.9) ranged from 0.05 to 0.11 m^2/day. Hence, there was little variation in magnitude between the values for these particular solvents. As discussed in Thomas[22] the diffusion of gases and vapors in unsaturated soil is a relatively slow process. The coefficients in Table 16.1.9 do not indicate the *rate* at which solvents can move in soil; such rates must be either measured experimentally or predicted using models that require input data such as soil porosity, moisture content, and the concentrations of the solvents in the vapor phase to calculate fluxes based solely on diffusion. Variations in water content, for example, will control vapor-phase movement. The presence of water can reduce the air porosity of soil, thereby reducing the soil diffusion coefficient. Moreover, relatively water-soluble chemicals may dissolve into water in the vadose zone. Hence, water can act as a barrier to the movement of solvent vapors from the subsurface to the surface.

Table 16.1.9. Estimated soil diffusion coefficients D_s [Data from Roy and Griffin].[26]

Solvent	D_s (m^2/day)
Alcohols	
n-Butyl alcohol	0.062 (25°C)
Isobutyl alcohol	0.050 (0°C)
Methanol	0.111 (25°C)
Benzene derivatives	
Benzene	0.060 (15°C)
Chlorobenzene	0.052 (30°C)
o-Cresol	0.053 (15°C)
o-Dichlorobenzene	0.049 (20°C)
Ethylbenzene	0.046 (0°C)
Nitrobenzene	0.050 (20°C)
Toluene	0.058 (25°C)
o-Xylene	0.049 (15°C)
Chlorinated aliphatic hydrocarbons	
Carbon tetrachloride	0.051 (25°C)
Methylene chloride	0.070 (15°C)
Tetrachloroethylene	0.051 (20°C)
1,1,1-Trichloroethane	0.075 (20°C)
Trichloroethylene	0.058 (15°C)
Ketones	
Acetone	0.076 (0°C)
Others	
Carbon disulfide	0.074 (25°C)
Diethyl ether	0.054 (0°C)
Ethyl acetate	0.059 (25°C)

Solvents spilled onto the surface of soil may volatilize into the atmosphere. The Dow Method[22] was used in this section to estimate half-life values of each solvent if spilled on the surface of a dry soil. The Dow Method is a simple relationship that was derived for the evaporation of pesticides from bare soil;

$$t_{1/2}\ (\text{days}) = 1.58 \times 10^{-8}\ (K_{oc}S/P_v) \qquad [16.1.6]$$

where:

$t_{1/2}$ evaporation half-life (days)
K_{oc} organic carbon-water partition coefficient (L/kg)

S solubility in water (mg/L), and
P_v vapor pressure (mm Hg at 20°C)

The resulting estimated half-life is inversely proportional to vapor pressure; the greater the vapor pressure, the greater the extent of volatilization. Conversely, the rate of volatilization will be reduced if the solvent readily dissolves into water or is adsorbed by the soil. Organic carbon-water partition coefficients (see 16.1.5.2), and vapor pressure data (Table 16.1.10) were compiled for each solvent. Excluding the solvents that are miscible with water, the resulting half-life estimates (Table 16.1.11) indicated that volatilization would be a major pathway if the liquid solvents were spilled on soil; all of the half-life estimates were less than one hour. Thomas[22] cautioned, however, that soil moisture, soil type, temperature, and wind conditions were not incorporated in the simple Dow Model.

Table 16.1.10. Vapor pressures (V_p) of the solvents at 25°C [Data from A. Wypych and G. Wypych][14]

	V_p (kPa)	Solvent
100 kPa	71.6	Diethyl ether
	58.0	Methylene chloride
	47.9	Carbon disulfide
	30.8	Acetone
	21.6	Tetrahydrofuran
	20.2	Hexane
	16.9	Methanol
	16.5	1,1,1-Trichloroethane
	15.3	Carbon tetrachloride
	12.7	Methyl ethyl ketone
	12.7	Benzene
	12.5	Ethyl acetate
10 kPa	9.20	Trichloroethylene
	3.78	Toluene
	2.65	Methyl isobutyl ketone
	2.47	Tetrachloroethylene
	2.00	Pyridine
	1.39	Isobutyl alcohol
	1.17	Chlorobenzene
	1.28	Ethylbenzene
1 kPa	0.89	n-Butyl alcohol
	0.88	o-Xylene
	0.58	Cyclohexanone
	0.17	Decane
	0.16	o-Dichlorobenzene

Table 16.1.10. Vapor pressures (V_p) of the solvents at 25°C [Data from A. Wypych and G. Wypych][14]

	V_p (kPa)	Solvent
0.1 kPa	0.03	o-Cresol
	0.02	Nitrobenzene

Table 16.1.11. Estimated soil evaporation half-lives

Solvent	Half-life (minutes)
o-Cresol	33
Nitrobenzene	21
n-Butyl alcohol	18
Isobutyl alcohol	6
Methyl isobutyl ketone	2
Methyl ethyl ketone	2
All other solvents except acetone, methanol, pyridine, and tetrahydrofuran which are miscible with water.	< 1

16.1.5.2 Adsorption by soils and sediments

Adsorption by soils and sediments can remove solvents dissolved in water. Furthermore, the rate of movement of dissolved solvents through porous geological material may be retarded by adsorption-desorption reactions between the solvents and the solid phases. The partitioning of solvents between the liquid phase and soil is usually described by an adsorption isotherm. The adsorption of solvents may be described by the Freundlich equation:

$$x/m = K_f C^{1/n} \qquad [16.1.7]$$

where:

- x the mass adsorbed
- m mass of sorbent
- K_f the Freundlich constant, a soil-specific term
- C the equilibrium concentration of the solvent in water, and
- n the Freundlich exponent which describes the degree of non-linearity of the isotherm.

When n is equal to one, the Freundlich equation becomes a relatively simple partition function:

$$x/m = KC \qquad [16.1.8]$$

where K is an adsorption or distribution coefficient which is sometimes written as K_d. It has been known since the 1960s that the extent of adsorption of hydrophobic (sparingly soluble in water) solvents often correlates with the amount of organic matter in the soil.[35]

When K_d is divided by the amount of organic carbon in the soil, the resulting coefficient is the organic carbon-water partition coefficient (K_{oc}):

$$K_d \times 100/\text{organic carbon (\%)} = K_{oc} \quad [16.1.9]$$

The organic carbon-water partition coefficient is a compound-specific term that allows the user to estimate the mobility of a solvent in saturated-soil water systems if the amount of organic carbon is known. For hydrophilic solvents, K_{oc} values have been measured for many compounds. Other values were derived from empirical relationships drawn between water solubility or octanol-water partition coefficients.[13]

Organic carbon-water partition coefficients were compiled (Table 16.1.12) for each of the solvents in Table 16.1.1. There is considerable variability in the numerical values for some of the solvents. This variability is the result of the heterogeneous nature of soil organic matter, and experimental error that is endemic to any laboratory measurements. A K_{oc} value is a measure of the *affinity* of a solvent to partition to organic matter which in turn will control the *mobility* of the solute in soil and groundwater under convective flow. Although the actual amount of organic matter will determine the extent of adsorption, a solvent with a K_{oc} value of less than 100 L/kg is generally regarded as relatively mobile in saturated materials. Hence, adsorption may not be a significant fate mechanism for alcohols, ketones, diethyl ether, ethyl acetate, pyridine, and tetrahydrofuran. In contrast, adsorption by organic matter may be a major fate mechanism controlling the fate of most of the benzene derivatives, and most of the chlorinated compounds. Hexane and decane would likely be relatively immobile. However, when the organic carbon content of an adsorbent is less than about 1 g/kg, the organic carbon fraction is not a valid predictor of the partitioning of nonpolar organic compounds,[50] and other properties such as pH, surface area, or surface chemistry contribute to or dominate the extent of adsorption. Moreover, pyridine occurs as a cation ($pK_a = 5.25$) over a wide pH range, and thus it is adsorbed by electrostatic interactions rather than by the hydrophobic mechanisms that are endemic to using K_{oc} values to predict mobility.

Table 16.1.12. Compilation of experimentally measured and estimated organic carbon-water partition coefficients (K_{oc}) for each solvent at 25°C.

Solvent	K_{oc} (L/g) and reference
Alcohols	
n-Butyl alcohol	72 (2), 72 (7)
Isobutyl alcohol	8 (35), 62 (7)
Methanol	< 1 (35), 2.75 (36)
Benzene derivatives	
Benzene	63 to 70 (9), 79, 85 (7), 97 (35)
Chlorobenzene	5, 81, 147, 313 (7), 318 (35), 331 (37)
o-Cresol	11 (38), 20 (15), 22 (39)
o-Dichlorobenzene	280, 320 (7), 324 (40)

Table 16.1.12. Compilation of experimentally measured and estimated organic carbon-water partition coefficients (K_{oc}) for each solvent at 25°C.

Solvent	K_{oc} (L/g) and reference
Ethylbenzene	164 (15), 240 (41)
Nitrobenzene	31, 43, 70, 89, 106, 170, 370 (7), 36 (29) 67 (35)
Toluene	37, 46, 160, 178 (7), 37 to 178 (19), 242 (23)
o-Xylene	24, 26, 68, 138 (7), 129 (42), 363 (13)
Chlorinated aliphatic hydrocarbons	
Carbon tetrachloride	71 (7), 110 (2, 43)
Methylene chloride	24 (7), 25 (35, 44)
Tetrachloroethylene	158 to 501 (45), 200, 210, 237 (7), 303 (35)
1,1,1-Trichloroethane	66, 120, 135, 151 (7), 107 (46), 155 (35)
Trichlororethylene	49, 58, 66, 72, 96, 100, 101, 110 (7), 107 to 457 (47), 152 (35)
Ketones	
Acetone	1 (13), 0 (7), 0.73 (28)
Cyclohexanone	10 (13), 15, 17 (7)
Methyl ethyl ketone	4 (35), 29, 34 (48)
Methyl isobutyl ketone	24 (13), 120 (7)
Others	
Carbon disulfide	63 (35, 49), 270 (7)
Diethyl ether	9 (13), 73 (7)
Ethyl acetate	8 (35), 59 (7)
Hexane	130 (7), 794 (20),
Decane	22,200 to 42,700 (7)
Pyridine	7 (35), 50 (7)
Tetrahydrofuran	< 1 (35), 18, 23 (48)

Desorption of solvents from soil has not been extensively measured. In the application of advection-dispersion models to predict solute movement, it is generally assumed that adsorption is reversible. However, the adsorption of the solutes in Table 16.1.1 may not be reversible. For example, hysteresis is often observed in pesticide adsorption-desorption studies with soils.[51] The measurement and interpretation of desorption data for solid-liquid systems is not well understood.[52,53] Once adsorbed, some adsorbates may react further to become covalently and irreversibly bound, while others may become physically trapped in the soil matrix.[51] The non-singularity of adsorption-desorption may sometimes result from experimental artifacts.[51,54]

16.1.5.3 Degradation in soil and sediments

Solvents may be degraded in soil by the same mechanisms as those in water. In biodegradation, microorganisms utilize the carbon of the solvents for cell growth and maintenance.

In general, the more similar a solvent is to one that is naturally occurring, the more likely that it can be biodegraded into other compound(s) because the carbon is more available to the microbes. Moreover, the probability of biodegradation increases with the extent of water solubility of the compound. It is difficult to make generalities about the extent or rate of solvent biodegradation that can be expected in soil. Biodegradation can depend on the concentration of the solvent itself, competing processes that can make the solvent less available to microbes (such as adsorption), the population and diversity of microorganisms, and numerous soil properties such as water content, temperature, and reduction-oxidation potential. The rate and extent of biodegradation reported in studies appears to depend on the conditions under which the measurement was made. Some results, for example, were based on sewage-treatment plant simulations or other biological treatment facilities that had been optimized in terms of nutrient content, microbial acclimation, mechanical mixing of reactants, or temperature. Hence, these results may overestimate the extent of biodegradation in ambient soil in a spill or waste-disposal scenario.

First-order kinetic models are commonly used to describe biodegradation because of their mathematical simplicity. First-order biodegradation is to be expected when the organisms are not increasing in abundance. A first-order model also lends itself to calculating a half-life ($t_{1/2}$) which is a convenient parameter to classify the persistence of a solvent. If a solvent has a soil half-life of six months, then about half of the compound will have degraded in six months. After one year, about one fourth the initial amount would still be present, and after 3 half-lives (1.5 years), about 1/8 of the initial amount would be present.

Howard *et al.*[33] also estimated soil half-life values (Figures 16.1.1 and 16.1.2) for the degradation of most of the solvents in Table 16.1.1. Biodegradation was cited as the most rapid process available to degrade solvents in a biologically active soil. The numerical values obtained were often the same as those estimated for surface water. Consequently, it appears likely that the alcohols, ketones, o-cresol, ethyl acetate, and pyridine will degrade rapidly in soil if "rapidly" is defined as having a half-life of 10 days or less. Most of the benzene derivatives, and the chlorinated aliphatic hydrocarbons may be relatively persistent in soil. Analogous information was not located for diethyl ether, hexane, decane, or tetrahydrofuran. For example, there is little information available for the degradation of n-hexane in soil.[20] It was suggested that n-hexane can degrade to alcohols, aldehydes, and fatty acids under aerobic conditions.

16.1.6 ORGANIC SOLVENTS IN AIR

16.1.6.1 Degradation of solvents in air

Organic solvents may be photodegraded in both water and air. Atmospheric chemical reactions have been studied in detail, particularly in the context of smog formation, ozone depletion, and acid rain. The absorption of light by chemical species generates free radicals which are atoms, or groups of atoms that have unpaired electrons. These free radicals are very reactive, and can degrade atmospheric solvents. Atmospheric ozone, which occurs in trace amounts in both the troposphere (sea level to about 11 km) and in the stratosphere (11 km to 50 km elevation), can degrade solvents. Ozone is produced by the photochemical reaction:

$$O_2 + h\nu \rightarrow O + O \quad [16.1.10]$$

$$O + O_2 \rightarrow O_3 + M \quad [16.1.11]$$

where M is another species such as molecular nitrogen that absorbs the excess energy given off by the reaction. Ozone-depleting substances include carbon tetrachloride in the stratosphere.

16.1.6.2 Atmospheric residence time of organic solvents

Vapor-phase solvents can dissolve into water vapor, and be subject to hydrolysis reactions and ultimately, precipitation (wet deposition), depending on the solubility of the given solvent. The solvents may also be adsorbed by particulate matter, and be subject to dry deposition. Lyman[55] asserted that atmospheric residence time cannot be directly measured; that it must be estimated using simple models of the atmosphere.

Once released into the atmosphere, the most rapid mechanism to reduce the vapor concentration of the solvents in Table 16.1.1 appears to be by photooxidation by hydroxyl radicals in the troposphere. The estimated half-life of each solvent in Table 16.1.1 was compiled (Table 16.1.13). It appeared that 14 of the solvents can be characterized by an atmospheric residence half-life of 10 days or less. Photooxidation of solvents yields products. For example, the reaction of hydroxyl radicals with n-hexane can yield aldehydes, ketones, and nitrates.[20]

Table 16.1.13. Estimated atmospheric half-life of the vapor-phase solvents when reacting with photochemically produced hydroxyl radicals [Data from HSDB].[7]

	Solvent	Half-life (days)
0.1 day	o-Cresol	0.38
	Tetrahydrofuran	0.96
1.0 day	Hexane	1.0
	Methyl ethyl ketone	1.1
	o-Xylene	1.2
	Diethyl ether	1.2
	Cyclohexanone	1.3
	n-Butyl alcohol	1.9
	Ethylbenzene	2.3
	Isobutyl alcohol	2.3
	Toluene	3.0
	Carbon disulfide	5.5
	Trichloroethylene	7.0
	Ethyl acetate	9.4

Table 16.1.13. Estimated atmospheric half-life of the vapor-phase solvents when reacting with photochemically produced hydroxyl radicals [Data from HSDB].[7]

	Solvent	Half-life (days)
10 days	Benzene	13
	Methyl ethyl ketone	14
	Methanol	17
	Chlorobenzene	21
	o-Dichlorobenzene	38
	Pyridine	43
	Acetone	79
	Tetrachloroethylene	96
100 days	Nitrobenzene	115
	Methylene chloride	119
> 1,000 days	1,1,1-Trichloroethane	1,720
	Carbon tetrachloride	1.3×10^5

The reaction of some of the solvents with ozone may be much slower. For example, the half-life for the reaction of nitrobenzene with hydroxyl radicals may be longer than 100 years.[29] Carbon tetrachloride and 1,1,1-trichloroethane may be relatively resistant to photooxidation. The major fate mechanism of atmospheric 1,1,1-trichloroethane, for example, may be wet deposition.[46]

REFERENCES

1 Calamari D (ed.) **Chemical Exposure Predictions**. *Lewis Publishers*, 1993.
2 Howard P H, **Handbook of Environmental Fate and Exposure Data for Organic Chemicals**. Vol. II Solvents. *Lewis Publishers*, Chelsea, Michigan, 1990.
3 Lyman W J, Reehl W F, Rosenblatt D H (eds). **Handbook of Chemical Property Estimation Methods**. *American Chemical Society*, Washington, D.C., 1990.
4 Ney R E, **Fate and Transport of Organic Chemicals in the Environment**. 2nd ed. *Government Institutes, Inc*. Rockville, MD, 1995.
5 Sawhney B L, Brown K (eds.). **Reactions and Movement of Organic Chemicals in Soils**. *Soil Science Society of America* Special Publication Number 22, 1989.
6 **Toxics Release Inventory** (TRI). *National Library of Medicine* [Online]. Available at http://www.toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TRI (2016).
7 **Hazardous Substances Data Bank** (HSBD). *National Library of Medicine* [Online]. Available at http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB (2013).
8 Agency for Toxic Substances and Disease Registry. **Toxicological Profile for Toluene**. *ATSDR*, Atlanta, Georgia, 2017.
9 Agency for Toxic Substances and Disease Registry. **Toxicological Profile for Benzene**. *ATSDR*, Atlanta, Georgia, 2007.
10 Agency for Toxic Substances and Disease Registry. **Toxicological Profile for Pyridine**. *ATSDR*, Atlanta, Georgia, 1992.
11 Roy W R, Groundwater contamination from municipal landfills in the USA, in Adriano D C, Iskandar A K, Murarka I P (eds.) **Contamination of Groundwaters**, *Science Reviews*, Northwood, UK., Chap. 14, 1994.
12 Staples C A, Peterson D R, Parkerton T F, Adams W J, *Chemosphere*, **35**, 667, 1997.
13 Hoekstra E J, de Leer E W B, Brinkman U A T, *Chemosphere*, **38**, 2875, 1999.
14 Wypych A, Wypych G, **Solvent Database**, 4th Edition, *ChemTec Publishing*, Toronto, 2014.
15 Howard P H, **Handbook of Environmental Fate and Exposure Data for Organic Chemicals**. Vol. I. Large Production and Priority Pollutants. *Lewis Publishers*, Chelsea, Michigan, 1989.

16 Yalkowsky S H, Yan H, **Handbook of Aqueous Solubility Data**: An Extensive Compilation of Aqueous Solubility Data for Organic Compounds Extracted from the AQUASOL dATAbASE. *CRC Press LLC*, Boca Raton, FL. 2003.
17 Banerjee S, Yalkowski S H, Valvani S C, *Environ. Sci. Techn.*, **14**, 227, 1980.
18 Horvath A L, Getzen F W, *J. Phys. Chem. Ref. Data*, **28**, 649, 1999.
19 Agency for Toxic Substances and Disease Registry. **Toxicological Profile for Toluene**. *ATSDR*, Atlanta, Georgia, 2017.
20 Agency for Toxic Substances and Disease Registry. **Toxicological Profile for Hexane**. *ATSDR*, Atlanta, Georgia, 1999.
21 MacKay D, Shiu W Y, *J. Phys. Chem. Ref. Data*, **4**, 1175, 1981.
22 Thomas R G, Volatilization From Water in Lyman W J, Reehl W F, Rosenblatt D H (eds). **Handbook of Chemical Property Estimation Methods**. *American Chemical Society*, Washington, D.C, Chap. 15, 1990.
23 Gosset J M, *Environ. Sci. Techn.*, **21**, 202, 1987.
24 Elliot S, *Atmos. Environ*., **23**, 177, 1989.
25 Staudinger J, Roberts P V, *Crit. Rev. Environ. Sci. Techn*., **26**, 205, 1996.
26 Roy W R, Griffin R A, *Environ. Geology Water Sci*., **15**, 101, 1990.
27 Cabani S, Conti G, Lepori L, *Trans. Faraday Soc*., **67**, 1943, 1971.
28 Agency for Toxic Substances and Disease Registry. **Toxicological Profile for Acetone**. *ATSDR*, Atlanta, Georgia, 1994.
29 Agency for Toxic Substances and Disease Registry. **Toxicological Profile for Nitrobenzene**. *ATSDR*, Atlanta, Georgia, 1990.
30 Gaffney J S, Streit G E, Spall W D, Hall J H, *Environ. Sci. Techn.*, **21**, 519, 1987.
31 Harris C, Rate of hydrolysis in Lyman W J, Reehl W F, Rosenblatt D H (eds). **Handbook of Chemical Property Estimation Methods**. *American Chemical Society*, Washington, D.C, Chap. 7, 1990.
32 Scow K M, Rate of biodegradation in Lyman W J, Reehl W F, Rosenblatt D H (eds). **Handbook of Chemical Property Estimation Methods**. *American Chemical Society*, Washington, D.C, Chap. 9, 1990.
33 Howard P H, Boethling R S, Jarvis W F, Meylan W M, Michalenko E M, **Handbook of Environmental Degradation Rates**. *Lewis Publishers*, Chelsea, Michigan, 1991.
34 Millington R J, *Science*, **130**, 100, 1959.
35 Roy W R, Griffin R A, *Environ. Geology Water Sci*., **7**, 241, 1985.
36 Schuurmann G, Ebert R U, Kuhne R, *Environ. Sci. Techn.*, **40**, 7005, 2006.
37 Agency for Toxic Substances and Disease Registry. **Toxicological Profile for Chlorobenzene**. *ATSDR*, Atlanta, Georgia, 1990.
38 Agency for Toxic Substances and Disease Registry. **Toxicological Profile for Cresols**. *ATSDR*, Atlanta, Georgia, 2008.
39 Shiu W Y, Ma K C, Varhanickova D, Mackay D, *Chemosphere*, **29**, 1155, 1994.
40 Agency for Toxic Substances and Disease Registry. **Toxicological Profile for Dichlorobenzenes**. *ATSDR*, Atlanta, Georgia, 2006.
41 Agency for Toxic Substances and Disease Registry. **Toxicological Profile for Ethylbenzene**. *ATSDR*, Atlanta, Georgia, 2010.
42 Agency for Toxic Substances and Disease Registry. **Toxicological Profile for Xylenes**. *ATSDR*, Atlanta, Georgia, 2007.
43 Agency for Toxic Substances and Disease Registry. **Toxicological Profile for Carbon Tetrachloride**. *ATSDR*, Atlanta, Georgia, 2005.
44 Agency for Toxic Substances and Disease Registry. **Toxicological Profile for Methylene Chloride**. *ATSDR*, Atlanta, Georgia, 2000.
45 Agency for Toxic Substances and Disease Registry. **Toxicological Profile for Tetrachloroethylene**. *ATSDR*, Atlanta, Georgia, 2014.
46 Agency for Toxic Substances and Disease Registry. **Toxicological Profile for 1,1,1-Trichloroethane**. *ATSDR*, Atlanta, Georgia, 2006.
47 Agency for Toxic Substances and Disease Registry. **Toxicological Profile for Trichlororethylene**. *ATSDR*, Atlanta, Georgia, 1997.
48 Walton B T, Hendricks M S, Anderson T A, Griest W H, Merriweather R, Beauchamp J J, Francis C W, *J. Environ. Quality*, **21**, 552, 1992.
49 Agency for Toxic Substances and Disease Registry. **Toxicological Profile for Carbon disulfide**. *ATSDR*, Atlanta, Georgia, 1996.
50 Stauffer T B, MacIntyre W G, *Environ. Toxic. Chem.*, **5**, 949, 1986.
51 Koskinen W C, Harper S S, The retention process: mechanisms. p. 51-77. In **Pesticides in the Soil**

Environment. *Soil Science Society of America* Book Series, no. 2, 1990.
52 Green R E, Davidson J M, Biggar J W, An assessment of methods for determining adsorption-desorption of organic chemicals. p. 73-82. In Bainn A, Kafkafi U (eds.), **Agrochemicals in Soils**, *Pergamon Press*, New York, 1980.
53 Calvet R, *Environ. Health Perspectives*, **83**, 145, 1989.
54 Bowman B T, Sans W W, *J. Environ. Quality*, **14**, 270, 1985.
55 Lyman W J, Atmospheric Residence Time in Lyman W J, Reehl W F, Rosenblatt D H (eds). **Handbook of Chemical Property Estimation Methods**. *American Chemical Society*, Washington, D.C, Chap. 10, 1990.

16.2 THE ENVIRONMENTAL CHEMISTRY OF IONIC LIQUIDS

William R. Roy
2404 Brookens Circle, Urbana, Illinois 61801-6621, USA

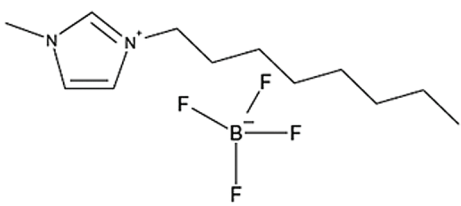


Figure 16.2.1. 1-methyl-3-octylimidazolium tetrafluoroborate Data from Matzke M, Thiele K, Muller A, Filser J, *Chemosphere*, **74**, 568, 2009].

16.2.1 INTRODUCTION

Ionic liquids have been recognized as a major advance in the development of novel solvents that have the potential to replace many of the conventional organic solvents discussed in Chapter 16.1. Ionic liquids occur as liquids at or near room temperature (close to it), and are typically nonflammable and, unlike conventional solvents, have no measurable vapor pressure. Because of these unique properties ionic liquids have been viewed as "green solvents" with respect to their potential environmental impacts.[1]

Ionic liquids are composed of two parts: a cation and an anion (Fig. 16.2.1). The cation is a relatively large organic moiety such as imidazole ($(CH)_2N(NH)CH$), an aromatic, planar, 5-membered ring with variable lengths of n-alkyl chains, the methyl group ($-CH_3$) being a simple example. The anionic part varies from being a monovalent halide such as chloride to more complex fluorinated organic moieties such as bis(trifluoromethyl)sulfonylimide. Because both the type of cation and anion can be varied, ionic liquids have the potential to be designed and synthesized with the end-use in mind such that the term "designer solvents" has been coined.[1] It has been speculated that there may be millions of possible cation-anion combinations as ionic liquids that could eventually be used in industrial and commercial applications.[3]

If ionic liquids attain wide-spread usage, it is inevitable that they will be released into the environment.[4-6] Stepnowski and Zaleska,[3] however, cautioned that there is a scarcity of relevant information to make assessments of the environmental fate and movement of ionic liquids when released. Other researchers have also concluded that little was known about how ionic liquids interact with natural systems such as soil.[7,8] There have been a number of studies conducted during the last 10 years to help fill this information gap. The goal of this chapter is to synthesize the current state-of-knowledge about the environmental chemistry of ionic liquids in soil, water, and air. The scope of the chapter does not include discussions about the possible toxicity of ionic liquids to terrestrial and aquatic organisms. The plethora of possible ionic liquid formulations limits the number of sweeping conclusions that can be made about how ionic liquids will behave in the environment. However, as a starting point imidazolium-based ionic liquids are currently the most widely studied, and have already been applied at the industrial scale.[9]

16.2.2 RELEASES TO THE ENVIRONMENT

No information was located about accidental or intentional releases of ionic liquids to land, water or air from industrial or commercial sources.

16.2.3 LEVELS IN THE ENVIRONMENT

There are no published data that demonstrate the presence of ionic liquids in the natural environment.[10]

16.2.4 IONIC LIQUIDS IN WATER

16.2.4.1 Solubility

One of the most important properties of an ionic liquid in the natural environment is its solubility in water. The greater the compound's aqueous solubility, the more likely that an ionic liquid will dissolve into water, and become part of the hydrologic cycle. Water solubility can affect the extent of leaching of solid wastes containing ionic liquids, and the movement and chemical fate of dissolved ionic liquids in rivers, lakes, groundwater, and in drinking-water supplies.

Because of the diversity of ionic liquid combinations, the solubility of this class of solvents is diverse and can depend on the chemical composition of the cation or the anion, and the length of the alkyl chain. When 1-alkyl-3-methylimidazolium cations are combined with halogen anions such as chloride, iodide, and BF_4^-, the ionic liquids are hydrophilic and miscible with water.[11] When combined with more hydrophobic anions, the solubility of the ionic liquid decreases. For example, Alfassi *et al.*[12] measured the solubility of 1-butyl-3-methylimidazolium hexafluorophosphate as 18.6 g/L, butylmethlpyrrolidinium bis(trifluoromethylsulfonyl)imide as 6.0 g/L, and methyltributylammonium bis(trifluoromethylsufonyl)imide as 0.7 g/L.

McFarlane *et al.*[13] measured the solubility of methylimidazolium-based bis[(trifluoromethane)sulfonyl]imides, and found that when the length of the alkyl chain increased from 1-butyl, 1-hexyl, to 1-octyl, the solubility of the ionic liquid decreased from 16 mM to 4.7 mM at 22°C. When the 1-butyl form was combined with a more hydrophilic anion (hexafluorophosphate), the solubility of that ionic liquid was 63 mM. The chemical composition of the anion affected the solubility of four alkylimidazolium-based ionic liquids.[14] When the anion was bis[(trifluoromethyl)sulfonyl]azanide, the ionic liquids were less soluble in water when the anion was hexafluorophosphate. For example, the solubility of 1-butyl-3-methylimidazolium hexafluorophosphate was 2.12 wt% whereas the solubility of the relatively more hydrophobic 1-butyl-2,3-dimethylimidazolium bis[(trifluoromethyl)sulfonyl]azanide was measured as 0.61 weight percent. Overall, the solubility of each ionic liquid did not exceed 0.075 mM.

When 1-methyl-3-octylimidazolium was combined with dicyanamide or trifluoromethyl-sulfonate, the combinations were completely miscible with water. When the organic cation was combined with relatively more hydrophobic anions (nonafluorobutyl sulfonate and bis(trifluoromethylsulfonyl)imide), the resulting solubility of the ionic liquid was 0.21 and 0.16% respectively.[15] Ranke *et al.*[16] measured the solubility of 13 ionic liquids, then derived a model to estimate the water solubility of cation-anion combinations for which no experimental measurements had been made. Expressed as the log of the mole

fraction, the solubility of the eight methylimidazolium-based ionic liquids ranged from –2.9 to –5.04. The most soluble was 1-butyl-3-methylimidazolium hexafluorophosphate, and its solubility on a weight basis was about 2.05%. The least soluble was 1-hexyl-3-methylimidazolium tris(trifluoromethylsulfonyl)methide; 293 mg/L. The solubility of the two pyridinium-based compounds was measured as –2.43 and –4.53, the latter being 4-(dimethylamino)-1-hexylpyridimium bis(trifluoromethylsulfonyl)imide. The solubility of three pyrrolidinium-based ionic liquids ranged from –3.57 to –4.12. The least soluble was 1-hexyl-1-methylpyrrolidinium bis(trifluoromethylsulfonyl)imide; 4.21 mM or about 0.188 wt%.

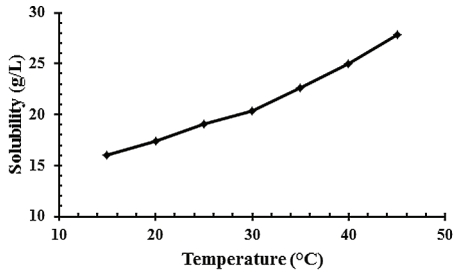


Figure 16.2.2. The solubility of 1-butyl-3-methylimidazolium hexafluorophosphate as a function of temperature [Data from Freire M G, Neves C, Carvalho P J, Gardas R L, Fernandes A M, Marrucho I M, Santos L, Coutinho J A P, *J. Phys. Chem. B*, **111**, 13082, 2007.]

Another example of how the selection of the anion will affect solubility is the study by Papaiconomou *et al.*[17] A portion of their results is shown in Table 16.2.1. For each ionic liquid, the organic cation was 1-octyl-4-methylpyridinium. When combined with one of nine increasingly hydrophobic anions, solubility decreased by four orders of magnitude. The most soluble ionic liquid was with dicyanamide as the anion, while tetraphenylborate rendered the pyridinium-based ionic liquid as the most hydrophobic.

Table 16.2.1. The solubility of 1-octyl-4-methylpyridinium when combined with nine different anions [Data from Papaiconomou N, Salminen J, Lee J M, Prausnitz J M, *J. Chem. Eng. Data*, **52**, 833, 2007].

Anion	% mass fraction
Dicyanamide	>5.0
Tetrafluoroborate	1.68
Trifluoromethylsulfonate	1.59
Trifluorophenylborate	0.49
Nonafluorobutylsulfonate	0.065
Hexafluoroarsenate	0.027
Bis(trifluoromethylsulfonyl)imide	0.022
Bis(pentafluoroethylsulfonyl)imide	0.013
Tetraphenylborate	<0.0005

The solubility of ionic liquids may depend on the temperature of the solution. Freire *at al.*[18,19] measured the solubility of imidazolium-, pyridinium-, pyrrolidinium-, and piperidinium-based ionic liquids. In general, the solubility of each ionic liquid increased with an increase in temperature. For example, the solubility of 1-butyl-3-methylimidazolium hexafluorophosphate increased by about 74% over a 30-degree temperature increase (Fig-

ure 16.2.2). The behavior of ionic liquids in solution may also be influenced by micelle formation much like surfactants. Working with 1-alkyl-3-methylimidazolium chloride solutions, Jungnickel *et al*.[20] presented evidence of the formation of micelles, but only when the alkyl chains were longer than six carbon atoms.

16.2.4.2 Volatilization from water

Ionic liquids dissolved in water may partition or volatilize into the atmosphere or into soil gases. A Henry's Law constant (K_H) can be used to classify the volatilization of ionic liquids from water. Henry's Law describes the ratio of the partial pressure of the vapor phase of an ideal gas (P_i) to its mole fraction (X_i) in a dilute solution:

$$K_{H(i)} = P_i/X_i \quad [16.2.1]$$

Henry's Law constants for ionic liquids have not been measured. One method of estimation is to divide the vapor pressure of the ionic liquid by its corresponding solubility in water (S_i) at the same temperature:

$$K_{H(i)} = P_i \text{ (atm)}/S_i \text{ (mol/m}^3 \text{ solvent)} \quad [16.2.2]$$

A major characteristic of ionic liquids, however, is that they have a nearly negligible vapor pressure which makes accurate measurements problematic. Although the possible number of ionic liquids formulations is large, there are only a limited number of studies that provide vapor-pressure data, and most of them were conducted at temperatures far in excess of relevant environmental conditions. For example, Zaitsau *et al*.[21] measured the vapor pressure of 1-n-alkyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide in the temperature range of 165 to 244°C.

Bier and Dietrich[22] presented experimental data suggesting that the vapor pressure of 1-ethyl-3-methylimidazolium bis(triflamide) was 8.9 x 10^{-12} Pa at –2.15°C, and for 1-octyl-3-methylimidazolium bis(triflamide), 7.8 x 10^{-14} Pa at –9.15°C. The vapor pressure of 1-butyl-3-methylimidazolium hexafluorophosphate has been estimated as 1 x 10^{-10} Pa at 25°C.[23] Using this value, a Henry's Law constant can be approximated:

$$K_H \approx (9.869 \times 10^{-16}\text{atm})/(670 \text{ moles/m}^3) = 1.5 \times 10^{-18}\text{atm-m}^3/\text{mole} \quad [16.2.3]$$

If K_H is less than about 3 x 10^{-7} atm-m^3/mole, the substance is less volatile than the water it is dissolved in, and its concentration will increase as the water evaporates.[24] The estimated value above suggests that volatilization from water is not likely. Therefore the few data available suggest that volatilization from surface or groundwater may not be a significant mechanism following the release of ionic liquids.

16.2.4.3 CHEMICAL DEGRADATION IN WATER

There is little information available to assess the extent of chemical or abiotic degradation of ionic liquids in solution under natural conditions. Ionic liquids are regarded as relatively stable in solution.[25] A sense of their stability may be gained by reviewing the results of relatively aggressive techniques that have been proposed for the treatment of wastewater containing ionic liquids. For example, in a pioneering study by Stepnowski and Zaleska,[3] applied three so-called "advanced oxidation processes" to solutions containing

imidazolium-based ionic liquids: ultraviolet (UV) photodegradation, UV hydrolysis of hydrogen peroxide, and photocatalysis on titanium oxide irradiated with UV light. Under the influence of UV radiation alone, the half-life of 1-butyl-3-methylimidazolium tetrafluoroborate was about 270 minutes. The combination of hydrogen peroxide and UV irradiation reduced the half-life of the same ionic liquid to about 100 minutes. The third combination reduced the half-life to about 85 minutes.

A combination of hydrogen peroxide and iron (II) was found to degrade 1-butyl-3-methylimidazolium chloride.[26] The iron was used as a source of hydroxyl radicals:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + \dot{O}H + OH^- \qquad [16.2.4]$$

The greatest extent of degradation of a 1 mM solution occurred at pH = 3 in the presence of 10 mM of H_2O_2. Itakura *et al*.[27] applied a combination of heat (200°C) in presence of calcium hydroxide followed by UV irradiation in the presence of ground titanium oxide or a platinum/titanium oxide reagent in a stirred container. This treatment combination was applied to imidazolium-based ionic liquids. The extent of decomposition varied from 24 to 99.9%.

Ultrasonic irradiation was applied to suspensions containing granular carbon and activated zero-valent iron and eight different imidazolium-based ionic liquids.[28] For example, about 90% of 1-alkyl-3-methylimidazolium bromide was degraded in about 110 minutes. Degradation products were also identified such as 1-alkyl-3-methyl-2,4,5,-trioxoimidazolidine.

While the results of these relatively aggressive treatment approaches are suggestive for future wastewater treatment, it is not clear how they could be extrapolated to natural systems. It may be that chemical degradation in natural waters may not be a major factor that influences the fate of ionic liquids.

16.2.4.4 Biodegradation in water

There is no information available about the biodegradation of ionic liquids in natural waters under environmental conditions. All of the studies conducted to date were aimed at assessing the extent of biodegradation in the context of wastewater treatment. Both the rate and extent of biodegradation of contaminants reported in the literature depend on the experimental conditions under which the measurement was made, and the results may not be applicable to other scenarios. Results from aerobic wastewater treatment procedures may have been optimized in terms of nutrient content, microbial acclimation, mechanical mixing of the reactants, and temperature. Hence, the results of such studies may underpredict the persistence of ionic liquids released into natural waters.

In an early pioneering study, Gathergood *et al*.[29] prepared 35 combinations of diallylimidazolium-based ionic liquids with five different anions (Br^-, BF_4^-, PF_6^-, $N(CN)_2^-$ and bis(trifluoromethylsulfonyl)imide). The investigators applied the Modified Sturm Test (Organization for Economic Co-operation and Development, OECD 301 B) and the Closed Bottle test (OECD 301 D). Both test procedures are relatively simple in which the ionic liquid is added to an aerobic aqueous solution that has been inoculated with wastewater microorganisms. In OECD 301 B, the evolution of carbon dioxide is measured whereas the depletion of dissolved oxygen is measured in OECD 301 D. Gathergood *et*

al.[29] observed that none of the ionic liquids could be classified as "readily biodegradable" (>60% degraded) after 28 days. However, 3-methyl-1-(ethoxycarbonylmethyl)imidazolium bromide yielded 48% by method 301 B, and 59% of 3-methyl-1-(ethoxycarbonylmethyl)imidazolium tetrafluoroborate degraded. The extent of biodegradation increased generally with an increase in the alkyl chain length of the 3-methyl-1-(alkyloxycarbonylmethyl)imidazolium bromides. The results indicated that 1-n-butyl-3-methylimidazolium-based ionic liquids appeared to be resistant to biodegradation as measured by the Closed Bottle test (OECD 301 D).

When applied to a series of ionic liquids composed of 1-butyl-3-methylimidazolium and 1-(propoxycarbonyl)methyl-3-methylimidazolium combined with various anions such as Br^-, BF_4^-, PF_6^- and $N(CN)_2^-$ was subjected to the Closed Bottle test, none of the cation-anion combinations were readily biodegradable (>60%).[30] The most biodegradable forms possessed the octyl sulfate anion. The source of the microorganisms was effluent from an activated sewage treatment plant. When the CO_2 Headspace test (ISO 14593) was applied to a series of 1-(alkoxycarbonyl)-3-methylimidazolium ionic liquids, the forms with an ester bond in the side chain and the octyl sulfate anion yielded sufficient biodegradation to be classified as readily biodegradable.[31] The solutions were inoculated with effluent from an activated sludge treatment plant.

When the OECD DOC Die-Away procedure (301 B) was applied to 1-butyl-3-methylpyridinium bromide and 1-hexyl-3-methylpyridinium bromide, both were reported as being almost completely degraded after 41 days, and 1-octyl-3-methylpyridinium met the same condition after 28 days.[32] The source of microorganisms was a sample of activated sewage sludge from a wastewater treatment facility. In the method, dissolved organic carbon is periodically measured during a 28-day interval.

When the Closed Bottle test (OECD 301 D) was applied to 1-ethyl, 1-hexyl, and 1-decyl-3-methylimidazolium bromide, the extent of biodegradation after 28 days was approximately 10, 12, and 26% respectively.[33] It was speculated that the extent of biodegradation was related to the length of the alkyl chain; the longer chains were more accessible to the bacteria. The source of the microorganisms was a sample of activated sewage sludge from a wastewater treatment plant in Poland. As with other studies, the test period was too short to estimate a half-life beyond concluding that it was greater than 28 days.

In contrast to other reports, a half-life of $\leq$ 10.5 days was observed during the application of the OECD DOC Die-Away procedure (301 B) to 1-methyl-octylimidazolium chloride.[34] The source of the microorganisms was a sample of activated sewage sludge from a wastewater treatment plant in Poland. The authors, however, cautioned that the results of the OECD tests cannot be easily extrapolated to natural environmental conditions. Coleman and Gathergood[35] provided a review of biodegradation studies of ionic liquids, but the comprehensive review did not identify any studies conducted under conditions that were intended to mimic natural conditions. The potential for even the more common ionic liquids to biodegrade in surface and groundwater remains unresolved.

16.2.4.5 Adsorption from water

Adsorption is a physicochemical process by which dissolved ionic liquids may be removed from the water and concentrated at solid-liquid interfaces such as water in con-

tact with soil or sediments. Once adsorbed, ionic liquids can be desorbed or released back into solution. The overall impact of adsorption-desorption reactions is that the movement of dissolved ionic liquids in soil and groundwater may be retarded which would limit the spread of the chemicals after a release. Gorman-Lewis and Fein[36] measured the adsorption of 1-butyl-3-methylimidazolium chloride by quartz, SiO_2, gibbsite, $Al(OH)_3$ and montmorillonite, a swelling clay mineral composed of $(Na,Ca)_{0.3}(Al,Mg)_2Si_4O_{10}(OH)_2 \cdot nH_2O$. Neither the quartz nor the gibbsite sample adsorbed measurable amounts of the ionic liquid from solution. The clay mineral, however, was more reactive. The authors speculated that 1-butyl-3-methylimidazolium chloride might be relatively mobile in groundwater moving within porous media that lacks clay minerals.

Stepnowski[37] may have first measured both the adsorption and desorption of ionic liquids with soil and sediment samples. Working with 1-hexyl, 1-amyl, 1-butyl, and 1-propyl-3-methylimidazolium tetrafluoroborate and 1-butyl-3-ethylimidazolium tetrafluoroborate, adsorption by two unidentified soil samples, peat, and a marine sediment sample collected in Poland was found to conform to the Freundlich equation:

$$x/m = K_f C^{1/n} \qquad [16.2.5]$$

where:

x	the mass adsorbed
m	mass of adsorbent
K_f	the Freundlich constant, a soil-specific term
C	the equilibrium concentration of the chemical in water, and
n	the Freundlich exponent which describes the degree of non-linearity of the isotherm.

Mrozik *et al.*[38] calculated soil organic carbon partition coefficients (K_{oc}) for four soil samples. An organic carbon-water partition coefficient is a compound-specific term that allows the user to estimate the mobility of a relatively hydrophobic chemical in saturated soil-water systems if the amount of organic carbon in the soil is known. A K_{oc} value is a measure of the affinity of a chemical to partition to organic matter which in turn will control the mobility of the solute in water. Although some variation in measured K_{oc} values is expected because of the heterogeneous nature of soil organic matter and experimental variation, Mrozik *et al.*[38] found that the K_{oc} values varied by one to three orders of magnitude. For example, K_{oc} for 1-hexyl-3-methylimidazolium ranged from 62 to 23,440 mg/kg. The lack of convergence to a single value was likely an indication that the extent of adsorption could not be explained by hydrophobic partitioning alone. The adsorption of 1-butyl-3-methylimidazolium chloride by four soil samples also greater than that predicted by the cation exchange capacity of each soil.[39] A study conducted using three soil samples, a glacial till, and a sample of beach sand collected in Poland also found that the extent of adsorption of three imidazolium-based ionic liquids was greater than that predicted by the cation exchange capacity of the sorbents.[40]

These observations, fueled by studies that followed it, have led researchers to propose that the adsorption of ionic liquids may result from both electrostatic interactions between the cationic moiety of the ionic liquid and negatively charged surfaces of clay-size minerals, as well as hydrophobic partitioning. As the hydrophobic alkyl chains are oriented away from the surface, the chains can attract additional chains thereby modifying

the surface of the mineral. Opinions vary as to the relative importance of the two mechanisms. Stepnowski[41] proposed that the predominant adsorption mechanism was likely ion exchange, and that hydrophobic interactions contribute when the length of the alkyl chain increases which enhances the hydrophobicity of the entire molecule. Other studies have also presented evidence of the evolution of a second layer of adsorbate as more ionic liquid molecules were retained.[9,10]

Other researchers[7] arrived at different conclusions when measuring the adsorption of four imidazolium-based ionic liquids by lake sediments. The extent of adsorption did not correlate with cation exchange capacity, and the organic matter content of the sediment samples appeared to be a major influence. However, because an increase in the length of the alkyl chain did not result in greater adsorption, the role of hydrophobic interactions was dismissed. It was proposed that hydrogen bonding between the imidazolium ring and the sediment organic matter was the major mechanism of adsorption.

The type of clay minerals present in the soil has also been found to influence the extent of ion liquid adsorption. Matzke *et al*.[2] measured the adsorption of 1-butyl-3-methyl-imidazolium tetrafluoroborate, 1-methyl-3-octyl-imidazolium tetrafluoroborate, and 1-butyl-3-methyl-imidazolium bis[(trifluoromethyl)sulfonyl]imide by an acidic, loamy soil mixed with different proportions of kaolinite and smectite. The addition of smectite increased the amount of each ionic liquid adsorbed whereas the addition of kaolinite did not result in a measurable change.

A recent study by Dong *et al*.[42] measured the sorption of six imidazolium-based ionic liquids by surface soil samples collected in China. The ionic liquids were 1-butyl-3-methyl-midazolium trifluoromethanesulfonate, 1-butyl-3-methylimidazolium tosylate, 1-butyl-3-methylimidazolium methylsufonate, 1-butyl-3mehylimidazolium tetrafluoroborate, 1-ethyl-3-methylimidazolium tetrafluoroborate, and 1-hexyl-3-methyl-imidazolium tetrafluoroborate. The experimental data conformed to the Freundlich Equation (16.2.5). The investigators concluded that the extent of sorption increased with an increase in the ally chain length of the cation moiety. Desorption was not measured.

The adsorption of ionic liquids appears to be an endothermic reaction. Reinert *et al*.[6] measured the adsorption of five imidazolium- and pyridinium-based ionic liquids by montmorillonite over a temperature range of 25 to 55°C. The extent of adsorption increased with temperature. Quasi-isosteric enthalpy values ranged from 5.4 kJ/mole (1-allyl-3-methylimidazolium chloride) to 9.9 kJ/mole (1-octylpyridinium bromide). The extent of adsorption by the clay mineral followed the order of 1-butylpyridinium bromide > 1-octylpyridinium bromide ~ 1-allyl-3-methylimidazolium chloride ~ 1-methyl-3-butylimidazolium chloride > 1-methyl-3-octylimidazolium chloride.

The desorption of ionic liquids has also received some attention. The extent of desorption appeared to decrease with an increase in the alkyl chain length. For example, only about 1.5% of the initially adsorbed was desorbed from a sediment sample under the experimental conditions imposed.[37] Ionic liquids such as 1-hexyl-3-methylimidazolium were reported as “irreversible bound.” Mrozik *et al.*[40] found that the extent of desorption from two soil samples, two subsurface soil samples, and a sample of beach sand seemed to depend on the organic matter content and the length of the alkyl chain (Fig. 16.2.3).

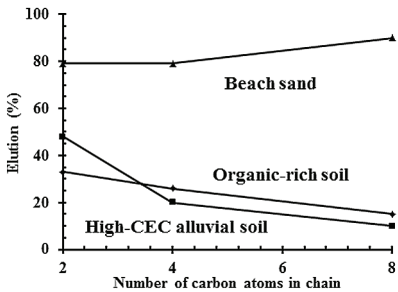


Figure 16.2.3. The extent of desorption of 1-ethyl, 1-butyl, and 1-octylimidazolium chloride from two soil samples and a beach sand [Data from Mrozik W, Jungnickel C, Ciborowski T, Pitner W R, Kumirska J, Kaczynski Z, Stepnowski P, *J. Soils Sediments*, **9**, 237, 2009].

Although there were too few adsorbent samples to be definitive, it also appeared that the cation exchange capacity and clay content influenced the extent of desorption. The addition of smectite to an acidic loamy soil also reduced the degree of desorption of imidazolium-based ionic liquids.[2]

The movement of dissolved ionic liquids may be facilitated by being adsorbed by dissolved organic matter in surface water. Zhang *et al.*[5] measured the adsorption of 1-butyl and 1-octyl-3-methylimidazolium by dissolved organic matter, and calculated relatively large distribution coefficients ($10^{4.2}$ to $10^{4.6}$). The magnitude of the partition coefficients suggest that if these ionic liquids were discharged into streams or rivers, that they could be mobile in the environment.

16.2.5 IONIC LIQUIDS IN SOILS AND SEDIMENTS

16.2.5.1 Volatilization

Volatilization of ionic liquids from soils and sediments has not been measured. The environmental properties that affect volatilization of any solvent are its vapor pressure, solubility in water and the properties of the soil such as organic matter content and texture.[24] In the absence of measured data, there are numerous methods to estimate the likely extent of volatilization of a solvent following, for example, a chemical spill. However, as discussed in Section 16.2.4.2, the vapor pressure of typical ionic liquids is negligible suggesting that volatilization from dry or wet soil would be insignificant.

16.2.5.2 Biodegradation in soils and sediments

There is no information available about the significance of biodegradation of ionic liquids in soils or sediments. As discussed in Section 16.2.4.4, all published biodegradation studies were conducted in the context of wastewater treatment plants. These studies suggest that first-generation ionic liquids may be relatively persistent under natural conditions.

There are no procedures for estimating the rate of biodegradation of chemicals because of the complexity of the biochemical reactions, and the diverse experimental conditions imposed in individual investigations.[43] The potential for even the more common imidazolium-based ionic liquids to biodegrade in soils and sediments remains unresolved.

16.2.6 IONIC LIQUIDS IN AQUATIC ORGANISMS

Analogous to the partitioning of ionic liquids from water to soil and sediments, another potential pathway for these chemicals is aquatic organisms. A solvent combination that has been used extensively to estimate the partitioning behavior between water and organisms living in the water is the n-octanol-water combination. Octanol is believed to best imitate living tissues. The resulting octanol-water partition coefficients (K_{ow}) have been correlated with aqueous solubility and soil organic carbon partition coefficients. Lyman[44]

generalized that a K_{ow} greater than 10,000 indicates that the chemical should partition significantly to organic phases such fish tissue. A compilation of the available K_{ow} values for ionic liquids (Table 16.2.2) indicated that partitioning to aquatic organisms may not be an important pathway.

Table 16.2.2. Compilation of octanol-water partition coefficients (K_{ow}) for ionic liquids.

Ionic liquid	K_{ow}	Ref.
1-butyl-3-methylimidazolium chloride	0.004	45
1-butyl-2,3-dimethylimidazolium chloride	0.004	7
1-hexyl-3-methylimidazolium chloride	1.4	7
1-octyl-3-methylimidazolium bromide	6.3	7
2,3-dimethyl-1-ethylimidazolium bis(trifluoromethylsulfonyl)imide	0.09 to 0.11	45
3-methyl-1-octylimidazolium bis(trifluoromethylsulfonyl)imide	6.3 to 11.1	45
1-propylpyridinium[1]	0.04	46
1-hexyl-3-methylpyridinium	1.39	46
1-(3-hydroxypropyl)pyridinium	0.02	46
1-(2-ethoxycarbonyl)methylpyridinium	0.003	46

[1]The anion for the pyridinium-based forms was bis(trifluoromethylsulfonyl)imide.

16.2.7 IONIC LIQUIDS IN THE ATMOSPHERE

Photochemical reactions can be important mechanisms to reduce the vapor-phase concentrations of conventional organic solvents (see Chapter 16.1). However, as discussed in Section 16.2.4.2, the vapor pressure of ionic liquids is negligible suggesting that it is unlikely that typical ionic liquids will occur as a vapor phase in the atmosphere. It is possible that ionic liquids could be transported in the atmosphere as an adsorbed phase on particulate matter that is subject to dry and wet deposition, but this pathway is only conjecture at this time.

16.2.8 CONCLUSIONS

The amount of information available about the environmental chemistry of ionic liquids in soil, water, and the air is limited. To date, ionic liquids have not yet been detected in the environment. Ionic liquids are composed of a relatively large cationic organic moiety with variable lengths of n-alkyl chains, and an anionic part composed of a variety of halides or complex organic moieties. The solubility of ionic liquids varies from being completely miscible with water to concentrations that are comparable with some hydrophobic conventional organic solvents (see Chapter 16.1). Typical ionic liquids have a negligible vapor pressure, and as a consequence, have little tendency to volatilize from water or from dry or wet soils into the atmosphere. Ionic liquids can be adsorbed from water by soils and sediments by a combination of mechanisms including ion exchange on hydrophobic interactions. Once adsorbed, it appears that the reaction is not fully reversible. Ionic liquids appear to be resistant to chemical degradation and biodegradation. All of the available

information on degradation, however, is from studies conducted in the context of wastewater treatment. Partitioning to aquatic organisms does not appear to be a significant pathway. If the use of ionic liquids increases in industrial and commercial applications, there is the need to conduct more studies to better assess the potential environmental impacts of this relatively new class of solvents.

REFERENCES

1 Earle M, Seddon K R, *Pure Appl. Chem*., **72**, 1391, 2000.
2 Matzke M, Thiele K, Muller A, Filser J, *Chemosphere*, **74**, 568, 2009.
3 Stepnowski P, Zaleska A, *J. Photochem. Photobiol. A: Chem.*, **170**, 45, 2004.
4 Modelli A, Sali A, Galletti P, Samori C, *Chemosphere*, **73**, 1322, 2008.
5 Zhang Z, Liu J, Cali X, Jiang W, Luo W, Jiang G, *Environ. Sci. Techn*., **45**, 1688, 2011.
6 Reinert L, Batouche K, Leveque J M, Muller F, Beny J M, Kebabi B, Duclaux L, Chem. Eng. J., **209**, 13, 2012.
7 Beaulieu J, Tank L, Kopacz M, *Chemosphere*, **70**, 1320, 2008.
8 Studzinska S, Sprynskyy M, Buszweski B, *Chemosphere*, **71**, 2121, 2008.
9 Markiewicz M, Mrozik W, Rezwan K, Thoming J, Hupka J, Jungnickel C, *Chemosphere*, **90**, 706, 2013
10 Mrozik W, Kotlowska A, Kamysz W, Stepnowski P, *Chemosphere*, **88**, 1202, 2012.
11 Huddleston J G, Visser A E, Reichert W M, Willauer H D, Broker G A, Rogers R D, *Green Chem*., **3**, 156, 2001.
12 Alfassi Z B, Huie R E, Milman B L, Neta P, *Anal. Bioanal. Chem*., **377**, 159, 2003.
13 McFarlane J, Ridenour W B, Luo H, Hunt R D, Depaoli D W, *Separation Sci. Techn*., **40**, 1245, 2005.
14 Shvedene N V, Borovskaya S V, Sviridov V V, Ismailova E R, Pletnev I V, *Anal. Bioanal. Chem*., **381**, 427, 2005.
15 Papaiconomou N, Yakelis N, Salminen J, Bergman R, Prausnitz J M, *J. Chem. Eng. D*ata, **51**, 1389, 2006.
16 Ranke J, Othman A, Fan P, Muller A, *Intern. J. Mol. Sci*., **10**, 1271, 2009.
17 Papaiconomou N, Salminen J, Lee J M, Prausnitz J M, *J. Chem. Eng. D*ata, **52**, 833, 2007.
18 Freire M G, Neves C, Carvalho P J, Gardas R L, Fernandes A M, Marrucho I M, Santos L, Coutinho J A P, *J. Phys. Chem. B*, **111**, 13082, 2007.
19 Freire, M G, Carvalho P J, Gardas R L, Marrucho I M, Santos L, and Coutinho J A P, 08. *J. Phys. Chem. B*, **112**, 1604, 2008.
20 Jungnickel C, Luczak J, Ranke J, Fernandez J F, Muller A, Thoming J, *Coll. Surf. A. Physicochem. Eng. Aspects*, **316**, 278, 2008.
21 Zaitsau D H, Kabo G J, Strechan A A, Paulechka Y U, Tschersich A, Verevkin S P, Heintz A, *J. Phys. Chem. A*, **110**, 7303, 2006
22 Bier M, Dietrich S, *Mol. Phys*., **108**, 211, 2010.
23 Paulechka Y U, Kabo G J, Blokhin A V, Vydrov O A, Magee J W, Frenkel M, *J. Chem. Eng. D*ata, **48**, 457, 2003.
24 Thomas R G, Volatilization from water in Lyman W L, Reehl W F, and Rosenblatt D H (eds). **Handbook of Chemical Property Estimation Methods**. *American Chemical Societ*y, Washington, D. C. Chap. 15, 1990.
25 Pham, T P T, Cho C W, Yun Y S, *Water Res*., **44**, 352, 2010.
26 Siedlecka E M, Mrozik W, Kaczynski Z, Stepnowski P, *J. Hazardous Mater*., **154**, 893, 2008.
27 Itakura T, Hirata K, Aoki M, Sasai R, Yoshida H, Itoh H, *Environ. Chem. Lett*., **7**, 343, 2009.
28 Zhou H, Lv P, Shen Y, Wang J, Fan J, *Water Res*, **47**, 3514, 2013.
29 Gathergood N, Garcia M T, Scammells P J, *Green Chem*., **6**, 166, 2004.
30 Garcia M T, Gathergood N, Scammells P J, *Green Chem*., **7**, 9, 2005.
31 Gathergood N, Scammells P J, Garcia M T. *Green Chem*., **8**, 156, 2006.
32 Docherty K M, Joyce M V, Kulacki K J, Kulpa C F, *Green Chem*., **12**, 701, 2010.
33 Liwarska-Bizukojc E, Gendaszewska D, *J. Biosci. Bioeng*., **115**, 71, 2013.
34 Markiewicz M, Stolte S, Lustig Z, Luczak J, Skup M, Hupka J, Jungnickel C, *J. Hazardous Mater*., **195**, 378, 2011.
35 Coleman D, Gathergood N, *Chem. Soc. Rev.*, **39**, 600, 2010.
36 Gorman-Lewis D J, Fein J B, *Environ. Sci. Techn*, **38**, 2491, 2004.
37 Stepnowski P, *Australian J. Chem*., **58**, 170, 2005.
38 Mrozik W, Nichthauser J, Markowska A, Golebiowski M, Kumirska J, Czerwicka G, Malinski E,

Stepnowski P. 2007. Investigation of sorption of ionic liquids onto selected natural soils in Proceedings of the 10th International Conference of Environmental Science and Technology, Kos Island Greece, Global Network for Environmental Science and Technology, Sept. 5-7, 2007.
39 Stepnowski P, Mrozik W, Nichthauser J, E*nviron. Sci. Techn.*, **41**, 511, 2007.
40 Mrozik W, Jungnickel C, Ciborowski T, Pitner W R, Kumirska J, Kaczynski Z, Stepnowski P, *J. Soils Sediments*, **9**, 237, 2009.
41 Stepnowski P, Sorption, lipophilicity and partitioning phenomena of ionic liquids in environmental systems in Letcher T M (ed.). **Thermodynamics, Solubility and Environmental Issues**, *Elsevier B V*, Chap. 16, 2007.
42 Dong, Z, Wei, L, Sun S, Shi X. Qui Y. *Ecotoxicology and Environmental Safety*, **147**, 480, 2018.
43 Scow K M, 1990. Rate of Biodegradation in Lyman W J, Reehl W F, Rosenblatt D H (eds). **Handbook of Chemical Property Estimation Methods**. *American Chemical Society*, Washington, D. C. Chap. 9, 1990.
44 Lyman, W J, 1990. Octanol/water partition coefficient in Lyman W J, Reehl W F, Rosenblatt D H (eds). **Handbook of Chemical Property Estimation Methods**. *American Chemical Society*, Washington, D. C., Chap. 1, 1990.
45 Ropel L, Belveze L S, Aki S N V K, Stadtherr M A, Brennecke J F, *Green Chem*., **7**, 83, 2005.
46 Deng Y, Besse-Hoggan P, Husson P, Sancelme M, Delort A, Stepnowski P, Paszkiewicz M, Golebiowski M, Gomes M F C, *Chemosphere*, **89**, 327, 2012.

16.3 ORGANIC SOLVENT IMPACTS ON TROPOSPHERIC AIR POLLUTION

Michelle Bergin and Armistead Russell
Georgia Institute of Technology, Atlanta, Georgia, USA

16.3.1 SOURCES AND IMPACTS OF VOLATILE SOLVENTS

Solvents, either by design or default, are often emitted into the air, and the total mass of emissions of solvents is not small. In a typical city in the United States, solvents can rival automobile exhaust as the largest source category of volatile organic compound (VOC) emissions into the atmosphere.[1] In the United Kingdom, solvent usage accounted for 36% of the estimated total VOC mass emissions in 1995.[2] Such widespread emission leads to increased concentrations of many different compounds in the ambient environment, and their release has diverse impacts on air quality.

A large variety of solvent-associated compounds are emitted, many of which are hydrocarbons and oxygenates. Those solvents may have multiple atmospheric impacts. For example, toluene is potentially toxic and can reach relatively high concentrations at small spatial scales, such as in a workplace. Toluene also contributes to the formation of tropospheric ozone at urban scales, while at regional scales toluene can lower the rate of tropospheric ozone formation. Other solvents likewise can have a range of impacts, ranging from local contamination to modification of the global climate system.

This diversity of potential impacts is due, in part, to differences in the chemical properties and reactions that a compound may undergo in the atmosphere, differences in emission patterns, and differences in the spatial and temporal scales of atmospheric phenomena. Transport and fate of chemical species are closely tied to the speed at which the compound degrades (from seconds to centuries, depending on the compound) as well as to the environmental conditions in which the compound is emitted. If a compound degrades very quickly, it may still have toxic effects near a source where concentrations can be high. In contrast, extremely stable compounds (such as chlorofluorocarbons; CFCs) are able to circumvent the globe, gradually accumulating to non-negligible concentrations.[3]

Of the myriad of solvents emitted into the air, the ones of primary concern are those with the greatest emissions rates, and/or those to which the environment has a high sensitivity. Compounds with very large emission rates include tri- and tetrachloroethylene (e.g., from dry-cleaning), aromatics (benzene, toluene, and xylenes, e.g., from coatings), alcohols, acetone and, historically, CFCs. While these compounds are often emitted from solvent use, other applications lead to their emission as well. For example, gasoline is rich in aromatics and alkanes, and in many cases, fuel use dominates emissions of those compounds. CFCs have been used as refrigerants and as blowing agents. This diversity of originating sources makes identifying the relative contribution of solvents to air quality somewhat difficult since there are large uncertainties in our ability to quantify emissions rates from various source categories.

Solvents with a high environmental sensitivity include benzene (a potent carcinogen), xylenes (which are very effective in producing ozone), formaldehyde (both toxic and a strong ozone precursor), and CFCs (ozone depleters and potential greenhouse gases). Most of the solvents of concern in terms of impacting ambient air are organic, either hydrocarbons, oxygenated organics (e.g., ethers, alcohols, and ketones) or halogenated organics (e.g., dichlorobenzene). Some roles of these compounds in the atmosphere are discussed below.

While the toxicity of some solvents is uncertain, the role of emissions on direct exposure is not in question. Indoors, vaporized solvents can accumulate to levels of concern for acute and/or chronic exposure. However, the toxicity of solvents outdoors is not typically of a great concern as indoors except very near sources. Outdoors, solvents have adverse effects other than toxicity. The importance of CFC emissions on stratospheric ozone, for example, is significant, but the problem is well understood and measures are in place to alleviate the problem. Reactive compounds can also aid in the formation of other pollutants, referred to as secondary pollutants because they are not emitted, but formed from directly emitted primary precursors. Of particular concern is tropospheric ozone, a primary constituent of photochemical smog. In the remainder of this chapter, the impacts of solvents on air quality are discussed, with particular attention given to the formation of tropospheric ozone. This emphasis is motivated by the current regulatory importance as well as by lingering scientific issues regarding the role of volatile organics in secondary pollution formation.

16.3.2 MODES AND SCALES OF IMPACT

Many organic solvents are toxic, and direct exposure to the compound through the atmosphere (e.g., *via* inhalation) can be harmful. While toxic effects of solvents rely on direct exposure, many solvents also contribute to the formation of secondary pollutants such as tropospheric ozone or particulate matter (PM), which cause health problems and damage the environment on larger spatial scales such as over urban areas and multistate/country regions. Very slowly reacting solvent compounds also impact the atmosphere on the global scale, which may cause imbalances in living systems and in the environment. While some mechanisms of environmental imbalance are understood, the risks associated with global atmospheric impacts are highly uncertain.

Transport of solvents in the atmosphere is similar to most other gaseous pollutants, and it is dominated by wind and turbulent diffusion. There is little difference between the transport of different solvent compounds, and the fact that most solvents have much higher molecular weights than air does not lead to enhanced levels at the ground. Heavy solvents are, for the most part, as readily diffused as lighter solvents, although they may not vaporize as fast. The higher levels of many solvents measured near the ground are due to proximity to emissions sources, which are near the surface, and the fact that most solvents degrade chemically as they mix upwards. A major difference in the evolution of various solvents is how fast they react chemically. Some, such as formaldehyde, have very short lifetimes while others, such as CFCs, last decades.

16.3.2.1 Direct exposure

Volatilization of solvents allows air to serve as a mode of direct exposure to many compounds known to be toxic. Generally, direct exposure is a risk near strong or contained sources, and can cause both acute and chronic responses. Most of the non-workplace exposure to solvents occurs indoors. This is not surprising since, on average, people spend a vast majority of their time indoors, and solvents are often used indoors. Outdoors, solvents rapidly disperse and can oxidize, leading to markedly lower levels than what is found indoors near a source. For example, indoor formaldehyde levels are often orders of magnitude greater than outdoors. There are still cases when outdoor exposure may be non-negligible, such as if one spends a significant amount of time near a major source. Toxic effects of solvents are fairly well understood, and many countries have developed regulatory structures to protect people from direct exposure. The toxic effects of solvent emissions on ecosystem are less well understood, but are of growing concern.

16.3.2.2 Formation of secondary compounds

In addition to transport, organic compounds emitted into the air may also participate in complex sets of chemical reactions. While many of these reactions "cleanse" the atmosphere (most organic compounds ultimately react to form carbon dioxide), a number of undesirable side-effects may also occur. Such adverse impacts include the formation of respiratory irritants and the destruction of protective components of the atmosphere. Ozone is a classic example of the complexity of secondary atmospheric impact. Ozone is a highly reactive molecule consisting of three oxygen atoms (O_3). In one part of the atmosphere ozone is beneficial, in another, it is a pollutant of major concern. Solvents and other organic emissions may either increase or decrease ozone concentration, depending on the compound, location of reaction, and background chemistry. The mechanisms of some adverse secondary responses are discussed below.

16.3.2.3 Spatial scales of secondary effects

Two layers of the Earth's atmosphere are known to be adversely impacted by solvents – the troposphere and the stratosphere. These two layers are closest to Earth, and have distinct chemical and physical properties. The troposphere (our breathable atmosphere) is the closest layer, extending from the Earth to a height of between 10 to 15 km. The rate of chemical reaction generally determines the spatial scale over which emissions have an impact in the troposphere. Most non-halogenated solvents have lifetimes of a week or less, and elevated concentrations will only be found near the sources.[4] Compounds that do not react rapidly in the troposphere (e.g., CFCs) are relatively uniformly distributed, and may eventually reach the stratosphere. The stratosphere is the next vertical layer of the atmosphere, extending from the tropopause (the top of the troposphere) to about 50 km in altitude. Little vertical mixing occurs in the stratosphere, and mixing between the troposphere and the stratosphere is slow.

Impacts on the stratosphere can be considered global in scale, while impacts on the troposphere are generally urban or regional in scale. Distinct chemical systems of interest concerning solvents in the atmosphere are stratospheric ozone depletion, global climate

change, and tropospheric photochemistry leading to enhanced production of ozone, particulate matter, and other secondary pollutants such as organonitrates.

16.3.2.3.1 Global impacts

Because some solvent compounds are nearly inert, they can eventually reach the stratosphere where they participate in global scale atmospheric dynamics such as the destruction of stratospheric ozone and unnatural forcing of the climate system. Stratospheric ozone depletion by chlorofluorocarbons (CFCs) is a well-known example of global scale impacts. CFCs were initially viewed as environmentally superior to organic solvents. They are generally less toxic than other similarly acting compounds, less flammable and are virtually inert in the troposphere. Replacing solvents using volatile organic compounds (VOCs) with CFCs was hoped to reduce the formation of tropospheric ozone and other secondary pollutants. Because of their inert properties, there are no effective routes for the troposphere to remove CFCs, and, over the decades, emissions of CFCs have caused their accumulation, enabling them to slowly leak into the stratosphere. In the stratosphere, the strong ultraviolet (UV) light photodissociates CFCs, releasing chlorine, which then catalytically attacks ozone. CFC use has been largely eliminated for that reason. Partially halogenated organic solvents do not contribute as seriously to this problem since they react faster in the troposphere than CFCs, so the associated chlorine does not reach the stratosphere as efficiently. CFCs and other solvent compounds also have a potential impact on global climate change.

16.3.2.3.2 Stratospheric ozone depletion

Natural concentrations of stratospheric O_3 are balanced by the production of ozone *via* photolysis of oxygen by strong UV light, and destruction by a number of pathways, including reactions with nitrogen oxides and oxidized hydrogen products that are present. Photolysis of an oxygen molecule leads to the production of two free oxygen atoms:

$$O_2 + h\nu \rightarrow O + O \qquad [16.3.1]$$

Each oxygen atom can then combine with an oxygen molecule to form ozone:

$$O + O_2 \rightarrow O_3 \qquad [16.3.2]$$

Ozone is then destroyed when it reacts with some other compound, e.g., with NO:

$$O_3 + NO \rightarrow NO_2 + O_2 \qquad [16.3.3]$$

Addition of either chlorine or bromine atoms leads to extra, and very efficient, pathways for ozone destruction. The free chlorine (or bromine) atom reacts with ozone, and the product of the reaction removes a free oxygen atom:

$$Cl + O_3 \rightarrow ClO + O_2 \qquad [16.3.4]$$

$$ClO + O \rightarrow Cl + O_2 \qquad [16.3.5]$$

$$\text{Net (reactions 4+5 together): } O_3 + O \rightarrow 2O_2 \qquad [16.3.6]$$

Removing a free oxygen atom also reduces ozone since one less ozone molecule will be formed *via* reaction 16.3.2. Thus, the chlorine atom reactions effectively remove two ozone molecules by destroying one and preventing the formation of another. Additionally, the original chlorine atom is regenerated to catalytically destroy more ozone. This reaction cycle can proceed thousands of times, destroying up to 100,000 molecules of O_3 before the chlorine is removed from the system (e.g., by the formation of HCl).

Reduction of ozone is greatly enhanced over the poles by a combination of extremely low temperatures, decreased transport and mixing, and the presence of polar stratospheric clouds that provide heterogeneous chemical pathways for the regeneration of atomic chlorine. The resulting rate of O_3 destruction is much greater than the rate at which it can be naturally replenished.

Current elevated levels of CFCs in the troposphere will provide a source of chlorine to the stratosphere for decades, such that the recent actions taken to reduce CFC emissions (through the Montreal Protocol) will have a delayed impact.

16.3.2.3 Global climate forcing

Over the past decade, the potential for non-negligible changes in climate caused by human activity has been an issue of great concern. Very large uncertainties are associated with both estimation of possible effects on climate as well as estimation of the potential impacts of changes in climate. However, current consensus in the international scientific community is that observations suggest "a discernible human influence on global climate".[3]

Solvent compounds, especially CFCs and their replacements, participate in climate change as "greenhouse gases". Greenhouse gases allow short-wave solar radiation to pass through, much of which the earth absorbs and reradiates as long-wave radiation. Greenhouse gases absorb the long-wave radiation, causing the atmosphere to heat up, thereby acting as a blanket to trap radiation that would normally vent back to space. Climate change is a controversial and complex issue, but it is likely that restrictions such as those from the Kyoto Protocol will be adopted for emissions of compounds strongly suspected of exacerbating climate change. Many countries have already adopted stringent policies to reduce greenhouse gas emissions.

16.3.2.4 Urban and regional scales

Another area of concern regarding outdoor air is exposure to secondary pollutants that are due, in part, to chemical reactions involving solvent compounds. Examples include the formation of elevated levels of ozone, formaldehyde, organonitrates, and particulate matter. Formaldehyde, a suspected carcinogen, is an oxidation product of organic compounds. Tropospheric ozone and organonitrates, as discussed below, are formed from a series of reactions of organic gases and nitrogen oxides in the presence of sunlight. Particulate matter formation is linked to ozone, and some solvents may react to form particulate matter. The particulate matter of concern is small (generally less than 2.5 μm in diameter) usually formed by gas-to-aerosol condensation of compounds *via* atmospheric chemical reactions. Ozone and particulate matter are both regulated as "criteria" pollutants in the United States because they have been identified as risks to human health. Ozone is believed to cause respiratory problems and trigger asthma attacks, and PM has a variety of suspected adverse health outcomes (e.g., respiratory and coronary stress and failure). Many organo-

nitrates, such as peroxyacetyl nitrate, are eye irritants and phytotoxins. Currently, the formation and effects of ozone are better understood than those of fine particulate matter and organonitrates. The following section of this chapter discusses the effects, formation, and control of tropospheric ozone. The role of solvents in forming particulate matter is currently viewed as less urgent.

16.3.3 TROPOSPHERIC OZONE

Tropospheric ozone, a primary constituent of photochemical smog, is naturally present at concentrations on the order of 20-40 parts per billion (ppb).[4] However, elevated levels of ground-level ozone are now found virtually worldwide, reaching in some cities concentrations of up to 10 times the natural background.

16.3.3.1 Effects

Ozone is believed to be responsible for both acute (short-term) and chronic (long-term) impacts on human health, especially on lung functions. Major acute effects of ozone are decreased lung function and increased susceptibility to respiratory problems such as asthma attacks and pulmonary infection. Short-term exposure can also cause eye irritation, coughing, and breathing discomfort.[5-7] Evidence of acute effects of ozone is believed to be "clear and compelling".[8] Chronic health effects may present a potentially far more serious problem; however, definitive evidence is difficult to obtain. Recent studies do suggest that ambient levels of ozone induce inflammation in human lungs, which is generally accepted as a precursor to irreversible lung damage,[6] and chronic animal exposure studies at concentrations within current ambient peak levels indicate progressive and persistent lung function and structural abnormalities.[5,8]

Crop damage caused by air pollution has also received much attention. It is estimated that 10% to 35% of the world's grain production occurs in regions where ozone pollution likely reduces crop yields.[9] Air pollution accounts for an estimated several billion dollar crop loss every year in the United States alone, and research and analysis suggests that about 90% of this crop loss can be directly or indirectly attributed to ozone.[10] Evidence also indicates that ozone may cause short- and long-term damage to the growth of forest trees,[11] as well as altering the biogenic hydrocarbon emissions of vegetation.[12]

16.3.3.2 Tropospheric photochemistry and ozone formation

In the lowest part of the atmosphere, chemical interactions are very complex. A large number of chemical compounds are present, the levels of many of these compounds are greatly elevated, and emissions vary due to both natural and anthropogenic sources. Ozone formation in the troposphere results from non-linear interactions between NO_x, VOCs, and sunlight.[4,13] In remote regions, ozone formation is driven essentially by methane,[14] however elsewhere most VOCs participate in ozone generation. For example, measurements of non-methane organic compounds in the South Coast Air Basin of California during the 1987 Southern California Air Quality Study, identified more than 280 ambient hydrocarbon and oxygenated organic species,[15] many of which originated from solvents and contribute in differing degrees to ozone generation.

The only significant process forming O_3 in the lower atmosphere is the photolysis of NO_2 (reaction with sunlight), followed by the rapid reactions of the oxygen atoms formed with O_2.

$$NO_2 + h\nu \rightarrow O(^3P) + NO \qquad [16.3.7]$$

$$O(^3P) + O_2 \rightarrow O_3 + M$$

This is reversed by the rapid reaction of O_3 with NO

$$O_3 + NO \rightarrow NO + O_2 \qquad [16.3.8]$$

This reaction cycle results in a photostationary state for O_3, where concentrations only depend on the amount of sunlight available, dictated by the NO_2 photolysis rate (k_1) and the $[NO_2]/[NO]$ concentration ratio.

$$[O_3]_{steady-state} = \frac{k_1[NO_2]}{k_2[NO]} \qquad [16.3.9]$$

Because of this photostationary state, ozone levels generally rise and fall with the sun, behavior that is referred to as "diurnal."

If the above NO_x cycle was the only chemical process at work, the steady-state concentrations of ozone would be relatively low. However, when VOCs such as organic solvent compounds are present, they react to form radicals that may either consume NO or convert NO to NO_2. This additional reaction cycle combined with the above photostationary state relationship causes O_3 to increase.

Although many types of reactions are involved,[4,13,16,17] the major processes for most VOCs can be summarized as follows:

$$VOC + OH \rightarrow RO_2 + products \qquad [16.3.10a]$$

$$RO_2 + NO \rightarrow NO_2 + radicals \qquad [16.3.10b]$$

$$radicals \rightarrow \ldots \rightarrow OH + products \qquad [16.3.10c]$$

$$products \rightarrow \ldots \rightarrow \ldots + CO_2 \qquad [16.3.10d]$$

The last two pseudo-reactions comprise many additional steps, and the products often include formaldehyde, carbon monoxide, and organonitrates. The rate of ozone increase caused by these processes depends on the amount of VOCs present, the type of VOCs present, and the level of OH radicals and other species with which the VOCs can react. One of the major determinants of a compound's impact on ozone is the rate of the reaction of the particular VOC with the hydroxyl radical *via* reaction [16.3.10a], above. The total amount of ozone formed is largely determined by the amount of VOC and NO_x available.

The dependence of O_3 production on the initial amounts of VOC and NO_x is frequently represented by means of an ozone isopleth diagram. An example of such a dia-

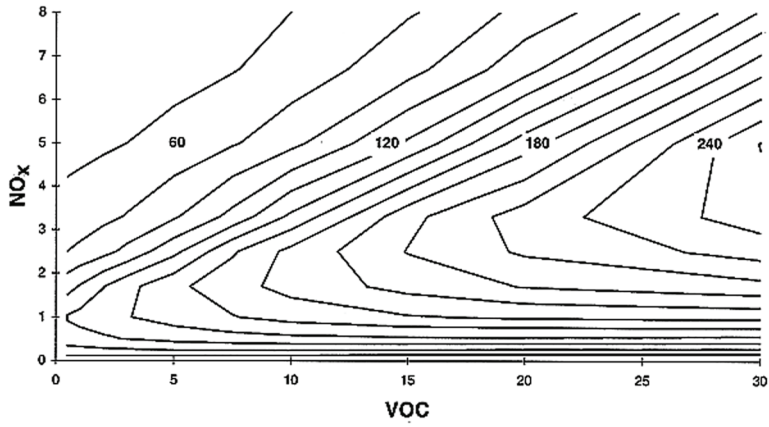


Figure 16.3.1. Ozone isopleth diagram showing the dependencies of ozone on varying levels of initial VOCs and NO_x. Concentrations are given in ppb. [Adapted from M.S. Bergin *et al*., *Enc. of Env. Analysis and Remediation*, **29**, 3029, (1998)].

gram is shown in Figure 16.3.1. The diagram is a contour plot of ozone maxima obtained from a large number of air quality model simulations using an atmospheric chemical mechanism. Initial concentrations of VOC and NO_x are varied; all other variables are held constant. Notice that there is a "ridge" along a certain VOC-to-NO_x ratio where the highest ozone concentrations occur at given VOC levels. This is referred to as the "optimum" VOC-to-NO_x ratio. While the atmosphere is more complicated than this idealized system, important features are very similar.

VOC-to-NO_x ratios sufficiently low to retard ozone formation from an optimum ratio (represented in the upper left quadrant of Figure 16.3.1) can occur in central cities and in plumes immediately downwind of strong NO_x sources. Rural environments tend to be characterized by fairly high VOC-to-NO_x ratios because of the relatively rapid removal of NO_x from non-local sources as compared to that of VOCs, coupled with the usual absence of strong local NO_x sources and the presence of natural VOC sources. In such rural environments, the formation of ozone is limited more by the absence of emissions of NO_x, and most ozone present was directly transported from upwind. Indeed, in most of the troposphere, except in areas of strong NO_x sources, the availability of NO_x governs ozone production.

16.3.3.3 Assessing solvent impacts on ozone and VOC reactivity

As mentioned previously, the contribution of solvents to the VOC levels, and hence ozone formation, is significant. For example, in Los Angeles, about 25% of the VOC mass is from solvent use.[1] This fraction is down from earlier years due to various controls such as using water-based paints and enclosing/controlling paint spraying operations. On the other hand, reduction in the use of CFCs as propellants has led to an increase in organic emissions from substituted compounds.[2] However, the impact on ozone formation by a specific source is not directly proportional to the amount of VOC emitted by that source. A major determinant of the ozone-forming potential is the reactivity of the compound or compound

mixture emitted. Reactivity can be viewed as the propensity for a compound to form ozone, and this propensity varies dramatically between compounds and between environments.[18,19]

As seen in Table 16.3.1, "box" model (single cell) simulations designed to represent summertime conditions in Los Angeles, California indicates that the amount of carbon associated with each class of compounds only roughly corresponds to the amount of ozone formed from those compounds. Methane, which reacts very slowly but comprises most of the carbon, contributes little to the ozone formation. Alkenes and aromatics are only a small part of the total carbon but lead to much of the ozone formation.

Table 16.3.1. Percentage of ozone production attributable to each organic. The percentages shown should be viewed as only approximate and will depend upon local emissions characteristics. [Adapted from F.M. Bowman and J.H. Seinfeld, J. Geophys. Res., 99, 5309, (1994) and M.S. Bergin *et al., Env. Sci. Technol.*, **29**, 3029 (1998).]

Compound Class	Percent of carbon in each specified class	Percent of ozone due to specified organic class
carbon monoxide*	35	6
methane	40	1
aldehydes and ketones	1	3
non-methane alkanes, ~4C	8	17
non-methane alkanes, ~8C	5	16
aromatics, including toluene	3	5
aromatics, including xylenes and others	3	13
ethene	2	12
biogenic alkenes and isoprene	1	10
other alkenes	2	17

*While not considered organic carbon, carbon monoxide acts to facilitate ozone formation similar to organic compounds.

16.3.3.3.1 Quantification of the effect of solvent emissions on ozone formation

Two methods are generally employed to quantify the role pollutants play in forming ozone: experimental and computational. Both types of estimation approaches have their limitations. In the case of physical experiments, it is difficult to fully simulate ambient conditions, so the results do not have general applicability. In the case of computational approaches, uncertainties, and approximations in the model for airshed conditions, in its formulation and in the chemical mechanism, cause uncertainties in the predicted ozone impacts. For these reasons, modeling predictions and experimental measurements are used together.

16.3.3.3.1.1 Experimental analysis

Experimental analysis is performed using environmental "smog" chambers, either with a series of single hydrocarbons irradiated in the presence of NO_x or using complex mixtures to simulate, for example, automobile exhaust emitted into characteristic urban ambient conditions. Such chambers are large reaction vessels (some with internal volumes of cubic meters), in which air and small amounts of hydrocarbons and NO_x are injected, and then irradiated with real or artificial light. Both indoor and outdoor chambers are used so behaviors can be evaluated under natural radiative conditions and under controlled conditions. While these experiments[18-23] clearly indicate differences in ozone formation from individual hydrocarbons, they do not represent some important physical systems of urban pollution such as the mixing processes and continuing emissions cycles. Such experiments have focused both on groups of compounds as well as specific VOCs, including solvents. A particular limitation has been in studying very low vapor pressure solvents because it is difficult to get enough of the compound into the vapor phase in the chamber to appreciably change the ozone levels. Another limitation is the expense of using smog chambers to simulate a large range of conditions that might occur in the atmosphere. On the other hand, smog chambers are very powerful, if not fundamental, for developing chemical mechanisms that describe the reaction pathways that can be used in computational approaches.

16.3.3.3.1.2 Computational analysis (air quality models)

Given the limitations of physical experiments to simulate atmospheric conditions, computer models have been developed to assess the impact of emission on ozone. These models, called airshed models, are computerized representations of the atmospheric processes responsible for air pollution, and are the core to air quality management.[23] They have been applied in two fashions to assess how solvents affect ozone. One approach is to conduct a number of simulations with varying levels of solvent emission.[2] The second approach is to evaluate individual compounds and then calculate the incremental reactivity of solvent mixtures.[19,21,24-28]

Derwent and Pearson[2] examined the impact of solvent emission on ozone by simulating air parcel trajectories ending in the United Kingdom and perturbing the emission to account for an anticipated 30% mass reduction in VOCs from solvents between 1995 and 2007. They found a small decrease in ozone from 78 to 77 ppb in the mean peak ozone in the UK and a 9 ppb reduction from 129 ppb outside of London. A more substantial decrease of 33 ppb from the 129 ppb peak outside of London was found from reducing non-solvent mass VOC emission by 30% outside of the UK and 40% within the UK. This suggests that the VOC emission from sources other than solvents have a higher average reactivity, as is discussed by McBride *et al*.[29]

While the types of simulations conducted by Derwent and Pearson[2] are important to understanding the net effect of solvent emission on ozone, there is an unanswered associated and important question: which solvents have the greatest impact.

This question is critical to assessing if one solvent leads to significantly more ozone formation than a viable substitute (or *vice versa*).

To evaluate the contribution of individual organic compounds to ozone formation, the use of incremental reactivities (IR) was proposed,[18-21] defined as the change in ozone

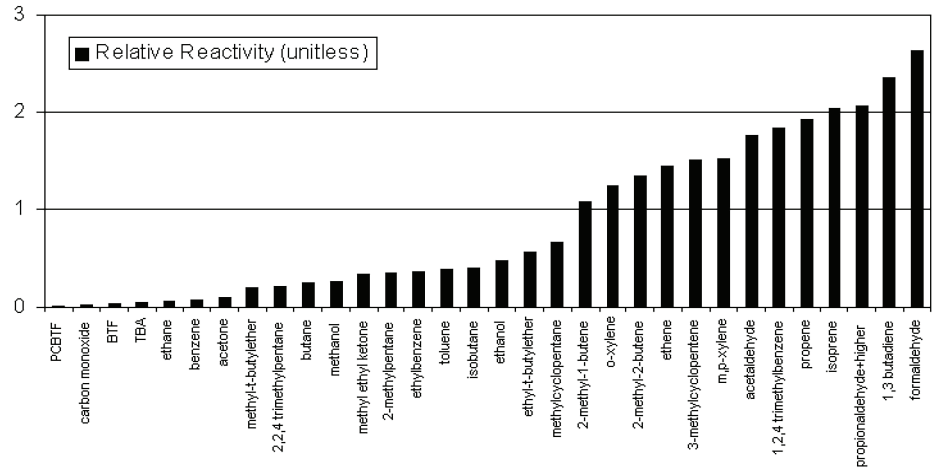


Figure 16.3.2. Relative reactivities of solvents based on mass of ozone formed per gram of solvent emitted into the gas phase. PCBTF is para-chlorobenzo-trifluoride, BTF is benzotrifluoride and TBA is tertiary butyl acetate. [Adapted from M.S. Bergin *et al.*, *Env. Sci. Technol.*, **29**, 3029 (1998) and M. Khan *et al.*, *Atmos. Env.*, **33**, 1085 (1999)].

caused by a change in the emission of a VOC in an air pollution episode. To remove the dependence on the amount of VOC added, incremental reactivity is defined by equation [16.3.11] as the limit as the amount of VOC added approaches zero, i.e., as the derivative of ozone with respect to VOC:

$$IR_i = \frac{\partial[O_3]}{\partial[VOC_i]} \qquad [16.3.11]$$

Here, IR_i is the incremental reactivity and the subscript i denotes the VOC being examined. This definition takes into account the effects of all aspects of the organic's reaction mechanism and the effects of the environment where the VOC is emitted. A similar quantity is a relative reactivity,[23] RR_i:

$$RR_i = \frac{R_i}{\sum_{i=1}^{N} F_{B_i} R_i} \qquad [16.3.12]$$

where:

F_{B_i} mass fraction of compound i in the reference mixture
IR_i^i incremental reactivity of species i (grams ozone formed per gram compound i emitted)

In this case, the incremental reactivity is normalized by the reactivities of a suite of organics, thus removing much of the environmental dependencies found when using IRs defined by [16.3.11]. This metric provides a means for directly comparing individual compounds to each other in terms of their likely impact on ozone.

A number of investigators have performed calculations to quantify incremental and/or relative reactivities for various solvents and other organics[23-28,30] and references therein. Those studies found very similar results for the relative reactivities of most compounds found in solvents. Figure 16.3.2 (based on references 23, 24 and 26) shows the relative reactivities for some of the more common compounds, as well as possible solvent substitutes and isoprene, a naturally emitted organic. (For a more extensive list of relative reactivities, see 19, 27 and 30.) As can be seen, even normalized compound reactivities can vary by orders of magnitude. Some compounds even exhibit "negative" reactivities, which means that their emission can lead to ozone decreases under specific conditions. In particular, negative reactivities are found most commonly when the levels of NO_x are low, e.g., in non-urban locations. For example, Kahn *et al.*,[26] found that a solvent can promote ozone formation in one area (e.g., near downtown Los Angeles), but retard ozone formation further downwind. Kahn also found that the relative reactivities of the eight different solvents studied were similar in very different locations, e.g., Los Angeles, Switzerland and Mexico City.

Looking at Figure 16.3.2, it is apparent that alkenes and aromatic hydrocarbons with multiple alkyl substitutions (e.g., xylenes and trimethylbenzene) have relatively high reactivities. Alcohols, ethers, and alkanes have lower reactivities. Halogenated organics have some of the lowest reactivities, so low that they are often considered unreactive. This suggests that there are two ways to mitigate how solvents contribute to air quality problems. The more traditional method is to reduce the mass of organic solvent emissions (e.g., by using water-based paints). A second approach is to reduce the overall reactivity of the solvent used, e.g., by switching to ethers, alcohols, alkanes or halogenated compounds. Solvent substitution, however, is complicated by the need to maintain product quality.

16.3.4 REGULATORY APPROACHES TO OZONE CONTROL AND SOLVENTS

Historically, regulatory approaches to reducing ozone concentrations have relied on reducing the mass emissions of VOCs,[2,4] and this has led to stringent controls on solvents. Two factors are important in determining if an organic solvent is considered a VOC: its reactivity (discussed above) and its vapor pressure. In the U.S., traditionally, if a compound was less reactive than ethane, it was considered unreactive. Such compounds include many halogenated species and some acetates and ethers. Recently, acetone was also added as an unreactive compound. A vapor pressure threshold is also used in many areas (e.g., Europe) since it is viewed that compounds with very low vapor pressures will not be emitted rapidly into the atmosphere. It has been argued that a vapor pressure limit may not be appropriate since, given time, even lower vapor pressure compounds will have ample time to evaporate. Just recently, California is considering regulations that more fully account for the full range of reactivities that solvents possess. This is due, in part, to make it easier for manufacturers to meet stringent regulations being adopted in that state to help them meet their air quality goals. It is likely that other areas will also have to employ increas-

ingly more stringent regulations, to both lower ozone and alleviate other environmental damage.

In many countries, greater focus is now being placed on reducing NO_x emissions to mitigate ozone formation. This has important ramifications for solvent use, indicating the regulatory focus is now turning from VOCs towards NO_x, the other main precursor to ozone. Another imminent regulatory issue is the control of ambient fine particulate matter. While the role of solvent emission in forming particulate matter is not well understood, studies to date do not suggest they are a major contributor.

A study conducted in Wuppertal, Germany found that while the German Emission Inventory indicated that 51% of the total non-methane volatile organic compounds emissions were attributed to solvent use and only 14% to traffic.[31] According to data presented by the European Environmental Agency from the national emissions reported to the Convention on Long-range Transboundary Air Pollution, the sector "Solvent and product use" contributed 3.4 million kt of emissions and accounted for 43.10% of the total non-methane volatile organic compounds emissions in Europe in 2011.[31] The non-methane volatile organic compounds speciation can have a significant effect on the amount of ozone produced in the troposphere.[31]

Ozone formation potential of the road marking paint currently used as a standard in Kraków was calculated to be more than twice the amount of VOCs it emits: 240 kg of solvents evaporating from one tonne of paint might cause the formation of over 550 kg of ozone in Kraków that means up to 42 tonnes of tropospheric ozone annually.[32]

16.3.5 SUMMARY

Solvents are, and will continue to be, one of the major classes of organic compounds emitted into the atmosphere. These compounds have a wide range of air quality impacts. Accumulation of toxic compounds indoors is of concern, although outdoors the concern of toxicity is significantly less substantial due to rapid dilution. In the stratosphere, some of the halogenated solvents lead to depletion of the protective layer of ozone, while in the troposphere solvents generally lead to increased ozone levels, where it adversely affects health and environment. The former has led to regulations of CFCs, and the latter to regulations of organic solvents. Some solvents are also considered to be precursors to the formation of secondary tropospheric pollutants other than ozone, such as particulate matter, however, these relationships are currently less certain.

In the aggregate, total VOC emissions from solvents in the U.S. are the second largest single source category in polluted urban areas, falling just behind motor vehicle VOC emissions both in terms of mass and urban ozone production. For now, regulations are designed to reduce the loss of ozone in the stratosphere and the formation of excess ozone in the troposphere. However, while some solvents are very reactive, others are substantially less reactive, suggesting that there is considerable opportunity to reduce urban ozone formation from solvents by utilizing substitutes with low ozone forming potentials. Currently, most regulations are targeted at reducing the mass of VOC emissions, not their relative impacts on ozone.

REFERENCES

1 SCAQMD (South Coast Air Quality Management District). (1996). 1997 Air Quality Management Plan. November.
2 R.G. Derwent and J.K. Pearson, *Environ. Technol.*, **18**, 1029 (1997).
3 **Climate Change 1995**: The Science of Climate Change. Contribution of Working Group I to the Second Assessment Report of the Intergovernmental Panel on Climate Change (IPCC). Ed. J.T. Houghton, *et al*. *Cambridge University Press*, Cambridge, Great Britain. 1996.
4 NRC (National Research Council). **Rethinking the Ozone Problem in Urban and Regional Air Pollution**. *National Academy Press*, Washington, DC. (1991).
5 OTA (U.S. Congress, Office of Technology Assessment). **Catching Our Breath: Next Steps for Reducing Urban Ozone**, OTA-O-412, *U.S. Government Printing Office*, Washington, DC. July,1989.
6 S.M. Horvath and D.J.McKee (1994). In D.J. McKee, ed., **Tropospheric Ozone: Human Health and Agricultural Impacts**, *CRC Press/Lewis Publishers*, Boca Raton, FL, Chapter 3.
7 M. Lippmann, *Environ. Sci. Technol*., **25** (12), 1954, (1991).
8 M. Lippmann, *J. Exposure Anal. Environ. Epidemiology*, **3** (1), 103, (1993).
9 W.L.Chameides, P.S. Kasibhatla, J Yienger, and H. Levy II., *Science*, **264** (5155), 74, (1994).
10 D.T. Tingey, D.M. Olszyk, A.A.Herstrom, and E.H. Lee, (1994). "Effects of Ozone on Crops" in D.J. McKee, ed., **Tropospheric Ozone: Human Health and Agricultural Impacts**, *CRC Press/Lewis Publishers*, Boca Raton, FL, Chapter 6.
11 S.B.McLaughlin and L.J. Downing, *Nature*, **374** (6519), 252, (1995).
12 W. Mehlhorn, *Nature*, **327**, 417, (1989).
13 J.H. Seinfeld and S.N. Pandis, **Atmospheric Chemistry and Physic: From Air Pollution to Climate Change**, New York: *J. Wiley & Sons*, (1998).
14 J.A. Logan, M.J. Pather, S.C. Wofsy, and M.B. McElroy, *J. Geophys. Res*., **86**, 7210, (1981).
15 F.W. Lurmann and H.H. Main, **Analysis of the Ambient VOC Data Collected in the Southern California Air Quality Study**, final report, Contract A832-130, *California Air Resources Board*, Sacramento, CA., 1992.
16 R. Atkinson, *Atmos. Environ*., **24A**, 1, (1990).
17 R. Atkinson, J. Phys. Chem. Ref. Data, Monograph No. 2, (1994).
18 W.P.L. Carter, *Atmos. Environ*., **24A**, 481, (1990).
19 W.P.L.Carter, (1991). **Development of Ozone Reactivity Scales for Volatile Organic Compounds**, EPA 600/3-91-050. *U.S. Environmental Protection Agency, Research Triangle Park, NC* (August).
20 W.P.L. Carter and R. Atkinson, *Environ. Sci. and Technol*., **23**, 864, (1989).
21 W.P.L. Carter, *Atmos. Environ*., **29**, 2513, (1995).
22 N.A. Kelly and P. Wang, (1996) **Part I: Indoor Smog Chamber Study of Reactivity** in Kelly, N.A.; Wang, P.; Japar, S.M.; Hurley, M.D.; and Wallington, T.J. (1996). Measurement of the Atmosphere Reactivity of Emissions from Gasoline and Alternative-Fueled Vehicles: Assessment of Available Methodologies, Second-Year Final Report, CRC Contract No. AQ-6-1-92 and NREL Contract No. AF-2-112961. *Environmental Research Consortium,* (September).
23 M.S. Bergin, A.G. Russell, W.P.L. Carter, B.E. Croes, and J.H. Seinfeld, Ozone Control and VOC Reactivity, in the **Encyclopedia of Environmental Analysis and Remediation**, Ed. R.A. Meyers, *J. Wiley & Sons, Inc*, New York, NY. 1998.
24 M.S. Bergin *et al., Env. Sci Technol*., **29**, 3029 (1998)
25 F.M. Bowman and J.H. Seinfeld, *J. Geophys. Res*., **99**, 5309, (1994a).
26 M. Khan *et al., Atmos. Env*., **33**, 1085 (1999).
27 W.P.L. Carter, *J. Air Waste Mgmt. Assoc*., **44**, 881, (1994a).
28 R.G. Derwent, and M.E. Jenkin, *Atmos. Environ*., **25**(A):1661-1673 (1991).
29 S. B. McBride *et al*., *Env. Sci. Technol*., **31**, 238a, (1997)
30 http://www.cert.ucr.edu/~carter/bycarter.htm
31 E. von Schneidemesser, J. Coates, H. A. C. D. van der Gon, A. J. H. Visschedijk, T. M. Butler, *Atmosph. Environ*., **135**, 59-72, 2015.
32 T. E. Burghardt, A. Pashkevich, L. Zakowska, *Transp. Res. Proc*., **14**, 714-23, 2016.

17

Concentration of Solvents in Various Industrial Environments

17.1 MEASUREMENT AND ESTIMATION OF SOLVENTS EMISSION AND ODOR

Margot Scheithauer
Institut für Holztechnologie Dresden, Germany

17.1.1 DEFINITIONS OF "SOLVENT" AND "VOLATILE ORGANIC COMPOUNDS" (VOC)

Solvents are generally understood to be substances that can physically dissolve other materials, more narrowly they are inorganic and organic liquids able to dissolve other gaseous, liquid, or solid substances. A qualifier for the suitability of a solvent is that, during the dissolution, neither the solvent nor the dissolved substance undergoes chemical change, i.e., the components of the solution may be recovered in their original form by physical separation processes, such as distillation, crystallization, sublimation, evaporation, adsorption (exception – the reactive solvents which are reactive by intent to decrease VOC after being used for lowering viscosity).

From a chemical point of view, solvents or volatile organic compounds, VOCs, vary widely. They are often classified using their boiling point and vapor pressure.

In the context of VOC, only organic solvents are of relevance. Therefore, in the following discussion, only organic solvents are discussed.

Definition of solvent according to Council Directive 2004/42/CE of 21 April, 2004[1]

"Organic solvent" means any VOC which is used alone or in combination with other agents to dissolve or dilute raw materials, products, or waste materials, or is used as a cleaning agent to dissolve contaminants, or as a dispersion medium, or as a viscosity adjuster, or as a surface tension adjuster, or as a plasticizer, or as a preservative.

Definition of solvent according to ISO 4618:2014[2]

Paints and varnishes – terms and definition for coating materials: Solvent: A single liquid or blends of liquids, volatile under specified drying conditions, and in which the binder is completely soluble.

Updated and revised by George Wypych, ChemTec Laboratories, Toronto, Canada

For certain applications, solvents are defined more specifically:

Technische Regeln für Gefahrstoffe TRGS 610 (Technical Regulations for Hazardous Substances) as applied to high solvent-containing primers and flooring glues the definition is:

Solvents in the context of this Technical Rule are volatile organic compounds and their mixtures with a boiling point ≤ 200°C, under standard conditions (20°C and 101.3 kPa) are liquid and can be used to dissolve other substances or to dilute the without chemical change.[3]

As can be seen, there are clear differences in the way VOCs are defined.[4] The most general, and hence least disputable, one is:

Definition of volatile organic compounds according to DIN 11890[5,6]

The solvent is generally any organic liquid and/or any organic solid substance, which evaporates by itself under prevailing conditions (temperature and pressure).

Definition of VOC according to Council Directive 2004/42/CE of 21 April, 2004[1]

Volatile organic compound (VOC) means any organic compound having an initial boiling point less than or equal to 250°C measured at a standard pressure of 101.3 kPa.

In the **Lösemittelverordnung LMV 2005 (Austrian Regulations on Solvents)** of 2005,[7] which on this issue corresponds to the österreichische **Lackieranlagen-Verordnung (Austrian Regulation on Varnishing Plants)** of 2002,[8] VOCs have a maximum boiling point of 200°C. Hence, the volatile compounds at a boiling point > 200°C are not included. These comprise, e.g., some film forming media, such as butyldiglycol, butyldiglycolacetate, and texanol. Similarly, reactive solvents are excluded from this regulation.

Definitions of VOCs in the USA according to ASTM D3960[9]

Volatile Organic Compound (VOC), means any compound of carbon, excluding carbon monoxide, carbon dioxide, carbonic acid, metallic carbides or carbonates, and ammonium carbonate, which participates in atmospheric photochemical reactions.

US Environmental Protection Agency proposed two definitions for outdoor (1) and indoor (2) conditions as follows

1. Volatile organic compound means any compound of carbon, excluding carbon monoxide, carbon dioxide, carbonic acid, metallic carbides or carbonates and ammonium carbonate, which participates in atmospheric photochemical reactions, except those designated by EPA as having negligible photochemical reactivity.
2. Volatile organic compound is an organic chemical compound whose composition makes it possible to evaporate under normal indoor atmospheric conditions of temperature and pressure

Since the volatility of a compound is generally higher for the lower boiling point substances, the volatility of an organic compound is frequently classified by its boiling point. For example, the European Union uses the boiling point, rather than its volatility in its definition of VOCs (VOC is any organic compound having an initial boiling point of less than or equal to 250°C measured at a standard atmospheric pressure of 101.3 kPa).

Certain organic compounds that may be released under the specified bake conditions are not classified as VOC as they do not participate in atmospheric photochemical reactions. Such non-photochemically active compounds are referred to as exempt volatile compounds in the practice.

An example of an exempt compound in the USA according to the EPA is tertiary-butyl-acetate (TBA, b.p. of 98°C). It is described as a substance not harmful in air.[10]

Substances contained in air are differentiated in their mixtures according to their volatility:[11]

Abbreviation	Compound class	Range of boiling point in °C
VVOC	very volatile organic compounds (e.g., propane, butane, methyl chloride)	< 0 up to 50÷100
VOC	volatile organic compounds (e.g., formaldehyde, d-limonene, toluene, acetone, ethanol, 2-propanol, hexanal)	50÷100 up to 240÷260
SVOC	semi-volatile organic compounds (e.g., plasticizers, fire retardants)	240÷260 up to 380÷400

17.1.2 REVIEW OF SOURCES OF SOLVENT EMISSIONS

17.1.2.1 Causes for emissions

The basic human needs include eating, drinking, and breathing. In a 75-years lifetime, a human being takes up about 49 t of food, 25-55 t of drink and 360 t of air.[12] Thus air pollution may have a large influence on human health. Room air quality is of the greatest interest, since the population stayed indoors more than 93% time (12 countries average) according to findings by Szalai[13] and more than 92.4% according to Klepeis et al.[14] in the US (residence – 68.7%, other indoor locations – 141%, vehicle – 5.5%, office/factory – 5.4%, bar/restaurant – 1.8%, outdoors – 7.6%).

These statistical data show that our emphasis may frequently be misconstrued and workplace may be by now one of the safest places, concerning the typical total ban of smoking, various regulations regarding pollution, and well-designed building code as opposed to the freedom of smoke at home, use of cheap chemicals and furniture which are known to pollute indoor environment, and driving cars which have “smell of a new vehicle” which can be translated to the emission of various additives included in the chemical content of the vehicle in addition to breathing air from exhausts of neighboring vehicles.

Sources for volatile substances in indoor air are diverse and originate, apart from that brought in with outside air and produced by the living occupants (people, pets) and their activities (e.g., smoking), from the materials themselves which have been applied for building and furnishing the rooms. These include:

- building materials
- glues
- floor coverings
- internal decorative textiles
- paints
- furniture, upholstered furniture
- mattresses, etc.

These materials may contain volatile organic, but also inorganic, compounds, which are evaporated during their use. The emission of these volatile compounds is influenced by a large number of factors, such as:

- chemical/physical structure of the material (thickness, surface structure)
- volatility, the polarity of the volatile compounds
- room temperature and humidity
- room load, i.e., the ratio of the area of the emitting surface and the volume of room air
- ventilation, the rate of air flow
- load of the external air entering (dust, substances)

The residual monomers from plastics, reactive products (e.g., formaldehyde), degradation products, flame protection media, softeners etc. may be emitted from building materials.

17.1.2.2 Emissions of VOCs from varnishes and paints

A substantial part of emitted materials belongs to solvents. They originate from varnishes, paints, and glues. Table 17.1.1 shows a survey of the main types of varnishes referring to their average solvent content.

Table 17.1.1. Solvent share in various types of varnishes.

Material	Solvent content, wt%
Stain	~95
Cellulose nitrate varnish	~75
PUR varnish	35-70
Polyester varnish	35
UV roller varnish based on acrylate	2-10

Despite the introduction of water-based and powder varnishes, cellulose nitrate varnishes with their high solvent content, are still widely used due to their easy application and their low prices. The current varnish application still requires the use of solvents. The chosen coating procedure determines the necessary processing viscosity, which may be adjusted in different ways:

- Thinning the binding agent/varnish with a solvent consisting of one or more organic compounds without altering the binding agent chemically. Today, the solvent can partially or almost totally be replaced by water.
- Thinning the binding agent with a reactive thinner, i.e., one or more monomers/oligomers included in the system, which react with the binding agent during the hardening process and are built into a molecule. According to the definition, they do not have characteristics of solvents. They take over the solvent function while they remain in the liquid state.
- A temperature increase of the coating system, which reduces the required amount of solvents.

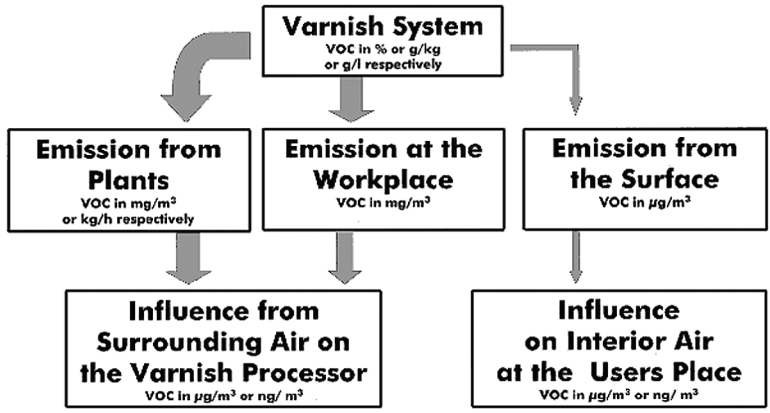


Figure 17.1.1. Emission of VOCs in the life-cycle of a varnish.

- Liquid application of a melted solid system

Profiled construction components form parts of complicated shapes, which must rely on the spraying of coatings for decorative and protective purposes. The spraying requires low-viscosity material. Viscosity reduction is usually achieved by adding solvents but sometimes by increasing the material temperature. Parts with large flat surfaces, however, may be coated by roller-coating, which tolerates higher viscosity materials. After fulfilling their function as solvents, they are expected to completely evaporate from the varnish system.

Emission of solvents from a varnish system occurs in the course of the "life-cycle" of a varnish in several different locations as the following survey shows (Figure 17.1.1). As early as on the production stage of the varnish system, solvent emissions contaminate the ambient air of the factory. About 90% of the solvents contained in the varnish system evaporates during its application which affects the air quality in the workplaces. These emissions are in the milligram per cubic meter of air range. The thinning effect decreases the solvent concentration in the ambient air in the varnisher's workplace into the microgram to nanogram per cubic meter.

About 10% of the solvent remains in the varnish and it is emitted, depending on the type of solvent and varnish, with the variable rate on their way to the consumers and in their living spaces.

The European furniture industry had the total consumption of 430,000 tonnes of solvent-based coatings in the year 2000.[15] Solvent Emissions Directive required to reduce VOC emissions in the Member States by 57% of 1990 levels by 2007. Since January 2007, the European Paints Directive 2004/42/EC has permitted 150 g/l for waterborne and 400 g/l for solvent-borne coatings.[16] As from January 2010, this was reduced to 130 g/l for waterborne and 300 g/l for solvent-borne wood coatings.[16]

Not all VOCs enter the air, however, since remedial efforts, such as absorption and solvent reclaim, after-burning of solvents, and the use of biofilters, result in the emission reduction.

Nevertheless, it is still evident that limitation of solvents, VOCs, reduction in varnishes and coatings may help in reducing emissions.

17.1.2.3 VOC emissions from emulsion paints

Although emulsion paints and plasters contain less than 2% VOCs these are produced in such large quantities (estimated from 3 million tons in 2018 in US17).[17] The consumption in the US alone produces 150,000 tons of VOCs per year. These amounts enter the environment in an uncontrolled way.

Prior to an interior application of the coating, there is no VOC in room atmosphere, unless sources already exist in the room. Then the load – from the beginning of the application – increases very rapidly. After the application, the VOC concentration in the ambient air decreases exponentially. If these emissions are to be monitored, it is desirable to have methods available to record VOC concentrations typical of emitting stages.[18]

17.1.3 MEASURING OF VOC-CONTENT IN PAINTS AND VARNISHES

17.1.3.1 Definition of low-emissive coating materials

In order to limit the sources of solvent emission in ambient air in the most effective manner, primary goal must be to reduce the VOC content in coating materials. In Germany, there was a Varnishing Plant Regulation[19] regulating the application of low-emissive varnishes, which will require that coating materials must initially not contain more than 420 g/l VOC. Four years after the introduction of the regulation this was reduced to 250 g/l VOC.

The “Jury Umweltzeichen” (Environmental Trade Mark) rewards certain products with the environmental trademark. Low pollutant paints and varnishes are into 3 groups with a maximum content of VOC of 2, 8, and 10 wt%.[20] This ecolabel helped to avoid emissions of more than 340,000 tons of organic solvents which would have been used in varnishes during 30 years of its existence.

Varnishing plants are exempt if they employ waste gas purification facilities corresponding to the EU VOC Guideline.[21]

The draft of the Varnishing Plant Regulation follows the US method according to ASTM D3960[9] in determining the VOC content.

17.1.3.2 Determination of the VOC content according to ASTM D3960

ASTM D3960 is the method used to determine the VOC content of coating materials. The VOC value is calculated as follows:

$$\text{VOC value [g/l]} = \frac{\text{mass of volatile components [g]} - \text{mass of water [g]}}{\text{volume of varnish [l]} - \text{volume of water [l]}} \quad [17.1.1]$$

For varnishes exclusively containing solvents, this formula results in high values. This calculation is, however, of dubious value for water-containing varnishes. The unit g/l does not refer to 1 liter of an actual varnish, but to a hypothetical product, which only expresses the binding agent in liters.

This is demonstrated in Example 1, which will then also be calculated according to other methods.

Example 1:
Water spray varnish: 30% solid matter (binding agent and pigments)
10% solvent content
60% water content
varnish density: 1.0 g/cm^3
VOC (g/l) = (700 g – 600 g)/(1 l – 0.6 l) = 250 g/l

17.1.3.3 Determination of the VOC content according to ISO 11890/1[5] and 2[6]

17.1.3.3.1 VOC content > 15%

The calculation according to ISO 11890/1 gives a more logical result. VOCs are given here as a mass share in % of the ready-to-use varnish. At a VOC content > 15% (of the mass share), the determination is made by the differential approach:

$$\text{VOC [\% of the mass share]} = 100 - \text{nfA} - m_w \qquad [17.1.2]$$

where:

nfA	non-volatile parts determined by ISO 325122 (1 h/110°C)
m_w	mass as water in % of the mass parts, determined according to ISO 76023 (after Karl-Fischer)

Many available techniques for water determination are not sufficiently common and thus are not considered.

Example 2:
Water solvent stain: 5% solid matter content = non-volatile parts
25% solvent
70% water share
VOC (wt%) = 100 – 5 – 70=25%
For density $\neq 1$

$$\text{VOC [g/l]} = 10(100 - \text{nfA} - m_w)\,\rho_s \qquad [17.1.3]$$

where:

ρ	varnish density in g/ml at 23°C

In this case, the VOC content refers to 1 l of actual varnish.

Example 3:
Solvent stain: 5% solid matter content
95% solvent share
VOC (g/l) = (100 – 5 – 0) × 0.9 = 855 g/l

Example 4:
Solvent/water stain: 5% solid matter content
70% solvent
25% water share
Density: 0.9 g/cm^3
VOC (g/l) = (100 – 5 – 25) × 0.9 × 10 = 630 g/l

ISO 11890 also allows the calculation to be made using the method prescribed by ASTM D3960:

$$VOC_{lw}\ [g/l] = 1000\frac{100 - nfA - m_w}{100 - \rho_s\frac{m_w}{\rho_w}}\rho_s \qquad [17.1.4]$$

where:

ρ_s	varnish density in g/ml at 23°C
nfA	non-volatile parts determined by ISO 325122 (1 h/110°C)
m_w	mass as water in wt%, determined acc. to ISO 76023 (after Karl-Fischer)
ρ_w	density, in g/ml, of water at 23°C (ρ_w = 0.997537 g/ml at 23°C)

Example 1

Water spray varnish: 30% solid matter content
10% solvent
60% water content
varnish density 1.0 g/cm^3
water density 1.0 g/cm^3
$VOC_{lw} = [(100 - 30 - 60)/(100 - 1.0 \times 60)] \times 1.0 \times 1000 = 250$ g/l

Example 2:

Water spray varnish but with a density of 0.9 g/cm^3
$VOC_{lw} = [(100 - 3 - 60)/(100 - 0.9 \times 60)] \times 0.9 \times 1000 = 196$ g/l
Or another example:
Example 3:
Water varnish primer: 15% solid matter content
10% solvent 75% water
varnish density 1.0 g/cm^3
$VOC_{lw} = [(100 - 15 - 75)/(100 - 1.0 \times 75)] \times 1.0 \times 1000 = 400$ g/l

The calculation permits the deduction of exempt compounds, which are defined as organic compounds which do not participate in photochemical reactions in the atmosphere.

$$VOC_{lwe}\ [g/l] = 1000\frac{100 - nfA - m_w\sum_{i=1}^{i=n} m_{eci}}{100 - \rho_s\frac{m_w}{\rho_w} - \rho_s\sum_{i=1}^{i=n}\frac{m_{eci}}{\rho_{eci}}}\rho_s \qquad [17.1.5]$$

where:

VOC_{lwe}	VOC content, in g/l, contained in the product in its ready-to-use condition minus water and minus exempt compounds
nfA	content of non-solvent parts, as a mass share in %
m_w	water content, as mass share in %
m_{eci}	content, as mass share in %, of the exempt compound i
ρ_s	density, in g/ml, of sample at 23°C
ρ_w	density, in g/ml, of water at 23°C (ρ_w = 0.997537 g/ml at 23°C);
1000	conversion factor × 1000 in g/l

Example 4:
Exempt compounds are propanol and ethanol
Solvent water stain (density 0.9 cm^3) 5% solid matter content
20% propanol (density 0.8 g/cm^3)
10% ethanol (density 0.79 g/cm^3)
40% other solvent
25% water

$$VOC_{lwe} = [(100 - 5 - 25 - (10))/\{100 - 0.9(25/1.0) - 0.9[(20/0.8) + (10/0.79)]\}] \times 0.9 \times 1000 = 825 \text{ g/l}$$

Calculated according to DIN ISO 11 890-1, for the same water stain applies (example 4)
after approach 1: 70%
after approach 2: 630 g/l
(propanol and ethanol are treated as VOC)

17.1.3.3.2 VOC content > 0.1 and < 15%

For VOC content > 0.1 (by mass) to < 15% the determination is made using gas chromatography (ISO 11890-2).[6] A hot or the cold injection is used depending on the sample properties.

After assessing the peak areas, the quantitative assessment and evaluation of the VOC content in the product in its ready-to-use condition, the calculation is made in the simplest case according to:

$$VOC\ [g/l] = \sum_{i=1}^{i=n} m_i \rho_s 1000 \qquad [17.1.6]$$

where:

VOC	VOC content, in g/l, of the ready-to-use product;
m_i	mass, in g, of compound i in 1 g of sample
ρ_s	density, in g/ml, of the sample at 23°C
1000	conversion factor × 1000 in g/l.

Table 17.1.2 shows how the application of the various formulas affects the result of the calculation. The VOC contents calculated according to ISO 11890 are credible for Examples 2, 3, 4. Values calculated according to ASTM, using ratio solvent – water in Examples 2 and 4, are almost the same as VOC contents calculated according to ISO/DIS.

Only by increasing the solid matter content, the VOC content can be reduced in examples calculated according to ASTM (cf. Examples 5 and 1), while an increase in the water content, in spite of the same solvent share, leads to an increase of the ASTM value, because a higher water content increases the sum of the denominator and consequently increases the VOC content.

Table 17.1.2. Examples for the VOC content calculated by various methods.

E[a]	Coating material, wt%	Non-volatile parts wt%	Solvent content wt%	Water content wt%	Density g/cm³	VOC content according to		
						ASTM D3960 g/l	ISO 11890/1	
							%	g/l
1	Water spray varnish	30	10	60	1.000 0.900	250 196	10 10	100 90
2	Water/solvent stain	5	25	70	1.00	833	25	250
3	Solvent stain	5	95	0	0.900	855	95	855
4	Solvent/water stain	5	70	25	0.900	839	70	630
5	Water varnish primer	15	10	75	1.000	400	10	100

[a] – Example number

17.1.3.4 Determination of VOC-content in water-thinnable emulsion paints (in-can VOC)

ISO 17895[24] describes an approach, which, *via* the so-called total evaporation method, assesses the content of volatile organic compounds in water-thinnable emulsion paints (in-can VOC).

Measuring principle:

The VOCs are totally evaporated from a very small amount (a few milliliters) of the thinned original sample by means of a head-space injector and subsequent gas chromatographic analysis.

All components, whose retention time is lower than the retention time of tetradecane (boiling point 252.6°C) are included as VOCs.

VOC content calculation:

$$\text{VOC [mg/kg]} = 1000\frac{m_{VOC}}{E_\rho} \qquad [17.1.7]$$

where:

m_{VOC} mass in mg VOC, related to originally weighted-in quantity of the original sample E_ρ
E_ρ originally weighted-in quantity in g of the original sample

$$\text{VOC [g/l]} = \frac{\text{VOC}_{[mg/kg]}\rho_{df}}{100} \qquad [17.1.8]$$

where:

ρ_{df} density in g/ml of the original sample (emulsion paint)

17.1.4 MEASUREMENT OF SOLVENT EMISSIONS IN INDUSTRIAL PLANTS

17.1.4.1 Plant requirements

In spite of considerable reductions in the use of organic solvents, the worldwide-adopted ozone values in the troposphere are not being attained. It is crucial to apply consistent measures worldwide to reduce solvent emissions.

In Europe, for example, the Council Directive 2004/42/CE[1] "On limiting emissions of volatile organic compounds, due to the use of organic solvents in certain activities and installations" came into force on April 21, 2004. The application area refers to activities in applying solvents, as enlisted in Appendix IIA of the EU-VOC-Richtlinie (Table 17.1.3).

Table 17.1.3. Summary of stricter VOC limits

Product Subcategory	Type	Phase I from 2007	Phase II from 2010
		g/l	
Interior matt walls and ceilings (Gloss <25@60°	WB	75	30
	SB	400	30
Interior glossy walls and ceilings (Gloss >25@60°)	WB	150	100
	SB	400	100
Exterior walls of mineral substrate	WB	75	40
	SB	450	430
Interior/exterior trim and cladding paints for wood and metal	WB	150	130
	SB	400	300
Interior/exterior trim varnishes and wood stains, including opaque wood stains	WB	150	130
	SB	500	400
Interior and exterior minimal build wood stains	WB	150	130
	SB	700	700
Primers	WB	50	30
	SB	450	350
Binding primers	WB	50	30
	SB	750	750
One-pack performance coatings	WB	140	140
	SB	600	500
Two-pack reactive performance coatings for specific end use such as floors	WB	140	140
	SB	550	500
Multi-colored coatings	WB	150	100
	SB	400	100
Decorative effect coatings	WB	300	200
	SB	500	200

An analysis of the activity requires data on solvent consumption as calculated from the amount of solvent purchased both as a pure solvent and included in the solvent containing materials less the amount of solvent retained and/or contained in the waste. The calculated difference includes all emissions including diffuse emissions such as the solvent loss from drying racks or solvent initially retained by pained, varnished, printed or dry cleaned articles. These measurements are essential if the statutes are to be enforced and emissions are to be effectively reduced.

Emissive limit values are stipulated for plants covered under this directive for exhaust-gases in mgC/Nm^3 as well as limits for diffuse emissions in % solvents input. If these data are not available, total emission limit values are used.

Definition of "Emission Limit Value:" The "Emission Limit Value" is understood as the mass of volatile organic compounds, the concentration, the percentage and/or the amount of emission – ascertained under normal conditions – expressed in certain specific parameters, which in one or several time periods must not be exceeded.[1]

Plant measurement must be made to provide data for analyzing the actual situation as well as to be able to prove the emission reduction which a business must attain.

17.1.4.2 The determination of the total carbon content in mg C/Nm^3

17.1.4.2.1 Flame ionization detector (FID)

The total C/Nm^3 is assessed according to the Guideline VDI 3481/page 3[25] by means of a flame ionization detector (FID). This device is the component of a mobile device for random sample tests or a continuous measuring device for total carbon concentration measurement in an exhaust-gas flow. This approach measures the total organic substance in an exhaust gas. Should the composition of the solvents contained in the exhaust air not be known, their concentration may be quoted in carbon equivalents as mgC/m^3.

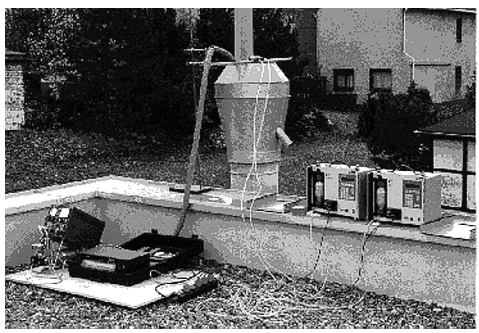


Figure 17.1.2. Emission measurement by FID.

Measuring principle:

An FID detects ionized organically compounded C atoms in a hydrogen flame. The ion flow developed in the induced electrical field is electrically amplified and measured. The ion flow arising when burning carbon compounds is proportional to the mass of carbon atoms exposed to the flame per time unit.

The detection of organic compounds with heteroatoms, e.g., N, O, S, Cl, is generally less sensitive. The calibration of the device is done in most cases with propane as the test gas. Figure 17.1.2 shows a measuring arrangement for assessment of emissions from a drying plant.

17.1.4.2.2 Silica gel approach

The determination of the total carbon concentration in the exhaust gas by means of the silica gel approach can be done according to the Guideline VDI 3481, p. 2.[26] A partial flow of the exhaust air to be tested is guided through a sorption pipe filled with silica gel.

The organic compounds are absorbed by the silica gel. Subsequently, the organic compounds are desorbed in an oxygen flow at an increased temperature and burnt to carbon dioxide (CO_2), which is determined quantitatively. This is a discontinuous method. The data reflect the concentration in the measured time intervals and the causes of deviations are difficult to ascertain.

17.1.4.3 Qualitative and quantitative assessment of individual components in the exhaust-gas

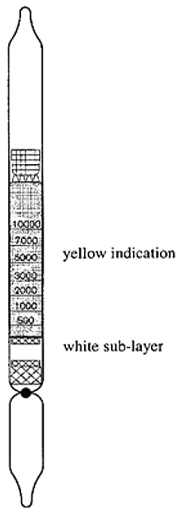


Figure 17.1.3. Indication tube for ethyl acetate 500/a-D.

While the methods mentioned under 17.1.4.2 reflect the total carbon concentration as a summary parameter, it is still necessary to know concentrations of the individual solvents to assess the plant emission.

17.1.4.3.1 Indicator tubes

For many solvents and other substances directly indicating detector tubes are available.[27] They are used for rapid assessment of emission. Since they often do not react specifically with a certain compound alone, errors have to be considered due to cross-sensitivity.

Detector tubes contain sorption-active agents. A gas flow of a defined rate is fed through and the substance in the gas flow produces a color reaction with the agent in the tube. The color intensity is checked against the scale on the test tube and the ppm value can be registered.

Figure 17.1.3 shows such a tube for determining ethyl acetate.[27] The color change, in this case, is from yellow to light green.

Reaction principle:

$$CH_3–COOC_2H_5 + Cr^{VI} \rightarrow Cr^{III} + \text{various oxidation products}$$

This reaction is not substance-specific. Other alcohols, at varying cross-sensitivity, as well as methyl ethyl ketone are reactive.

17.1.4.3.2 Quantitative solvent determination in exhaust gas of plants by means of gas-chromatography

A defined amount of exhaust gas is fed into an adsorption medium (activated carbon, Tenax, etc.) and its concentration is enriched. There is a subsequent extraction by means of a solvent. The mixture is then injected into a gas chromatograph. The individual components are determined according to Guideline VDI 34 82, page 1.[28]

Measuring principle:

A heatable capillary coated on the inside with various materials (polyester or silicone resins, silica gel) is used as a separating unit. The gaseous substance mixture is transported by means of an inert gas (nitrogen, argon, etc.). The individual solvents remain in the column for different time periods depending on their polarity. After leaving the column, the solvent is detected by sensitive physical methods. By combining the highly resolving capillary gas chromatography with a mass spectrometer even unknown substances may be identified in the mixtures. The quantitative evaluation of the gas chromatograms is automatically done with appropriate software.

1st Example: Emission measurement in an industrial varnishing plant

The measurement was done in a furniture company, which applies different varnish systems on several varnishing lines.[29]

For preliminary investigations, four chimneys were selected for the measurement as typical sources of emission. Based on the analysis of the varnish materials and measurements performed over extended periods of time, it is certain that the materials and concentrations processed during the measuring gave a representative cross-section of the production activity. Table 17.1.4 shows a summary of the varnish and solvent amounts processed per day, which were emitted from chimneys 1 to 4.

Table 17.1.4. Summary of the varnish and solvent amounts processed in the 1st example.

Measuring point chimney	Varnish	Solvent share, %	Varnish processed, l/day	Total solvent, l/day
1	1	34	10 - 15	~40 - 45
	2	76		
	3	80	30 - 35	
	3	80	5	
	4	80	5	
2	5	56	50 - 60	37
	6	34	10	
3	7	38	30	12.5
	6	34	3	
4	1	34	~240	~170
	8	52.88	120-130	
	6	34	50	

At the chimneys, the following exhaust air parameters were established:

Chimney diameter	mm
Exhaust air flow rate	m/s
Exhaust air temperature	°C
Humidity	%
Volume flow (operation)	m^3/h
Volume flow	Nm^3/h
Heat flow	MW

Table 17.1.5 contains a summary of the established emission values expressed in mg C total/Nm^3 as well as the mass flow g C/h.

Table 17.1.5. Measuring results for total carbon concentration at different measuring points.

Measuring point chimney	Time	Volume flow, Nm^3/h	Carbon concentr., mgC/Nm^3	Mass flow, go/h	Odorant concentr.(1), GE/m^3	Mass flow, TGE/m^3
1	10.35-11.20	35,200	112.6	3,964	93	3,519
	11.45-12.00		96.5	3,397	87	3,292
	13.45-14.35		128.6	4,527		
2	11.25-12.00	39,240	72.4	2 841	91	4,151
	12.45-13.10		56.3	2 209	87	3,969
	13.10-14.30		56.3	2 209	93	4,242
3	13.50-14.40	33,900	48.2	1 634	100	3,747
	09.25-09.55		56.3	1 908	115	4,309
	09.55-10.25		64.3	2 180		
4	09.15-09.45	108,650	112.5	12 223	98	12,837
	09.45-10.15		152.8	16 602	213	27,900
	10.15-10.45		160.8	17 471		

(1)The odorant concentration does not refer to the times stated.

The EU VOC Directive for plants for wood coating with a solvent consumption of 15-25 t/year requires an emission limit of 100 mg C/Nm^3. In the example, this is only met at chimneys 2 and 3.

In addition to these measurements, using activated carbon tubes and subsequent gas chromatographic evaluation, it was determined that the main components of VOCs were acetone, ethyl acetate, toluene, butyl acetate, xylene, ethylbenzene (Table 17.1.6). Butyl acetate and ethyl acetate were the main components in the respective solvent mixtures.

Table 17.1.6. Measured results for individual components at different measuring points

M*	Acetone		Ethyl acetate		Toluene		Butyl acetate		Ethyl benzene		Xylene	
	C^a	MF^b	C^a	MF^b	C^a	MF^b	C^a	MF^b	C^a	MF^b	C^a	MF^b
1	6.5	229	15.5	546	9.0	317	15.5	545	1.0	352	4.2	158
	4.5	158	11.0	387	5.5	194	11.0	387	1.0	352	2.5	88
2	11.0	432	24.5	961	14.5	569	24.5	961	1.0	39	6.5	255
	4.5	176	9.0	353	6.5	255	14.5	569	–	–	–	–
3	–	–	4.5	152	2.0	68	3.5	118	0.5	17	2.0	68
	–	–	15.5	525	5.5	186	8.0	271	1.0	34	5.5	186
4	9.0	978	20.0	2173	9.0	978	17.0	1847	2.0	217	8.0	869
	5.5	597	27.0	2933	18.0	1956	37.0	4020	3.5	380	17.0	1847

*M = Measuring point chimney; [a]concentration in mg/Nm^3; [b]MF = mass flow in g/h

2nd Example: Emissions measured in a spray-room

The usual technique of measuring VOC emissions in plants by means of the FID according to VDI 3481/page 3 has the shortcomings that individual components in the gas mixture cannot be measured separately, but only determined as total carbon. Also, the device needs to be placed in the immediate vicinity of the measuring point and requires frequent calibration.

Figure 17.1.4. Photoacoustic Gas Monitor Innova 1412i.

A portable Gas Monitor 1412i (Figure 17.1.4) enables sampling in six places up to 50 m away from the monitor. It can determine at each measuring point, the concentration of up to a maximum 5 components as well as the humidity. This is done by a multipoint sampler with a dosing apparatus controlled by system software. The device needs calibration only 1-2 times a year. Beyond that, the device may also be used for determining the total C concentration. It is expandable up to 24 locations using 1309 Multipoint Sampler.

Measuring principle (Figure 17.1.5)

3. An air sample is drawn into the measurement chamber and the chamber is sealed by valves.
4. Radiation from the IR-source passes through a chopper and optical filter into the chamber, where it is absorbed, generating heat and pressure variations.
5. The pressure variations correspond to the chopper frequency, creating a pressure wave which can be detected by the microphones.
6. The microphone signal, proportional to the gas concentration, is post-processed and the measurement result is calculated.
7. Optional remote control capability is available.

The measurements are quasi-continuous. When measuring a single gas, the measuring value is updated every 30 s, with five gases and humidity the update time is 105 s. The measured values are stored, statistically evaluated, and numerical or graphical output can be obtained either immediately or on demand. Such devices make the emission measurement effort much easier than with the older, less automated equipment.

Figure 17.1.6 shows the results of emission investigations in the spray-room of a joiner's with and without ventilation.[31] Windows and doors were closed. The varnisher was standing in front of a spray-wall, opposite to him was placed a platform rack truck for shelving the varnished parts. Those areas in the joiner's, which showed roughly the same emission values of n-butyl acetate, are marked on each drawing.

The emission load in the room was decreased by the technical ventilation to about a tenth of the values.

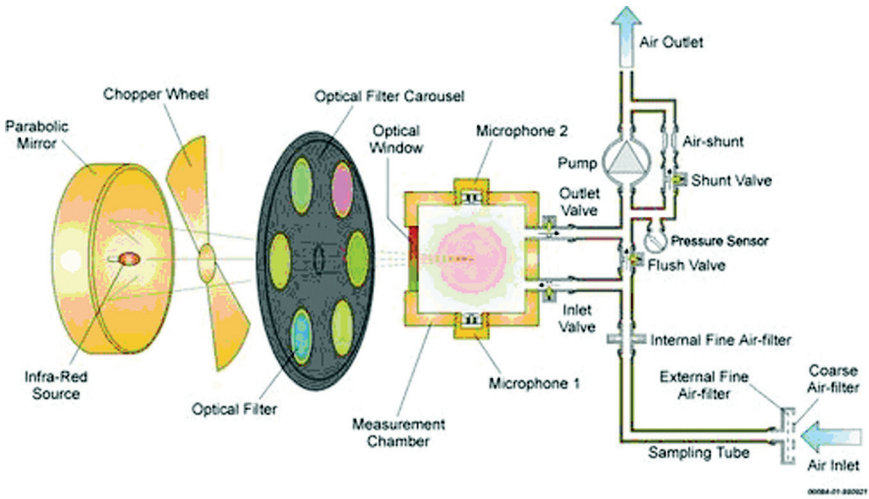
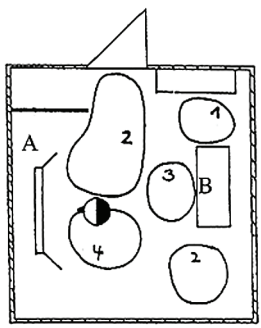


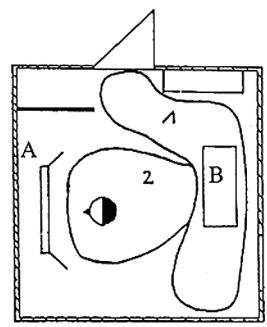
Figure 17.1.5. Measurement principle of Photoacoustic Gas Monitor Innova 1412i.

Natural Ventilation



area	mg/m^3
1	3650
2	4430
	4910
	4530
3	5580
4	6690

Technical Ventilation



area	mg/m^3
1	489
	483
	499
2	662
	614
	564

Figure 17.1.6. Maximum concentration of n-butyl acetate in the spray-room of a joiner's with windows and door closed. A – Spray wall, B – Rack track for shelving the varnished parts.

17.1.5 "ODOR" DEFINITION

One of the senses of the living organism is the sense of smell. Smell is largely dependent on the chemical structure. of the substance. The odorous substances perceived by human are suspended in the air as volatile substances. The degree of response to a substance depends on its vapor pressure, thus, in turn on its concentration in the air and its molecular weight. An odorant also has to be sufficiently water and fat-soluble, which enables it to interact with the olfactory receptors.

Whether an odorous impression is considered pleasant or unpleasant, it is largely determined by the functional groups of the chemical compounds (Table 17.1.7).

Table 17.1.7. Scent qualities of various chemical compounds in relation to their functional groups.[33,34]

Odorous impression	Functional group	Substance group
Pleasant	–OH	Alcohols
	–OR	Ethers
	–CHO	Aldehydes
	–COR	Ketones
	–COOR	Esters
	–CN	Cyanogen compounds
	$–NO_2$	Nitro compounds
Unpleasant	–SH	Mercaptans
	–SR	Thioethers
	–CSR	Thioketones
	–NC	Nitriles
	$–NH_2$	Amines

The above assignment of odorous impressions should be, however, only regarded as a rough guideline, since the so-called "pleasant" odor, at higher concentrations, can easily be perceived as very "unpleasant". Also, the perception of smell depends on personal preferences. Almost all solvents, such as ketones, esters, glycols, alcohols, aromatic and aliphatic hydrocarbons, contribute to a more or less intensive smell.

"Odor" is not a parameter of substance, but a summarized parameter of effects. Its determination is based on the fact that the sense of a smell can be used subjectively to evaluate certain substances (odorants). The concentration of those substances suspended in the air can be determined, which is called odorant concentration.

Odor threshold or perception threshold[35-38]

The odor threshold is the concentration of the odorant in the air, given in mg/m^3. The odor threshold corresponds to an odor unit (GE). It is the amount of odorous substance, which – distributed in 1 m^3 of scent-neutral synthetic air – initiates in at least 50% of the evaluators a perception of smell and in the other 50% no response.

The odor threshold is very specific to substance. It is determined in several measuring series and the results from a Gaussian distribution curve. Since this is ultimately a sub-

jective evaluation, one should not be surprised to find more as well as, less, reliable data in the literature. Examples are shown in Table 17.1.8.

Table 17.1.8. Odor thresholds of selected compounds from literature [Geruchs-Immissions-Richtlinie][34]

Compound	Odor threshold, mg/m^3	Compound	Odor threshold, mg/m^3
Butyl acetate	0.03	Ethanol	19.1
Ethyl acetate	22	1-Butanol	0.4
Benzene	16.2	Acetone	48
Toluene	7.6	Ethyl acrylate	0.002
Xylene	0.35	Dichloromethane	706

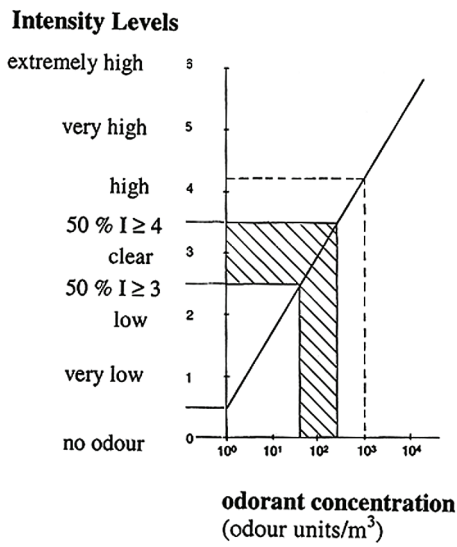


Figure 17.1.7. Interdependence of odorant concentration and odor intensity in an artificial example.

Table 17.1.9. Correlation of odor with an intensity level

Odor	Intensity level
Extremely high	6
Very high	5
High	4
Moderate	3
Low	2
Very low	1
No scent	0

Odorant concentration

The odorant concentration of a sample is the multiple of the odor threshold and it is determined in odor units (GE) per 1 m³ neutral air.

Odor intensity[35]

Since the odor threshold alone is an insufficient evaluation criterion for an odorant, the increase in response with increasing odorant concentration may additionally be taken into account as a scale of reference.

The increase in response is mainly material and/or mixture dependent for a given odorant concentration and is called odor intensity.[32]

Figure 17.1.7 shows the interaction between odorant concentration and odor intensity in an artificial example.[39]

Odor intensity is assessed by means of a scale from 1 to 6 [VDI 3882/1][35] (Table 17.1.9).

Hedonic odor tone

An odor may be quantified by determining the odor concentration, the character of the odor (pleasant or unpleasant) is not considered. Unpleasant odors may result in deteriorating health and should, therefore, be avoided.

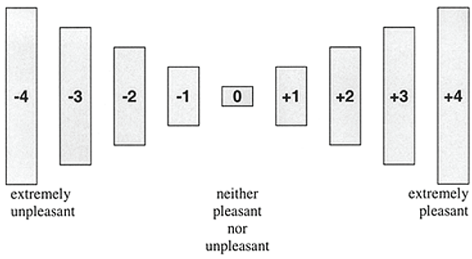


Figure 17.1.8. Evaluation of the hedonic effect of an odor sample [VDI 3882/2].[40]

By determining the hedonic odor effect, the emotional reaction initiated by an irritation to the sense of smell may be included. It should not be confused with the kind of smell (it smells like...) or with the odor intensity (it smells "strong" to "weak"). It may be determined not only for a single odorant but also for an odorant mixture. Odor samples of an odorant concentration above the odor threshold are ranked by evaluators according to the odorants' position in the following response range between "extremely unpleasant" to "extremely pleasant" (Figure 17.1.8].

In many cases of odor evaluation, there are big differences between the results among the individual evaluators, since they have a widely varied background of experience.

17.1.6 MEASUREMENT OF ODOR IN MATERIALS AND INDUSTRIAL PLANTS

17.1.6.1 Introduction

Various methods are known for determining odors. One of particular interest is pupil dilatation. This is based on the fact, that pupils dilate when a strong odor is sensed, as may be caused by concentrated ammonia.

A simple sampling of odors is based on the Öko-Tex Standard 200.[40] The samples are conditioned in a desiccator and their odor is subsequently judged by 6 evaluators according to a five-point scale:

1 odorless
2 low odor
3 bearable odor
4 annoying odor
5 unbearable odor

Such a scale is also used by the "Deutsche Gütegemeinschaft Möbel" (German Quality Association of Furniture Manufacturers) as a methodical approach for evaluation of odors of furniture, cover fabric, leather, etc.

In principle, odors may be determined by means of sample recognition with the help of arrays of gas sensors, so-called electronic noses.[33] Unknown samples are compared with known samples. Hence, olfactometric investigations need to precede. Such a measuring device is applicable only in a specific case and has to be trained prior to use. Odor can become a controllable quality feature of a product. Samples of good quality can be made distinguishable from samples of bad quality.

In practice, odor determination by means of the olfactometer has been widely applied and generally adopted.

17.1.6.2 Odor determination by means of the "electronic nose"

The principle of odor determination in different fields of application has been discussed in detail, elsewhere by Moy and Collins[41] and Schulz.[42]

Measuring principle:

The substance mixture in question, which causes the odor, undergoes an overall investigation by means of a sensor array. In doing so, the device makes use of the semi-conductive properties of various metal oxides, which are on the surface of 12 sensors which react to the gaseous substances which come in contact with them. The response also depends on the temperature, humidity and flow rate of the gas. Each sensor issues its own reply signal as soon as the sample of air touches its surface.

The measurement is done within about two minutes, readjustment of the sensors takes about 4 minutes. The measuring device is linked to a computer with relevant software.

Each odor is, according to the twelve sensors, represented by 12 graphs showing a characteristic "profile" ("fingerprint"). These sensor-specific, time-dependent, series of electric conductivity data, which are produced by the presence of the odorous substances provide the data for the evaluation. They are processed by means of neuronal networks.

The available odor samples can be shown as two or three-dimensional. Comparative or referential samples are treated in the same way. By means of sample series, they may serve the purposes of the identification of new samples.

It remains an issue, that odor-relevant compounds exist in much lower concentration in most cases than the less odorous compounds, thus they are also less influential on the sensor signal. Much research effort has yet to be undertaken to apply the electronic nose in the future.

More information on the odor perception and the odor measurement can be found in the specialized monographic source.[33]

17.1.6.3 Odor determination by means of the olfactometer

The method of odor determination by means of the olfactometer is based on the guidelines Richtlinien VDI 3881, pages 1 to 4[35-38] and VDI 3882, pages 1 and 2.

Measuring principle:

An odorant sample is diluted in a defined way with neutral air in an olfactometer and offered to test persons as an odor sample. The test persons are exposed to several dilution levels. Should an odor be perceived, it shall be confirmed by pressing a button. An olfactometric determination requires at least 5, and preferably 8 evaluators. These evaluators need to pass a suitability test in accordance with guidelines of VDI 3882, p. 2. The principle of an olfactometer[43] is shown in Figure 17.1.9.

The results are presented in odor units/m^3 of neutral air and they are automatically displayed as the averaged data of the panel's evaluation.

17.1.6.4 Example for odor determination for selected materials: Determination of odorant concentration in varnished furniture surfaces

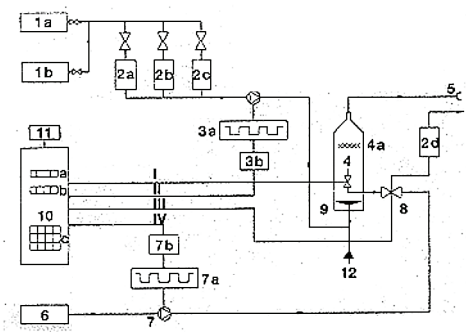


Figure 17.1.9. Principle of an olfactometer. 1 diluent air a) outer air, b) synthetic air (bottle); 2 acitvated charcoal filter air from 2d to rinse by-pass, 3 glass bulb pump with electronically controlled drive (a,b); 4 mix chamber (with installation a); 5 evaluator.s mask; 6 sample air (if necessary pre-mixed); 7 glass bulb pump with electronically controlled drive (a,b); 8 by-pass valve; 9 mix chamber valve; 10 control terminal, a) display (programme step), b) display, c) terminal keyboard; 11 printer: I-IV control line; 12 additional pump (24 l x min^{-1}).

The odor potential of furniture is determined primarily by the applied varnishes although adhesives also play a minor role. Furniture varnishes may contain up to 80% solvents. The residual solvents remaining in the varnish thus determine the VOC and odorant concentration of furniture surfaces.

A specific test method has been developed for determining the VOC and odorant concentration of coated surfaces,[44-46] as shown schematically in Figure 17.1.10. Similar to formaldehyde determination,[47] sample testing is done using a test chamber approach. After some atmospheric conditioning of the varnished furniture, the samples are stored in a test chamber (typically 1 m^3) under the following conditions: 23°C±0.5; 45±3% relative humidity; charged with 1 = 1 m^2 of emitting sample surface per 1 m^3 test chamber volume air flow rate at sample surface: between 0.1 and 0.3 m/s. The samples remain in the test chamber for 48 hours without an air exchange in the test chamber, in order to simulate the "worst case scenario", i.e., that, for instance, the new furniture is sealed off air-tight during transport, so that residual solvents accumulate. After 48 h of storage time without an air exchange, air samples are taken in parallel for the determination of VOC emission by means of gas chromatography and for determination of odor by the olfactometer. Subsequently, there is an air exchange of one air change per hour, and the slow-down curve of VOC and odorant concentration is determined.

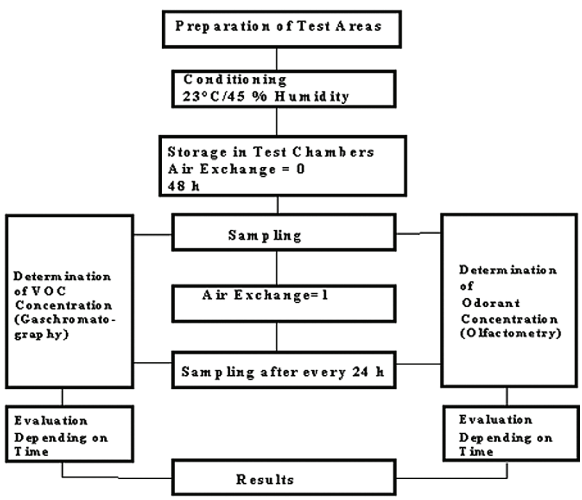


Figure 17.1.10. Test approach for the determination of VOC and odorant concentration in coated surfaces.

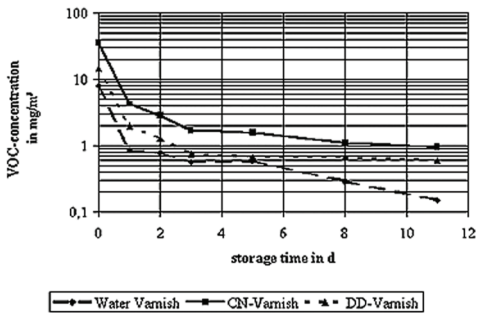


Figure 17.1.11. VOC concentration depending on the storage time in the test chamber with air exchange 1.

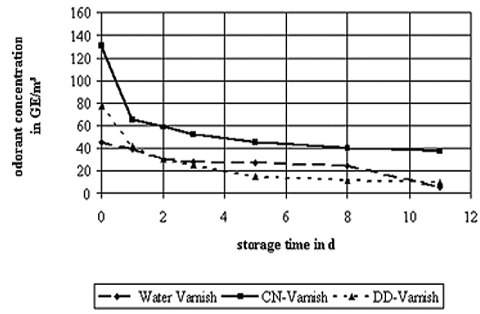


Figure 17.1.12. Decreasing odorant concentration depending on the storage time in the test chamber with air exchange 1.

Figure 17.1.11 shows the decreasing VOC concentration depending on the storage time in the test chamber with an air exchange 1,[48,44] and Figure 17.1.12 shows the decreasing odorant under the same test conditions.[48,44]

The curves for VOC and the odorant concentration follow a similar pattern, they are, however, not identical. While the VOC concentration in water varnish is the lowest after 11 days, the odorant concentration after this time is equally high with both DD-varnish and water varnish. This, however, does not generally apply to these types of varnish. Also, DD-varnishes of different origins may differ greatly in emitting the residual solvents.

In the single-solvent systems, it is easy to see the interdependence between VOC and odorant concentration. This does not necessarily apply to solvent mixtures. This is due to the large variations in odor thresholds and the different evaporating behavior of the various solvents.

Acrylate varnishes, for example, need to contain only a few µg of ethyl acrylate in order to produce odor, since odor threshold level is at 0.002 mg/m^3. Thus, the determination of the VOC concentration alone is not sufficient for determining the quality of coated surfaces.

17.1.6.5 Example of odor determination in industrial plants: Odor measurement in an industrial varnishing plant

In a study parallel to the measurements of the VOC emission in the varnishing lines of the furniture company, as described in Section 17.1.4.3.2, 1st Example, the odorant concentrations were sampled in the exhaust air from the individual chimneys by means of olfactometry.[29] All conditions of measurement described in Section 17.1.4.3.2 also apply to the determination of the odorant concentration.

The results are contained in Table 17.1.5 as odorant concentration in GE (odorant units)/m^3 and in the mass flow in TGE/h (one thousand odorant units per hour). The main components were butyl acetate and ethyl acetate. Due to the very low odorant threshold of butyl acetate (0.03 mg/m^3), as compared to other available substances, (ethyl acetate 22 mg/m^3), butyl acetate may be assumed to be responsible for the bulk of detectable odor.

An immediate comparison of samples taken at the same point of time resulted in the following data:

concentration of butyl acetate: 8 mg/m^3
odorant concentration: 115 GE (odorant units)/m^3

Adopting the value quoted in the literature for the odorous threshold of butyl acetate at 0.03 mg/m^3, which equals one odorant unit, the odorant concentration estimates a butyl acetate concentration of about 4 mg/m^3. This value is in the same range as the value established for butyl acetate by gas chromatography. In these comparisons, one has to consider that odorant thresholds may deviate by one to two exponents to even ten, according to literature sources.[49]

Measurements taken in the housing area about 300 m away from the chimneys of the varnishing plants could not establish any solvent-typical components in the gas analysis. The maximum concentration value for TVOC was at 0.004 mg/m^3.

Also, the spreading calculation, which was carried out on the basis of the determined solvent concentration, showed that there should be no significant odor annoyance in the vicinity of the emission source. The results of the spreading calculation on the basis of measured solvent concentrations are considerably more precise, since solvent concentrations may be determined more exactly than odorant concentrations.

The spreading calculation was done using the software package "IMMPROG-P" by AIRINFO AG, Switzerland, and carried out according to a method of the Odor Emission Guideline of the German State of Northrhine-Westfalia/Geruchsimmissions-Richtlinie des Deutschen Bundeslandes Nordrhein-Westfalen.[34]

REFERENCES

1 Council Directive 2004/42/CE of 21 April, 2004 on the limitation of emissions of volatile organic compounds due to the use of organic solvents in certain paints and varnishes and vehicle refinishing products and amending Directive 1999/13/EC
2 ISO 4618:2014, Paints and varnishes - Terms and definitions.
3 Ersatzstoffe und Ersatzverfahren für stark lösemittelhaltige Vorstriche und Klebstoffe für den Bodenbereich (TRGS 610). Ausgabe: Januar 2011. GMBl 2011 Nr. 8 S. 163-165 (02.03.2011)
4 M. Scheithauer, *I-Lack,* 66, 325 - 331 (1998).
5 ISO 11890-1:2007, Paints and varnishes -- Determination of volatile organic compound (VOC) content -- Part 1: Difference method.
6 ISO 11890-2:2013, Paints and varnishes -- Determination of volatile organic compound (VOC) content -- Part 2: Gas-chromatographic method.
7 Lösungsmittelverordnung, LMV 2005: Federal Law Gazette (BGBl.) II No. 398/2005
8 Lackieranlagen-Verordnung 2002 in Österreich 301/2002 im Bundesgesetzblatt für die Republik Österreich.
9 ASTM D 3960-05(2013). Standard Practice for Determining Volatile Organic Compound (VOC) Content of Paints and Related Coatings.
10 *Farbe und Lack*, **105**, 12/99, 111 (1999).
11 B. Seifert, **Richtwerte für die Innenraumluft; Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz 3**; *Springer-Verlag*, Berlin, 2015, pp. 505-12.
World Health Organization, 1989. Indoor air quality: organic pollutants. Report on a WHO Meeting, Berlin, 23-27 August 1987. EURO Reports and Studies 111. Copenhagen, World Health Organization Regional Office for Europe.
12 National Health and Nutrition Examination Survey, 2011. National Geographic, 2011.
13 A. Szalai, The use of Time: Daily activities of urban and suburban populations in twelve countries, Den Haag, Paris: Mouton, 1972.
14 N. E. Klepeis, W. C. Nelson, W. R. Ott, J. P. Robinson, A M Tsang, P. Switzer, J. V. Behar, S. C. Hern, W. H. Robinson, *J. Expos. Anal. Environ. Epidem.*, **11**, 231-52, 2001.

15 M.-L. Roux, Different coating alternatives to meet the European VOC Directive, COST E-18, seminar, 2004.
16 C. Philipp, *Eur. Coat. J*., **2010**, 1, 1-3, 2010.
17 Emulsion Polymer Market. Grandview Research, Inc., Report 978-6808-202-0, 2016.
18 H. Zeh, 4. Freiberger Polymertag, Freiberg, May 27-28, 1999, Conference paper P/2.
19 Lackieranlagen-Verordnung in Deutschland (Varnishing Plant Regulation): Umweltbundesamt Deutschland III 3.2 - 52337/7); draft April 1, 1996.
20 Low-Emission and Low-Pollutant Paints and Varnishes. RAL-UZ 12a. Der Blaue Engel. August 2011.
21 M. Große Ophoff, *Holz- und Kunststoffverarbeitung*, 12/96, 52-55 (1996).
22 ISO 3251: 2008. Paints and varnishes - Determination of non-volatile matter content.
23 ISO 760: 1978. Determination of water - Karl-Fischer method (general method).
24 ISO 17895:2005. Paints and varnishes - Determination of volatile organic compounds content of low-VOC emulsion paints (in-can VOC).
25 Richtlinie VDI 3481 / Blatt 3: Gaseous emission measurement - Determination of volatile organic compounds, especially solvent, flame ionisation detector (FID), 10.95.
26 Richtlinie VDI 3481 / Blatt 2 E: Messen gasförmiger Emissionen (Gaseous emission measurement) Bestimmung des durch Adsorption an Kieselgel erfassbaren organisch gebundenen Kohlenstoffs in Abgasen; 11.96.
27 Dräger, **Dräger-Röhrchen Handbuch**, Lübeck, 1991, 249.
P. de Kettenis, **Practical guide for measuring solvent vapor concentrations using chemical indicator tubes**. *European Solvents Industry*. www.esig.org
28 Richtlinie VDI 3482/Blatt 1. Gaseous air pollution measurement; gas-chromatographic determination of organic compounds, fundamentals; 02.86.
29 M. Broege, **Gutachten zu von Lackieranlagen verursachten Geruchsimmissionen**, *Institut für Holztechnologie Dresden*, 1993.
30 Photoacoustic Gas Monitor INNOVA 1412i, Product Data from LumaSense Technologies, Inc., US.
31 R. Kusian, M. Henkel, Forschungsbericht des Institutes für Holztechnologie Dresden, Germany (1997): Untersuchung der Emissionsverhältnisse bei der Oberflächenbehandlung von Holz und Holzwerkstoffen.
32 M. Schön, R. Hübner, **Geruch-Messung und Beseitigung**, *Vogel-Buchverlag*, Würzburg, 1996.
33 G. Wypych, **Handbook of Odors in Plastic Materials**, 2nd Ed. **ChemTec Publishing**, 2017.
34 Feststellung und Beurteilung von Geruchsimmissionen (Geruchsimmissionsrichtlinie, GJR); Der Minister für Umwelt, Raumordnung und Landwirtschaft des Landes Nordrhein-Westfalen, Stand 15.02.1993, Anhang B.Richtlinie VDI 3881.
35 Blatt 1: Olfactometry; determination of odor intensity. VDI 3882 Blatt 1. Audited and confirmed 2015-04.
36 Blatt 2: Olfactometry, determination of hedonic odor tone; VDI 3882 Blatt 2:1994-09. Audited and confirmed 2015-04.
37 Blatt 3: Olfactometry; odor threshold determination; olfactometers with gas jet dilution; 11/1986. Withdrawn.
38 Blatt 4: Olfaktometrie; Geruchsschwellenbestimmung; Anwendungsvorschriften und Verfahrenskenngrößen; 12/86 Richtlinie VDI 3882. Withdrawn.
39 M. Paduch, VDI-Berichte 1059, “Aktuelle Aufgaben der Messtechnik in der Luftreinhaltung” zum Kolloquium Heidelberg, Düsseldorf, Juni 2-4, 1993, pp. 593-607.
40 Öko-Tex Standard 200: Prüfverfahren für die Vergabe der Berechtigung zur Kennzeichnung von Teppichböden mit “Schadstoff geprüft nach Öko-Tex Standard 100” (Österreichisches Forschungsinstitut) 2010.
41 L. Moy, M. Collins, *LaborPraxis - Journal für Labor und Analytik*, **20**, 5, 14-18 (1996).
42 H. Schulz, 4. Freiberger Polymertag, Freiberg, May 27-28, 1999, conference paper C 4/5.
43 Ströhlein, Labor-, Mess- und Umwelttechnik, Kaarst, Germany, Product Data p. 25, principle of an olfactometer.
44 M. Scheithauer, K. Aehlig, M. Broege, *Holz- und Kunststoffverarbeitung*, 1/96, 58-61 (1996).
45 M. Scheithauer, K. Aehlig, Konferenz im ITD, Poznan (Poland), 1995.
46 K. Aehlig, M. Scheithauer, M. Broege, *Holz*, **5**, 26-32; (1996).
47 prENV 717-1: 1998: Holzwerkstoffe Bestimmung der Formaldehydabgabe Teil 1: Formaldehydabgabe nach der Prüfkammer-Methode (1998).
48 M. Broege, K. Aehlig, 4. Freiberger Polymertag, Freiberg, Mai 27-28, 1999, conference paper R 4/5.
49 G. Scharfenberger, *Chemie in Labor und Biotechnik*, **42**, 498-502 (1991).

17.2 EMISSION OF ORGANIC SOLVENTS DURING USAGE OF ECOLOGICAL PAINTS

Krzysztof M. Benczek and Joanna Kurpiewska
Central Institute for Labour Protection, National Research Institute, Warsaw, Poland

17.2.1 INTRODUCTION

Directive 2004/42/CE placed limits on the emission of volatile organic compounds due to the use of organic solvents in paints and varnishes as well as vehicle refinishing products. It also amended Directive 1999/13/EC on the limitation of emissions of volatile organic compounds due to the use of organic solvents in certain activities and installations imposing high demands on the limitation of volatile organic compounds (VOCs) in the production of coating materials.[1,2] The aim of these Directives is to limit the total content of VOCs in certain paints and varnishes and vehicle refinishing products in order to prevent or reduce air pollution resulting from the contribution of VOCs to the formation of tropospheric ozone. A common way to reduce emissions of organic solvents is to replace conventional paint products, containing significant amounts of solvents, by water-based or powder paints, which can be substantially solvent-free. The fact that the powder coatings emit much less organic compounds than the classic paints does not mean that they do not emit any harmful substances. The type of emitted substances cannot be determined on the basis of available information on used paint. The paints' MSDSs are not very helpful in this matter because the data they usually present are incomplete.

The application of the coating is a basic process of surface treatment applied to reduce a material susceptibility to corrosion and to provide a longer performance.

Until recently, paints containing significant amounts of organic solvents were frequently used. Such conventional paint composition consisted of up to 60% solvents, 30% binder, 7-8% pigments and fillers, and 2-3% additives.[1] The most common solvents in these paints are aliphatic hydrocarbons, aromatic hydrocarbons, ketones, alcohols, esters, and glycolic ethers.

These are the most frequently used solvents:

- Toluene – good solvent for many resins, which can be mixed with drying oils (e.g., linseed oil); it is applied in a mixture with other solvents of the so-called oil paints.
- Xylenes – solvents for many resins, which are characterized by a high rate of evaporation, and, therefore, are widely used as a component of fast-drying and thermoset paints.
- Ketones – solvents for many resins; especially methyl isobutyl ketone is widely used in thermoset enamels (glaze, lacquer) and varnishes.

To provide specific technical and operational properties small amounts of specific solvents are also added to the solid paints.

17.2.2 TYPES OF ECOLOGICAL PAINTS

The need to reduce emissions of volatile organic compounds (VOC) led to the development of a number of paints with a reduced concentration of these substances. These paints can be divided into the following groups:

High-solids paints with a high content of solid components are characterized by lower emissions of solvents (up to 50% less compared to the conventional paints), good coverage, and the possibility of application of thick coatings with a reduced number of layers, and a smaller fire hazard. They can be applied using the conventional equipment. However, this type normally contains 10 to 40% organic solvents. Special types of these paints contain 100% solids and no solvents, but their viscosity is about 10 times higher than normal paint and they require special methods of application (heating).

Water-based paints are currently the most popular "green" paints, in which the main liquid phase is water accounting for up to 80% of the paint. The advantage of using such paint is in a significant reduction of emission of organic solvents (usually their content does not exceed 35% of the amount of water they contain), reducing the risk of fire, long shelf-life, good film properties, and decrease in the workers exposure to the organic substances contained in the air.

The latest achievement in the field is two-component paint produced without the addition of auxiliary organic solvents. Two-component, waterborne epoxy coatings have properties similar to the solvent-based paints.

Powder paints consist of powdered resin containing solid additives.[3] The powder is applied to the painted surface by dipping in a fluidized bed, spraying, or electrostatic spraying. After application, the powder coating is usually melted to form a durable, corrosion-resistant, and a high-quality coating. The advantages of this type of paint include the complete elimination of solvents, solids reduction, cost-effective use, the potential for recycling of powder, elimination of direct contact of paint with industrial wastewater, the easiness of obtaining thick coatings, energy efficiency, etc.

17.2.3 THE TYPES OF VOC PRESENT IN ECOLOGICAL PAINTS

The composition of organic solvents in the air over the covered surface of 52 different types of water-based paints, was analyzed by gas chromatography.[4] Test specimens were taken from the paint by evaporation of volatile organic compounds, which were absorbed on fiberglass bearing Carbowax. After thermal desorption volatiles were subjected to gas chromatographic analysis. The following compounds were identified in the tested paints:

- Texanol (2,2,4-trimethyl-1,3-pentanediol-monoisobutyrate)
- Propylene glycol
- Butyl ether of diethylene glycol
- Ethylene glycol
- Butyl ether of ethylene glycol
- Isopropanol
- Methanol
- N-methyl pyrrolidone
- Ethyl ether of diethylene glycol
- Dibutyl phthalate

- Methyl ether of diethylene glycol
- Ethanol
- Butyl ether of propylene glycol
- 2-Butanol
- Aminomethyl propanol
- Ethyl ether of diethylene glycol
- Diethylene glycol
- Butyl ether of dipropylene glycol
- Glycerol
- Hexylene glycol
- 2-Heptanone (methyl amyl ketone)
- Methyl ether of propylene glycol
- Propyl ether of propylene glycol

Classic water-based paints may contain from 3 to 12% organic solvents, waterborne paints of the third generation theoretically do not contain solvents. In reality, it is possible to detect trace quantities of impurities from the intermediates. It should be noted that the solvents used in these paints are generally more harmful (lower TLV value) then the solvents used in the classical paints.[6]

The greatest potential for reducing wastes and reducing the emission of VOCs are attributable to powder coatings. They are intended to be solventless, and because of the use of powder coating booths, they completely utilize coating material. Powder coating technologies are not absolutely free from pollutants – components used to prepare surface and products utilized in the curing process are emitted into the environment.

The amount of emitted substances is less than 1% of the used epoxy resin, in the case of polyesters, it is from 1% to 2%, and for polyurethanes from 5% to 7%. Analyzing the substances emitted in the proper curing process of the different coatings following compounds were found:[3,6,8]

- Epoxy resins – mainly methyl isobutyl ketone;
- Epoxy-polyester – methyl isobutyl ketone, tetrahydrophthalic anhydride, benzoine (α-hydroxy-α-phenylacetophenone), and glycol
- Polyester – tetrahydrophthalic anhydride, benzene, toluene, xylenes, and glycol
- Polyurethane – caprolactam

Quantities of emitted substances are small when the proper process temperature is provided. An interviewed supervisors of furnaces suggested that increase of the oven temperature and overheating of paint causes a significant increase in the amount of emitted substances, but no data were found in the literature.

17.2.4 WATER-SOLUBLE PAINTS

Hazardous substances contained in the composition of a paint should be listed in the data sheet, however, manufacturers rather underestimate quantities of hazardous substances in their products as comes from the VOC analysis of two water-based paints.[11]

Paint A – red, water-based, thixotropic paint produced for thick, flexible coatings on iron, steel, cast iron, also galvanized materials, according to the data sheet, had only one hazardous substance in its composition – 5.5% zinc orthophosphate.

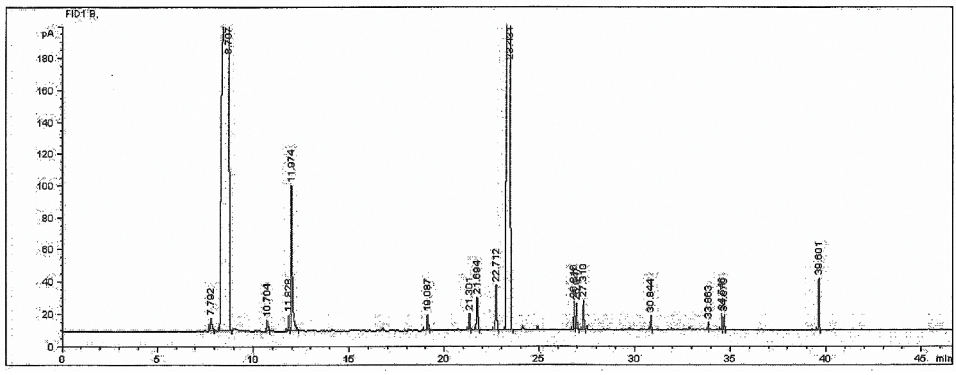


Figure 17.2.1. Gas chromatogram of paint A.

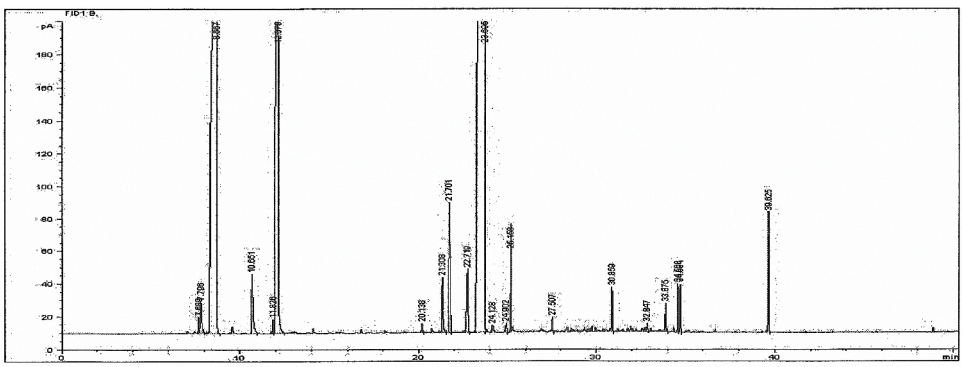


Figure 17.2.2. Gas chromatogram of paint B.

Paint B – green, waterborne paint, based on acrylic copolymers, was designed to apply thick, flexible coating on plated elements, also suitable for the renovation of old coatings. According to the data sheet, paint does not contain any harmful substances.

Substances emitted from paints were analyzed using gas chromatography.

Figures 17.2.1 and 17.2.2 present the chromatograms of paints A and B, respectively.

Chromatograms show that both paints contain numerous volatile organic substances. Using identification by mass spectroscopy, the following substances were detected in the paint A:

- Xylene, (auxiliary solvent)
- Isobutanol, (auxiliary solvent)
- Butyl acrylate (component of acrylic resin)
- 2-Butoxyethanol, (popular solvent in water-based paints)
- Diethylhexyl adipate, (softener)
- Diisooctyl ester of 1,2-benzenedicarboxylic acid (softener)

The following substances were found in the paint B:

- Ethylbenzene
- 1,3-Dimethylbenzene
- 2-Propanebutylate
- 2-Butoxyethanol
- Decane
- 1,2-Dimethylcyclohexane
- n-Dodecane
- Tripropylene glycol
- Dimethyl phthalate

In addition to these compounds, some small unidentified peaks were also present. They likely come from impurities in the raw materials. It can be concluded that information given in the safety data sheet does not necessarily reflect a real composition.

Particularly suspected are the cases in which the manufacturer declares that the paint does not contain volatile organic compounds, whereas the simple organoleptic test shows a strong odor characteristic of VOCs.

17.2.5 POWDER COATINGS

An assessment of exposure to substances emitted during powder coating in two selected paint shops was conducted.[12] During the curing of coatings, the concentration of VOCs did not exceed the limiting values. The measured concentrations were:

Epoxy-polyester paint

Cyclohexane	0.53 mg/m^3	TLV – 300 mg/m^3
Methylcyclohexane	0.17 mg/m^3	TLV – 1600 mg/m^3
Ethylcyclohexane	0.11 mg/m^3	TLV – not established
Heptane	0.77 mg/m^3	TLV – 1200 mg/m^3
Toluene	0.91 mg/m^3	TLV – 100 mg/m^3
Cumulative exposure = 0.01		

Polyester paint 1

Cyclohexane	0.13 mg/m^3	TLV – 300 mg/m^3
Methylcyclohexane	0.41 mg/m^3	TLV – 1600 mg/m^3
Ethylcyclohexane	0.20 mg/m^3	TLV – not established
Heptane	0.21 mg/m^3	TLV – 1200 mg/m^3
Toluene	1.75 mg/m^3	TLV – 100 mg/m^3
Cumulative exposure = 0.02		

Polyamide paint

p-Xylene	1.3 mg/m^3	TLV – 100 mg/m^3
Methylethylbenzene	10 mg/m^3	TLV – not established
Propylbenzene	7 mg/m^3	TLV – not established
Trimethylbenzene	35 mg/m^3	TLV – 100 mg/m^3

Using TLV values for methylethylbenzene and propylbenzene the same as the values for xylenes and trimethylbenzenes (TLV 100 mg/m^3) one can obtain the level of **cumulative exposure** equal **0.5**.

17.2.6 HOW TO EVALUATE THE HARMFUL EFFECT OF PAINTS?

High-solids paints and especially waterborne paints contain much smaller amounts of organic solvents and are generally regarded as "green" paints with a low hazard to human health. However, these paints typically contain 5 to 12% solvents and compounds with higher toxicity than the solvents typical of "classical" paints. When analyzing the harmfulness of a given material, the hazard index, a parameter defined as the sum of the ratios of contents of each VOC in the product and the value of the maximum permissible concentration of this component, can be considered.[5,7]

$$I = \sum \frac{C_i}{TLV_i} \times 10^6$$

where:

I hazard index
C_i content of solvent in the product [g/dm^3]
TLV limit value for the solvent [mg/m^3]

Usability of "hazard index" can be presented as an example in comparison of two types of paints: classical, solvent-based paint containing 35% of toluene and "green", water-based paint containing 10% of ethoxyethanol.

For classical paint

$I = 35/100 = 0.35$

For waterborne paint

$I = 10/20 = 0.5$

The above comparison shows that waterborne paint can be more harmful than the classical solvent paint.

In addition to the respiratory system, also the skin of hands – the most exposed part of the body – contacts these toxic substances. The best protection is given by the protective gloves. These gloves often make work too difficult, thus it is not always possible to use them. Then, the skin protective measures (SPM) such as creams, gels, and ointments can be used to protect skin. Well selected SPM protects the skin against non-polar organic solvents absorption as well as against the action of lubricants, paints, oils, and greases.[9,10]

REFERENCES

1 **Alternatives to Solvent-Borne Coatings. A Manual for Technical Assistance Providers**, editor NEWMOA and Il WMRC 1998
2 Directive 2004/42/CE of the European Parliament and of the Council of 21 April 2004 on the limitation of emissions of volatile organic compounds due to the use of organic solvents in certain paints and varnishes and vehicle refinishing products and amending Directive 1999/13/EC
3 S. Gorzkowski, Stan i perspektywy rozwoju technologii malowania proszkowego. Materialy z Konferencji KOROZJA, 2002 Warszawa 19-20 luty 2002.
4 A. C. Censullo, D. R. Jones, M. T. Wills; Direct VOC Analysis of Water-Based Coatings By Gas Chromatography and Solid-Phase Microextraction, *J. Coat. Technol*., **69**, 897, 33-41 (1997).
5 S. Gorzkowski, L. Kwiatkowski, Zagadnienia ekologiczne w procesach malarskich, Materialy z Konferencji KOROZJA 1998, Warszawa 25. 2.1998.
6 T. Ladra, Niektóre problemy ekologiczne w malarniach proszkowych, Materialy z Konferencji KOROZJA 2002 Warszawa 19-20 luty 2002.
7 K. Kazimierczak, S. Gorzkowski, Ekologiczne technologie wytwarzania powlok organicznych, Informator IChP, 1999, pp. 205-210.
8 K. M. Benczek, E. Gawlda, J. Kurpiewska, *JOSE*, **5**, 35-43, (2000).
9 J. Kurpiewska, J. Liwkowicz, K. M. Benczek K.M., **Dilemas and Issues of Modern Ergonomics and Work Safety Education and Research**, *Institute of Management Engineering Poznan University of Technology,* 2004 pp 267-276.
10 J. Kurpiewska, J. Liwkowicz, *J. Physiol. Pharmacol.*, **58**, Suppl 4, 75 (2007).
11 K. M. Benczek, S. Gorzkowski, Ocena szkodliwosci farb, *Bezpieczenstwo Pracy*, **3**, 8-10 (2006).
12 K. M. Benczek, Zagrozenia chemiczne przy stosowaniu farb proszkowych - ograniczyc emisje szkodliwych substancji, *Lakiernictwo przemyslowe*, **1**, 70-72 (2008).

17.3 SOLVENT LEVELS IN THE VEHICLE COLLISION REPAIR INDUSTRY

Samuel Keer
Centre for Public Health Research, Massey University, Wellington Campus, PO Box 756, Wellington 6140, New Zealand

17.3.1 INTRODUCTION

In the US alone, approximately 220,000 people are employed in 35,800 vehicle collision repair businesses.[1,2] The majority of workshops employ ≤4 workers, and only around 20% have ≥10 employees.[2] In the European Union, the total number of "body shops" (vehicle refinishing/collision repair enterprises) was estimated at 60,330 enterprises employing around 250,000 workers in 2007, with the value of the market estimated at €1.6 billion (in 2001).[3] The vehicle collision repair process (bodywork repair, refinishing, and spray painting) has traditionally involved the use of large quantities of solvent mixes for preparation work, cleaning of refurbished panels, and thinning of paint. This and the subsequent spraying of solvent-containing paints may result in elevated airborne solvent levels.[4] Many of the products used in the collision repair process contain solvents. The main products used, their uses and the combination of solvents they generally contain are shown in Table 17.3.1.

Table 17.3.1. Solvent-based products used in the vehicle collision repair industry.

Product	Uses	Solvent constituents
Preparatory degreasing/ cleaning fluids	Removing oily contaminants, road tar, etc. from bodywork and other vehicle parts prior to/ after initial disassembly, and immediately prior to painting	A variable combination of aromatic/aliphatic hydrocarbons, ketones, and propanols, the main constituents usually being petroleum naphtha, toluene, xylene and isopropanol
Polyester resin-based fillers	Repairing, filling and truing damaged bodywork	Predominantly styrene
Primer, color and topcoat paint thinners	Carrier solvent for various paints (primers, color coats, and top coats)	A variable combination of aromatic/aliphatic hydrocarbons and esters, the main constituents usually being butyl acetate, toluene and xylene
Equipment/spray gun cleaning fluids	Cleaning residual paint from spray guns and paint spray equipment	A variable combination of (primarily) aromatic hydrocarbons, ketones and esters, the main constituents usually being toluene, acetone, MEK and MIK, isopropanol and ethyl/butyl acetates

17.3.2 THE COLLISION REPAIR PROCESS

17.3.2.1 Job Roles

Based on work tasks, there are three main job roles in the collision repair industry: vehicle refinishing technicians, or spray painters; auto-body repair technicians, or panel beaters, and; management and administrative staff. In addition, some, particularly larger shops will employ workers who perform a range of general tasks on the workshop floor, including basic preparation/cleaning work, post-repair vehicle valeting and generally assisting the technical staff. There may also be a number of apprentice technical staff who perform some or all of the tasks associated with vehicle repair and refinishing. Due to differences in the work tasks performed and products used, solvent exposures differ between job roles.[5,6]

17.3.2.2 Work tasks associated with specific job roles

As workshops are often small to medium-sized enterprises (SMEs) with limited staff numbers,[7] spray painting work is variable and includes a range of tasks, including sanding of panels prior to painting; degreasing immediately prior to painting; masking areas of vehicles/panels to avoid paint overspray; mixing of paint; spray painting primer, color and clearcoat (topcoat) paints, and; cleaning spray equipment. Panel beaters are primarily responsible for; disassembly and replacement or repair of damaged parts (including chassis realignment and cutting, welding and grinding of steel/aluminum/plastic); planishing to restore (steel or aluminum) panels; degreasing of panels/parts after disassembly and prior to repair; filling of damaged panels with polyester resin, and; sanding of repaired areas. They may also apply limited quantities of primer paint from an aerosol can, often in non-mechanically ventilated work areas.[5,7]

Spray painting and panel beating are generally performed in designated areas, often without physical barriers between them, particularly in smaller workshops. However, some, particularly larger shops have separate buildings for panel beating and spray painting, although usually with open internal access between them. Panel beating and prepainting preparation are done in the main workshop(s), where ventilation is often restricted to open roller doors, or occasionally mechanical ventilation in the form of roof-mounted extractor fans.[5]

Painting is primarily conducted inside spray booths, most of which are commercially produced single vehicle units with downdraft extraction systems (ceiling to floor air flow).[5,7] Some workshops also use cross-draft booths (horizontal air flow), some of which may be owner-built. Additionally, particularly in larger shops, commercial or owner-built preparation painting bays are used. These units are often open-sided, with cross-draft ventilation. They are principally used to apply primer paint to bare or refurbished parts.[1,7-10]

Paint is generally mixed in a dedicated space for preparing paint and spraying equipment. This space is also used for storing paint, paint tints, and raw bulk solvents (for cleaning, degreasing and thinning of paint). The spray equipment washer used by the majority of workshops is a purpose-built cabinet that can be open-sided or enclosed, sometimes with its own local exhaust ventilation (LEV) system. Equipment may also be cleaned by hand using brushes and cloths.[5,6]

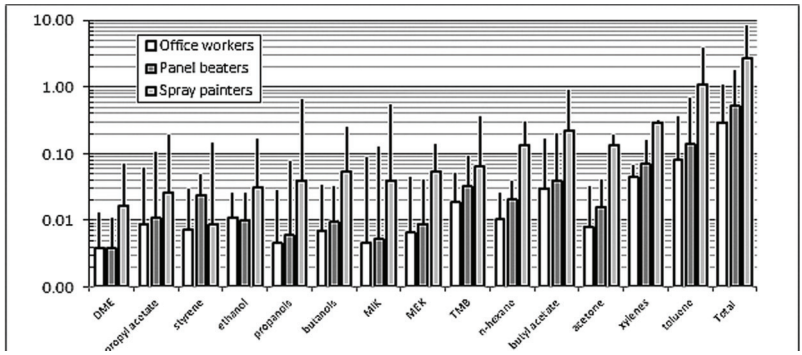


Figure 17.3.1. Full work-shift equivalent geometric mean personal airborne solvent concentrations (compound specific and summed total, in parts per million (ppm)) in samples from New Zealand collision repair workers. DME - dimethoxyethane, MIK - methyl isobutyl ketone, MEK - methyl ethyl ketone, TMB - trimethylbenzene. Error bars on columns indicate geometric standard deviation. [Adapted, by permission, from
Source: S. Keer *et al*., Determinants of airborne solvent exposures in the New Zealand collision repair industry, *Ann. Work Expo Health*, **62** (7), 871-883, 2018.]

17.3.2.3 Airborne solvent exposures in the collision repair industry

The most likely route by which collision repair workers are exposed to solvents is *via* inhalation, but dermal exposures may also be significant,[11-14] particularly when effective respiratory protection is worn.[13-16] Figure 17.3.1 shows the results of airborne exposure monitoring in a recent study in the New Zealand collision repair industry.[5] The solvents found in greatest abundance were aromatics, namely toluene and xylene, followed by butyl acetate, trimethylbenzene, and n-hexane, which is consistent with the findings of previous studies in this industry.[17-19]

17.3.2.4 Exposure levels

Assessments of global trends of occupational solvent exposures indicate a steady decline in levels across a range of industries over the past 40 years,[20-22] including the vehicle collision repair industry, most likely as a result of changes in product formulations, workplace conditions, worker behaviors, and health and safety practices. However, aside from the New Zealand study described above,[5] few studies have assessed exposure levels in the collision repair industry, particularly in the past decade. Results from studies in the collision repair industry which have included quantitative monitoring of personal airborne exposures (e.g., collected in the worker's breathing zone)[23] are shown in Table 17.3.2.

Table 17.3.2. Results of airborne mixed solvent exposure monitoring from studies in the vehicle spray painting/collision repair industry

Ref. #	# of samples	Sampling method/device (sorbent medium)	Average sampling duration	# solvents measured	Mean mixed solvent level ppm	%*
24	54	–	1 h. (task-based)	9	61.3	31.8
25	106	–	not specified	12	62.3	30.0
8	11	Active – tubes (activated carbon)	30 min. (task-based)	18	117.0	160.0
26	137	Passive – dosimeters (activated carbon)	full-shift	2	16.4	8.4
27	67	Passive – dosimeters (activated carbon)	full-shift	6**	33.2	19.3
17	70	Active – tubes (activated carbon)	4-7 h. (full shift)	15	52.3	19.0
28	30	Active – tubes (activated carbon)	15 min. – 5 h. (combination of task-based/full shift)	12	13.7	–
29	–	Passive – dosimeters (activated carbon)	3-5 h. (full-shift)	6	4.6	–
19	51/28	Active – tubes (activated carbon)	6-8 h. (full-shift)	10	2.3/0.8	19.0/7.0
30	8	Passive – dosimeters (activated carbon)	4-5.5 h. (full-shift)	5	22.5	<100
18	6	Active – tubes (Tentax TA polymer resin)	3 h. (full-shift)	18	20.2	–
5	92	Active – 400cc Stainless steel canisters and flow controllers	4-7 h. (full-shift)	14	1.2	8.0

%* – Estimated percentage of relevant workplace exposure standard (at the time of the study) - Additive limit value (ALV)[v]; ** most prevalent; [v] Exposure Indices – Calculated by dividing the concentration of each compound detected in the sample by its relevant exposure standard (see American Conference of Governmental Industrial Hygienists[32] for examples), and summing the resultant values together (values are taken from the manuscripts for each study, therefore the method used to calculate the ALV varies between studies, e.g., due to changes in exposure standards over time). If this number exceeds 1, it is deemed that the exposure standard has been exceeded for the mixture of solvents detected.

As shown in Table 17.3.2, the average airborne exposure levels in earlier studies were generally higher than in later studies, which is consistent with suggestions that occupational solvent exposures may have declined globally.[5,20-22] However, aside from the New Zealand study described above, few studies of solvent levels in this industry have been conducted in the past decade, so a worldwide decline in exposures in this industry has not been confirmed. Also, suggestions of a general decline in occupational exposures are based primarily on European data, and may, therefore, not be applicable to the industry in other, particularly developing countries, where workplace conditions differ.[22]

17.3.2.5 Determinants of exposures in the collision repair industry and the effectiveness of control measures.

If true, the decline in solvent exposures in this industry over the past ten years[22] may be due to technological advances in the products, equipment and exposure control measures used. Advances in paint technology have led to the development of low VOC and water-borne paints,[33] which have both been associated with lower airborne solvent levels.[19] Engineering control technologies have also improved, and their use becomes more widespread over the past few decades, due to increased pressure on the control exposures, regulation of environmental emissions, and specifically for the vehicle collision repair industry,[13,33] the superior quality and consistency of paint finish they produce.[9,34] As discussed above, active ventilation in contemporary collision repair workshops consists of spray booths and mechanical extraction of specific or general work areas.[5,10] In addition to improving the consistency and quality of paint finish, evidence suggests they are effective in reducing worker exposures.[21,22,35] Both LEV and the general ventilation of the workspace have been shown to reduce levels of various airborne contaminants, including solvents.[36-39]

Relatively few studies have assessed the specific determinants of solvent exposures in the collision repair industry. The New Zealand study described above[5] included an assessment of exposure determinants and showed a number of factors related to workshop layout, equipment design, workplace practices, and worker behaviors were associated with exposure levels. For example, certain arrangements of LEV in the paint mixing room (extraction vents located on the opposite wall to the main paint mixing bench) and spray booth (e.g., downdraft air-flow) were associated with lower exposures. Also, time spent mixing paint, cleaning equipment with solvents, spraying primer, and spraying clearcoat paint was associated with higher exposure levels. The combined non-spray painting tasks (mixing paint, degreasing, and cleaning equipment) were more strongly associated with exposure than the combined spray painting tasks, suggesting exposures outside the spray booth were less well controlled (than in the spray booth). Similar observations have been reported by others.[19] An assessment of 'peaks' in exposure conducted as part of the same study showed equipment cleaning and pre-painting preparatory work (e.g., degreasing panels) were associated with elevated and sustained peaks in mixed solvent levels (measured using a photo-ionization detector)[40] of 80-160 ppm during paint mixing and 10-1150 ppm during spray equipment cleaning. Levels were below the limit of detection of the instrument (0.1 ppm) during spray painting in a downdraft spray booth, suggesting these booths are highly effective at controlling airborne exposures. However, brief peaks of around 300 ppm were observed in a booth with cross-draft extraction,[5] suggesting such booths are less effective. The inferior performance of cross-draft compared to down-draft spray booths has been observed in several other studies.[27,28,32]

17.3.2.6 Solvent-related health effects in vehicle collision repair workers

Occupational solvent exposure may result in a range of systemic effects, including organ damage and carcinogenesis,[41,42] but acute and chronic effects on the brain and nervous system are perhaps most well recognized.[4,43,44] Symptoms associated with acute exposure to solvents are well documented[45-47] and include irritation of the mucosal membranes (rhi-

nitis, sore/itchy eyes, etc.)[48,49] nausea, dizziness, feelings of intoxication and headache[4,28] which in extreme cases of very high exposure may result in unconsciousness and even death (e.g., through respiratory depression).[4,50] The transient effects of solvents on brain chemistry are largely responsible for acute symptoms and are unlikely to reflect actual neurotoxic damage. On the other hand, damage to the central and peripheral nervous systems and an increased risk of permanent and evident neurological damage has been associated with one-off incidents of extremely high exposure, as well as low-level exposures over a period of years to decades.[4,51-55] In severe cases, workers may be diagnosed with "chronic solvent-induced encephalopathy" (CSE), a condition characterized by neurobehavioral symptoms associated with central nervous system depression and deficits in neurobehavioral performance, which may persist even upon cessation of exposure.[56] Individuals diagnosed with CSE most commonly have a history of employment in industrial, automotive and metal painting and refinishing, particularly spray painting.[51,57] Cases of CSE are most often exposed to aromatic hydrocarbons, particularly mixtures containing toluene and xylene,[51] which are amongst the primary constituents of many solvent-based products used in the vehicle collision repair industry.[8,33]

A number of epidemiological studies have been conducted in the collision repair industry over the past half-century which has included assessments of symptoms of neurotoxicity and cognitive performance.[25,29,31,52,58,59] Despite some inconsistencies, particularly regarding the results of objective tests of cognitive function, most studies suggest vehicle and other spray painters are at greater risk of neurobehavioral effects compared to unexposed workers.[28,60] Effects are most commonly observed in the functional domains of attention (concentration), mood, memory (particularly short-term), information processing speed, and manual speed/dexterity.[24,25,27,29,31,52,59-61] These effects have also often been observed in workers with full-shift average airborne exposures at or below relevant workplace exposure standards ("safe" levels set by various international scientific advisory and regulatory groups.)[31,32,52,62] Peak exposures (which contribute little to average levels, described above)[63,64] may be more important in the development of neurobehavioral effects, but as few studies in the collision repair industry have measured them, this remains unclear. In addition, dermal (skin) exposures may be more strongly associated with symptoms than average airborne exposures, especially when effective respiratory protection is in place,[11,13,14] but again few studies have assessed these exposures in the collision repair industry.

REFERENCES

1. Bejan, A., L.M. Brosseau, and D.L. Parker, Exposure Assessment in Auto Collision Repair Shops. *J. Occup. Environ. Hyg*., 2011. **8**(7): p. 401-408.
2. United States Census Bureau, Statistics of U.S. Businesses (SUSB). Available online, URL: https://www.census.gov/programs-surveys/susb.html.
3. Entec UK, Reducing VOC Emissions from the Vehicle Refinishing Sector, Final Report by Entec UK Limited and the Paint Research Association for the European Commission, Environment Directorate-General. 2000.
4. Dick, F.D., Solvent neurotoxicity. *Occup. Environ. Med.*, 2006. **63**(3): p. 221-6, 179.
5. Keer, S., et al., Determinants of Airborne Solvent Exposure in the Collision Repair Industry. *Ann Work Expo Health*, 2018: p. wxy047-wxy047.
6. Keer, S., et al., Effects of Personal Protective Equipment Use and Good Workplace Hygiene on Symptoms of Neurotoxicity in Solvent-Exposed Vehicle Spray Painters. *Ann Work Expo Health*, 2018. **62**(3):

p. 307-320.
7. Brosseau, L., et al., Workplace safety and health programs, practices, and conditions in auto collision repair businesses. *J. Occup. Environ. Hyg*., 2014. **11**(6): p. 354-365.
8. De Medinilla, J. and M. Espigares, Contamination by organic solvents in auto paint shops. *Ann. Occup. Hyg.*, 1988. **32**(4): p. 509-513.
9. Heitbrink, W.A., et al., Control of Paint Overspray in Autobody Repair Shops. *Am. Ind. Hyg. Assoc. J*., 1995. **56**(10): p. 1023-1032.
10. Woskie, S.R., et al., Determinants of Isocyanate Exposures in Auto Body Repair and Refinishing Shops. *Ann. Occup. Hyg*., 2004. **48**(5): p. 393-403.
11. Fiserova-Bergerova, V., J.T. Pierce, and P. Droz, Dermal absorption potential of industrial chemicals: criteria for skin notation. *Am. J. Ind. Med.*, 1990. **17**(5): p. 617-635.
12. World Health Organization, Dermal Exposure, in Environmental Health Criteria. 2014, Inter-Organization Programme for the Sound Management of Chemicals, World Health Organization: Geneva, Switzerland.
13. Semple, S., Dermal exposure to chemicals in the workplace: just how important is skin absorption? *Occup. Environ. Med*., 2004. **61**(4): p. 376-82.
14. Semple, S., et al., A dermal model for spray painters. Part II: Estimating the deposition and uptake of solvents. *Ann. Occup. Hyg*., 2001. **45**(1): p. 25-33.
15. Chang, F.-K., *et al*., Evaluation of dermal absorption and protective effectiveness of respirators for xylene in spray painters. *Int. Arch. Occup. Environ. Health*, 2007. **81**(2): p. 145-150.
16. Vermeulen, R., et al., Identification of dermal exposure pathways in the rubber manufacturing industry. *Ann. Occup. Hyg*., 2000. **44**(7): p. 533-541.
17. Winder, C. and P.J. Turner, Solvent exposure and related work practices amongst apprentice spray painters in automotive body repair workshops. *Ann. Occup. Hyg*., 1992. **36**(4): p. 385-394.
18. Caro, J. and M. Gallego, Environmental and biological monitoring of volatile organic compounds in the workplace. *Chemosphere*, 2009. **77**(3): p. 426-433.
19. Bråtveit, M., B.E. Hollund, and B.E. Moen, Reduced exposure to organic solvents by use of water-based paint systems in car repair shops. *Int. Arch. Occup. Environ. Health*, 2004. **77**(1): p. 31-38.
20. Caldwell, D.J., *et al*., Hydrocarbon solvent exposure data: compilation and analysis of the literature. *Am. Ind. Hyg. Assoc. J*., 2000. **61**(6): p. 881-94.
21. Burstyn, I. and H. Kromhout, Trends in inhalation exposure to hydrocarbons among commercial painters in The Netherlands. *Scand. J. Work Environ. Health*, 2002. **28**(6): p. 429-438.
22. Kauppinen, T., et al., Trends of Occupational Exposure to Chemical Agents in Finland in 1950-2020. *Ann. Occup. Hyg*., 2013. **57**(5): p. 593-609.
23. Checkoway, H., N.E. Pearce, and D. Kriebel, **Research Methods in Occupational Epidemiology**. 2 ed. Monographs in Epidemiology and Biostatistics. 2004, New York: *Oxford University Press*. 386.
24. Hänninen, H., et al., Behavioral effects of long-term exposure to a mixture of organic solvents. *Scand. J. Work. Environ. Health*, 1976. **2**(4): p. 240-55.
25. Elofsson, S.A., et al., Exposure to organic solvents. A cross-sectional epidemiologic investigation on occupationally exposed care and industrial spray painters with special reference to the nervous system. *Scand. J. Work. Environ. Health*, 1980. **6**(4): p. 239-73.
26. Daniell, W., et al., The contributions to solvent uptake by skin and inhalation exposure. *Am. Ind. Hyg. Assoc. J.*, 1992. **53**(2): p. 124-129.
27. Daniell, W., et al., Neuropsychological performance and solvent exposure among car body repair shop workers. *Br. J. Ind. Med.*, 1993. **50**(4): p. 368-77.
28. Moen, B.E. and B.E. Hollund, Exposure to organic solvents among car painters in Bergen, Norway. *Ann. Occup. Hyg.*, 2000. **44**(3): p. 185-189.
29. Böckelmann, I., et al., The psychological effects of exposure to mixed organic solvents on car painters. *Disabil. Rehabil.*, 2002. **24**(9): p. 455-461.
30. Vitali, M., et al., Exposure to organic solvents among handicraft car painters: a pilot study in Italy. *Ind. Health*, 2006. **44**(2): p. 310-317.
31. Keer, S., et al., Neuropsychological performance in solvent-exposed vehicle collision repair workers in New Zealand. *PLoS One*, 2017. **12**(12): p. e0189108.
32. American Conference of Governmental Industrial Hygienists, TLVs and BEIs: Threshold limit values for chemical substances and physical agents biological exposure indices. 2015, Cincinnati, OH.
33. Akafuah, N.K., et al., Evolution of the automotive body coating process-a review. *Coatings*, 2016. **6**(2): p. 24.
34. Eklund, B.M. and T.P. Nelson, Evaluation of VOC emission measurement methods for paint spray booths. *J. Air Waste Manage. Assoc.*, 1995. **45**(3): p. 196-205.

35. Leung, M.K., C.-H. Liu, and A.H. Chan, Occupational exposure to volatile organic compounds and mitigation by push-pull local exhaust ventilation in printing plants. *J. Occup. Health,* 2005. **47**(6): p. 540-547.
36. Tjoe Nij, E., et al., Dust Control Measures in the Construction Industry. *Ann. Occup. Hyg*., 2003. **47**(3): p. 211-218.
37. Jafari, M.J., A. Karimi, and M.R. Azari, The role of exhaust ventilation systems in reducing occupational exposure to organic solvents in a paint manufacturing factory. *Indian J. Occup. Environ. Med*., 2008. **12**(2): p. 82.
38. Kromhout, H., E. Symanski, and S.M. Rappaport, A comprehensive evaluation of within-and between-worker components of occupational exposure to chemical agents. *Ann. Occup. Hyg*., 1993. **37**(3): p. 253-270.
39. Coy, J.D., et al., Field Evaluation of a Portable Photoionization Detector for Assessing Exposure to Solvent Mixtures. *Am. Ind. Hyg. Assoc. J*., 2000. **61**(2): p. 268-274.
40. Lynge, E., A. Anttila, and K. Hemminki, Organic solvents and cancer. *Cancer Causes Control*, 1997. **8**(3): p. 406-419.
41. Brautbar, N. and J. Williams, Industrial solvents and liver toxicity: risk assessment, risk factors and mechanisms. *Int. J. Hyg. Environ. Health*, 2002. **205**(6): p. 479-491.
42. Chen, R., F. Dick, and A. Seaton, Health effects of solvent exposure among dockyard painters: mortality and neuropsychological symptoms. *Occup. Environ. Med*., 1999. **56**(6): p. 383-7.
43. Baker, E.L., A review of recent research on health effects of human occupational exposure to organic solvents. A critical review. *J. Occup. Med*., 1994. **36**(10): p. 1079-92.
44. Lammers, J., *et al*., Neurobehavioral effects of acute exposure to normal (n-) paraffins. *Int. J. Toxicol*., 2011. **30**(1): p. 47-58.
45. McKee, R.H., *et al*., Neurobehavioral effects of acute exposure to aromatic hydrocarbons. *Int. J. Toxicol*., 2010. **29**(3): p. 277-290.
46. Kobald, S.O., *et al*., Neurobehavioral and neurophysiological effects after acute exposure to a single peak of 200 ppm toluene in healthy volunteers. *Neurotoxicology*, 2015. **48**: p. 50-59.
47. Bælum, J., *et al*., Response of solvent-exposed printers and unexposed controls to six-hour toluene exposure. *Scand. J. Work Environ. Health*, 1985: p. 271-280.
48. Wang, J.D. and J.D. Chen, Acute and Chronic Neurological Symptoms Among Paint Workers Exposed to Mixtures of Organic Solvents. *Environ. Res*., 1993. **61**(1): p. 107-116.
49. Shepherd, R., Mechanism of sudden death associated with volatile substance abuse. *Hum. Toxicol*., 1989. **8**(4): p. 287-291.
50. Keski-Santti, P., *et al*., Occupational chronic solvent encephalopathy in Finland 1995-2007: incidence and exposure. *Int. Arch. Occup. Environ. Health*, 2010. **83**(6): p. 703-12.
51. Keer, S., *et al.*, Solvent neurotoxicity in vehicle collision repair workers in New Zealand. *Neurotoxicology*, 2016. **57**: p. 223-229.
52. Dryson, E., Chronic Organic Solvent Neurotoxicity: Diagnostic Criteria. 1992, 1998, Occupational Safety and Health Service, New Zealand Department of Labour: Wellington, New Zealand.
53. Gamble, J.F., Low-level hydrocarbon solvent exposure and neurobehavioural effects. *Occup. Med.* (Lond.), 2000. **50**(2): p. 81-102.
54. Ihrig, A., *et al*., Longitudinal study to explore chronic neuropsychologic effects on solvent exposed workers. *Ind. Health*, 2005. **43**(3): p. 588-596.
55. van der Hoek, F.J.A., M.M. Verberk, and G. Hageman, Criteria for solvent-induced chronic toxic encephalopathy: a systematic review. *Int. Arch. Occup. Environ. Healt*h, 2000. **73**(6): p. 362-368.
56. Dryson, E.W. and J.A. Ogden, Chronic solvent neurotoxicity in New Zealand: notified cases between 1993 and 1997. *N. Z. Med. J.,* 1998. **111**(1077): p. 425-427.
57. Meyer-Baron, M., *et al.*, The impact of solvent mixtures on neurobehavioral performance: conclusions from epidemiological data. *Neurotoxicology*, 2008. **29**(3): p. 349-60.
58. Husman, K., Symptoms of car painters with long-term exposure to a mixture of organic solvents. *Scand. J. Work. Environ. Health*, 1980. **6**(1): p. 19-32.
59. Triebig, G., *et al*., Neurotoxicity of solvent mixtures in spray painters. II. Neurologic, psychiatric, psychological, and neuroradiologic findings. *Int. Arch. Occup. Environ. Health*, 1992. **64**(5): p. 361-72.
60. Lee, S., A study on the neurobehavioral effects of occupational exposure to organic solvents in Korean workers. *Environ. Res*., 1993. **60**(2): p. 227-232.
61. Worksafe New Zealand, Workplace Exposure Standards and Biological Exposure Indices. 9 ed. 2017, Wellington, NZ.
62. Morrow, L.A., et al., Risk factors associated with persistence of neuropsychological deficits in persons with

organic solvent exposure. *J. Nerv. Ment. Dis*., 1991. **179**(9): p. 540-5.
63. Checkoway, H. and C.H. Rice, Time-weighted averages, peaks, and other indices of exposure in occupational epidemiology. *Am. J. Ind. Med.*, 1992. **21**(1): p. 25-33.

18

Regulations

18.1 REGULATIONS IN NORTH AMERICA

Carlos M. Nunez
U.S. Environmental Protection Agency National Risk Management Research Laboratory, Research Triangle Park, NC, USA

18.1.1 INTRODUCTION

Since the Clean Air Act Amendments of 1970, when a war against pollution was declared, solvents have been on the U.S. regulatory radar screen.[1] This represented the beginning of new environmental policies which led to today's more stringent regulations with a greater focus on toxic substances.[2] In the U.S., historically, these policies and regulations have been divided by medium (air, water, and land), which has represented a challenge to the regulated industries and the Federal, State, and local regulatory communities. Later, however, the U.S. Congress and the Environmental Protection Agency (EPA) have recognized the need to address environmental problems from a more holistic approach considering multimedia and innovative environmental management strategies.[3] Hence, various programs and initiatives have emerged, which have proven to be extremely successful, encouraging voluntary industry participation rather than the old command and control approach.[4]

Almost all solvents are volatile organic compounds (VOCs) and hazardous air pollutants (HAPs), and their evaporation creates environmental problems that have become the focus of many domestic and international regulations and initiatives. A VOC solvent is defined by EPA as follows:

- Volatile organic compounds (VOC) means any compound of carbon, excluding carbon monoxide, carbon dioxide, carbonic acid, metallic carbides or carbonates and ammonium carbonate, which participates in atmospheric photochemical reactions, except those designated by EPA as having negligible photochemical reactivity.
- Volatile organic compounds or VOCs are organic chemical compounds whose composition makes it possible for them to evaporate under normal indoor atmospheric conditions of temperature and pressure.[5]

In 1996, an estimated 19 million tons of VOCs have been emitted in the U.S. of which 33 percent came from solvent utilization (see Table 18.1.1).[6] This compares with 13 million tons emitted in 2012.[6]

In the lower atmosphere VOC solvents participate in photochemical reactions to form, to varying degrees, ground-level ozone and other oxidants which affect health, as well as cause damage to materials, crops, and forests. (Ozone concentration was decreased in the USA by 25% in 2012 as compared with 1980).[6] Between 1980 and 2016, there was a 31% decrease in the national average of the ground-level of ozone concentration.[6] Ozone impairs the normal functioning of the lungs and reduces the ability to perform physical exercise. Such effects are more severe in individuals with sensitive respiratory systems. Even healthy adults can experience symptoms and reduction in lung function during moderate exercise at ozone levels below the current ozone standard.

Table 18.1.1. Major categories in the solvent utilization sector and their estimated VOC emissions[6]

Source category	Estimated Emissions, 1996	
	Quantity, tons	Distribution in solvent utilization sector, %
Degreasing	661,000	11
Graphic arts	389,000	6
Dry cleaning	190,000	3
Surface coating	2,881,000	46
Other industrial and non-industrial processes	2,153,000	34
Total emissions	**6,274,000**	**100**

It is expected that the solvent consumption in the USA in 2020 will be 4.3 million tonnes.

Solvents are pollutants that have been associated with serious health effects such as cancer, liver or kidney damage, reproductive disorders, and developmental or neurological problems.[7,8] They also have detrimental environmental effects on wildlife and degrade water or habitat quality. The Clean Air Act of 1990 in section 112(b) lists 188 HAPs,[9] some of which are solvents (see Table 18.1.2),[10-14] for which sources are identified and regulated. The contents of Table 18.1.2 will be discussed in more detail later.

Table 18.1.2. Classification of solvents by their codes, exposure limits, and environmental effects.

CAS #	Chemical Name	EPA Code[10]	[a]Permissive Exposure Limits (PEL)[13,14]		[b]TLV[14] ppmv	Environmental Effect			
			ppmv	mg/m^3		O	T	D	G
50-00-0	Formaldehyde	K009; K010; K040; K156; K157	see 29 CFR 1910.1048		0.1	✓	✓		
50-21-5	Lactic acid					✓			
50-70-4	Sorbitol					✓			

Table 18.1.2. Classification of solvents by their codes, exposure limits, and environmental effects.

CAS #	Chemical Name	EPA Code[10]	[a]Permissive Exposure Limits (PEL)[13,14]		[b]TLV[14] ppmv	Environmental Effect			
			ppmv	mg/m^3		O	T	D	G
56-23-5	Carbon tetrachloride	F001; F024; F025; K016; K019; K020; K021; K073; K116; K150; K151; K157; U211; D019	10		5	✓			
56-38-2	Parathion	P089		(S) 0.1	0.1 mg/ m^3	✓			
56-81-5	Glycerine			5		✓			
56-93-9	Benzyltrimethyl-ammonium chloride					✓			
57-14-7	1,1-Dimethyl hydrazine	K017; K108; K109; K110; U098	0.5	1	0.01	✓			
57-55-6	Propylene glycol					✓			
57-57-8	β-Propiolactone		see 29 CFR 1910.1013		0.5	✓	✓		
60-29-7	Ethyl ether	U117	400	1200	400	✓			
60-34-4	Methyl hydrazine	P068	(C) 0.2	(C) 0.35	0.01	✓	✓		
62-53-3	Aniline	K083; K103; K104; U012	(S) 5	(S) 19	2	✓	✓		
62-75-9	N-Nitrosodimethylamine	P082	see 29 CFR 1910.1016			✓	✓		
64-17-5	Ethyl alcohol		1000	1900	(ST) 1000	✓			
64-18-6	Formic acid	K009; K010; U123	5	9	5	✓			
64-19-7	Acetic acid		10	25	10	✓			
64-67-5	Diethyl sulfate					✓	✓		
67-56-1	Methanol	U154	200	260	200	✓	✓		
67-63-0	Isopropyl alcohol		400	980	200	✓			
67-64-1	Acetone	U002	1000	2400	250	ε			
67-66-3	Chloroform	K009; K010; K019; K020; K021; K029; K073; K116; K149; K150; K151; U044; D022	(C) 50	(C) 240	10	✓	✓		
67-68-5	Dimethyl sulfoxide					✓			
68-12-2	Dimethyl formamide		10	30	10	✓	✓		
71-23-8	n-Propyl alcohol		200	500	100	✓			
71-36-3	n-Butyl alcohol	U031	100	300		✓			

Table 18.1.2. Classification of solvents by their codes, exposure limits, and environmental effects.

CAS #	Chemical Name	EPA Code[10]	[a]Permissive Exposure Limits (PEL)[13,14]		[b]TLV[14] ppmv	Environmental Effect			
			ppmv	mg/m^3		O	T	D	G
71-43-2	Benzene	F005; F024; F025; F037; F038; K085; K104; K105; K141; K142; K143; K144; K145; K147; K151; K159; K169; U019; D018	see 29 CFR 1910.1028 Table Z-2		0.5	✓	✓		
71-55-6	1,1,1-Trichloroethane	F001, F002, F024, F025, K019, K020, K028, K029, U226	350	1900	350	ε	✓	✓	✓
74-88-4	Methyl iodide	U138	5	28	2	✓	✓		
74-96-4	Ethyl bromide		200	890	5	✓			
75-00-3	Ethyl chloride	K018	1000	2600	100	✓	✓		
75-04-7	Ethylamine		10	18	5	✓			
75-05-8	Acetonitrile	K011; K013; K014; U003	40	70	20	✓	✓		
75-07-0	Acetaldehyde	U001	200	360		✓	✓		
75-08-1	Ethyl mercaptan		(C) 10	(C) 25	0.5	✓			
75-09-2	Dichloromethane	F001; F002; F024; F025; K009; K010; K156; K158; U080		(2)	50	ε	✓		
75-15-0	Carbon disulfide	F005; P022		(2)	10	✓	✓		
75-18-3	Dimethyl sulfide					✓			
75-25-2	Bromoform	U225	(S) 0.5	(S) 5	0.5	✓	✓		
75-31-0	Isopropylamine		5	12	5	✓			
75-33-2	Isopropyl mercaptan					✓			
75-34-3	1,1-Dichloroethane	F024, F025; U076	100	400	100	✓	✓		
75-35-4	Vinylidene chloride	F024; F025; K019; K020; K029; U078; D029			5	✓	✓		
75-52-5	Nitromethane		100	250	20	✓			
75-55-8	Propyleneimine	P067	2	5	0.2	✓	✓		
75-56-9	Propylene oxide		100	240	2	✓	✓		
75-64-9	tert-Butylamine					✓			
75-65-0	tert-Butyl alcohol		100	300	100	✓			
75-68-3	1-Chloro-1,1-difluoroethane (HCFC-142b)	F001				ε		✓	✓

Table 18.1.2. Classification of solvents by their codes, exposure limits, and environmental effects.

CAS #	Chemical Name	EPA Code[10]	[a]Permissive Exposure Limits (PEL)[13,14]		[b]TLV[14] ppmv	Environmental Effect			
			ppmv	mg/m^3		O	T	D	G
75-69-4	Trichlorofluoromethane (CFC-11)	F001; F002; F024; F025; U121	1000	5600	1000	ε		✓	✓
75-83-2	Neohexane					✓			
76-13-1	1,1,2-Trichloro-1,2,2-trifluoroethane (CFC-113)	F001; F002	1000	7600	1000	ε		✓	✓
76-14-2	1,2-Dichloro-1,1,2,2-tetrafluoroethane(CFC-114)	F001	1000	7000	1000			✓	✓
77-47-4	Hexachlorocyclopentadiene	F024; F025; K032; K033; K034; U130			0.01	✓	✓		
77-78-1	Dimethyl sulfate	K131; U103	1	5	0.1	✓	✓		
78-59-1	Isophorone		25	140	(C) 5	✓	✓		
78-78-4	Isopentane					✓			
78-81-9	Isobutylamine					✓			
78-83-1	Isobutyl alcohol	F005; U140	100	300	50	✓			
78-84-2	Isobutyraldehyde					✓			
78-87-5	1,2-Dichloropropane	U083	75	350	10	✓	✓		
78-88-6	2,3-Dichloropropene	F024; F025				✓			
78-92-2	sec-Butyl alcohol		150	450	100	✓			
78-93-3	Methyl ethyl ketone	F005; U159; D035	200	590	200	✓			
78-96-6	Monoisopropanolamine					✓			
79-01-6	Trichloroethylene	F001; F002; F024; F025; K018; K019; K020; U228; D040		(2)		✓	✓		
79-04-9	Chloroacetyl chloride				0.05 (S)	✓			
79-09-4	Propionic acid				10	✓			
79-10-7	Acrylic acid	U008			2	✓	✓		
79-20-9	Methyl acetate		200	610	200	ε			
79-21-0	Peracetic acid					✓			
79-24-3	Nitroethane		100	310	100	✓			
79-34-5	1,1,2,2-Tetrachloroethane	F001; F024; F025; K019; K020; K030; K073; K095; K150; U209	5	35	1	ε	✓		
79-44-7	Dimethyl carbamoyl chloride	U097				✓	✓		
79-46-9	2-Nitropropane	F005; U171	25	90	10	✓	✓		

Table 18.1.2. Classification of solvents by their codes, exposure limits, and environmental effects.

CAS #	Chemical Name	EPA Code[10]	[a]Permissive Exposure Limits (PEL)[13,14]		[b]TLV[14] ppmv	Environmental Effect			
			ppmv	mg/m^3		O	T	D	G
80-62-6	Methyl methacrylate	U162	100	410	50	✓	✓		
84-66-2	Diethyl phthalate	U088			5	✓			
84-74-2	Dibutyl phthalate	U069		5	5 mg/m^3	✓			
85-68-7	Butyl benzyl phthalate					✓			
87-68-3	Hexachlorobutadiene	F024; F025; K016; K018; K030; D033			0.02	✓	✓		
90-02-8	Salicylic aldehyde					✓			
91-17-8	Decahydronapthalene					✓			
91-22-5	Quinoline					✓	✓		
95-47-6	o-Xylene	U239	100	435	100	✓	✓		
95-50-1	1,2-Dichlorobenzene	F024; F025; K042; K085; K105; U070	(C) 50	(C) 300	25	✓			
96-09-3	Styrene oxide					✓	✓		
96-12-8	1,2-Dibromo-3-chloropropane	U066	see 29 CFR 1910.1044			✓	✓		
96-33-3	Methyl acrylate		10	35	2	✓			
96-37-7	Methyl cyclopentane					✓			
97-63-2	Ethyl methacrylate					✓			
97-64-3	Ethyl lactate					✓			
97-88-1	n-Butyl methacrylate					✓			
98-00-0	Furfuryl alcohol		50	200	0.2	✓			
98-01-1	Furfural	U125	5	20	0.2	✓			
98-07-7	Benzotrichloride	K015; K149; U023				✓	✓		
98-56-6	p-Chlorobenzotrifluoride					ε			
98-82-8	Cumene	U055	(S) 50	(S) 245	50	✓	✓		
98-95-3	Nitrobenzene	F004; K083; K103; K104; U169; D036	1	5	1	✓	✓		
99-87-6	p-Cymene					✓			
100-37-8	Diethylethanolamine		10	50	2	✓			
100-39-0	Benzyl bromide					✓			
100-41-4	Ethyl benzene		100	415	20	✓	✓		
100-42-5	Styrene			(2)	20	✓	✓		
100-44-7	Benzyl chloride	K015; K149; K085; P028	1	5	1	✓	✓		

Table 18.1.2. Classification of solvents by their codes, exposure limits, and environmental effects.

CAS #	Chemical Name	EPA Code[10]	[a]Permissive Exposure Limits (PEL)[13,14]		[b]TLV[14] ppmv	Environmental Effect			
			ppmv	mg/m^3		O	T	D	G
100-46-9	Benzylamine					✓			
100-47-0	Benzonitrile					✓			
100-51-6	Benzyl alcohol					✓			
100-52-7	Benzaldehyde					✓			
100-61-8	N-Methylaniline		2	9	0.5	✓			
101-84-8	Diphenyl ether		1	7	1	✓			
103-11-7	2-Ethylhexyl acrylate					✓			
103-23-1	Dioctyl adipate					✓			
104-72-3	Decylbenzene					✓			
104-76-7	2-Ethyl hexanol					✓			
105-39-5	Ethyl chloroacetate					✓			
105-46-4	sec-Butyl acetate		200	950		✓			
105-54-4	Ethyl butyrate					✓			
105-58-8	Diethyl carbonate					✓			
106-35-4	Ethyl butyl ketone		50	230	50	✓			
106-42-3	p-Xylene	U239	100	435	100	✓	✓		
106-43-4	p-Chlorotoluene					✓			
106-63-8	Isobutyl acrylate					✓			
106-88-7	1,2-Epoxybutane				0.3	✓	✓		
106-89-8	Epichlorohydrin	K017; U041	(S) 5	(S) 19		✓	✓		
106-91-2	Glycidyl methacrylate					✓			
106-93-4	Dibromoethane	U067		(2)		✓	✓		
106-99-0	Butadiene		1		2	✓	✓		
107-02-8	Acrolein	P003	0.1	0.25	0.1	✓	✓		
107-03-9	n-Propyl mercaptan					✓			
107-05-1	Allyl chloride	F024, F025	1	3	1	✓	✓		
107-06-2	1,2-Dichloroethane	F024; F025; K019; K020; K029; K030; U077; D028		(2)	10	✓	✓		
107-07-3	Ethylene chlorohydrin		5	16	(C) 1	✓			
107-10-8	n-Propylamine					✓			
107-13-1	Acrylonitrile	K011; K013; U009	see 29 CFR 1910.1006		2	✓	✓		

Table 18.1.2. Classification of solvents by their codes, exposure limits, and environmental effects.

CAS #	Chemical Name	EPA Code[10]	[a]Permissive Exposure Limits (PEL)[13,14]		[b]TLV[14] ppmv	Environmental Effect			
			ppmv	mg/m^3		O	T	D	G
107-15-3	Ethylenediamine		10	25	10	✓			
107-18-6	Allyl alcohol	P005	2	5	0.5	✓			
107-21-1	Ethylene glycol					✓	✓		
107-30-2	Chloromethyl methyl ether	U046	see 29 CFR 1910.1006			✓	✓		
107-31-3	Methyl formate		100	250	50	✓			
107-39-1	Diisobutylene					✓			
107-41-5	Hexylene glycol					✓			
107-66-4	Dibutylphosphate		1	5	1	✓			
107-83-5	Isohexane					✓			
107-87-9	Methyl propyl ketone		200	700	(ST) 150	✓			
107-92-6	n-Butyric acid					✓			
107-98-2	Propylene glycol methyl ether				100	✓			
108-03-2	1-Nitropropane		25	90	25	✓			
108-10-1	Methyl isobutyl ketone	U161	100	410	20	✓	✓		
108-11-2	Methylamyl alcohol		(S) 25	(S) 100		✓			
108-18-9	Diisopropylamine		5	20	5	✓			
108-20-3	Isopropyl ether		500	2100	250	✓			
108-21-4	Isopropyl acetate		250	950	100	✓			
108-38-3	m-Xylene	U239	100	435	100	✓	✓		
108-39-4	m-Cresol	F004; U052; D024	(S) 5	(S) 22	5	✓	✓		
108-82-7	Diisobutylcarbinol					✓			
108-83-8	Diisobutyl ketone		50	290	25	✓			
108-84-9	Methyl amyl acetate		50	300	50	✓			
108-86-1	Bromobenzene					✓			
108-87-2	Methylcyclohexane		500	2000	400	✓			
108-88-3	Toluene	F005; F024; F025; K015; K027; K036; K037; K149; U220		(2)	50	✓	✓		
108-90-7	Chlorobenzene	F002; F024; F025; K015; K085; K105; U037; D021	75	350	10	✓	✓		
108-91-8	Cyclohexylamine				10	✓			
108-93-0	Cyclohexanol		50	200	50	✓			

Table 18.1.2. Classification of solvents by their codes, exposure limits, and environmental effects.

CAS #	Chemical Name	EPA Code[10]	[a]Permissive Exposure Limits (PEL)[13,14]		[b]TLV[14] ppmv	Environmental Effect			
			ppmv	mg/m^3		O	T	D	G
108-94-1	Cyclohexanone	U057	50	200	25	✓			
108-95-2	Phenol	K001; K022; K050; K060; K087; U188	(S) 5	(S) 19	5	✓	✓		
109-06-8	2-Methylpyridine	U191				✓			
109-60-4	n-Propyl acetate		200	840	200	✓			
109-66-0	Pentane		1000	2950	1000	✓			
109-67-1	1-Pentene					✓			
109-73-9	Butylamine		(C) 5	(C) 15	(C) 5	✓			
109-78-4	Ethylene cyanohydrin					✓			
109-79-5	n-Butyl mercaptan		10	35	0.5	✓			
109-86-4	Ethylene glycol monomethyl ether		25	80	0.1	✓			
109-86-4	Methyl cellosolve		25	80	0.1	✓			
109-87-5	Dimethoxymethane		1000	3100		✓			
109-87-5	Methyl formal		1000	3100	1000	✓			
109-89-7	Diethylamine		25	75	5	✓			
109-94-4	Ethyl formate		100	300	(ST) 100	✓			
109-99-9	Tetrahydrofuran		200	590	50	✓			
110-12-3	Methyl isoamyl ketone		100	475	20	✓			
110-19-0	Isobutyl acetate		150	700		✓			
110-43-0	Methyl n-amyl ketone		100	465	50	✓			
110-49-6	Methyl cellosolve acetate		25	120	0.1	✓			
110-54-3	Hexane		500	1800	50	✓	✓		
110-63-4	1,4-Butanediol					✓			
110-66-7	n-Amyl mercaptan					✓			
110-71-4	Ethylene glycol dimethyl ether					✓			
110-80-5	Cellosolve	F005; U359	200	740	5	✓			
110-82-7	Cyclohexane	U056	300	1050	(300)	✓			
110-86-1	Pyridine	F005; K026; K157; U196; D038	5	15	1	✓			
110-87-2	Dihydropyran					✓			
110-91-8	Morpholine		20	70	20	✓			

Table 18.1.2. Classification of solvents by their codes, exposure limits, and environmental effects.

CAS #	Chemical Name	EPA Code[10]	[a]Permissive Exposure Limits (PEL)[13,14]		[b]TLV[14] ppmv	Environmental Effect			
			ppmv	mg/m^3		O	T	D	G
111-15-9	Cellosolve acetate		100	540	5	✓			
111-27-3	n-Hexanol					✓			
111-40-0	Diethylenetriamine				(S) 1	✓			
111-42-2	Diethanolamine				2 mg/m^3	✓	✓		
111-46-6	Diethylene glycol					✓			
111-49-9	Hexamethyleneimine					✓			
111-55-7	Ethylene glycol diacetate					✓			
111-65-9	Octane		500	2350	300	✓			
111-66-0	1-Octene					✓			
111-76-2	2-Butoxyethanol		(S) 50	(S) 240	20	✓			
111-76-2	Ethylene glycol monobutyl ether					✓			
111-77-3	Diethylene glycol monomethyl ether					✓			
111-84-2	Nonane				200	✓			
111-90-0	Diethylene glycol monoethyl ether					✓			
111-92-2	Di-n-butylamine					✓			
111-96-6	Diethylene glycol dimethyl ether					✓			
112-07-2	Ethylene glycol monobutyl ether acetate					✓			
112-30-1	n-Decyl alcohol					✓			
112-34-5	Diethylene glycol monobutyl ether					✓			
112-41-4	1-Dodecene					✓			
112-50-5	Ethoxy triglycol					✓			
112-55-0	Lauryl mercaptan					✓			
112-80-1	Oleic acid					✓			
115-10-6	Dimethyl ether					✓			
117-81-7	Bis(2-ethylhexyl)phthalate	U028		5	5 mg/m^3	✓	✓		

Table 18.1.2. Classification of solvents by their codes, exposure limits, and environmental effects.

CAS #	Chemical Name	EPA Code[10]	[a]Permissive Exposure Limits (PEL)[13,14]		[b]TLV[14] ppmv	Environmental Effect			
			ppmv	mg/m^3		O	T	D	G
121-44-8	Triethylamine	K156; K157; U404	25	100	0.5	✓	✓		
121-69-7	N,N-dimethylaniline		5	25	5	✓	✓		
123-38-6	Propionaldehyde		see 29 CFR 1910.1013			✓	✓		
123-42-2	Diacetone alcohol		50	240	50	✓			
123-51-3	Isoamyl alcohol		100	360	100	✓			
123-62-6	Propionic anhydride					✓			
123-63-7	Paraldehyde	K009; K010; K026; U182				✓			
123-72-8	n-Butyraldehyde					✓			
123-86-4	n-Butyl acetate		150	710		✓			
123-91-1	1,4-Dioxane	U108	100	360	20	✓	✓		
123-92-2	Isoamyl acetate		100	525	50	✓			
124-11-8	1-Nonene					✓			
124-17-4	Diethylene glycol monobutyl ether acetate					✓			
124-38-9	Carbon dioxide		5000	9000	5000				✓
124-40-3	Dimethylamine	U092	10	18	5	✓			
126-33-0	Sulfolane					✓			
126-99-8	Chloroprene		(S) 25	(S) 90	1	✓	✓		
127-18-4	Tetrachloroethylene	F001; F002; F024; F025; K116; K019; K020; K073; K150; K151; U210; D039		(2)	25	ε	✓		
127-19-5	N,N-Dimethylacetamide		10	35	10	✓			
131-11-3	Dimethyl phthalate	U102		5	5 mg/m^3	✓	✓		
131-18-0	Di-n-amyl phthalate					✓			
140-88-5	Ethyl acrylate	U113	25	100	5	✓	✓		
141-32-2	n-Butyl acrylate				10	✓			
141-43-5	Ethanolamine		3	6	3	✓			
141-78-6	Ethyl acetate	U112	400	1400	400	✓			
141-79-7	Mesityl oxide		25	100	15	✓			
141-97-9	Ethyl acetoacetate					✓			
142-82-5	Heptane		500	2000	400	✓			
142-84-7	Di-n-propylamine	U110				✓			

Table 18.1.2. Classification of solvents by their codes, exposure limits, and environmental effects.

CAS #	Chemical Name	EPA Code[10]	[a]Permissive Exposure Limits (PEL)[13,14]		[b]TLV[14] ppmv	Environmental Effect			
			ppmv	mg/m^3		O	T	D	G
142-96-1	Di-n-butyl ether					✓			
151-56-4	Aziridine (ethylene imine)	P054	see 29 CFR 1910.1012		0.5	✓	✓		
287-92-3	Cyclopentane				600	✓			
298-07-7	Di-(2-ethylhexyl) phosphoric acid					✓			
302-01-2	Hydrazine	U133	(S) 1	(S) 1.3	0.01	✓	✓		
306-83-2	2,2-Dichloro-1,1,1-trifluoro ethane (HCFC-123)	F001				ε		✓	✓
502-56-7	Di-n-butyl ketone					✓			
510-15-6	Chlorobenzylate	U038				✓	✓		
513-37-1	Methallyl chloride					✓			
540-59-0	1,2-Dichloroethylene	F024; F025; K073	200	790	200	✓			
540-84-1	2,2,4-Trimethylpentane					✓	✓		
540-88-5	tert-Butyl acetate		200	950		✓			
541-41-3	Ethyl chloroformate					✓			
541-85-5	Ethyl amyl ketone		25	130	10	✓			
542-75-6	1,3-Dichloropropene	F024; F025; U084			1	✓	✓		
542-88-1	Bis(chloromethyl)ether	K017; P016			0.001	✓	✓		
543-59-9	n-Amyl chloride					✓			
584-84-9	2,4-Toluene diisocyanate	K027	(C) 0.02	(C) 0.14	0.005	✓	✓		
591-78-6	Methyl n-butyl ketone		100	410	5	✓			
592-41-6	1-Hexene				30	✓			
592-76-7	1-Heptene					✓			
594-42-3	Perchloromethyl mercaptan		0.1	0.8	0.1	✓			
624-83-9	Methyl isocyanate		(S) 0.02	(S) 0.05	0.02	✓	✓		
628-63-7	n-Amyl acetate		100	525	50	✓			
626-38-0	sec-Amyl acetate		125	650	50	✓			
629-14-1	Ethylene glycol diethyl ether					✓			
629-76-5	Pentadecanol					✓			
680-31-9	Hexamethylphosphoramide					✓	✓		
696-28-6	Phenyldichloroarsine					✓			
763-29-1	2-Methyl-1-pentene					✓			

Table 18.1.2. Classification of solvents by their codes, exposure limits, and environmental effects.

CAS #	Chemical Name	EPA Code[10]	[a]Permissive Exposure Limits (PEL)[13,14]		[b]TLV[14] ppmv	Environmental Effect			
			ppmv	mg/m^3		O	T	D	G
822-06-0	Hexamethylene-1,6-diisocyanate				0.005	✓	✓		
872-05-9	1-Decene					✓			
872-50-4	N-Methylpyrrolidinone					✓			
1191-17-9	2,2-Dichloroethyl ether					✓			
1300-71-6	Xylenol					✓			
1330-20-7	Xylene (isomer mixtures)	U239	100	435	100	✓	✓		
1336-36-3	Polychlorinated biphenyls					✓	✓		
1338-24-5	Naphthenic acids mixtures					✓			
1634-04-4	Methyl tert-butyl ether					✓	✓		
1717-00-6	1,1-Dichloro-1-fluoroethane (HCFC-141b)	F001				ε		✓	✓
2837-89-0	2-Chloro-1,1,1,2-tetrafluoro ethane (HCFC-124)	F001				ε		✓	✓
4170-30-3	Crotonaldehyde	U053				✓			
7664-39-3	Hydrofluoric acid	U134				✓	✓		
7785-26-4	Dipentene					✓			
8006-64-2	Turpentine		100	560	20				
8030-30-6	Naphtha: coal tar	K022	100	400		✓			
8032-32-4	Petroleum naphtha or naphtha: VM & P				300	✓			
8052-41-3	Naphtha: Stoddard solvent		500	2900	100	✓			
13360-63-9	N-Ethyl-n-butylamine					✓			
13952-84-6	sec-Butylamine					✓			
25154-52-3	Nonylphenol					✓			
25265-71-8	Dipropylene glycol					✓			
25322-69-4	Polypropylene glycol					✓			
25340-17-4	Diethylbenzene					✓			
25378-22-7	Dodecene					✓			
26761-40-0	Diisodecyl phthalate					✓			
26952-21-6	Isooctyl alcohol				50	✓			
27215-95-8	Nonene					✓			
28473-21-3	Nonanol					✓			

Table 18.1.2. Classification of solvents by their codes, exposure limits, and environmental effects.

CAS #	Chemical Name	EPA Code[10]	[a]Permissive Exposure Limits (PEL)[13,14]		[b]TLV[14] ppmv	Environmental Effect			
			ppmv	mg/m^3		O	T	D	G
29063-28-3	Octanol					✓			
34590-94-8	Dipropylene glycol methyl ether		100	600	100	✓			
53535-33-4	Heptanol					✓			
64742-81-0	Kerosene					✓			
74806-04-5	Carene					✓			

(ε) Exempt VOC.
[a]Permissible Exposure Limits (PELs) are 8-hour time-weighted averages (TWAs) unless a number is preceded with a (C) which denotes a ceiling limit. When an entry is in the mg/m^3 column only, the value is exact; otherwise, it is approximate.
[b]Threshold Limit Values (TLVs) are the time-weighted average concentrations for a conventional 8-hour workday and a 40-hour workweek.
(C) Indicates ceiling limit, or a concentration that should not be exceeded during any part of the working exposure.
(S) Denotes skin designation as the basis for the value.
O Classified as a volatile organic compound (VOC). VOC can react in the lower atmosphere to form ozone and other oxidants. VOC means any compound of carbon, excluding carbon monoxide, carbon dioxide, carbonic acid, metallic carbides or carbonates, and ammonium carbonate, which participates in atmospheric photochemical reactions. Some compounds are specifically exempted from this definition which is found in 40 C.F.R.51.100(s).
T Considered a hazardous air pollutant (HAP) and listed in Title III of the Clean Air Act Amendments of 1990.
D A regulated stratospheric ozone layer depleter.
G May impact climate change.

Other solvents, known as chlorofluorocarbons (CFCs), cause stratospheric ozone depletion. They gradually release chlorine and other halogens into the atmosphere, which are effective in destroying the ozone layer,[15] our natural protection from damaging ultraviolet light (UV). They also have high global warming potentials (GWPs).[16] These solvents are generally not considered significant precursors of ground-level ozone formation. The production and use of many CFCs have been banned[17,18] and new chemicals have been synthesized and are becoming available for various applications (see Table 18.1.3).[19,20]

Table 18.1.3. List of acceptable replacement chemicals for ozone-depleting solvents (ODS).[20]

Substitutes	CFC-113[a]				Methyl chloroform[a]				HCFC-141[b]			
	C	E	M	P	C	E	M	P	C	E	M	P
Alternative Technologies (e.g., powder, hot melt, thermoplastic plasma spray, radiation- cured, moisture-cured, chemical-cured, and reactive liquid)	c											
Aqueous cleaners		c	c	c		c	c	c				
Benzotrifluorides	d	d	d	d	d	d	d	d				
HFC-123				c				c				
HFC-225ca/cb		d		d		d		d				
HFC-4310mee		d	c	c		d	c	c		c	c	
High-solids formulations	c											
Hydrofluorether (HFE)		c	c	c		c	c	c		c	c	c
Methoxynanofluorobutane, iso and normal		c	c	c		c	c	c		c	c	c
Methylene chloride	c	c	c	c		c	c	c				
Monochlorotoluenes	d	d	d	d	d	d	d	d				
No clean alternatives		c				c						
Oxygenated solvents (alcohols, ketones, esters, ethers)	c											
Perchloroethylene	c	c	c	c		c	c	c				
Perfluorocarbons (C5F12, C6F12, C6F14, C7F16, C8F18, C5F11NO, C6F13NO, C7F15NO, and C8F16)		e		e		e		e				
Perfluoropolyethers		e		e		e		e				
Petroleum hydrocarbons	c											
Plasma cleaning		c		c		c		c				
Semi-aqueous cleaners		c	c	c		c	c	c				
Straight organic solvent cleaning		c	c	c		c	c	c				
Supercritical fluids		c	c	c		c	c	c				
Terpenes	c											
Trans-1,2-dichloroethylene	d	c	c	c	d	c	c	c				
Trichloroethylene	c	c	c	c		c	c	c				
UV/ozone cleaning		c		c		c		c				

Table 18.1.3. List of acceptable replacement chemicals for ozone-depleting solvents (ODS).[20]

Substitutes	CFC-113[a]				Methyl chloroform[a]				HCFC-141[b]			
	C	E	M	P	C	E	M	P	C	E	M	P
Varnishing oils												
Volatile methyl siloxanes		c	c	c		c	c	c				
Water-based formulations	c											

where:

a Class I ODS – substance with an ozone depletion potential of 0.2 or higher
b Class II ODS – substance with an ozone depletion potential of less than 0.2
c Acceptable
d Acceptable, subject to use conditions
e Acceptable, subject to narrowed use limit
C Adhesive, coating, and ink applications
E Electronics cleaning
M Metals cleaning
P Precision cleaning

Solvents are used commercially and industrially for numerous applications. Some of those applications include polymer synthesis, coating formulations, cleaning (e.g., electronic circuit board, fabrics, ink supply lines, application equipment, and degreasing), and chemical processes. More than 300 solvents are currently used in the U.S.[21]

Organic chemical solvents are also widely used as ingredients in household products. Paints, varnishes, and wax all contain organic solvents, as well as many cleaning, disinfecting, cosmetic, degreasing, and hobby products.[21] These consumer products can release organic compounds while in use and even when stored. Their release indoors can cause health problems, especially considering that we spend around 90 percent of our time indoors.[22]

All of the environmental and health problems aforementioned have prompted a number of regulations specifically designed to promote and maintain a cleaner and sustainable environment as well as a healthier and safer workplace. This chapter discusses the environmental and safety laws and regulations and the regulatory process in the U.S. Some international regulatory perspectives will also be provided. The purpose of the chapter is to present some key elements of relevant laws and regulations affecting the use of solvents. Solvent users can use this information to understand the range and basic structure of laws and regulations that may affect solvent use. State and federal regulators can use this information to gain a better understanding of the full scope of requirements across all media. In sections 18.1.2 to 18.1.4, the discussion follows the single-medium-based regulatory approach used in the U.S. Recognizing, however, that environmental problems may cross medium lines, section 18.1.5 of this chapter provides a brief discussion of multimedia laws and regulations. Section 18.1.6 discusses laws and regulations to protect workers from exposure to hazardous chemicals. An overview of Canadian environmental laws and regulations is given in section 18.1.7.

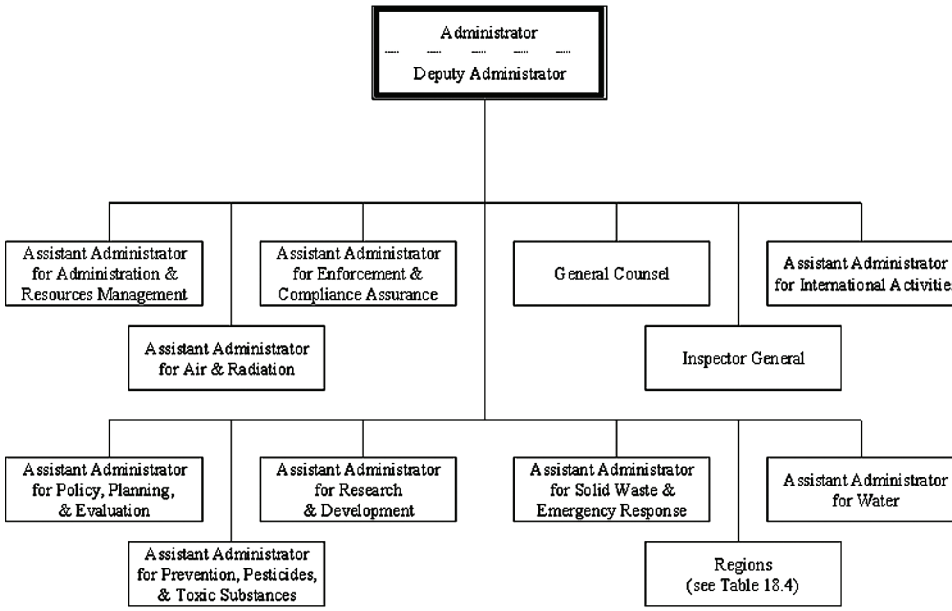


Figure 18.1.1. EPA organizational structure.

18.1.2 AIR LAWS AND REGULATIONS

18.1.2.1 Clean air act amendments of 1990[9]

18.1.2.1.1 Background

In the seventies, the Air Quality Act of 1967 was amended twice: first in 1970 and then in 1977. These amendments brought, among other things, the establishment of national ambient air quality standards (NAAQS), new source performance standards (NSPS) for major new or modified stationary sources, and the national emission standards for hazardous air pollutants (NESHAPS). Also in 1970, the decentralized environmental quality programs and oversight were integrated with the founding of EPA.[23] EPA became the federal agency with primary environmental regulatory responsibility in the U.S with 10 Regional Offices located in major cities (see Figure 18.1.1 and Table 18.1.4). The Clean Air Act was amended once again in 1990, building on earlier editions while incorporating some significant changes. The old command and control policy changed to a more cooperative effort on the part of the federal government, state agencies, local municipalities, and industry. Similar approaches were implemented as early as 1979. Then, EPA tried to develop market-based concepts in an attempt to limit and control pollution within a given area, also known as a bubble, while permitting some level of flexibility for the affected facilities. Facilities achieving greater control than required were allowed to sell their excess pollution reduction credit to other facilities within that area provided the overall pollution level was not exceeded.[24] These attempts did not achieve the desired pollution reduction, which prompted revisions and amendments to the CAA.

The legal authority for federal programs regarding air pollution control is based on the 1990 Clean Air Act Amendments (1990 CAAA). These are the latest in a series of amendments made to the Clean Air Act (CAA). This legislation modified and extended federal legal authority provided by the earlier Clean Air Acts of 1963 and 1970. New regulatory programs were authorized for control of acid deposition (acid rain) and for the issuance of the stationary source operating permits.

Despite substantial revisions and amendments to the CAA, prior EPA, state, or local laws or regulations were not repealed. In fact, even today, many states still follow prior CAA amendments.[25]

Table 18.1.4. List of EPA's regional offices.

EPA Region	States	Address	Phone number
1	Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont	EPA New England Headquarters 5 Post Office Square – Suite 100 Boston, MA 02109-3912	(617) 918-3912
2	New Jersey, New York, Puerto Rico, Virgin Islands	290 Broadway, New York, NY 10007-1866	(212) 637-3000
3	Delaware, District of Columbia, Maryland, Pennsylvania, Virginia, West Virginia	1650 Arch Street, Philadelphia, PA 19103-2029	(215) 814-5000
4	Alabama, Florida, Georgia, Kentucky, Mississippi, North Carolina, South Carolina, Tennessee	61 Forsyth Street, SW, Atlanta, GA 30303-3104	(404) 562-9900
5	Illinois, Indiana, Michigan, Minnesota, Ohio, Wisconsin	77 West Jackson Boulevard, Chicago, IL 60604-3507	(312) 353-2000
6	Arkansas, Louisiana, New Mexico, Oklahoma, Texas	Fountain Place 12th Floor, Suite 1200 1445 Ross Avenue Dallas, TX 75202-2733	(214) 665-2200
7	Iowa, Kansas, Missouri, Nebraska	11201 Renner Blvd. Lenexa, KS 66219	(913) 551-7003
8	Colorado, Montana, North Dakota, South Dakota, Utah, Wyoming	1595 Wynkoop St. Denver, CO 80202-1129	(303) 312-6312
9	American Samoa, Arizona, California, Guam, Hawaii, Nevada	75 Hawthorne Street, San Francisco, CA 94105	(415) 947-8000
10	Alaska, Idaho, Oregon, Washington	1200 Sixth Avenue, Suite 900 Seattle, WA 98101	(206) 553-1200

The CAA of 1990 contains six titles and related provisions designed to “encourage” air pollution abatement and reduction. These provisions address several environmental pollution problems that affect us all, such as tropospheric ozone, hazardous pollution, mobile emissions, urban pollution, acid deposition, and stratospheric ozone depletion. Because the scope of this chapter is on solvents and the regulations that impact their use, only Titles I, III, V, and VI and their relevance to solvents will be discussed.

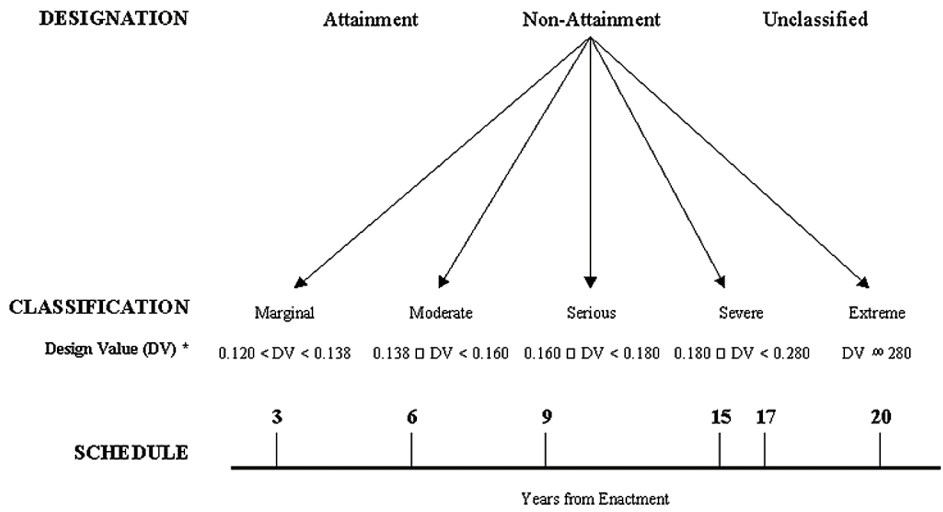
18.1.2.1.2 Title I – Provisions for Attainment and Maintenance of National Ambient Air Quality Standards

Under this Title (Section 108), EPA has issued National Ambient Air Quality Standards (NAAQS) for six criteria pollutants – referred to as traditional pollutants in Canada and the European Union (EU):[26] ground-level ozone, nitrogen oxides, carbon monoxide, sulfur dioxide, particulate matter less than 10 μm in aerodynamic diameter (PM_{10}), and lead. They are called criteria pollutants because EPA has developed health-based criteria or science-based guidelines as the basis for establishing permissible levels. The air quality criteria established by EPA must "accurately reflect the latest scientific knowledge useful in indicating the kind and extent of all identifiable effects on public health and welfare which may be expected from the presence of such pollutants in the ambient air."[9] These ambient air pollutants or NAAQS pollutants are generally present nationally and may be detected through the use of ambient monitoring detectors. Other air pollutants may be regulated as HAPs under Section 112 of Title III if they pose danger to human health but their effect is confined to a localized area.[25] NAAQS include standards to allow for an adequate protection of health (primary) and standards to prevent environmental and property damage from anticipated adverse effects (secondary). In July 1997, EPA published its revision to the ozone NAAQS. The ozone NAAQS limit was 80 ppb and it was based on an 8-hour air measurement average.

On October 1, 2015, EPA strengthened the National Ambient Air Quality Standards (NAAQS) for ground-level ozone to 70 parts per billion (ppb), based on extensive scientific evidence about ozone's effects on public health and welfare. Studies provided information clearly showing that ozone at 72 ppb can be harmful to healthy exercising adults. Several clinical studies have shown effects in some adults following exposure to ozone at levels as low as 60 ppb. The updated standards will improve public health protection, particularly for at-risk groups including children, older adults, people of all ages who have lung diseases such as asthma, and people who are active outdoors, especially outdoor workers. They also will improve the health of trees, plants, and ecosystems.

Areas that do not meet the established NAAQS or that affect the ambient air quality in a nearby area that does not meet NAAQS for the pollutant are known as non-attainment areas.[9] In the U.S., an estimated 90 million people live in these areas. These areas may be further classified based on the severity of non-attainment and the availability and flexibility of the pollution control measures believed necessary to achieve attainment.[9] A State Implementation Plan (SIP) must be prepared and submitted by each state with a non-attainment area. The SIP must contain strategies to achieve compliance within the state's borders and "Air Quality Control Regions." Once a non-attainment area meets the NAAQS for a given pollutant, it is then classified as a maintenance area.

Ozone non-attainment areas are classified according to the severity of the pollution problem (see Figure 18.1.2). These areas also have to achieve VOC reduction as determined by the non-attainment classification. A 15 percent VOC reduction in non-attainment areas, classified as moderate and above, was required by 1996. Also, Section 182(c)(2)(B) requires that non-attainment areas classified as serious and above follow with a 3 percent VOC reduction per year.[9]



* Measured in parts per million (ppm).

Figure 18.1.2. Designation and classification of ozone areas.

Each state with a non-attainment area selects reasonable control measures, known as Reasonably Available Control Technologies (RACTs), for major sources to achieve the required reduction. Specific information about RACTs can be found in the EPA published Control Technology Guideline (CTG) documents, which are designed to assist state agencies to achieve VOC reduction and ozone NAAQS compliance. States are primarily responsible for meeting NAAQS following measures laid out in their SIPs. States work with stationary and mobile sources to ensure that criteria pollutant levels (ozone in the case of solvents) allow the states to meet NAAQS requirements. If a state is not doing an adequate job in improving and maintaining air quality through the activities identified in the SIP, EPA may step in and insist on more stringent measures. EPA promulgates Federal Implementation Plans (FIPs) to correct inadequacies in SIPs. A FIP includes enforceable emission limitations or other control measures and techniques or economic incentives so compliance with the NAAQS is achieved.

In the case of new major stationary sources, the states try to stay or come into attainment through the New Source Review (NSR) program. The NSR program, sometimes called preconstruction permitting, addresses emissions from new major stationary sources; i.e., entire facilities or major modifications to existing facilities. Requirements depend on whether the facility is in a non-attainment area or is in a prevention of significant deterioration (PSD) area. Major sources for these areas must obtain a permit before any construction or modification is started. CAA defines a major VOC source as one that emits 9.1 Mg/year in an area classified as severe.[26]

Facilities in PSD areas are required to apply Best Available Control Technology (BACT) which takes into account economic impact. BACT is analyzed by regulators and

applied to facilities on a case by case basis. BACT determination must result in emissions reduction as stringent as the federal New Source Performance Standard (NSPS) rule.

Facilities located in non-attainment areas or that are increasing emissions in such areas must apply for a state permit prior to starting construction. The permit must codify that they are applying Lowest Achievable Emissions Rate (LAER). LAER is also established on a case by case basis. They also need to obtain equivalent offsetting emissions reductions (Offsets) from existing sources within the non-attainment area. Unlike BACT, a LAER determination does not consider economic, energy, or other cross-media impacts.

Information about emission control technology, work practices, and reformulations that have been determined to be BACT and LAER for various types of sources is made available to the states through a central database called the RACT/BACT/LAER Clearinghouse.

Most organic solvents in this book are classified as VOCs and are found in commercial and consumer products such as paints, coatings, containers, and packaging (see Table 18.1.2 for a list of these VOC solvents and exempt solvents). They contribute to the formation of ozone and are regulated under this Title, Section 183(e).[9] Fuels and fuel additives are not the focus of Section 183(e). VOCs, nitrogen oxides, and oxygen undergo a photochemical reaction in the presence of sunlight resulting in the formation of tropospheric or ground-level ozone, the primary component of smog. Heat also increases the reaction rates of these reactions. The contribution of some solvents to the photochemical reaction may be considered negligible. As a result, some VOC solvents may be reclassified as exempt solvents; e.g., acetone. This reclassification begins with industry submitting a petition to EPA for a solvent or solvents to be reclassified as exempt. As of December 3, 1999, EPA had a list of 18 compounds for which petitions requesting VOC exempt status (see Table 18.1.5) had been received.[27]

Table 18.1.5. List of VOCs with requested VOC exempt status.

Compound	Submitting		Accepted
	Organization	Date	
Acetone			06/16/95
Chlorobromomethane	ICF Kaiser	11/10/95	
Bromopropane	Enviro Tech International	05/10/96	
	Albemarle Corp.	11/18/97	
Methyl bromide	Chemical Manufacturers Association	07/19/96	
n-Alkanes (C_{12} - C_{18})	The Aluminum Association	11/27/96	
Technical white oils	The Printing Industries of America	12/20/96	
	Pennzoil Products Company	12/20/96	
t-Butyl acetate	ARCO Chemical Company (now Lyondell)	01/17/97	12/29/04
Benzotrifluoride	Occidental Chemical Company	03/11/97	

Table 18.1.5. List of VOCs with requested VOC exempt status.

Compound	Submitting		Accepted
	Organization	Date	
Carbonyl sulfide	E.I. du Pont de Nemours and Company	08/11/97	
	Texas Mid-Continent Oil & Gas Association	12/05/97	
trans-1,2-Dichloroethylene	3M Corporation	10/08/97	
Dimethyl succinate and dimethyl glutarate	Dibasic Esters Group, affiliated with the Synthetic Organic Chemical Manufacturers Association, Inc.	10/14/97	
Carbon disulfide	Texas Mid-Continent Oil & Gas Association	12/05/97	
Acetonitrile	BP Chemicals	01/21/98	
	GNI Chemicals Corporation	01/21/98	
Toluene diisocyanate (TDI)	Chemical Manufacturers Association	01/22/98	
1,1,1,2,3,3,3-heptafluoropropane (HFC-227)	Great Lakes Chemical Corporation	02/18/98	12/29/04
Methyl acetate	Eastman Chemical	04/09/98	05/11/98
Methylene diphenyl diisocyanate (MDI)	Chemical Manufacturers Association	08/19/98	
1,1,1,2,2,3,3-Heptafluoro-3-methoxy-propane	3M Performance and Fluids Division	02/05/99	
Propylene carbonate	Huntsman Corporation	07/27/99	
Methyl pivalate	Exxon Chemical Company	11/22/99	
Dimethyl carbonate	Kowa Chemical Company	07/29/04	
Hydrofluoropolyethers	Solvay Solexis, Inc.	02/10/05	
1,1,2,2-tetrafluoro-1-(2,2,2-trifluoroethoxy)ethane	AGC Chemicals Americas, Inc.	02/05/07	
Methyl iodide (iodomethane)	Arysta LifeScience North America	04/21/08	
Propylene carbonate			02/20/09
Dimethyl carbonate			02/20/09
HFE-7300			01/18/07
1,1,1,2,2,3,3-Heptafluoro-3-methoxy-propane HFE-7000	3M Performance Chemicals	02/05/99	12/29/04
3-ethoxy-1,1,1,2,3,4,4,5,5,6,6,6-Dodeca-fluoro-2-(trifluoromethyl) hexane (HFE-7500, HFE-s702, T-7145, or L-15381)	3M Performance Chemicals	08/21/00	12/29/04
Methyl formate	Foam Supplies, Inc.	02/12/02	12/29/04

Note: As of November 20, 2008, EPA had not published final actions on these chemicals.

In 1995, under Section 183(e), EPA generated a list of consumer and commercial products categories to be regulated which accounted for at least 80 percent of the VOC emissions from such products in ozone non-attainment areas.[28] The list was divided into four groups, and each group is to be regulated every 2 years (starting in 1997) based on the best available controls (BACs). These four groups are listed in Table 18.1.6.[29] The term control is broad, including not only end-of-pipe control technology but also source reduction alternatives. The product categories were selected for regulation based on eight criteria developed to address five factors outlined in Section 183(e)(2):

1. utility
2. commercial demand
3. health or safety functions
4. content of highly reactive compounds
5. availability of alternatives
6. cost-effectiveness of controls
7. magnitude of annual VOC emissions
8. regulatory efficiency and program considerations

Table 18.1.6. Consumer and commercial products categories.

Group I (1997) Aerospace Coatings, Architectural Coatings, Autobody Refinishing Coatings, Consumer Products (24 categories), Shipbuilding and Repair Coatings, Wood Furniture Coatings
Group II (1999) Flexible Packaging Printing Materials
Group III (2001) Aerosol Spray Paints, Industrial Cleaning Solvents, Flat Wood Paneling Coating, Lithographic Printing Materials
Group IV (2003) Auto and Light Duty Truck Assembly Coatings, Fiberglass Boat Manufacturing Materials, Large Appliance Coatings, Letterpress Printing Materials, Metal Furniture Coatings, Miscellaneous Industrial Adhesives, Miscellaneous Metal Products Coatings, Paper, Film, and Foil Coatings, Petroleum Drycleaning Solvents, Plastic Parts Coatings

This table reflects the regulatory schedule revised on March 18, 1999, Federal Register (64 FR 13422).

18.1.2.1.3 Title III – Hazardous Air Pollutants

Section 112 of Title III of the CAA of 1990 lists 188 HAP compounds or groups of compounds (the original list had 189, but caprolactam was removed from the list) which are believed to be carcinogens or can otherwise pose serious health effects. HAP solvents can cause a number of health problems such as cancer, kidney and liver damage, developmental problems in children, nervous system problems, respiratory irritation, birth defects, and miscarriages.[7,8] It may take minutes or years for these health effects to manifest themselves. Approximately half (90 compounds) of the HAP compounds are solvents and are found in many of the source categories regulated under Title III. EPA has the authority to delete chemicals from or add new chemicals to this original list, but no criteria pollutant can be added, only its precursors. If a petition to add or delete a chemical is submitted to EPA, EPA has 18 months to respond with a written explanation of its denial or concur-

rence. Before the 1990 CAA, EPA listed only eight substances as HAPs (beryllium, mercury, vinyl chloride, asbestos, benzene, radionuclides, arsenic, and coke oven emissions) and issued standards for seven (coke oven emissions were not regulated before the 1990 CAA). After the enactment of the CAA of 1990, a substantially greater number (187) of source categories were identified to be regulated within a period of 10 years. In other words, EPA would promulgate regulations for 187 source categories in half the time that it took to promulgate regulations for only seven. This number of categories to be regulated has been reduced because of subcategorization or deletion of categories.

Many of these categories are major stationary sources which emit HAP or toxic solvents to the atmosphere (see Table 18.1.2) and are scheduled to be regulated by the year 2000. These regulations are technology-based standards, known as Maximum Achievable Control Technology (MACT) standards. MACT standards are EPA's regulatory means to establish emission limits for air toxics. MACT standards have already been promulgated for 39 source categories (see Table 18.1.7). EPA will not be developing MACT standards for seven of the originally listed major source categories. There are 66 source categories that remain to be regulated.

Table 18.1.7. Categories of sources of HAPs for which Maximum Achievable Control Technology (MACT) standards have already been developed.[30]

Schedule	Source Categories	Compliance Date
2-Year	Dry Cleaning	09/23/96
	Hazardous Organic NESHAP	F/G – 05/14/01; H – 05/12/99; New Sources – 05/12/98
4-Year	Aerospace Industry	09/01/98
	Asbestos	Delisted
	Chromium Electroplating	Deco - 0 1/25/96; Others -01/25/97
	Coke Ovens	Not available
	Commercial Sterilizers	12/06/98
	Degreasing Organic Cleaners (Halogenated Solvent Cleaning)	12/02/97
	Gasoline Distribution (Stage 1)	12/15/97
	Hazardous Waste Combustion	06/19/01
	Industrial Cooling Towers	03/08/95
	Magnetic Tape	w/o new control devices – 12/15/96; w/new control devices – 12/15/97
	Marine Vessel Loading Operations	MACT – 09/19/99; RACT – 09/19/98
	Off-Site Waste Recovery Operations	07/01/00
	Petroleum Refineries	08/18/98
	Polymers & Resins I: Butyl Rubber, Epichlorohydrin Elastomers, Ethylene Propylene Rubber, Hypalon (TM) Production, Neoprene Production, Nitrile Butadiene Rubber, Polybutadiene Rubber, Polysulfide Rubber, Styrene-Butadiene Rubber & Latex	07/31/97
	Polymers & Resins II: Epoxy Resins Production, Non-Nylon Polyamides Production	03/03/98
	Polymers & Resins IV: Acrylonitrile-Butadiene-Styrene, Methyl Methacrylate-Acrylonitrile, Methyl Methacrylate-Butadiene, Polystyrene, Styrene Acrylonitrile, Polyethylene Terephthalate	07/31/97
	Printing & Publishing	05/30/99
	Secondary Lead Smelters	06/23/97
	Shipbuilding & Ship Repair	12/16/96
	Wood Furniture	11/21/97

Table 18.1.7. Categories of sources of HAPs for which Maximum Achievable Control Technology (MACT) standards have already been developed.[30]

Schedule	Source Categories	Compliance Date
7-Year	Chromium Chemical Manufacturing	Delisted
	Electro Arc Furnace: Stainless & Non-Stainless Steel	Delisted
	Ferroalloys Production	05/20/01
	Flexible Polyurethane Foam Production	10/08/01
	Generic MACT: Acetal Resins, Hydrogen Fluoride, Polycarbonates Production, Acrylic/Modacrylic Fibers	06/29/02
	Mineral Wool Production	06/01/02
	Nylon 66 Production	Delisted
	Oil & Natural Gas Production	06/17/02
	Pesticide Active Ingredient Production: 4-Chlor-2-Methyl Acid Production; 2,4 Salts & Esters Production; 4,6-dinitro-o-cresol Production; Butadiene Furfural Cotrimer; Captafol Production; Captan Production; Chloroneb Production; Dacthal™ Production; Sodium Pentachlorophenate Production; Tordon™ Acid Production	06/30/02
	Pharmaceutical Production	09/21/01
	Phosphoric Acid / Phosphate Fertilizers	06/10/02
	Polyether Polyols Production	06/01/02
	Portland Cement Manufacturing	Not available
	Primary Aluminum Production	10/07/99
	Primary Lead Smelting	06/04/02
	Pulp & Paper (non-combust) - MACT I	04/15/01
	Pulp & Paper (non-combust) - MACT III	04/16/01
	Steel Pickling - HCl Process	06/22/01
	Tetrahydrobenzaldehyde Manufacture (formerly known as Butadiene Dimers Production)	05/12/01
	Wood Treatment MACT	Delisted
	Wool Fiberglass Manufacturing	06/14/01
10-Year	Cyanuric Chloride Production	Delisted
	Lead Acid Battery Manufacturing	Delisted
	Natural Gas Transmission & S	06/17/02

Under Section 112 of Title III of the CAA of 1990, EPA will regulate all major sources and area sources deemed appropriate. A major source is a stationary source located within a contiguous area under common control that emits or has the potential to emit $\geq$ 9.1 Mg/yr (10 tons/yr) of a single HAP or $\geq$ 23.7 Mg/yr (25 tons/yr) of a combination of HAPs. An area source is a non-major stationary source. Under Section 112, EPA is required to promulgate 40 categories by 1992, 25 percent of the listed categories by 1994, an additional 25 percent by 1997, and all categories by the year 2000. A list of sources was developed by EPA in 1992[31] and modified 4 years later.[32] Each MACT standard allows existing sources 3 years to comply. Additional years may be granted to complete the installation of controls, to dry and cover mining waste, and for coke ovens. A

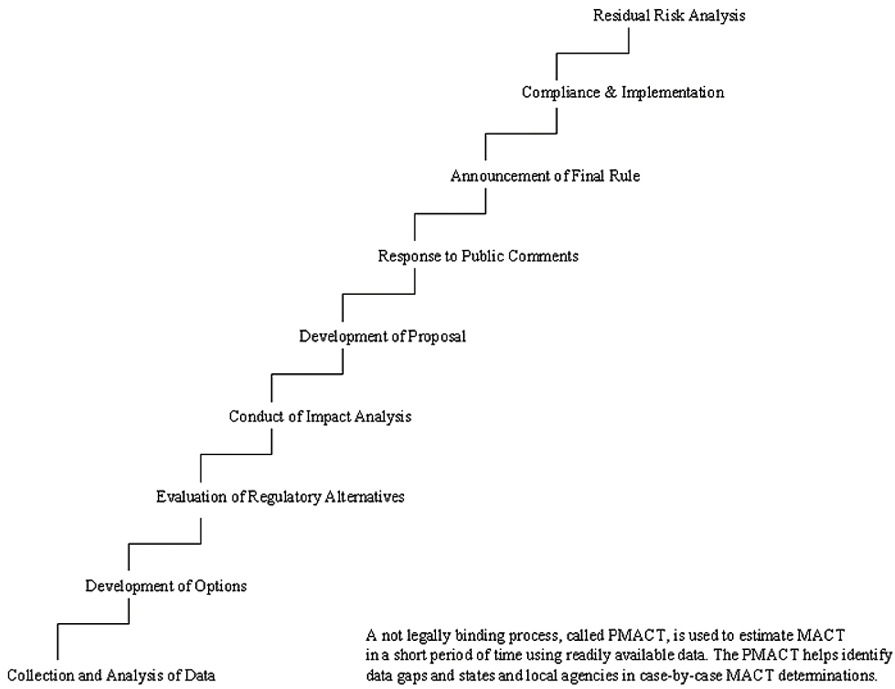


Figure 18.1.3. Steps for the development of MACT regulations.

new source that began construction after the date a MACT standard was proposed will begin compliance at startup or by the date the final standard is issued, whichever is later. Under the early reduction program, additional time may be given to a facility to meet HAP reduction requirements if about 90 percent of the HAP emissions are reduced before a MACT standard is in effect. Once MACT standards are promulgated, the CAA requires EPA to conduct a risk assessment, if considered necessary for public health, to:

- assess the level of risk or "residual risk" remaining to public health,
- estimate the public health significance of the estimated residual risk,
- identify the technological and commercially available methods and costs to reduce the residual risk,
- estimate the actual health effects in the vicinity of sources,
- identify any health studies and uncertainties in the available risk assessment
- determine any negative health and environmental impacts resulting from the reduction of the residual risk, and
- produce recommendations leading to legislation for the residual risk.

This may result in even more stringent regulations for solvent users. Figure 18.1.3 outlines basic steps involved in the development of a MACT regulatory standard.[28]

The CAA provides for potential delays in the promulgation of MACTs for major HAP sources; i.e., Section 112(j). This is known also as the MACT Hammer.[25] This provi-

sion requires major HAP sources to apply for a permit 18 months after the MACT standard scheduled promulgation date. The State must then make a case-by-case determination of MACT for the source. If the delayed MACT standard is later promulgated, the permit will be revised to reflect any new emission limitation requirements and the affected source may be given up to 8 years to comply.[9]

Air toxics have also been regulated at the state level under various air toxic state programs. In the U.S., the State of California has one of the more stringent and complex air toxics programs. California leads with air toxic programs such as Assembly Bill 1807 (AB 1807) that targets emissions that pose the greatest risk to public health and Senate Bill 1731 (SB 1731) that regulates air toxics through facility-based controls rather than risk-based controls.[33]

18.1.2.1.4 Title V – Permits

Title V was added to the CAA, in the 1990 CAA Amendments, to establish a permit program, federally mandated, to be implemented by the states. Under this Title, EPA has established 10 minimum "elements" for an operating permit program to be administered by the states. These elements serve as basic guidelines to be used when establishing an operating permit program. They include requirements for applications, monitoring and reporting, and annual fees to the owner or operator of sources subject to a permit. They also include the following elements to ensure the effectiveness of an operating permit program:

- adequate personnel, funding, and permitting authority to administer the program;
- procedures to expeditiously evaluate permit applications, prevent unreasonable delay by the permitting authority, and allow for revisions and needed changes to existing permits; and
- provisions to allow permitted facilities to change without requiring permit revision.[9]

Each state is required to develop and submit a permit program. By 1997, EPA had approved nearly all states' permit programs, and some sources have already applied for Title V permits.[25] The idea of an operating permit is to consolidate all CAA requirements for a source in one regulatory vehicle. This includes all applicable SIP air emission limitations, monitoring, and reporting requirements along with CAA regulations (HAP regulations, NSPS, etc.).[25]

18.1.2.1.5 Title VI – Stratospheric Ozone Protection

Title VI of the CAA deals with chemicals, CFCs, and other ozone-depleting substances (ODS) that can cause deterioration of the stratospheric ozone layer. Some of these chemicals are used as solvents in cleaning operations (cleaning of metals, electronics, and precision equipment), coatings, adhesives, and inks. Their production and use have been banned both domestically and internationally[34] (except for a few countries). An unprecedented international effort by 20 countries and the Commission of the European Communities resulted in the 1987 Montreal Protocol. The Montreal Protocol became effective on January 1, 1989. In the U.S., the CAA Amendments of 1990 were the domestic response to such a critical environmental issue of global proportions and provided EPA with the regulatory agenda.

ODS solvents are required to be replaced with non-depleting chemicals. Controlling these substances is not an alternative. ODS solvents are listed in Table 18.1.3. Substitute solvents deemed acceptable have been identified for some of these ODS solvents under EPA's Significant New Alternatives Policy (SNAP), but other health concerns have limited their use. Some exemptions to the use of phase out ODS exist for essential uses as long as they are consistent with the Montreal Protocol.[25]

The SNAP program was established to control the commercialization of ODS substitutes and to ensure that such substitutes do not pose greater harm to the environment than the original chemicals. Through the SNAP program, EPA identifies, classifies, restricts, or prohibits the use of ODS substitutes. Many new rules, notices, and proposals for replacement are consistently published on EPA side.[30]

18.1.3 WATER LAWS AND REGULATIONS

18.1.3.1 Clean water act

18.1.3.1.1 Background

In 1972, Congress enacted the Federal Water Pollution and Control Act (FWPCA), also known as the Clean Water Act (CWA).[35] The CWA is the primary federal legislation that regulates the quality of streams, lakes, estuaries, and coastal waters in the U.S. The CWA has been amended three times: 1977, 1982, and 1987.[36-39] The CWA is divided into six titles. Its purpose is to restore and maintain the chemical, physical, and biological integrity of the Nation's waters by eliminating the discharge of pollutants into navigable waters or municipal sewer systems.[39] Waters can become contaminated by pollutants discharged from point sources, non-point sources, stormwater, and by pollutants from the degradation of wetlands. Point source discharges originate from industrial and sewage treatment plants while non-point discharges are generated from diffuse sources such as sediment run-off from construction sites, leaks from faulty septic systems, and fertilizer and herbicide run-off from agricultural and residential activities. Point sources are "discernible, confined, and discrete conveyances."[38] Examples of a point source include pipes, ditches, channels, tunnels, conduits, discrete fissures, or containers. These sources are regulated and controlled through the National Pollutant Discharge Elimination System (NPDES) permit program.

In 1976, EPA's focus changed from the control of conventional pollutants (biological oxygen demand and suspended solids) to control of toxic pollutants. This shift in EPA's focus was the result of a lawsuit in 1976 which resulted in the Flannery Decree and in the 1977 amendments.[36,40] These amendments established a permit program for point source discharges to focus on 21 major industrial categories and 65 priority pollutants (see Table 18.1.2 for a list of priority pollutant solvents). Today's list of priority pollutants has been expanded to include 129 toxic pollutants from 34 industrial categories.

In the 1987 amendments of the CWA, Congress incorporated Section 319 to establish a national program to control non-point source discharges which provided a regulatory schedule for stormwater. These amendments also established a revolving loan fund for construction of sewage treatment plants and provided EPA with enhanced enforcement tools.[38]

18.1.3.1.2 Effluent Limitations

Under Title III of the CWA, effluent limitations provide the control conditions for a facility's wastewater discharge under an NPDES permit which regulates the quantity and rate of discharges to navigable waters. Guidelines, called the effluent limitations guidelines, have been developed to establish technology-based limits for all types of industrial discharges. Over 50 industry-specific technology-based effluent guidelines have already been promulgated.[40] There are five technology-based treatment standards currently established by the CWA to establish the minimum level of control to be required by a permit. They are the Best Practicable Control Technology (BPT), Best Available Technology Economically Achievable (BAT), Best Conventional Pollutant Control Technology (BCT), Best Available Demonstrated Technology (BDT), and Best Management Practices (BMPs). Industries that do not discharge directly into surface waters but into publicly operated treatment works (POTWs) are subject to pretreatment standards under Section 307(b) of the CWA.[38]

18.1.3.1.3 Permit Program

The CWA, under Section 301 (effluent limitations), prohibits the discharge of any pollutant unless the source obtains a permit and ensures compliance. The NPDES permit program, pursuant to Section 402 of the CWA, requires that commercial and industrial facilities and POTWs apply for permits issued by EPA or a designated state. A permit regulates the amount, concentration, and rate of discharge of each regulated pollutant. According to the CWA, a pollutant includes dredged soil, solid waste, incinerator residue, sewage, garbage, sewage sludge, munitions, chemical wastes, biological and radioactive materials, wrecked or discarded equipment, rock, sand, cellar dirt, and industrial, municipal, and agricultural waste.[39] These pollutants are further classified in three categories: conventional, toxic, and non-conventional. Virtually, any material and characteristics such as toxicity or acidity are considered a pollutant.[40] Solvents fall under the category of toxic pollutants.

An NPDES permit can be issued by EPA or by a state that has received EPA permitting approval. As of 1996, 40 states and territories had received EPA's approval.[40] States and territories that are not authorized to administer the NPDES program are Alaska, Arizona, District of Columbia, Idaho, Louisiana, Maine, Massachusetts, New Hampshire, New Mexico, the Pacific Territories, Puerto Rico, and Texas. For these states and territories, the 10 EPA Regional Offices will issue and administer the NPDES permits. The permit process is elaborate and requires extensive information and numerous steps. First a number of forms need to be completed to provide information about the facility, its operation, and the nature of the discharges. This is followed by a period of discussion between EPA and the discharging facility, and the draft permit is announced for comments from the public for 30 days. Once the comments are reviewed, responded to, and implemented, then the final NPDES permit is issued.

18.1.3.2 Safe drinking water act

18.1.3.2.1 Background

Enacted in 1974, the Safe Drinking Water Act (SDWA) was established to ensure safe drinking water in public water systems. It required that EPA has identified substances in drinking water which could adversely affect public health.[41] SDWA safeguards drinking

water with two standards. Primary drinking water standards with a maximum contaminant level (MCL) designed to protect human health and secondary drinking water standards to protect public welfare. The secondary standards involve physical characteristics of drinking water such as color, taste, and smell. A total of 95 contaminants are regulated under the SDWA including inorganic chemicals, organic chemicals, pesticides, waterborne pathogens, biological toxins, disinfection by-products, disinfectants, pharmaceutical products, and radiological contaminants.

In 1986, the SDWA was amended to greatly increase the responsibilities of EPA and state agencies. Under the 1986 amendments, EPA has directed to schedule the promulgation of primary public drinking water regulations, impose civil and criminal penalties for tampering with public water systems, and enforce more stringent standards.[2] Also, under the 1986 amendments, the wellhead protection program was established to focus on potential contamination of surface and subsurface surrounding a well.[42] In 1988, Congress passed the Lead Contamination Control Act (LCCA) as an additional amendment to the SDWA to protect the public against the contamination of drinking water by lead.

In 1996, the SDWA was amended again to place emphasis on sound science and a risk-based standard approach, small water supply systems, and water infrastructure assistance through a revolving loan fund.[43]

Later amendments were done in 1998, 2005, 2009, and 2016.[43]

18.1.3.2.2 National Primary Drinking Water Regulations

National Primary Drinking Water Regulations (NPDWRs) are enforceable, unlike secondary regulations that are only considered advisable, and established by EPA for contaminants that may cause adverse health effects. The promulgation of the NPDWRs begins with the publication of the advanced notice of the proposed rule. This notice presents the current scientific and technical knowledge about the contaminant and the approach EPA is taking toward its regulation. During this period, EPA seeks comments and any additional information through public meetings, workshops, etc. Comments are then reviewed, and a proposed rule is announced in the Federal Register which includes MCLs and non-enforceable health goals called maximum contaminant level goals (MCLGs). After additional public comments, the final regulation is announced and promulgated. The schedule for this regulatory development is contained in the SDWA amendments of 1986. The first 9 contaminants were to be regulated by EPA within 1 year of enactment, followed by another 40 contaminants within 2 years of enactment, and 34 contaminants within 3 years of enactment for a total of 83 by 1989. The SDWA of 1986 also required EPA to regulate 25 additional contaminants every 3 years. EPA regulated these 95 contaminants except for arsenic, sulfate, and radionuclides. These three are addressed under the 1996 amendments. With the 1996 amendments of the SDWA, beginning in 2001, EPA is required to make regulatory decisions for a minimum of five listed contaminants every 5 years.

Along with the regulatory development, EPA prepares criteria documents which provide technical support for the final rules. These criteria documents identify fundamental information regarding health effects of contaminants in drinking water. Health-effects-related data such as physical and chemical properties, toxicokinetics, human exposure,

health effects in animals and humans, mechanisms of toxicity, and quantification of toxicological effects are evaluated and serve as supporting documentation for the MCLGs.[44]

18.1.4 LAND LAWS & REGULATIONS

18.1.4.1 Resource conservation and recovery act (RCRA)[10]

18.1.4.1.1 Background

The law that regulates solid and hazardous waste management is called RCRA. It was passed as a law in 1976 as an amendment to the Solid Waste Disposal Act (SWDA), and amended in 1980 and 1984, to regulate solid hazardous waste from its creation all the way to its disposal. The 1984 amendments are called the Hazardous and Solid Waste Amendments (HSWAs). Until 2017, 237 rulemakings were published and are available on EPA web.[45] These amendments made RCRA a more stringent law giving EPA increased authority to enforce tighter hazardous waste management standards. They also provided for EPA to revisit problems associated with underground storage tanks. More specifically, Subtitle C regulates hazardous waste while Section D regulates non-hazardous waste such as municipal solid waste and sewage sludge.[45] RCRA requirements were also amended to include small businesses that manage specified amounts of hazardous waste and show an increase in the number of hazardous wastes.[46]

18.1.4.1.2 RCRA, Subtitle C – Hazardous Waste

Subtitle C is RCRA's regulatory arm to deal with the management of hazardous solid waste. A waste is considered hazardous if it appears on EPA's list of hazardous wastes or if hazardous characteristics can be identified. However, the person generating the solid waste is responsible for determining if the generated solid waste is hazardous. Over 500 solid wastes have been identified and listed by EPA as hazardous. Once a waste appears on the EPA hazardous list (wastes classified as F, K, P, U, or so-called "listed" wastes), such a waste is always considered hazardous regardless of its chemical composition. However, EPA is currently working on developing "exit criteria" for certain chemicals in listed wastes that would allow these wastes to be managed as non-hazardous solid wastes if the chemical concentrations are below specified levels. In Part 26, EPA classifies hazardous wastes by the following codes[10] (see Table 18.1.2 for EPA's hazardous codes for solvents):

F wastes from non-specific sources K wastes from specific sources
P discarded acutely hazardous commercial chemical products U discarded commercial chemical products
D wastes for which the above codes do not apply – considered hazardous only if they exhibit ignitability (I), corrosivity (C), reactivity (R), and/or toxicity (E/H/T).

A solid waste considered hazardous will always maintain its listed classification even if it is found mixed with any other waste or a residue derived from a listed hazardous waste.[10] In addition, land disposal of a hazardous waste is prohibited by RCRA unless it is demonstrated that hazardous constituents will not migrate from the disposal unit, causing harm to the environment and public health (40 CFR 268).[10] Hazardous solid waste generators are classified as small quantity generators (SQGs) (i.e., 100 to 1000 kg/month) or large quantity generators (LQGs) (i.e., ≥ 1000 kg/month or >1 kg of an acutely toxic

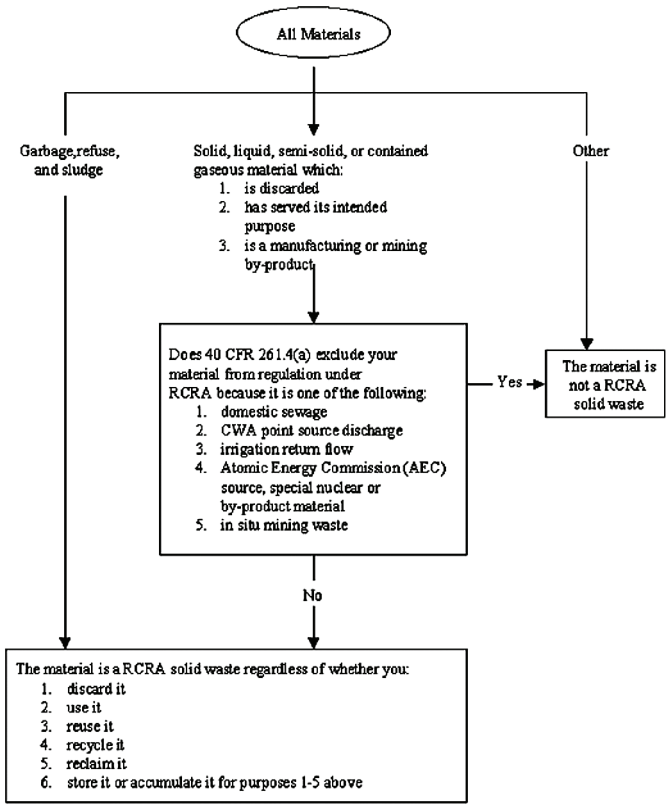


Figure 18.1.4. Definition of a solid waste (Figure 1 – 40CFR 260, Appendix I).

hazardous waste). These waste quantities apply to each month, not the average over the year. For example, if a facility generates 5 kg in each of the first 11 months and 1200 kg in the last month, such a facility would be considered a large quantity generator (LQG) even though its average is less than 1000 kg/month. Generators can be further classified as conditionally exempt small quantity generators (CESQGs) if they produce < 100 kg/month of hazardous waste and do not accumulate more than 1000 kg of hazardous waste. CESQGs are exempt from all RCRA notification, reporting, and manifesting requirements. Waste from CESQGs must be sent to properly permitted, licensed, or registered treatment, storage, and disposal (TSD) facilities, recycling/reclamation facilities, or facilities authorized to manage industrial or municipal solid waste.[2]

RCRA regulations also provide for states to have primary responsibility for managing and implementing the RCRA hazardous waste program (40 CFR 271). Currently, most states and territories have been granted this authority. States can receive an interim authorization (40 CFR 271, Subpart B) as a temporary vehicle while developing a program for final authorization, which is fully equivalent to the federal program. Hence, for a state to obtain final authorization, it must also be consistent with and no less stringent than the Federal program.

RCRA also addresses the transportation of hazardous waste (40 CFR 263). Any transporter of hazardous waste must also comply with the Department of Transportation (DOT) rules under the Hazardous Materials Transportation Act (HMTA) regarding proper labeling, packaging, handling, and placarding.[47]

Finally, a facility generating waste can determine if its waste is regulated under Subtitles C or D by following the steps outlined in the Code of Federal Regulations, Title 40 Part 260, Appendix I (see Figures 18.1.4, 18.1.5, and 18.1.6).

Other provisions exist if the solid waste will be incinerated.

18.1.5 MULTIMEDIA LAWS AND REGULATIONS

18.1.5.1 Pollution prevention act of 1990[3]

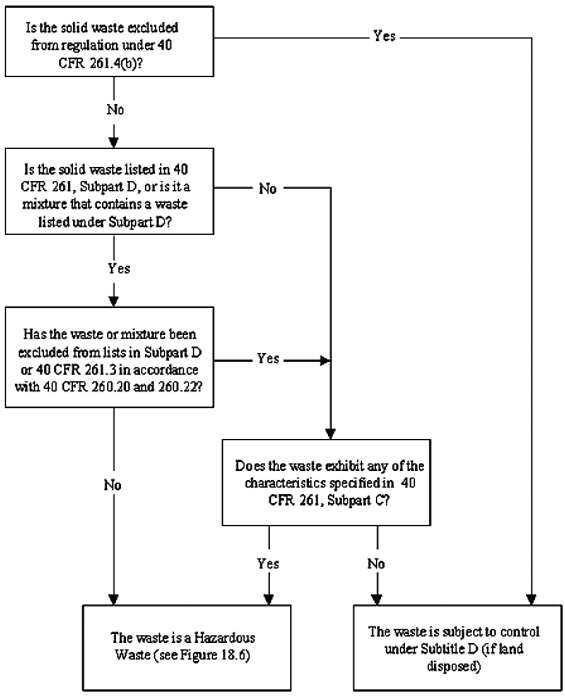


Figure 18.1.5. Definition of a hazardous waste (Figure 2 – 40CFR260, Appendix I).

18.1.5.1.1 Background

Before 1990, most regulations in the U.S. were issued based on the use of conventional pollution management practices usually considering waste management and end-of-pipe control technologies. Only a handful of government activities were considering reduction of pollution at the source. In the area of waste minimization, recycling approaches were employed in addition to add-on control technology to achieve pollution reduction. However, reducing pollution at the source refers to the top of the hierarchy. Although add-on control technology has its place in many applications, new approaches need to be considered to obtain emissions reduction required by new regulations.

In 1990, Congress passed the Pollution Prevention (P2) Act, recognizing that to attain greater levels of pollution reduction, reduction or prevention of pollution at the source "through cost-effective changes in production, operation, and raw materials use" needed to be encouraged and implemented.[3] A fundamental belief expressed in the P2 Act is that these changes would not only help the environment but would benefit industry's bottom line through the reduction of raw material, pollution control, and liability costs.[3]

18.1.5.1.2 Source reduction provisions

The P2 Act is an attempt by the U.S. to establish a framework for integrated multimedia environmental initiatives. The P2 Act provides for a multimedia, integrated, and cost-effective approach to solving environmental problems while encouraging sustainable development. P2 or source reduction includes any practice that reduces or eliminates the creation of pollutants through increased efficiency in the use of raw materials, energy,

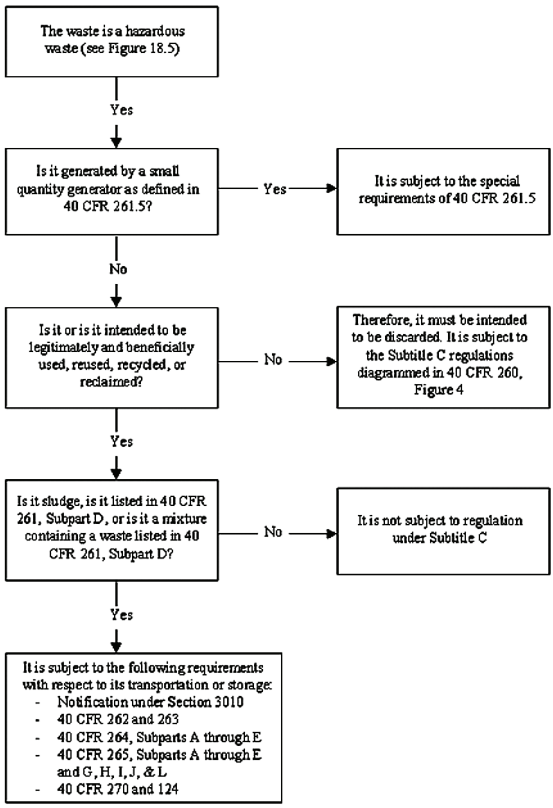


Figure 18.1.6. Special provisions for certain hazardous wastes. (Figure 3 – 40 CFR 260, Appendix I).

water, or other resources or protection of natural resources by conservation. Pollution may be reduced by modifying equipment or technology, modifying processes, reformulating products, substituting raw materials, and improving housekeeping, maintenance, training, or inventory control.[3] The P2 Act encourages the reduction or elimination of wastes of all types and requires that facilities reporting to the Toxic Release Inventory (TRI) provide documentation of their P2/waste minimization or reuse efforts for TRI-reportable chemicals.

The P2 Act required EPA to establish an Office of Pollution Prevention with the authority of promoting source reduction through a multimedia perspective. The Office of Pollution Prevention already existed under The Office of Policy, Planning, and Evaluation (OPPE). It was established by EPA 2 years prior the enactment of the P2 Act. In response to the P2 Act, in 1991, this office developed a source reduction strategy.

The P2 Act also includes provisions aimed at improving the collection and public access of data. Under the Emergency Planning and Community Right-to-Know Act of 1986, industrial facilities are required to report on their annual releases of toxic chemicals to the environment. In response to the P2 Act, the report must include information on their efforts on source reduction and recycling.

In response to the P2 Act and to help promote source reduction, EPA established various prevention programs and initiatives:

- 33/50 Program – A very successful EPA experimental program based on voluntary industry participation. Companies that reported to TRI any of the 17 target chemicals were encouraged to participate voluntarily to meet a 33 and 50 percent reduction by 1992 and 1995, respectively. Over 1000 companies participated in this program achieving a 55 percent reduction, which translates to an overall reduction of 340 x 106 kg (750 x 106 lb) of toxic chemical releases and trans-

fers.[4] More information about this program can be obtained by contacting the EPA's Office of Pollution Prevention and Toxics website at http://www.epa.gov/opptintr/3350/.

- Common Sense Initiative (CSI) – This initiative consisted of six pilot sectors: automobile manufacturing, computer and electronics, iron and steel, metal finishing, printing, and petroleum refining. The CSI idea was to focus on environmental management by industrial sector rather than by environmental medium.[48]
- Source Reduction Review Project (SRRP)[49] – This was a pilot program designed to ensure that source reduction measures and multimedia issues were considered during the development of air, water, and hazardous waste regulations affecting 17 industrial categories. The SRRP was established to provide a model for the regulatory development process throughout EPA. Some progress has been made, but most regulations are still developed primarily based on a single medium and, while source reduction is encouraged, add-on control technologies are the basis of the regulations.
- Project XL (eXcellence and Leadership) – This is another pilot program established by EPA to promote the use of innovative approaches rather than conventional regulatory and policy strategies to achieve more cost-effective environmental results. The XL project has three key elements: superior environmental performance (SEP), regulatory flexibility to encourage participation and maximize success, and stakeholder involvement to assist in development and implementation of the project.[50]

Other examples of voluntary programs and initiatives include: AgStar, Climate Wise, Coalbed Methane Outreach, Design for the Environment, Energy Star Buildings, Energy Star Residential, Energy Star Office Equipment, Energy Star Transformer, Environmental Accounting, Environmental Leadership Program, Green Chemistry, Green Lights, Indoor Environments, P2 Information Clearinghouse, P2 Grant Program, Transportation Partners, U.S. Initiative on Joint Implementation, WAVE, Waste Minimization National Plan, and WasteWi$e. The Pollution Prevention Grant Program has announced the availability to fund grants and/or cooperative agreements for 2018 and 2019 to provide technical assistance and/or training to businesses/facilities about source reduction techniques to help them adopt and implement source reduction approaches, and to increase the development, adoption, and market penetration of greener products and sustainable manufacturing practices as well as to identify, develop, document and share P2 best management practices and innovations so this information may inform future technical assistance, and these P2 approaches and outcomes may be replicated by others.[50]

18.1.5.2 Toxic substances control act

18.1.5.2.1 Background

Also referred to by some as the sleeping giant of environmental regulations,[51] the Toxic Substances Control Act (TSCA) was enacted in 1976 to regulate chemicals in commerce that may cause adverse environmental and health effects.[52] TSCA requires testing of manufactured substances to determine the character of their effect and regulates the manufacture, distribution, use, and disposal of new and existing substances. In 1986, TSCA was

amended to include the Asbestos Hazardous Emergency Response Act (AHERA). The 1990 amendments provided for coverage of all public and commercial buildings. TSCA does not regulate food and food products, tobacco or tobacco products, and pesticide manufacturing, processing, or distribution in commerce. These areas are regulated under the Federal Food, Drug, and Cosmetic Act (FFDCA) and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). TSCA's regulatory responsibility is not delegated to states, as may be the case with the other regulations previously mentioned. Since the focus of this book is on solvents, only some key provisions of Title I will be briefly discussed.

18.1.5.2.2 Controlling Toxic Substances

Under Title I of TSCA (Section 4), manufacturers, importers, and processors of chemical substances and mixtures may be required by EPA to obtain health and environmental data on their health and environmental effects if:

- their manufacture, processing, use, distribution in commerce, and disposal, or any combination of such activities, poses an unreasonable risk to human health or the environment;
- they are or will be produced and enter the environment in substantial quantities;
- human exposure is significant; and
- data and experience to determine the chemicals' potential impact on human health and the environment are insufficient.

TSCA (Section 5) also provides EPA with the authority to regulate and control the introduction of new chemicals either through manufacture or import, or the processing of an existing chemical for a significant new use. Such manufacturers and importers must file a Premanufacture Notification (PMN) 90 days before producing or importing the chemical. Once a PMN is filed, EPA assesses the information and determines if the chemical poses an unreasonable risk of injury to health or the environment. An additional 90 days may be required by EPA to complete the revision of the PMN. If during the first 90 days, EPA does not respond to the PMN, the manufacture or import of the chemical can begin. EPA has the authority to limit, prohibit, or ban the production of chemicals based on insufficient evidence to conduct a reasonable evaluation of the risk or because the chemical poses an unreasonable risk to human health and the environment (Section 6). Examples of prohibited substances by TSCA include asbestos, halogenated chlorofluoroalkanes, and polychlorinated biphenyls (PCBs).

TSCA provides specific guidance and requirements for data gathering and reporting. This includes information such as production volume, plant size, the amount lost to the environment during production or import, the quantity of releases, and worker exposure information pertaining to controlled or uncontrolled releases. Companies are also required to maintain records of allegations of significant health or environmental effects (Section 8).

Since 1979, EPA has maintained and published a list of chemical substances manufactured, imported, or processed for commercial purposes. This list, known as the TSCA Inventory, currently has almost 80,000 chemicals.

On June 22, 2016, TSCA has been amended to create primary chemical management law. It includes mandatory requirement for EPA to evaluate existing chemicals with clear

and enforceable deadlines; new risk-based safety standard; increased public transparency for chemical information; and consistent source of funding for EPA to carry out the responsibilities under the new law. One year later, on June 22, 2017, EPA announced a number of implementation activities which have enabled EPA to meet its first-year statutory responsibilities.

18.1.6 OCCUPATIONAL LAWS AND REGULATIONS

18.1.6.1 Occupational safety and health act[53]

18.1.6.1.1 Background

In April 1971, the Occupational Safety and Health (OSH) Act of 1970 was enacted and resulted in the creation of the Occupational Safety and Health Administration (OSHA) and the National Institute for Occupational Safety and Health (NIOSH). The purpose of this Act is to ensure that workers are provided with workplaces free from recognized safety, health, and environmental hazards. OSHA is part of the Department of Labor (DOL) and responsible for developing and enforcing rules to ensure workplace safety and health. NIOSH is a research agency, part of the Centers for Disease Control and Prevention (CDC), under the Department of Health and Human Services. NIOSH is responsible for developing and establishing new and improved OSH standards and identify potential hazards of new work technologies and practices.

Since 1970, OSHA has issued more than 500 rules dealing with all aspects of worker safety and protection in the workplace. Recent amendments to the 1970 Act require employers to notify employees of potential workplace health hazards, including chemicals. OSHA regulates exposure to about 400 hazardous and toxic substances in the workplace that can cause harm.[54] Under Section 18 of the OSH Act, states are allowed to assume the responsibility for developing and enforcing their own safety and health programs.[53] The 26 states, Puerto Rico, and the Virgin Island have OSHA-approved state plans.[55]

Under the OSH Act, employers are required to provide employees with a workplace free from "recognized hazards." Employers are also required to maintain accurate records of employees' exposure to potentially toxic materials required to be monitored or measured, conduct periodic inspections, and notify employees if they are exposed to toxic materials at higher levels than those prescribed by existing health and safety regulations.

18.1.6.1.2 Air Contaminants Exposure Limits[12-14]

Information on exposure limits to solvent emissions in the workplace is provided in Table 18.1.2. These permissible exposure limit (PEL) values were obtained from OSHA's Tables Z-1, Z-2, and Z-3.[13] They are the maximum allowed PELs legally enforceable by OSHA. For comparison purposes, Table 18.1.2 provides exposure limit values generated by the American Conference of Governmental Industrial Hygienists (ACGIH) which for many of the listed chemicals are the only values currently available.[14] Usually, the ACGIH values are more stringent than the OSHA values. Both ACGIH and NIOSH have proposed more stringent PELs for over 35 and 25 solvents, respectively.[14,56] Although Table Z-1 has not been formally updated since 1987, new toxicological data on specific chemicals could be used by OSHA to produce directives intended to amend old exposure limit requirements or to add new chemicals to the regulated list. An OSHA PEL is based on an 8-hour,

time weighted-average (TWA) concentration. These were initially based on ACGHI TLV/TWA values in place since 1971, and many have not been revised since.[57] The lower the value, the more toxic the solvent. PEL values in Table 18.1.2 are given in parts per million by volume (ppmv) of contaminated air volume and the equivalent milligrams of solvent in a cubic meter of air (mg/m^3). These values are focused only on inhalation exposure, which has been strongly criticized.[54] Although this is the most common exposure route to solvent emissions in the workplace, other exposure risks exist such as skin absorption and eye contamination. It is then very important to observe toxicological data compiled in the Material Safety and Data Sheets (MSDSs). Chemical manufacturers and importers are responsible to produce or obtain an MSDS for each hazardous chemical they produce or import, distributors must provide their customers with a copy of MSDSs, and employers are responsible to maintain a copy of MSDSs for each hazardous chemical used in their facility and make them available to their employees.

There are various sources of additional helpful information on the safe use of solvents in the workplace. The Hazard Evaluation System and Information Service (HESIS) of California's Department of Health Services has a 50-page document (Using Solvent Safely) that describes methods of using solvents in the workplace. This document includes information on solvents that pose reproductive problems to both women and men.

18.1.6.1.3 Hazard Communication Standard

The Hazard Communication Standard (HCS) was established to provide workers the "right-to-know" of potential hazards associated with their jobs. HCS is a proactive measure to disseminate information to workers and employers about the health hazards pertaining to the chemicals they handle and the protection required. Employers are required to prepare and implement a hazard communication (HAZCOM) program, ensure that all containers have appropriate labels, provide employees easy access to MSDSs, and conduct training programs. The HAZCOM program is the written plan of action that describes the standard implementation strategy for a given facility.

18.1.7 CANADA[59]

In Canada, Environment Canada, which was created in 1971, is the organization responsible for environmental regulation and protection. Environment Canada is divided into five Regional Offices: Ontario, Atlantic, Prairie and Northern Region, Quebec, and Pacific and Yukon. Its environmental services are administered through the Canadian Environment Protection Act (CEPA) which includes the Air Quality Act, the Canadian Water Act, the Ocean Dumping Act, the Environment Contaminant Act, and the Department of the Environment Act. CEPA was recently amended (September 1999), placing more emphasis on pollution prevention and toxic substances. It also provides an increased enforcement authority and resources to carry out necessary research and development activities.

In 1978, Canada signed the Great Lakes Water Quality Agreement with the U.S. which identified specific objectives for minimum levels of water quality for more than 35 substances and compounds.[60] Although this is an international agreement, it has certainly impacted and, to some extent, shaped Canada's domestic environmental laws.

As a result of these statutes, the federal government establishes objectives, guidelines, and emission standards for five national air quality pollutants (carbon monoxide,

nitrogen oxides, ozone, sulfur dioxide, and suspended particulate matter). In the case of stationary sources, the regulatory responsibility usually falls under the jurisdiction of 10 provinces. The jurisdiction of water quality management is divided between the provinces and the federal government. The provinces' primary responsibility is to regulate freshwater resources, while the federal government's jurisdiction is over seacoast and inland fisheries, navigation and fisheries, and trade and commerce. The 10 provinces are also primarily responsible for regulating the management of the household, non-hazardous, and hazardous solid wastes.

18.1.8 TOOLS AND RESOURCES FOR SOLVENTS

Various software tools have been developed to identify environmentally benign alternative solvents or equipment modifications to reduce the amount of toxic and volatile solvents. Some tools have attempted to consider life cycle impact in their selection methodologies, but these are the exceptions rather than the rule. This section provides a brief description of some of the tools and resources available to assist in solvent and equipment replacement. In addition, a hotline listing is provided (Table 18.1.8). Some of these tools are the result of years of research and development by the National Risk Management Research Laboratory of EPA's Office of Research and Development. This laboratory has been researching solvent abatement,[66] replacement, reduction,[67] complete elimination for cleaning and coating operations, and developing tools[68] to assess the overall environmental impact of alternative approaches.

Table 18.1.8. List of hotlines in the U.S.[69]

Name	Description	E-mail	Phone #
Air RISC Hotline	Information on health effects, urban toxics, risk assessment, human health, and exposure.	air.risc@epa.gov	919-541-0888
EPA Test Methods Hotline		nelson.peg@epa.gov	617-918-1991
Ozone Protection Hotline		N/A	1-800-296-1996
RACT/LAER Clearinghouse	Provides information on air pollution prevention and control technologies, permit requirements at stationary air pollution sources, and related Federal air pollution emission standards.	N/A	919-541-0800
RCRA Information Center	Provides access to all regulatory materials supporting EPA's actions under RCRA.	N/A	703-603-9230 800-424-9346
RCRA Information Hotline	Responds to requests regarding hazardous waste concerning identification, generators, transporters, treatment, storage and disposal facilities, recycling sites, export, and import.	N/A	703-603-9230
Safe Drinking Water Hotline	Provides information and assistance regarding drinking water regulations, the wellhead protection program, source water protection and guidance, and education materials.	hotline-sdwa@epa-mail.epa.gov	800-426-4791

Table 18.1.8. List of hotlines in the U.S.[69]

Name	Description	E-mail	Phone #
Subsurface Remediation Information Center	Provides technical and scientific information on groundwater protection and remediation.	N/A	580-436-8651
TSCA Assistance Information Center	Provides TSCA regulation information.	tsca-hotline @epamail.epa.gov	202-554-1404
WasteWise Helpline	WasteWise is a voluntary program to encourage businesses to reduce solid waste.	OSWWaste wise@epa.gov	800-372-9473

- Solvent Alternatives Guide (SAGE): SAGE is an Internet-based tool developed by the Surface Cleaning Program at Research Triangle Institute (RTI) in cooperation with EPA's Air Pollution Prevention and Control Division to identify solvent and process alternatives for parts cleaning and degreasing. SAGE works as an expert system asking the user a series of questions concerning the part's size and volume, nature of the soil to be removed, production rate, etc. SAGE then produces a ranked list of candidate processes and chemistries most likely to work for a given situation. Since SAGE is based on readily available and proven processes and chemistries, it does not assist in the design of new solvents.
- Coating Alternatives Guide (CAGE): CAGE is based on similar principles found in SAGE but focuses on identifying alternatives for paint and coating formulations. CAGE was also developed by RTI in cooperation with EPA. It is an expert system designed to provide recommendations on low VOC/HAP coating alternatives for various substrates. It also provides the user with links to other useful websites.
- Program for Assisting the Replacement of Industrial Solvents (PARIS II): PARIS is a solvent design software system developed by EPA, the National Research Council, and RTI to substitute offending solvents with a single chemical or a mixture of solvents based on physical and chemical properties and activity coefficients. PARIS also evaluates and considers the environmental properties of the substitute chemicals. The program’s recommended alternatives may require testing to validate their performance.[69]

18.1.9 SUMMARY

Solvent releases can affect the quality of air, water, and soil which can then have adverse effects on human health and the environment. More stringent environmental laws and regulations have been established to control their utilization and ensure a safer and healthier environment and a sustainable future. They are placing greater emphasis on the elimination or reduction of such releases at the source and the preservation of limited natural resources. However, replacing offensive solvents requires a comprehensive assessment of their overall environmental impact. This will ensure that substitute chemicals will not impose more stress on our environment and human health by transferring the problem to other media.

This chapter was intended to provide a "bird's eye view" of key environmental laws and regulations for solvents. This chapter will not serve as a replacement of the laws discussed herein.

REFERENCES

1 Clean Air Act Amendments of 1970, Public Law 91-604, December 31, 1970. http://www.epa.gov/air/caa/
Clean Air Act. The most current version: http://epa.gov/oar/caa/title1.html

2 N.P. Cheremisinoff and M.L. Graffia, **Environmental and Health & Safety Management: A Guide to Compliance**, **Noyes Publication**s, New York, NY, 1995.

3 Pollution Prevention Act of 1990, United States Code Title 42, The Public Health And Welfare, Chapter 133. http://www.epa.gov/p2/pubs/p2policy/act1990.htm

4 U.S. Environmental Protection Agency, 33/50 Program: The Final Record, EPA-745/R-99-004, Office of Pollution Prevention and Toxics, Washington, DC, 1999. http://www.epa.gov/opptintr/3350/3350-fnl.pdf

5 Code of Federal Regulations, 40: Chapter 1, Subchapter C, Part 51, Subpart F, 51100. EXIT accessed 8 February 2009.

6 S.V. Nizich, T. Pierce, A.A. Pope, P. Carlson, and B. Barnard, National Air Pollutant Emission Trends, 1900-1996, EPA-454/R-97-011, NTIS PB98-153158, Office of Air Quality Planning and Standards, Research Triangle Park, NC, December 1997.
https://www.epa.gov/air-trends/ozone-trends
1970 - 2013 Average annual emissions, all criteria pollutants in MS Excel - December 2013.
http://www.epa.gov/ttnchie1/trends/
EPA. Air Quality Trends. http://www.epa.gov/airtrends/aqtrends.html

7 National Institute for Occupational Safety and Health Pocket Guide to Chemical Hazards (Publication No. 94-116), Cincinnati, OH (1994).
NIOSH Pocket Guide to Chemical Hazards. Publication No. 2010-168c. http://www.cdc.gov/niosh/npg/

8 I. Lundberg, G. Nise, G. Hedenberg, M. Högberg, and O. Vesterberg, Liver function tests and urinary albumin in-house painters with previous heavy exposure to organic solvents, Occup. and Environ. Med., 51, 347 (1994).

9 Clean Air Act Amendments of 1990, Public Law 101-549, November 15, 1990.

10 Identification and Listing of Hazardous Waste 40 CFR §261.4(b): Exclusions: Solid Wastes which are Not Hazardous Wastes. A User-Friendly Reference Document Version 1: October 2009

11 2012 Emergency Response Guidebook, J.J. Keller & Associates, Inc., Washington, DC, 2012.

12 U.S. Environmental Protection Agency, Title III List of Lists, Consolidated List of Chemicals Subject to the Emergency Planning and Community Right-to-Know Act (EPCRA) and Section 112(r) of the Clean Air Act, as Amended, EPA 550-B-01-003, Chemical Emergency Preparedness and Prevention Office, October 2006.

13 Occupational Safety and Health Standards, 29 Code of Federal Regulations, Chapter XVII, Part 1910.

14 United States Department of Labor. Occupational Safety and Health Administration. Permissible Exposure Limits. OSHA Annotated Table Z-1. OSHA PEL values 2018; ACGIH TLV 2017.

15 S. Solomon and D. Albritton, Time-Dependent Ozone Depletion Potentials for Long- and Short-Term Forecasts, *Nature*, **357**, 33 (1992).

16 J.T. Houghton, L.G. Meira Filho, B.A. Callander, N. Harris, A. Kattenberg, and K. Maskell, Eds, **Climate Change 1995**, **The Science of Climate Change, Contribution of Working Group 1 to the Second Assessment Report of the Intergovernmental Panel on Climate Change**, *Cambridge University Press*, Cambridge, UK (1996).

17 Montreal Protocol, *The International Lawyer*, **26**, 148 (1992).

18 The Montreal Protocol, *Harvard Environmental Law Review*, **15**, 275 (1991).

19 J.S. Nimitz, Development of Nonflammable, Environmentally Compliant Fluoroiodocarbon Solvents: Phase I Final Report, Prepared for U.S.A.F. Wright Laboratories under contract F33615-94-C-5003, ETEC 95-2 (1995).

20 U.S. Environmental Protection Agency, List of Substitutes for Ozone-Depleting Substances, last update August 2010, http://www.epa.gov/ozone/snap/lists/index.html. August 19, 2010.

21 Technical Guide No. 6, **Handbook of Organic Industrial Solvents**, *American Mutual Insurance Alliance*, Chicago, IL, 1980.

22 J.P. Robinson and W.C. Nelson, National Human Activity Pattern Survey Data Base, U.S. EPA, Atmospheric Research and Exposure Assessment Laboratory, Research Triangle Park, NC, 1995.

23 Reorganization Plan No. 3 of 1970, 3 CFR 1072.

24 M. Seralgeldin, Symp. Environmentally Acceptable Inhibitors and Coatings, The Electrochemical Society, Impact of the Regulatory Environment on Green Technologies, Pennington, NJ, 1997, pp. 1-16.
25 R.J. Martineau, Jr. and D.P. Novello, **The Clean Air Act Handbook**, 2nd Edition, *American Bar Association*, Chicago, IL, 2004.
26 P.E.T. Douben and M.A. Serageldin, **Pollution Risk Assessment and Management**, P.E.T. Douben, Ed., *John Wiley & Sons Ltd.*, New York, NY, 2000.
27 Communication with William Johnson on December 7, 1999, EPA's Office of Air Quality Planning and Standards, Research Triangle Park, NC (1999).
28 Coating Regulations Workshop, April 8-9, 1997, EPA's Office of Air Quality Planning and Standards, Durham, NC.
29 Federal Register 64: 13422, Consumer and Commercial Products: Schedule for Regulation, Notice of revisions to schedule for regulation (1999).
30 U.S. Environmental Protection Agency's Technology Transfer Network, Unified Air Toxics Website: Rules and Implementation, http://www.epa.gov/ttn/uatw/eparules.html, Office of Air Quality Planning and Standards, Research Triangle Park, NC, March 21, 2011. https://www.epa.gov/snap/snap-regulations
31 Federal Register 57: 31576, Initial list of Categories of Sources Under Section 112(c)(1) of the Clean Air Act Amendments of 1990, Notice of initial list of categories of major and area sources. U.S. Environmental Protection Agency (1992).
32 Federal Register 61: 28197 and 37542, Revision of list of Categories of Sources and Schedules for Standards Under 112(c) and (e) of the Clean Air Act Amendments of 1990, Notice of revisions of initial list.
33 G.S. Koch and P.R. Ammann, Current Trends in Federal Regulation of Hazardous Air Pollutants, *J. Environ. Reg.*, **4**, 25 (1994).
34 P. Zurer, Ozone Treaty Tightened, CFC Substitutes Controlled, *Chem. Eng. News*, **70**, 5 (1992).
35 Federal Water Pollution Control Act, Public Law 92-500 (1972).
36 Clean Water Act Amendments of 1977, Public Law 95-217 (1977).
37 Clean Water Act Amendments of 1982, Public Law 97-117 (1982).
38 Clean Water Act of 1987 (Clean Water Act), Public Law 100-4 (1987).
39 Navigation and Navigable Waters, 33 U.S.C. 1251-1387.
40 L.M. Gallagher and L.A. Miller, **Clean Water Handbook**, *Government Institutes, Inc*., Rockville, MD, 1996.
41 Safe Drinking Water Act, 42 U.S.C 300f et seq. (1974).
42 Safe Drinking Water Act Amendments of 1986, Public Law 99-339 (1986).
43 Safe Drinking Water Act Amendments of 1996, Public Law 104-182 (1996). Understanding the Safe Drinking Water Act. June 2004. http://water.epa.gov/lawsregs/rulesregs/sdwa/ https://www.epa.gov/ccl
44 E.J. Calabrese, C.E. Gilbert, and H. Pastides, **Safe Drinking Water Act: Amendments, Regulations and Standards**, *Lewis Publishers*, Chelsea, MI, 1989.
45 RCRA: Reducing Risk from Waste, EPA-530/K-97-004, Office of Solid Waste and Emergency Response, Washington, DC, September 1997. https://www.epa.gov/rcra/rule-checklists-applications-state-authorization-under-resource-conservation-and-recovery-act
46 Understanding the Hazardous Waste Rules: A Handbook for Small Businesses - 1996 Update, EPA-530/K-95-001, Office of Solid Waste and Emergency Response, Washington, DC, June 1996.
47 Regulations Relating to Transportation, 49 Code of Federal Regulations 171-195. The most current amendments: http://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&tpl=/ecfrbrowse/Title49/49tab_02.tpl
48 U.S. Environmental Protection Agency, The Common Sense Initiative, Lessons Learned About Protecting the Environment in Common Sense, Cost-Effective Ways, EPA-100/R-98-011, Office of Reinvention, Washington, DC, December 1998.
49 U.S. Environmental Protection Agency, Source Reduction Review Project, EPA-100/R-92/002, Office of Pollution Prevention and Toxics, Washington, DC, August 1992.
50 U.S. Environmental Protection Agency, Project XL 1999 Comprehensive Report, EPA-100/R-99-008, Office of the Administrator, Washington, DC, 1999. https://www.epa.gov/p2/fy-2018-and-fy-2019-pollution-prevention-grant-program-request-proposals
51 J.W. Vincoli, **Basic Guide to Environmental Compliance**, *John Wiley*, New York, NY, 1993.
52 Commerce and Trade, 15 U.S.C. 2601, 2011.
53 Occupational Safety and Health Act of 1970, 29 U.S.C. 651 as amended through January 1, 2004.

54 B. Plog, **Fundamentals of Industrial Hygiene**, *National Safety Council*, Itasca, IL, 2002.
55 OSHA. State Occupational Safety and Health Plans. https://www.osha.gov/dcsp/osp/. 2012.
56 National Institute for Occupational Safety and Health recommendations for occupational safety and health: Compendium of policy documents and statements, Publication No. 92-100, Cincinnati, OH (1992).
57 G. G. Noll, M. S. Hildebrand, G. Rudner, R. Schnepp, **Hazardous Materials: Managing the Incident**, 4th Ed., J*ones & Bartlett Learning*, Nov. 2012.
58 California Department of Health Services. http://www.dhs.ca.gov/, Sacramento, CA.
59 Commission for Environmental Cooperation. Summary of Environmental Law in North America, Last update 2013, http://www.cec.org/Page.asp?PageID=1115&AA_SiteLanguageID=1, Montreal, Canada.
60 L.K. Caldwell, P.S. Weiland, International Environmental Policy: From the Twentieth to the Twenty-First Century, 4th Ed. *Apple i*Book, 2014.
61 B.J.S. Hoetjes, **Environmental Law and Policy in the European Union and the United States**, R. Baker, Ed., *Praeger Publishers*, Westport, CT, 1997, pp. 31-44.
62 K.Hanf, **Environmental Law and Policy in the European Union and the United States,** R. Baker, Ed., *Praeger Publishers*, Westport, CT, 1997, pp. 125-146.
63 J. Ebbesson, **Compatibility of International and National Environmental Law**, *Kluwer Law International*, 1996.
64 C.H.V. de Villeneuve, **Environmental Law and Policy in the European Union and the United States**, R. Baker, Ed., *Praeger Publisher*s, Westport, CT, 1997, pp. 159-168.
65 I.J. Koppen, **Environmental Law and Policy in the European Union and the United States**, R. Baker, Ed., *Praeger Publishers*, Westport, CT, 1997, pp. 234-247.
66 C.M. Nunez, G.H. Ramsey, W.H. Ponder, J.H. Abbott, L.E. Hamel, and P.H. Kariher, Corona Destruction: An Innovative Control Technology for VOCs and Air Toxics, *J. Air & Waste Management Assoc*., **43**, 242-247 (1993).
67 C.M. Nunez, A.L. Andrady, R.K. Guo, J.N. Baskir, and D.R. Morgan, Mechanical Properties of Blends of PAMAM Dendrimers with Poly(vinyl chloride) and Poly(vinyl acetate), *J. Polymer Sci., Part A - Polym. Chem*., **36**, 2111-2117 (1998).
68 C.M. Nunez, G.H. Ramsey, M.A. Bahner, and C.A. Clayton, An Empirical Model to Predict Styrene Emissions from Fiber-Reinforced Plastics Fabrication Processes, *J. Air & Waste Management Assoc.*, **49**, 1168-1178 (1999).
69 U.S. Environmental Protection Agency, http://www2.epa.gov/aboutepa/mailing-addresses-and-phone-numbers.
Paris II. Computer aided solvent design for pollution prevention
http://www.epa.gov/nrmrl/std/paris/paris.htm

ACRONYMS

ACGIH	American Conference of Governmental Industrial Hygienists
AEC	Atomic Energy Commission
AHERA	Asbestos Hazardous Emergency Response Act
BAC	Best Available Control
BACT	Best Available Control Technology
BAT	Best Available Technology Economically Achievable
BCT	Best Conventional Pollutant Control Technology
BDT	Best Available Demonstrated Technology
BMP	Best Management Practices
BPT	Best Practicable Control Technology
CAA	Clean Air Act
CAGE	Coating Alternatives Guide
CAMD	Computer-Aided Molecular Design
CAS	Clean Air Solvent
CDC	Centers for Disease Control and Prevention
CEPA	Canadian Environment Protection Act
CESQG	conditionally exempt small quantity generator
CFC	chlorofluorocarbon
CSI	Common Sense Initiative
CTG	Control Technology Guideline

CWA	Clean Water Act
DEPH	bis (2-ethylhexyl)phthalate
DOL	Department of Labor
DOT	Department of Transportation
DV	Design Value
EAP	Environmental Action Programme
EC	European Community
ECSC	European Coal and Steel Community
EEA	European Environment Agency
EEC	European Economic Community
ENVIROENE	public environmental information system
EPA	U.S. Environmental Protection Agency
ETV	Environmental Technology Verification
EU	European Union
EURATOM	European Atomic Energy Community
FFDCA	Federal Food, Drug, and Cosmetic Act
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FIP	Federal Implementation Plan
FWPCA	Federal Water Pollution and Control Act
GWP	global warming potential
HAP	hazardous air pollutant
HAZCOM	hazard communication
HCFC	hydrochlorofluorocarbon
HCS	Hazard Communication Standard
HESIS	Hazard Evaluation System and Information Service HFE hydrofluoroether
HMTA	Hazardous Materials Transportation Act
HSWA	Hazardous and Solid Waste Amendments
LAER	Lowest Achievable Emissions Rate
LCCA	Lead Contamination Control Act
LQG	large quantity generator
MACT	Maximum Achievable Control Technology
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MSDS	Material Safety and Data Sheet
NAAQS	national ambient air quality standards
NESHAP	national emission standards for hazardous air pollutants
NIOSH	National Institute for Occupational Safety and Health
NPDES	National Pollutant Discharge Elimination System
NPDWR	National Primary Drinking Water Regulations
NSPS	new source performance standards
NSR	New Source Review
ODS	ozone depleting substance
OPPE	Office of Policy, Planning, and Evaluation
OPPT	Office of Pollution Prevention and Toxics
OSH	Occupational Safety and Health
OSHA	Occupational Safety and Health Administration
P2	Pollution Prevention
PARIS	Program for Assisting the Replacement of Industrial Solvents
PCB	polychlorinated biphenyl
PCBTF	p-chlorobenzotrifluoride
PEL	permissible exposure limit
PM10	particulate matter of 10 micrometers in aerodynamic diameter or smaller
PMACT	Preliminary Maximum Achievable Control Technology
PMN	Premanufacture Notification
POTW	publicly operated treatment works
PPIC	Pollution Prevention Information Clearinghouse
PSD	prevention of significant deterioration
RACT	Reasonable Available Control Technology

RCRA	Resource Conservation and Recovery Act
RISC	Risk Information Support Center
SAGE	Solvent Alternatives Guide
SCAQMD	South Coast Air Quality Management District
SDWA	Safe Drinking Water Act
SEP	superior environmental performance
SIP	State Implementation Plan
SNAP	Significant New Alternatives Policy
SQG	small quantity generator
SRRP	Source Reduction Review Project
SWDA	Solid Waste Disposal Act
TLV®	Threshold Limit Value
TRI	Toxic Release Inventory
TSCA	Toxic Substances Control Act
TSD	treatment, storage, and disposal
TWA	time weighted average
UN	United Nations
UV	ultraviolet light
VOC	volatile organic compound
XL	eXcellence and Leadership

18.2 REGULATIONS IN EUROPE

Tilman Hahn, Konrad Botzenhart, Fritz Schweinsberg
Institut für Allgemeine Hygiene und Umwelthygiene, Universität Tübingen, Tübingen, Germany

The legislative and executive regulations in Europe are generally based on EEC regulations which are converted to and coordinated by national regulations as it is a rule in Europe. Some EEC regulations do not exist or they are not always converted effectively in the EEC Member States.

In Europe environmental law, especially concerning chemical and hazardous substances, was first introduced about 30-40 years ago.[1] Main aims of EEC regulations are the registration and the classification of a wide variety of chemical substances, the environmental protection, the health protection, harmonization of national laws, and the liberalization of the market. For these reasons, several EEC regulations were created and completed (see Section 18.2.1). Changes of regulations intended to optimize some aspects, e.g., environmental and health aspects by the obligation of registration and test procedures.[7] The list in Section 18.2.1 shows all relevant regulations in Europe concerning solvents. The amended versions of these regulations (if they exist) are given below each original regulation.[1-40]

Relevant German regulations concerning solvents are listed in Section 18.2.2 as an example of the conversion of EEC regulations in the Member States. In Germany, the application of chemical and hazardous substances are based on a few regulations.[41-46] Special and practical applications of these basic regulations are put in concrete terms in different standards, e.g., TRGS[44] or DIN.[41-68]

18.2.1 EEC REGULATIONS

1 67/548/EEC, Council Directive of 27 June 1967 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the classification, packaging, and labeling of dangerous substances, ABl. EG Nr. L 196/1, 1967.
Regulation (EC) No 1272/2008 - classification, labelling, and packaging of substances and mixtures. of the European Parliament and of the Council of 16 December 2008 on classification, labeling, and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006 (Text with EEA relevance).

2 73/173/EEC, Council Directive of 4 June 1973 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the classification, packaging, and labeling of dangerous preparations (solvents), ABl. EEC Nr. L 189, 1973.
189/1983 - European Communities (Dangerous Preparations) (Solvents) (Classification, Packaging and Labelling) Regulations, 1983.

3 Council Declaration (EC) and of the Member States of 22 November 1973 concerning an environmental program (EC), ABl. EG Nr. C 112/1, 1973.

4 75/442/EEC, Council Directive of 15 July 1975 on waste, ABl. EEC Nr. L 194/47, 1975.
Regulation (EC) No 1882/2003 of the European Parliament and of the Council of 29 September 2003
Directive 2008/98/EC of the European Parliament and of the Council of 19 November 2008 on waste and repealing certain Directives

5 76/769/EEC, Council Directive of 27 July 1976 on the approximation of the laws, regulations and administrative provisions of the Member States relating to limitations of the use of certain dangerous substances and preparations, ABl. EEC Nr. L 262/201, 1976.

6 77/728/EWG, Council Directive of 7 November 1977 on the approximation of the laws, regulations and

administrative provisions of the Member States relating to the classification, packaging, and labeling of paints, varnishes, printing paints, adhesives etc., ABl. EEC Nr. L 303/23, 1977.

7 79/831/EEC, Council Directive of 18 September 1979 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the classification, packaging and labeling of dangerous preparations, ABl. EEC Nr. L 154/1, 1979.
Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006

8 88/379/EEC, Council Directive of 7 June 1988 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the classification, packaging, and labeling of dangerous preparations, ABl. EEC Nr. L 187/14, 1988.

9 88/344/EEC, Council Directive of 13 June 1988 on the approximation of the law of the Member States on extraction solvents used in the production of foodstuffs and food ingredients, ABl. EEC Nr. L 57/28, 1988.
Directive 2009/32/EC of the European Parliament and of the Council of 23 April 2009 on the approximation of the laws of the Member States on extraction solvents used in the production of foodstuffs and food ingredients

10 89/349/EEC, Commission Recommendation of 13 April 1989 on the reduction of chlorofluorocarbons by the aerosol industry, Abl. EG Nr. L 144/56, 1989.

11 91/155/EEC, Commission Directive of 5 March 1991 defining and laying down the detailed arrangements of the system of specific information relating to dangerous preparations in implementation of Article 10 of Directive 88/379/EEC, ABl. EEC Nr. L 76/35, 1991.

12 91/689/EEG, Council Directive of 12 December 1991 on hazardous waste, ABl. EG Nr. L 23/29, 1993.

13 92/2455/EEC, Council Regulation (EEC) of 23 July 1992 concerning the export and import of certain dangerous chemicals, ABl. EEC Nr. L 251/13, 1992.

14 93/793/EEC, Corrigendum to Council Regulation (EEC) No. 793/93 of 23 March 1993 on the evaluation and control of the risks of existing substances, ABl. EEC Nr. L 224/34, 1993.

15 93/67/EEC, Commission Directive of 20 July 1993 laying down the principles for assessment of risks to man and the environment of substances notified in accordance with Council Directive 67/548/EEC, ABl. EEC Nr. L 227/9, 1994.
Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).

16 Council Regulation (EEC) No. 259/93 of 1 February 1993 on the supervision and control of waste within, into and out of the European Community, ABl. EG Nr. L 30/1, 1993,

17 Commission decision of 20 December 1993 concerning a list of hazardous waste pursuant to Article 1(a) of Council Directive 91/689/EEC on hazardous waste, ABl. EG Nr. L5/15, 1994.
Directive 2008/98/EC of the European Parliament and of the Council of 19 November 2008 on waste

18 94/1179/EEC, Commission Regulation of 25 May 1994 concerning the first list of priority substances as foreseen under Council Regulation (EEC) No. 793/93, ABl. EEC Nr. L 161/3, 1994.

19 94/1488/EEC, Commission Regulation of 28 June 1994 laying down the principles of the assessment of risks to mass and the environment of existing substances in accordance with Council Regulation No. 793/93, ABl. EEC Nr. L 161/3, 1994.

20 Council Regulation (EEC) No. 3093/94 of 15 December 1994 on substances that deplete the ozone layer, ABl. EG Nr. L 333/1, 1994.
COM/2008/0505 final - COD 2008/0165. Communication from the Commission to the Council, the European Parliament, the Economic and Social Committee and the Committee of the Regions - Completing the phase-out of substances that deplete the ozone layer

21 94/904/EEC, Council Decision of 22 December 1994 establishing a list of hazardous waste pursuant to Article 1(4) of Council Directive 91/689/EEC on hazardous waste, ABl. EG Nr. L 356/4, 1994.

22 95/365/EEC, Commission Decision of 25 July 1995 establishing the ecological criteria for the award of the Community eco-label to laundry detergents, ABl. EG Nr. L 217/14, 1995.

23 95/2268/EEC, Commission Regulation of 27 September 1995 concerning the second list of priority substances as foreseen under Council Regulation No. 793/93, ABl. EEC Nr. L 231/18, 1995.

24 96/61/EEC, Council Directive of 24 September 1996 concerning integrated pollution prevention and control, ABl. EG Nr. L 257/26, 1996.

25 97/142/EEC, Commission Regulation of 27 January 1997 concerning the delivery of information about certain existing substances, ABl. EEC Nr. L 25/11, 1997.

26 Directive 2004/42/CE of the European Parliament and of the Council of 21 April 2004 on the limitation of emissions of volatile organic compounds due to the use of organic solvents in certain paints and varnishes

and vehicle refinishing products
27 Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency
28 Directive 2010/75/EU of the European Parliament and of the Council of 24 November 2010 on industrial emissions (integrated pollution prevention and control).
29 Regulation 10/2011 Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food Text with EEA relevance
Union Guidance on Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food as regards information in the supply chain. 28.11.2013
Commission Regulation (EU) 2016/1416 of 24 August 2016 amending and correcting Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food
30 Guidance on Storage Handling of Chlorinated Solvents. Drum reconditioning and disposal of chlorinated solvents. Fifth Edition, February 2016. ECSA. www.chlorinated-solvents.eu
31 Directive 2008/99/EC – protecting the environment by means of criminal law
32 Regulation (EU) No 517/2014 of the European Parliament and of the Council of 16 April 2014 on fluorinated greenhouse gases and repealing Regulation (EC) No 842/2006. (cuts 2/3 of the present level by 2030)
33 Directive 2009/32/EC of the European Parliament and of the Council of 23 April 2009 on the approximation of the laws of the Member States on extraction solvents used in the production of foodstuffs and food ingredients (permitted solvents are propane, butane, ethyl acetate, ethanol, carbon dioxide, acetone, and nitrous oxide)
34 Regulation (EC) No 1005/2009 of the European Parliament and of the Council of 16 September 2009 on substances that deplete the ozone layer.
35 Directive 2012/18/EU of the European Parliament and of the Council of 4 July 2012 on the control of major-accident hazards involving dangerous substances, amending and subsequently repealing Council Directive 96/82/EC Text with EEA relevance
36 Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency
37 Regulation (EC) No 1935/2004 of the European Parliament and of the Council of 27 October 2004 on materials and articles intended to come into contact with food and repealing Directives 80/590/EEC and 89/109/EEC
38 Directive 2004/42/CE of the European Parliament and of the Council of 21 April 2004 on the limitation of emissions of volatile organic compounds due to the use of organic solvents in certain paints and varnishes and vehicle refinishing products and amending Directive 1999/13/EC
39 Directive 2010/75/EU of the European Parliament and of the Council of 24 November 2010 on industrial emissions (integrated pollution prevention and control) Text with EEA relevance
40 Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products (Text with EEA relevance)

18.2.2 GERMAN REGULATIONS

41 Verordnung über Höchstmengen an bestimmten Lösemitteln in Lebensmitteln (Lösemittel-HöchstmengenVerordnung - LHmV) vom 27. Juli 19. Regulation concerning maximum quantities of certain solvents in foods (LHmV) of 27 July 1989, BGBl., 1568 (1989).
42 Verordnung über die Entsorgung gebrauchter halogenierter Lösemittel (HKWAbfV) vom 23. Oktober 1989 (BGBl. I S. 1918), die durch Artikel 7b der Verordnung vom 20. Oktober 2006.
43 Verordnung zum Schutz vor gefährlichen Stoffen (Gefahrstoffverordnung - GefStoffV) vom 26.11.2010. Regulation concerning the protection against hazardous substances of 26 November 2010. Artikel 148 des Gesetzes vom 29. März 2017 (BGBl. I S 626)
44 Technische Regeln für Gefahrstoffe (TRGS). Technical Regulations concerning hazardous substances (TRGS), e.g. TRGS 002, TRGS 003, TRGS 101, TRGS 102, TRGS 150, TRGS 220, TRGS 222, TRGS 400, TRGS 402, TRGS 403, TRGS 404, TRGS 415, TRGS 420, TRGS 512, TRGS 519, TRGS 531, TRGS 900, TRGS 903, TRGS 905, TRGS 906, TRGS 910.
45 Gesetz zum Schutz vor gefährlichen Stoffen (Chemikaliengesetz - ChemG) vom 25. Juli 1994. Law concerning the protection against hazardous substances of 25 July 1994, BGBl. I, 1703 (1994).
46 DIN 51405, General principles governing the gas chromatographic analysis of petroleum products and related liquids and solvents used in paint sand varnishes, 2004.

47 DIN 53170, Solvents for paints and similar coating materials; determination of the evaporation rate, 2009.
48 DIN 53171, Solvents for paints and varnishes; determination of distillation characteristics (boiling range and boiling temperature as a function of distilled volume), 2009.
49 DIN 53172, Solvents for paints and varnishes; determination of evaporation residue, 2009.
50 DIN 53173, Solvents for paints and varnishes; determination of carbonyl value, 2009.
51 DIN 53245, Solvents for paints and varnishes; alcohols; supply specification, further properties and methods of test, 2009.
52 DIN 53246, Solvents for paints and varnishes - Acetic esters - Delivery specification, further requirements and methods of test, 2009.
53 DIN 53247, Solvents for paints and varnishes - Ketones - Supply specifications, further requirements and methods of test, 2009.
54 DIN 53248, Solvents for paints, varnishes and similar coating materials - Gum spirit of turpentine and wood turpentines - Requirements and methods of test, 2006.
55 DIN 53249, Solvents for paints, varnishes and similar coating materials - Dipentene - Requirements and methods of test, 2007.
56 DIN 55651, Solvents for paints and varnishes - Symbols, 2000.
57 DIN 55682, Solvents for paints and varnishes - Determination of solvents in water-thinnable coating materials - Gas chromatographic method, 2000.
58 DIN 55683, Solvents for paints and varnishes - Determination of solvents in coating materials containing organic solvents only - Gas chromatographic method, 2009.
59 DIN 55685, Solvents for paints and varnishes; alcohols; gas chromatographic determination of the degree of purity, 2009.
60 DIN 55686, Solvents for paints and varnishes; acetic esters; gas chromatographic determination of the degree of purity, 2006.
61 DIN 55687, Solvents for paints and varnishes; ketones; gas chromatographic determination of the degree of purity, 2009.
62 DIN 55688, Solvents for paints and varnishes - Ethylene glycol ethers - Gas chromatographic determination of the degree of purity, 2006.
63 DIN 55689, Solvents for paints and varnishes - Propylene glycol ethers - Gas chromatographic determination of the degree of purity, 2006.
64 DIN 55997, Solvents for paints and varnishes - Deionized water - Requirements and methods of test, 2000.
65 DIN 55998, Solvents for paints and varnishes - Propylene glycol ethers - Supply specification, further requirements and methods of test, 2009.
66 DIN 55999, Solvents for paints and varnishes, ethylene glycol ethers; supply specification, further properties and methods of test, 2009.
67 DIN EN 13649, Stationary source emissions determination of the mass concentration of individual gaseous organic compounds - activated carbon and solvent desorption method, 2015.
68 DIN EN 14662-2, Ambient air quality - standard method for measurement of benzene concentrations part 2: pumped sampling followed by solvent desorption and gas chromatography, 2005.

19

Toxic Effects of Solvent Exposure

19.1 TOXICOKINETICS, TOXICODYNAMICS, AND TOXICOLOGY

Tilman Hahn, Konrad Botzenhart, Fritz Schweinsberg
Institut für Allgemeine Hygiene und Umwelthygiene Universität Tübingen, Tübingen, Germany

19.1.1 TOXICOKINETICS AND TOXICODYNAMICS

19.1.1.1 Exposure

Highest exposures can be found in the workplace (e.g., evaporation of solvents) or during special processes (e.g., leaks of normally closed systems). Acute and severe solvent accidents often happen in workplaces (high solvent concentrations, intermittent high-level exposures, high duration of exposure). Apart from working sites, various other emission sources of solvents should be considered, e.g., consumer products.

The description of exposure parameters (a type of solvents, concentrations, duration, routes of exposure) is important for the evaluation of toxicokinetics. Solvents and other chemicals are usually emitted as a mixture of various substances. Therefore, the risk assessment of emitted solvents is difficult to ascertain.[1,2] Solvent concentrations and duration of exposure vary in most cases (intermittent high-value peaks, periods of low exposure). The exposure is influenced essentially by surrounding occupational and environmental conditions, such as working climate, protective equipment and by individual parameters such as eating habits.

The exposure to solvents is regulated by relevant threshold limit values.[1,2] Exposure and exposure values can be controlled by defined methods (e.g., ambient and biological monitoring).

19.1.1.2 Uptake

Relevant uptake routes of solvents are absorption from the lung and percutaneous absorption. The intestinal uptake is usually caused by accidents or by intent. The absorption rate is influenced by various factors.

19.1.1.2.1 Inhalation

Inhalation is the most common pathway of solvent absorption, especially at working sites. The pulmonary absorption of solvents depends on the following parameters:[3-6]

- Exposure (concentrations and concentration fluctuations in the ambient air, exposure time, physical exertion). The alveolar concentration of solvents or the differ-

ence between air and blood concentration levels determine the diffusion process into alveolar blood vessels. Physical exertion influences lung parameters, especially ventilation, and consequently alveolar and blood concentrations.

- Lung parameters (pulmonary and alveolar ventilation, pulmonary perfusion, air-blood coefficient, blood-tissue coefficient). These coefficients describe the number of solvents which can diffuse. The blood-tissue partition coefficient influences the tissue equilibrium concentrations, e.g., solvents with stronger hydrophobic properties (e.g., toluene) reach equilibrium more rapidly because of a low tissue-blood coefficient. Intraindividual differences such as child/adult are also of significance.
- Physicochemical characteristics of solvents (solubility such as hydrophobic and hydrophilic properties, state such as liquid or gaseous and degree of volatility).

19.1.1.2.2 Dermal uptake

Dermal uptake of solvents requires skin contact and depends on the area of contact, skin thickness, dermal state (e.g., eczema and defects in the stratum corneum), exposure parameters (contact time, etc.) and solvent properties.[7,8]

The main barriers against percutaneous uptake of solvents are structures of the stratum corneum, especially intercellular lipids and fibrous keratin. Removal of lipids by polar solvents such as ethanol or hydration in the stratum corneum is associated with an increase of skin permeability. Defects or lack of stratum corneum that may occur in skin diseases, at particular skin locations such as hair follicles or glandular regions enhance the percutaneous movement of solvents. The absorption through mucous membranes is facilitated because of the lack of the stratum corneum.

Skin defects or diseases can be provoked by solvents which cause irritation, cellular hyperplasia, and swelling, or removal of lipids. Skin defects are provoked mainly by frequent use of solvents thus enhancing their absorption.

Other characteristics, which influence percutaneous absorption, are solvent concentration gradients, solvent partitioning (water/lipid partition coefficient) and permeability constants.

Lipophilic chemicals are absorbed most easily (for example, benzene). These can include liquid solvents or solvents having low vapor pressure.[9-11] Vapors absorbed by dermal uptake can significantly contribute to the body burden as a result of the whole body exposure: e.g., 1-2% of xylene or toluene, up to 5-10% 1-methoxypropane-2-ol.[10] For other substances, much higher skin absorption rates were measured after the whole body exposure: 2-methoxyethanol up to 55%, 2-ethoxy-ethanol up to 42%.[12]

It is important to consider that the dermal uptake of vapors is especially significant when using a respirator.[10] In addition to inhalation measurements, measurement of percutaneous absorption is an important method for assessing health or environmental risks.

Dermal absorption of solvents is shown in Table 19.1.1.

Table 19.1.1. Dermal uptake of solvents according to the German MAK-list.[2,64]

Acetonitrile	Diacetone alcohol	Ethyl formate	Pyridine
Benzene	1,2-Dichlorobenzene	Formamide	Pyrrolidine
Benzyl alcohol	1,2-Dichloroethane	2-Hexanone	1,1,2,2-Tetrachloroethane
Bromomethane	Dichloromethane	Limonene	Tetrachloroethylene
2-Butanone	Diethylene glycol	Methanol	Tetrahydrofuran
2-Butoxyethanol	dimethyl ether	2-Methoxyethanol	Toluene
Carbon disulfide	Dimethylacetamide	Methyl chloride	Toluidine(s)
Carbon tetrachloride	Dimethylformamide	Methyl formate	Tributyl phosphate
2-Chloroethanol	Dimethylsulfoxide	Nitrobenzene	Trichlorobenzene
Chloroform	1,4-Dioxane	Nitrotoluene(s)	Trichloroethane
Cresol(s)	2-Ethoxyethanol	Phenol	Turpentine
Cyclohexanol	Ethylbenzene	Propylene glycol	Xylene(s)
Cyclohexanone	Ethylene glycol	2-methyl ether	Xylidine

19.1.1.2 Metabolism, distribution, excretion

Specific toxicity of solvents is directly related to their metabolism which is predominantly catalyzed by cytochrome P-450 mixed-function oxidases in the liver or other tissues.

Relevant examples of specific metabolism are toxic epoxides of benzene (hemopoietic toxicity), n-hexane 2,5-hexanedione (peripheral neurotoxic effects), metabolites of ethylene glycol ethers (reproductive toxicity), and unidentified metabolites from trichloroethylene (renal-toxic effects).[13] It should be emphasized that only the metabolites of these solvents are associated with toxic effects.

Other relevant metabolic pathways result in detoxified substances, such as biotransformation processes in the liver – conjugation with glycine, glucuronic acid and sulfuric acid (e.g., *via* hydroxylation of toluene) or biotransformation by hydrolysis, oxidation, and conjugation (e.g., glycol ethers).

It should be noted that metabolic processes vary according to the following conditions:[14]

- Species, sex, age, genetics, e.g. variability of enzymatic factors such as polymorphisms (cytochrome systems) or tissue repair mechanisms.[15]
- Lifestyle, e.g., diet, smoking, drug consumption, physical activity.
- Saturation. Massive concentrations of solvents result in saturation of metabolic pathways. This is important with regard to detoxification.
- Induction of enzymes. Specific induction of enzyme systems by chemicals (solvents as well as other chemicals such as drugs) may consequently provoke an increase or decrease of solvent toxicity.
- Interactions may be involved in enhancing or reducing the toxicity of solvents. For example, Bloch *et al.*[16] showed that in cases of alcohol abuse an increase in the toxic effects of benzene and other lipophilic petroleum derivatives occurs. Also, it has been shown that benzene inhibits the metabolism of toluene.[17]

Solvents can be excreted *via* various pathways:

- Exhalation (unchanged).
- Urine tract and biliary tract (unchanged or metabolites, e.g., water-soluble conjugates).

19.1.1.3 Modeling of toxicokinetics and modifying factors

The complexity of toxicokinetic processes of solvents can be described in models, e.g., predicting exposure situations and distribution phenomena in the human body and quantifying these processes (e.g., dose-effect response relationships). This applies especially to the simulation of physiological and physicochemical parameters[18] or to assessing low exposures to complex chemical mixtures.[19]

19.1.2 TOXICOLOGY

19.1.2.1 General effects

General effects of solvents concern primarily acute exposures to high solvent concentrations. Despite some variations of symptoms, the resulting effects on the central nervous system (CNS) are rather stereotypical.[20]

Several solvents have depressant or narcotic effects, and hence, some solvents are used as anesthetics.[21] The main acute health hazards result from the narcotic effects. Their intensity is proportional to the solvent concentrations in brain tissue and is caused by the solvents themselves (physical and chemical interactions with neural membranes, nerve cells or neurotransmitters of the CNS).

General CNS dysfunctions after solvent exposure, are initially euphoria and disinhibition, higher exposures result in pre-narcotic symptoms such as dizziness, euphoria, disorientation and confusion, nausea, headache, vomiting, ataxia, paresthesia, increased salivation, and tachycardia.[22,23] The symptoms are rapidly reversible when the solvents are removed.

In addition to the non-specific acute narcotic effects of solvents mentioned above, alterations of behavioral, cognitive and psychomotoric functions are typically found after short-term exposure to solvent levels close to the TLV. Over-exposure leads to convulsions, coma, and death. Typical changes are paresthesias, visual and auditory deficits, cognitive deficits (short-term and long-term memory loss), confusion, disorientation, affective deficits (nervousness, irritability, depression, apathy, compulsive behavior) and motor deficits (weakness in extremities, incoordination, fatigue, tremor).[24,25]

It is difficult to develop useful methods and models for testing these behavioral effects of solvents but for this purpose tests of attention and reaction, cognitive tests and other test systems are used.[26,27]

Acute CNS dysfunction diseases can show mild (organic affective syndrome), moderate or severe (acute toxic encephalopathy) symptoms.[28,29]

Unspecific irritations of skin and mucosal membrane structures can be caused by solvents. Various solvents are significant occupational irritants, e.g., solvents which cause irritant contact dermatitis.[30] Intact skin structures can be destroyed by solvents which dissolve grease and fat. Typically, the dermatitis is characterized by dryness, scaling, and fis-

suring and is usually located on the hands. It is often caused by handling solvent-contaminated products or by cleaning procedures.[31,32]

Unspecific irritation of mucous membranes is often caused by solvent vapors, e.g., irritation of the eyes and various sections of the airways.

19.1.2.2 Specific non-immunological effects

Table 19.1.2 summarizes the main specific effects of solvents:[33-47]

- Hepatotoxicity,
- Nephrotoxicity,
- Reproductive toxicity,
- Hemopoietic toxicity,
- Neurotoxicity,
- Ocular toxicity.

Table 19.1.2. Examples for specific effects of selected solvents.

Organ-system	Solvents	Symptoms
Liver	halogenated hydrocarbons (e.g., carbon tetrachloride, tetrachloroethane, chloroform), ethanol, 1,1,1-trichloroethane, trichloroethylene, bromobenzene, dimethylformamide	acute (necrosis, steatosis) and chronic (cirrhosis) hepatotoxic symptoms
Kidney	halogenated hydrocarbons (e.g. carbon tetrachloride), toluene, dioxane, diethylene glycol, ethylene glycol, glycol ethers, conjugates of trichloroethylene	acute tubular necrosis, glomerular and tubular dysfunctions (e.g., albuminuria, proteinuria), glomerulonephritis, note: modification of solvent effects caused by renal dysfunctions possible
Reproductive system	carbon disulfide, benzene, glycol ethers, nitrobenzene	disturbance of menstrual cycle, reduced sperm counts, embryotoxic effects
Hemopoietic system	benzene metabolites (e.g. benzoquinone, hydroquinone)	marrow depression, myelotoxic effects
Nerval system	n-hexane, ethanol, styrene, tetrachloroethylene	peripheral neuropathy (especially distal axons, axon swelling and degeneration, loss of sensibility, muscular atrophy, loss of tendon reflexes)
Eye	methanol	impaired vision

Note: the data shown come predominantly from occupational exposure.

These and other specific effects of solvents are discussed in more detail in separate sections following the present section.

19.1.2.3 Immunological effects

Various solvents have well-known allergic potentials. Allergic symptoms of the respiratory tract (rhinitis, tracheitis, bronchitis, asthma), allergic contact dermatitis and conjunctivitis can be provoked by solvents. The allergic effects of solvents can also contribute to other diseases such as MCS, autoimmune diseases.

Solvents or by-products with allergic potential occur mainly at workplaces and, to a lesser degree, in consumer products. According to EG regulations, solvent ingredients of some consumer products, e.g., cosmetic products, must be labeled. It is often difficult to detect the causative solvent allergen (allergens which cause cross-allergies, secondary products of solvents such as oxygenated terpenes, unknown allergens). Various specific test systems are available for carrying out individual test diagnoses: e.g., chamber tests,[48] skin tests such as patch-tests[49] and special applications of biological monitoring.

Solvent-induced allergies can occur at a variety of worksites, e.g., in shoe factories,[50] in electronic industries,[51] in synthetic chemical industries,[52] in metal industries[53] or in perfume and potter industries (oil of turpentine and other solvents).[54] Similar occurrence of solvents can be found in consumer products, e.g., in nail polishes (e.g., toluene).[55] Allergic solvent substances are listed in various catalogues and databases.[1,2,49]

Examples of allergic solvents are terpene products with high sensitivity potential, which can cause positive test reactions (patch-test) or even allergic diseases (contact sensitization and dermatitis). Allergic dermatitis can even be provoked by d-limonene in the air.[56] Terpenes and terpenoid substances are found especially in “natural products”, e.g., cosmetic products, foods, and plants (oilseed rape).[57,58]

The allergic potential of solvent products depends on the typical solvent structure. For example, in glycol ethers, their allergic potential is proportional to the charge of interacting molecules.[59]

Allergic effects can also be associated with other skin conditions caused by solvents such as irritations. Multiple areas of skin damage, including solvent allergies, can change the skin structure and provoke severe skin disease.[60]

In addition to other substances (pesticides, food additives, dust, smoke, etc.), allergic effects of solvents are discussed as an initial cause of MCS.[61]

Organic solvents are associated with human autoimmune diseases, but defined pathomechanisms of these solvents have not yet been detected (role of solvents in the initiation or progression of autoimmune diseases).[62]

19.1.2.4 Toxic effects of solvents on other organisms

In addition to humans, microorganisms animals and plants are also exposed to solvents. The interaction between organisms and solvents are often specific. For example, the reactions elicited by certain solvents depend on the species and abilities of the particular organism affected.

Hydrophobic organic solvents, in particular, are toxic to living organisms, primarily because they disrupt cell membrane structure and mechanisms. Some living organisms, especially certain bacterial species, are able to adapt to these solvents by invoking mechanisms such as accelerating repair processes (through changes in the rate of phospholipid biosynthesis), reduction of the diffusion rate of the solvent and active reduction of the

intracellular concentration of the solvent. More information and examples are shown in Chapter 13.4.2.

19.1.2.5 Carcinogenicity

The term carcinogenicity is used for toxicants that are able to induce malignant neoplasms. Carcinogens can be effective at different stages of the carcinogenic process, e. g., initiation, promotion and progression. They may interact with other noxes and thereby enhance tumor development. Interactive carcinogenesis can be described as co- and syn-carcinogenesis. A co-carcinogen is defined as a non-carcinogenic compound that is able to enhance tumor development induced by a given carcinogen. In syn-carcinogenesis, two or more carcinogens, each occurring in small amounts that are usually not sufficient to induce a tumor in a specific target organ, may interact to lead to tumor formation in that organ.

As with all carcinogens, the carcinogenic potency of solvents has been assessed by short-term *in vitro* tests, e. g., Ames assay, by long-term tumor induction experiments in animals and – especially important for the evaluation of the carcinogenic action in humans prospective and retrospective epidemiological studies, for solvent exposure mainly in workplaces.

From this data, it is generally not possible to evaluate the carcinogenic action of solvent mixtures, which occur in the majority of exposure situations. It is also important to note, that for a number of reasons, e.g., very long latency period of tumor generation, accumulation of single hits in the target cells, the significance of repair mechanisms it is not possible to define TLVs for carcinogens.

In accordance with the evidence available, different classes of chemical carcinogens have been developed by health authority organizations.[1,2,34-36] Examples of the classification of carcinogenic solvents are presented in Table 19.1.3.

Table 19.1.3. Carcinogenicity – Survey of selected solvents.

Solvent	Organ-System	Category*				
		MAK	EG	ACGIH	IARC	NTP
Acetonitrile	respiratory system, cardiovascular system, central nervous system, liver, kidneys	2		A4		n.c.
Benzene	hemopoietic system	1	K1	A1	1	K
Bromomethane	upper gastrointestinal, tract and respiratory, tract (animals)	3B	K3	n.c.**	3	n.1 **
Carbon tetrachloride	lymphatic system, liver (mice, rats), mamma (rats), suprarenal gland (mice)	4	K3	A2	2B	R
1-Chloro-2,3-epoxypropane (epichlorohydrin)	*lung, CNS*, forestomach (rats), nasal cavity, skin (mice)	2	K2	A3	2A	R
Chloroethane	uterus (mice)	3B	K3	A3	3	n.1
Cyclohexanone	suprarenal gland (rats)	3B	n.c.	n.1	3	n.1

Table 19.1.3. Carcinogenicity – Survey of selected solvents.

Solvent	Organ-System	Category*				
		MAK	EG	ACGIH	IARC	NTP
1,2-Dibromoethane	forestomach (mice), lung (mice, rats), nasal cavity, peritoneum, mamma, connective tissue (rats)	2	K2	A3	n.1	R
1,2-Dichloroethane	*brain, lymphatic and hemopoietic system, stomach, pancreas;* lung, mamma, stomach (mice, rats), lymphatic system (mice)	2	K2	n.1	2B	R
Dichloromethane	liver, lung (mice, rats), mamma (rats), lymphosarcomas (mice)	5A	K3	A3	2B	R
1,2-Dichloropropane	liver (mice), mamma (rats)	3B	K3	n.1	n.1	n.1
Dimethylformamide	*testes*	4	n.c.	n.1	3	n.1
1,4-Dioxane	liver (rats, guinea pigs), biliary tract (guinea pigs), mamma, peritoneum (rats), nasal cavity (mice)	4	n.i. **	A3	2B	R
Ethanol	eyes, skin, respiratory system, central nervous system, liver, blood, reproductive system	5		A4		
Ethylbenzene	respiratory system, central nervous system	4				
Hexamethyl phosphoramide	nasal cavity, lung (rats), liver (rats)	2	n.i.	A3	2B	R
Isophorone	respiratory system, central nervous system, liver, kidneys	3B		A3		
Methyl chloride	central nervous system, liver, kidneys, reproductive system	3B				
Nitrobenzene	lung, thyroid gland, mamma (mice), liver, kidney, uterus (rats)	4	K3	A3	2B	R
2-Nitropropane	liver (rats)	2	n.1	A3	2B	R
2- Nitrotoluene	epididymis (rats)	2	K2	n.c. BEI**	3	R
Phenol	lymphatic system, hemopoietic system suprarenal gland, thyroid gland, skin (mice, rats)	3B	n.c.	n.c. BEI	3	n.1
Pyridine	central nervous system, liver, kidneys, gastrointestinal tract	3B			3	
Tetrachloroethane	liver (mice)	3B	K3	A3	2B	n.1
Tetrachloroethylene	oesophagus, kidney, hemopoietic system, lymphatic system; liver (mice), hemopoietic system (rats)	3B	K3	A3	2A	R
Tetrahydrofuran	respiratory system, central nervous system	4				
o-Toluidine	mamma, skin, bladder, liver, spleen, peritoneum, connective tissue (rats), vessels (mice)	1	n.i.	A3	1	R
1,1,2-Trichloroethane	liver, suprarenal gland (mice)	3B	K3	A3	3	n.1

Table 19.1.3. Carcinogenicity – Survey of selected solvents.

Solvent	Organ-System	Category*				
		MAK	EG	ACGIH	IARC	NTP
Trichloroethylene	kidney; liver, biliary tract, kidney, lung, cervix, testes, lymphatic system (rats, mice)	1	K3	A2	1	R
Trichloromethane (Chloroform)	stomach, liver, kidney, thyroid gland (mice, rats)	4	K3	A3	2B	R
1,2,3-Trichloropropane	oral mucosa (mice, rats), uterus (mice), liver, pancreas, forestomach, kidney, mamma (rats)	2	n.i.	A3	2A	R
Xylidine	respiratory system, blood, liver, kidneys, cardiovascular system	2-3A		A3		

*Categories

MAK (German regulations)[2]

1. substances that cause cancer in humans and can be assumed to make a significant contribution to cancer risk. Epidemiological studies provide adequate evidence of a positive correlation between the exposure of humans and the occurrence of cancer. Limited epidemiological data can be substantiated by evidence that the substance causes cancer by a mode of action that is relevant to humans.
2. substances that are considered to be carcinogenic for humans because sufficient data from long-term animal studies or limited evidence from animal studies substantiated by evidence from epidemiological studies indicate that they can make a significant contribution to cancer risk. Limited data from animal studies can be supported by evidence that the substance causes cancer by a mode of action that is relevant to humans and by results of in vitro tests and short-term animal studies.
3. substances that cause concern that they could be carcinogenic for humans but cannot be assessed conclusively because of lack of data. In vitro tests or animal studies have yielded evidence in one of the other categories. The classification in Category 3 is provisional. Further studies are required before a final decision can be made. A MAK value can be established provided no genotoxic effects have been detected.
4. substances with carcinogenic potential for which genotoxicity plays no or at most a minor role. No significant contribution to human cancer risk is expected provided the MAK value is observed. The classification is supported especially by evidence that increases in cellular proliferation or changes in cellular differentiation are important in the mode of action. To characterize the cancer risk, the manifold mechanisms contributing to carcinogenesis and their characteristic dose-time-response relationships are taken into consideration.
5. substances with carcinogenic and genotoxic potential, the potency of which is considered to be so low that, provided the MAK value is observed, no significant contribution to human cancer risk is to be expected. The classification is supported by information on the mode of action, dose-dependence, and toxicokinetic data pertinent to species comparison.

EG[65]

K1: confirmed human carcinogen
K2: compounds which should be considered as a carcinogen
K3: compounds with possible carcinogenic evidence

ACGIH[2]

A1: confirmed human carcinogen
A2: suspected human carcinogen
A3: confirmed animal carcinogen with unknown relevance to humans
A4: not classifiable as a human carcinogen
A5: not suspected as a human carcinogen

IARC[34-36]

1: carcinogenic to humans
2A: probably carcinogenic to humans
2B: possibly carcinogenic to humans
3: not classifiable as to its carcinogenicity to humans

NTP[66]

K: Known to be a Human Carcinogen
R: Reasonably Anticipated to be a Human Carcinogen (RAHC)

**Notes:
n.c.: not classified as carcinogenic
n.i.: no information available
n.l.: not listed
BEI: not classified as carcinogenic but biological monitoring is recommended

19.1.2.6 Risk assessment

For risk assessment of solvent exposure, and, in addition to factors for general risk assessment (age, gender, race, diet, physical activity, stress, physical noxes, etc.), it is important to consider:

- Occupational exposure (high doses) and environmental exposure (low doses) to solvents separately.
- The effect of exposure time, e.g., life-long environmental low exposure or occupational intermittent high exposure.
- Exposure assessment (generally the most neglected aspect of risk assessment). This involves extensive ambient monitoring over a long period of time. Only a small amount of data on biological monitoring of solvents and/or metabolites (representing the "effective" dose) is available.
- The high volatility of solvents, e.g., VOCs and the fast biotransformation rate (in the environment and within the human body) for most solvents.
- Complex mixtures and numerous sources of environmental exposure.
- Especially for environmental solvent exposure. High-to-low-dose extrapolation for evaluation of adverse health effects.
- Consideration of "environmental diseases", e.g., sick building syndrome, chronic fatigue syndrome, multiple chemical sensitivity syndrome.
- Overlaying factors, e.g., smoking and alcohol consumption, as adverse health effects of which may dominate in cases of low solvent exposure.
- The risk in this context is defined in terms of the probability of occurrence of a particular adverse health effect, e.g., 1 in 10^6.
- Finally, as in the general risk assessment, the definition of a risk level that is acceptable.

19.1.3 CONCLUSIONS

- For solvent exposure at workplaces, considerable amount of evidence for adverse health effects has been gathered.
- In this regard, specific and carcinogenic effects, in particular, have been discussed (see Table 19.1.2 and 19.1.3).
- For environmental solvent exposure, only a few examples of adverse health effects have been documented.
- It is rather unlikely that potentially toxic environmental solvent exposures, e.g., benzene or halogenated hydrocarbons, can be prevented in a short-term.

- Many suspicions, but only a small amount of scientific data demonstrates a correlation between "environmental diseases", e.g., sick building syndrome and solvent exposure.
- It has been hypothesized that – as a rule – exposure to mixtures of solvents at low non-toxic doses of the individual constituent represents no danger to health.[63]
- There exists overwhelming evidence of adverse health effects caused by accepted environmental noxes such as tobacco smoke and the consumption of alcoholic beverages.

REFERENCES

1 ACGIH, **TLV´s and BEI´s**, *ACGIH*, Cincinnati, 2018.
2 **List of MAK and BAT Values 2017: Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area**. **Report 53**, *Wiley-VCH*, Weinheim, 2017.
3 I. Astrand, *Scand. J. Work Environ. Health,* **1**, 199, 1975.
4 I. Astrand in **Occupational Health Hazards of Solvents**, A. England, K. Ringen, M.A. Mehlman, Eds., *Princeton*, NJ, 1986, pp. 141-142.
5 K.H. Cohr, in **Safety and Health Aspects of Organic Solvents**, V. Riihimäki, U. Ulfvarson, Eds., Alan R. Liss, N.Y., 1986, pp. 45-60.
6 J.J.G. Opdam, *Br. J. Ind. Med.*, **46**, 831 (1989).
7 M.K. Bahl, *J. Soc. Cosmet. Chem*., **36**, 287 (1985).
8 M. Bird, *Ann. Occup. Hyg*., **24**, 235 (1981).
9 J. Angerer, E. Lichterbeck, J. Bergerow, S. Jekel, G. Lehnert, *Int. Arch. Occup. Environ. Health*, **62**, 123 (1990).
10 I. Brooke, J. Cocker, I. Delic, M. Payne, K. Jones, N.C. Gregg, D. Dyne, *Ann Occup. Hyg*., **42**, 531 (1998).
11 G. Johanson, *Toxicol. Lett*., **43**, 5 (1988).
12 S. Kezic, K. Mahieu, A.C. Monster, F.A. de Wolff, *Occup. Environ. Med*., **54**, 38 (1997).
13 E.A. Lock, *Crit. Rev. Toxicol.*, **19**, 23 (1988).
14 A. Lof, G. Johanson, *Crit. Rev. Toxicol*., **28**, 571 (1998).
15 H.M. Mehendale, *Toxicology*, **105**, 251 (1995).
16 P. Bloch, A. Kulig, M. Paradowski, T. Wybrzak-Wrobel, *Pol. J. Occup. Med.*, **3**, 69 (1990).
17 O. Inoue, K. Seiji, T. Watanabe, M. Kasahara, H. Nakatsuka, S.N. Yin, G.L. Li, S.X. Cai, C. Jin, M. Ikeda, *Int. Arch. Occup. Environ. Health*, **60**, 15 (1988).
18 V. Fiserova-Bergerova, *Scand. J. Work Environ. Health*, **11**, 7 (1985).
19 S. Haddad, K. Krishnan, *Environ. Health Perspect*., **106**, 1377 (1998).
20 W.K. Anger in **Neurobehavioral Toxicology**, Z. Annau, Ed., *John Hopkins University Press*, Baltimore, MD, 1986, pp. 331-347.
21 A. Laine, V. Riihimäki in **Safety and Health Aspects of Organic Solvents**, V. Riihimäki, U. Ulfvarson, Eds., Alan R. Liss, N.Y., 1986, pp. 123-126.
22 E. Browning, **Toxicity and Metabolism of Industrial Solvents**, *Elsevier Publishing Co*., N. Y., 1965.
23 R.E. Gosselin, R.P. Smith, H.E. Hodge, **Clinical Toxicology of Commercial Products**, Williams and Wilkins, Baltimore, 1984.
24 E.L. Baker, *Ann. Rev. Public Health*, **9**, 233 (1988).
25 P. Grasso, M. Sharratt, D. M., Davies, D. Irvine, *Food Chem. Toxicol.*, **22**, 819 (1984).
26 R.B. Dick, *Neurotoxicol. Teratol.*, **10**, 39 (1988).
27 W.K. Anger, *Neurotoxicology*, **11**, 627 (1990).
28 P. Arlien-Soborg, L. Hansen, O. Ladefoged, L. Simonsen, *Neurotoxicol. Teratol*., **14**, 81 (1992).
29 **WHO, Organic solvents and the central nervous system**, *WHO* European Office Copenhagen, (1985).
30 J.F.Fowler, *Dermatology*, **10**, 216 (1998).
31 K.E. Andersen in **Safety and Health Aspects of Organic Solvents**, V. Riihimäki, U. Ulfvarson, Eds., Alan R. Liss, N. Y., 1986, pp. 133-138, 1986.
32 C.G.T. Mathias, *Occup. Med. State of the Art Rev.,* **1**, 205 (1986).
33 M. Hodgson, A.E. Heyl, D.H. Van Thiel, *Arch. Intern. Med*., **149**, 1793 (1989):
34 **IARC, IARC Monographs on the evaluation of carcinogenic risks to humans. IARC Monographs on the evaluation of carcinogenic risks to humans**, Vol. 100F, *IARC*, Lyon, 2012.
35 **IARC, IARC Monographs on the evaluation of carcinogenic risks to humans. Dry cleaning,**

some chlorinated solvents and other industrial chemicals, *WHO*, 63, IARC, Lyon, 1995.
36 **IARC, IARC Monographs on the evaluation of carcinogenic risks to humans. Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide**. *WHO*, 71, IARC, Lyon, 1999.
37 **DFG, Gesundheitsschädliche Arbeitsstoffe. Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werten**, *VCH*, Weinheim, 2005.
38 R.R. Lauwerys, A. Bernard, C. Viau, J.P. Buchet, *Scand. J. Work Environ. Health*, **11**, 83 (1985).
39 E.A. Lock, *Crit. Rev. Toxicol.*, **19**, 23 (1988).
40 N.A. Nelson, T.G. Robins, F.K. Port, *Am. J. Nephrol*., **10**, 10 (1990).
41 H.J. Mason, A.J. Stevenson, G.M. Bell, *Ren. Fail.*, **21**, 413 (1999).
42 O. Ladefoged, H.R. Lam, G. Ostergaard, E.V. Hansen, U. Hass, S.P. Lund, L. Simonsen, *Neurotoxicology*, **19**, 721 (1998).
43 A.M. Seppalainen, *Crit. Rev. Toxicol.*, **18**, 245 (1988).
44 P.S. Spencer, H.H. Schaumburg, *Scand. J. Work Environ. Health*, **11**, 53 (1985).
45 L.H. Welch, S.M. Schrader, T.W. Turner, M.R. Cullen, *Am. J. Ind. Med*., **14**, 509 (1988).
46 I.J Yu, J.Y. Lee, Y.H. Chung, K.J. Kim, J.H. Han, G.Y. Cha, W.G. Chung, Y.M. Cha, J.D. Park, Y.M. Lee, Y.H. Moon, *Toxicol. Letters*, **109**, 11 (1999).
47 W.G. Chung, I.J. Yu, C.S. Park, K.H. Lee, H.K. Roh, Y.N. Cha, *Toxicol. Letters*, **104**, 143 (1999).
48 J.C.Selner, *Regul. Toxicol. Pharmacol.*, **24**, 87 (1996).
49 K.E. Andersen, S.C. Rastogi, L. Carlsen, *Acta Derm. Venereol.*, **76**, 136 (1996).
50 G. Mancuso, M. Reggiani, R.M. Berdodini, *Contact Dermatitis*, **34**, 17 (1996).
51 H.H. Tau, M. Tsu Li-Chan, C.L. Goh, *Am. J. Contact. Dermat.*, **8**, 210 (1997).
52 T. Chida, T. Uehata, *Sangyo Igaku*, **29**, 358 (1987).
53 P.J. Coenraads, S.C. Foo, W.O. Phoon, K.C. Lun, *Contact Dermatitis*, **12**, 155 (1985).
54 J.T. Lear, A.H. Heagerty, B.B. Tan, A.G. Smith, J.S. English, *Contact Dermatitis*, **35**, 169 (1996).
55 E.L. Sainio, K. Engstrom, M.L. Henriks-Eckerman, L. Kanerva, *Contact Dermatitis*, **37**, 155 (1997).
56 A.T. Karlberg, A. Dooms-Goossens, A., *Contact Dermatitis*, **36**, 201 (1997).
57 D.M. Rubel, S. Freeman, I.A. Southwell, *Australas J. Dermatol.*, **39**, 244 (1998).
58 M. McEwan, W.H. McFarlane-Smith, *Clin. Exp. Allergy,* **28**, 332 (1998).
59 G. Angelini, L. Rigano, C. Foti, M. Grandolfo, G.A. Vena, D. Bonamonte, L. Soleo, A.A. Scorpiniti, A.A., *Contact Dermatitis*, **35**, 11 (1996).
60 J. van de Walter, S.A. Jimenez, M.E. Gershwin, *Int. Rev. Immunol.*, **12**, 201 (1995).
61 D. Eis, *Allergologie*, **22**, 538 (1999).
62 J.J. Powell, J. Van-de-Water, M.E. Gershwin, *Environ. Health Perspect*., **197**, 667 (1999).
63 F.R. Cassee, **Crit. Rev. Toxicol**., 28, 73 (1998).
64 **Römpp, Lexikon Chemie**, J. Falbe, M. Regitz, Eds., *Thieme*, Stuttgart (2013).
65 GISBAU, WINGIS, Bau-Berufsgenossenschaften (Professional Associations of the Building Industry in Germany), 1999.
66 *U. S. Department of Health and Human Services, National Toxicology Program*, **14th Report on Carcinogens**, 2016.

19.2 SOLVENT EXPOSURE IN PREGNANCY

SC Mitchell* and RH Waring**
***Computational and Systems Medicine, Faculty of Medicine, Imperial College, London, SW7 2AZ, UK**
****School of Biosciences, University of Birmingham, Birmingham B15 2TT UK**

19.2.1 PREGNANCY

The events that occur from fertilization to birth are extremely complex and there is still a lack of understanding about many aspects. Approximately 30 hours after fertilization, as the zygote is passing down the fallopian tube, it undergoes division to yield two daughter cells known as blastomeres. Following this first successful cleavage, the zygote experiences a series of mitotic events resulting in the generation of a clump of cells (about 12-16 blastomeres at around 3 days) after which it is known as a morula. During the fourth day, the morula arrives at the uterus and cavities begin to appear within this ball of cells as uterine fluid enters helping to separate these cells into two groups. The outer cell layer forms the trophoblast which develops into part of the placenta whereas the inner cell mass gives rise to the embryo proper. Once coalescence has occurred and a single cavity, the blastocele, is formed within the morula, it is then termed a blastocyst. At about 5 to 6 days post-fertilization, the blastocyst attaches itself to the endometrial epithelium of the uterus and the trophoblast grows rapidly into the endometrial tissues leading to a superficial implantation by the end of the first week. During the second week the rapid proliferation of the trophoblast occurs and a primitive uteroplacental circulation is established. The conceptus becomes completely embedded within the endometrium where the cell mass differentiates and forms a bilaminar germ disc. Another small space appears which is to become the amniotic cavity. The characteristic event of the third week of development is the formation of the primitive streak, destined to be the site and inducer of the vertebral column and spinal cord. A third cellular sheet known as the mesodermal cell layer is formed and its establishment is called gastrulation. From these three layers (trilaminar germ disc) all tissues and organs of the embryo will develop. This initial phase (0 to 3rd week) is referred to as the 'predifferentiation stage' or 'pregerm layer stage'.

During the 'embryonic period' (4th to 8th weeks) each of the three germ layers gives rise to a number of tissues and organs of the body. Principally, the ectodermal layer is associated with organs and structures that will eventually maintain contact with the external environment, including the nervous system and integument. The mesodermal layer produces the somites which develop into the supporting tissues of the body (bones, cartilage, muscle, and subcutaneous tissue) and also the vascular and urogenital systems. The ectodermal germ layer provides epithelial linings of the gastrointestinal and respiratory tracts, the urinary bladder and also parenchyma of various organs. By the end of the embryonic period, the rudiments of the main organs have been established. With this the embryonic disc begins to fold in a head-tail direction and also transversely establishing a

rounded body shape. Thus, by the end of the eighth week the major features of the external body form are recognizable. The "foetal period" (9th week to birth) is characterized by the maturation of tissues and organs, with several structures including the respiratory and central nervous systems in particular continuing to differentiate. An increase in length is most striking during the 3rd to 5th months although there is a slowdown in the growth of the head relative to the rest of the body. By the 5th month foetal movements are present which may be plainly identified by the mother and continue until parturition. During the final months of gestation, there is a rapid increase in weight in preparation for birth at the end of interuterine life, enabling the establishment of a separate and viable individual.

It is generally accepted that contact with a chemical teratogen during the first trimester of pregnancy (0 to 12th week) may elicit the greatest amount of damage and should under all circumstances be avoided. Exposure during the "predifferentiation stage" may interfere with implantation of the blastocyst or injure all or the majority of cells within the conceptus resulting in death and subsequent abortion. Limited damage to a few cells may be repaired by the "regulative" potentialities of the conceptus thereby permitting normal development. However, if mitotic nondisjunction occurs during cleavage then chromosomal abnormalities may ensue. Also, the teratogen may remain within the maternal system to be presented *via* the placenta at a later stage. Development is most easily disturbed during the period of intensive differentiation and organogenesis, usually spanning a few days either side (3rd to 9th week) of the "embryonic period". At this time most teratogens are highly effective and may be lethal but are more likely to produce numerous malformations. Which particular organ system is affected depends critically on the window of exposure, but greatest susceptibility appears to be at the early stages of their differentiation, with the various body organs becoming vulnerable one after the other. Proneness to teratogenic influences declines rapidly during the "foetal period" although the central nervous system and some urogenital structures continue to develop and are liable to damage. Minor morphological alterations, functional disturbances and physiological problems are more likely to arise during the "foetal period" but the major feature of disturbances at this time is a general retardation of growth leading to an underweight neonate.[1,2]

Constant exposure during the entire pregnancy may lead to a host of problems dependent upon the subtle and specific susceptibilities of each developing tissue and organ system. The interaction of these aspects with other environmental, nutritional, and genetic factors leads to a complex and dynamic interplay that is difficult to predict and may only become apparent from retrospective studies. Also, in addition to chemicals that may pass across the placenta and enter the developing conceptus to induce and elicit damage, it must be borne in mind that these and other chemicals that do not have access may nevertheless have an effect upon the pregnant mother and, by default, compromise the efficient functioning of the placenta thereby threatening its vital role in the essential support of the developing embryo and foetus within the uterus. Furthermore, a substantial burden of chemicals may have accumulated *via* equilibrium from previous contact, especially within the adipose tissues if the substances are lipophilic, and once exposure is reduced or removed these chemicals will become mobilized from their storage reservoirs. This subsequent release back into the mother's bloodstream, on the way to elimination, will enable

potential exposure of the growing conceptus if placental transfer allows. The confirmation of pregnancy during the early days is difficult with tests usually relying on the detection of human chorionic gonadotrophin produced by the placenta following implantation. Even if exposure is then halted, up until this time chemicals may have been accumulating in the mother's body. It would be wise not to permit women of childbearing age to work in potentially harmful environments.

19.2.2 FACTORS INVOLVED IN INITIATION AND MAINTENANCE OF PREGNANCY

Although most research has been concentrated on women, some solvents damage sperm production or quality so that any subsequent pregnancy may be at risk of developing foetal abnormalities. In females, exposure to solvents during the first trimester has led to an increased risk of spontaneous abortion.[3,4] This usually occurs during the early days of pregnancy or when the dosage is relatively high (e.g., solvent abuse). Such embryolethality may disguise the insidious effects that would otherwise lead to malformation if carried to full term. As might be expected, the conceptus is particularly susceptible to non-polar solvents which readily pass through the placental tissue. Once within the foetal circulation, they can disrupt developmental processes, particularly where the tissues involved contain large amounts of triglycerides and other fats. Those most affected are the constituents of the central nervous system (CNS) and also the bone marrow.

19.2.3 POLYMORPHISMS OF XENOBIOTIC METABOLISM

Generally lipophilic chemicals, including xenobiotics such as solvents, are readily absorbed across membranes into the blood stream. Depending on volatility, they may then be excreted unchanged on the breath or *via* skin pores or chemically altered by hepatic enzymes to form polar metabolites which are largely excreted in urine or bile. The enzymes involved are 'polymorphic', with subsets of the population having different activities and therefore different susceptibilities to toxicity. Relatively little work has been undertaken on the correlation of polymorphisms of xenobiotic metabolism with responses to solvent intake. Exposure to solvents in pregnancy is known to increase the risk of major birth defects in the offspring[5] and the question must arise as to whether the parent solvent or its metabolites are responsible for the toxic effects which may act at different points on the developmental pathway. Many solvents (X) are metabolized by linkage to the thiol (-SH) group of the tripeptide glutathione (GSG, glutamine-cysteine-glycine) *via* glutathione-S-transferases (GST). One study on solvent exposure in pregnancy showed that the mother's metabolic capacity for this reaction was not linked to subsequent neonatal deformities. Neonates with non-active (null) GST (GST-M) were much less susceptible than those with the active form of the isoenzyme,[6] suggesting that the teratogen was a metabolite of the parent compound, possibly the thiol adduct (X-SH) formed from further metabolism of the primary metabolite within the conceptus. Conversely, a study on mother-infant pairs showed that where both had the null variant of GST (GST-T1), there was a significant association with shorter gestation,[7] suggesting that the parent solvent(s) and not their GST-mediated metabolites were responsible for the effect. Obviously further studies are needed.

19.2.4 SOLVENT MIXTURES AND LITERATURE ASSESSMENT

Many reports in the literature on solvent toxicity in pregnancy only refer to mixtures of solvents used in particular industrial applications, rather than to any one individual chemical. This of course renders the results from epidemiology (already problematic) even less precise. One of the major difficulties in attempting to draw definite conclusions is that there are many conflicting reports within the literature. Such inconsistencies may occur for many reasons, with small samples sizes, inadequate or inappropriate controls, inaccurate assignment of exposure levels and localized environmental or socio-economic factors being amongst them. Also, work practices and potential exposure to solvents in the modern world hopefully differ from those that existed in the past making comparisons and selection for meta-analyses difficult. For example, early studies indicated that exposure to organic solvents during pregnancy led to offspring being born with central nervous system problems[8] but this association disappeared when the numbers were increased.[9] Further investigations indicated that exposure of the mother to relatively low levels of organic solvents during pregnancy was not associated with adverse neurodevelopmental outcome.[10] However, more recently, this initial association has been reasserted with emphasis turning to low level exposure and subtler effects such as behavioral problems[11,12] which become evident as the child grows older.

Mathematical processing of data offers little help. An odds ratio (OR) above 1.0 indicates that having one property (exposure to solvents) raises the odds of having another property (chemical damage), that it is associated although it does not establish a causal relationship since both measured parameters may be resultant of a third unknown factor. In this case, it compares the occurrence of an event with solvent exposure to that without solvent exposure. Values quoted in studies are quite low, usually below 2.0 with wide 95% confidence intervals, indicating little more than a passing association or one obscured by various and as yet perhaps unappreciated factors. Nevertheless, some associations do emerge, especially when confounding factors have been taken into account.

19.2.4.1 Organic solvent mixtures

Solvents in general seem to have an adverse effect on the reproductive process. Paternal exposure to organic solvents appears to damage sperm quality – it reduced the implantation rate in couples undergoing IVF treatment and increased the risk of neural tube defects in their offspring; a meta-analysis found ORs of 2.18 for anencephaly and 1.59 for spina bifida respectively.[13] Organic solvent exposure is also damaging in women and several studies have linked it with reduced fertility.[14,15] Work exposure to organic solvents also affects the foetus, reducing intrauterine growth and increasing the risk of foetal malformations and the probability that the baby will be small for its gestational age.[16] An increased likelihood of spontaneous abortion has been reported in exposed workers in the dry-cleaning and shoe industries.[17,18] Even when pregnancy continues to term, the mother is more likely to suffer an elevated risk of complications from pregnancy-induced hypertension while the baby may have a lower Apgar score,[19] the latter being a quick way to indicate the physical health of a neonate (the backronym: Appearance, Pulse, Grimace (reflexes), Activity, Respiration).

Lung function can also be affected – hay fever is more common in children with mothers exposed to organic solvents in pregnancy and upper respiratory tract damage and wheezing were more common in children of mothers exposed to sprays, air fresheners and solvents in pregnancy although there was no increase in asthma.[20]

Effects on the CNS can occur which are usually more obvious as the child develops. The visual system is an important target for organic solvent toxicity in adults and similar effects are seen in children with prenatal exposure to these compounds. Subtle selective deficits (reduced contrast sensitivity and abnormal red-green vision) were identified and these persisted into later life.[21] There are also hints in the literature that prenatal solvent exposure can cause behavioral problems and increased susceptibility to schizophrenia[22] and ADHD[11] although the reported numbers are small.

19.2.4.2 Aliphatic hydrocarbons

N-hexane is commonly used as a solvent for leather dyes in shoe manufacture. It is neurotoxic in adults but its reported effects on female employees in the shoe industry appear to be reduction in fertility and an increased likelihood of spontaneous abortion.[18] N-hexane and its metabolites are known to cross the placenta in rodents and high-level exposure during the gestational period gave an increase in inter-uterine mortality, low birth weights and delayed brain development although no malformations were reported, suggesting n-hexane is not teratogenic in rodents.[23] However, this data may not be indicative of the human situation as there was an increased risk of childhood leukaemia (OR 4.3) when there was maternal exposure to aliphatic hydrocarbons in the preconception period.[24]

19.2.4.3 Aromatic hydrocarbons

The solvents most frequently studied are toluene and benzene, both of which are widely used in industrial processes. Toluene is often substituted for benzene as an apparently less toxic compound. However, prenatal exposure to toluene has been linked to the development of testicular germ cell tumors (TGCT) with an OR of 1.67.[25] Prenatal toluene exposure also leads to "foetal solvent syndrome", where affected children have neurodevelopmental disabilities which are similar to those seen with excess alcohol exposure,[26] possibly due to reduced neurite outgrowth and disruption of synapse formation.[27] The effects of toluene abuse owing to deliberate solvent inhalation have been investigated;[27-29] the high acute levels typically found in solvent abusers seem to be more damaging to foetal development than the considerably lower but chronic occupational levels.[30] Benzene is now much less used industrially, primarily because the solvent has been linked with the development of leukaemia in workers. This disruption of bone marrow function also extends to the unborn child. A meta-analysis of maternal benzene exposure during pregnancy, where data from 16,695 cases was compared with 1,472,786 controls, concluded that the OR for the risk of childhood acute lymphoblastic leukaemia (ALL) in the subsequent offspring was 1.25.[31] The SETIL study similarly found an increased risk of ALL with maternal exposure to aromatic hydrocarbons in general[23] in the pre-conception period (OR 3.8). The statistics are compelling for the development of childhood brain tumors (CBT), where paternal exposure to benzene in the year before conception[32] was associated with an increased risk (OR 2.72). Other aromatic solvents, probably largely toluene, gave an increased OR of 1.76. There was an increased (OR 5.3) risk of neural crest

malformations in offspring of female laboratory workers who had been exposed to benzene around the conception/organogenesis stages[33] although these figures were based on relatively small numbers (3003 pregnancies). Styrene has been reported as causing neurobehavioral and developmental effects in animals;[34] although there seem to be no studies on its effects in humans, it would be expected to have similar neurotoxicity.

19.2.4.4 Chlorinated solvents

Most exposure to chlorinated solvents comes from the commercial use of perchloroethylene (tetrachloroethylene, 'perc', PCE), particularly in the dry-cleaning, textile processing, and metal-cleaning industries, and from the presence of PCE from the vinyl liners of water pipes for domestic supplies. PCE seems to have many different effects; it has been associated with paternal occupational exposure and the development of TGCT in the offspring[24] and with a small increased risk of mental health dysfunction (bipolar disorder, post-traumatic stress disorder) in those who were exposed prenatally.[35] High prenatal exposure increased the risk of using 2 or more major illicit drugs in teens and adults, suggesting altered neurotransmitter pathways.[36] Studies on the same population showed a small increased risk of epilepsy (OR 1.8) although the authors thought that the findings should be interpreted with caution.[37] A prospective population-based cohort of 88,829 offspring found an increased incidence of schizophrenia in those whose parents were dry-cleaners but the numbers involved were again small.[22] Spontaneous abortion was reported as being more common in women employed in dry-cleaning work and exposed to PCE, as opposed to women in the same industry who were unexposed to the solvent.[17]

Both the developing brain and heart seem to be particularly susceptible to solvent exposure at critical times in early pregnancy. Neural tube defects[38] have been linked with exposure to chlorinated solvents (OR 1.96) with a higher association for spina bifida (OR 2.26). Chlorinated solvents have also been connected with heart defects (OR 1.7) and solvents in general with aortic stenosis (OR 2.1).[39]

19.2.4.5 Oxygen-containing solvents

These include glycol ethers, acetone, other ketones, aliphatic alcohols, esters and aliphatic aldehydes. The industrial solvent ethylene glycol monomethyl ether (EGME), used in the semi-conductor industry, is metabolized to methoxyacetic acid (MAA) which primarily affects tissues with rapidly dividing cells including those in testes, thymus and the foetus. Testicular toxicity is partly mediated by oxidative stress[40] and involves the down-regulation of spermatogenesis, potentially affecting reproduction by producing fewer or less viable sperm. In a nested case-control study, urinary concentrations of metabolites of glycol ethers were measured in women in early pregnancy and the results correlated with congenital malformations in the offspring.[41] Detection of glycol ether metabolites and trichloracetic acid in urine was associated with increased risks of oral clefts, urinary tract and limb defects although the numbers were small. These compounds appeared to be occupationally derived and to be common at low levels in nurses, nursing aides, cleaners and hairdressers.[42] The risk of oral clefts was increased in another study with an OR of 1.8; the authors reported that the risk increased linearly with the level of exposure to all the different types of oxygenated solvents.[43] Working with acetone, normally considered non-toxic, was associated with reduced fertility in female laboratory workers.[14]

Prenatal exposure to high levels of ethyl alcohol can lead to 'Fetal Alcohol Syndrome' (FAS). This latter condition has been appreciated for many years and presents a clinical picture of signs including a short height and low body weight, abnormal facial features, poor coordination, and relatively low intelligence, with ethanol disturbing brain growth at all phases from neurogenesis to myelination.[44] Affected children present with midline craniofacial dysmorphology, microcephaly, and reductions in brain volume and corpus callosum. Binge drinking and sustained chronic alcohol intake during any trimester of pregnancy increase the risk of FAS. The causes are still not clear – dilation of foetal cerebral arteries, thiamine deficiency, mitochondrial damage, reactive oxygen species and lipid peroxidation are some of the many factors which appear to interact to give the final syndrome.[45,46]

19.2.4.6 Petrol and Paint fumes

Two separate studies[23,47] on exposure of parents to petrol or exhaust fumes at any stage of pregnancy showed links with the development of acute lymphoblastic leukaemia (ALL) in the offspring (OR, 1.97 and 1.42). The progeny of two mothers who had heavily abused petrol (gasoline) *via* inhalation during their pregnancies were born with profound *growth retardation*, abnormal skull formation, and neuromuscular problems. However, concomitant alcohol (and other substance) abuse had also occurred in this limited sample.[48] Several other studies have been undertaken but these are mainly concerned with the effects of particulate matter arising from petrol and diesel engine exhausts[49,50] although it is possible that the micro- and nano-particles present are synergistic with the solvent constituents.

Exposure to organic solvents from paint fumes in residential settings[51] during the first trimester of pregnancy was associated with neonatal congenital abnormalities of the nervous system (OR 2.19), ear, face and neck (OR 2,15) and renal system (OR 2.16). In addition, an increased risk of giving birth to offspring with various congenital heart defects (CHD) (OR 1.89 to 4.00) has been reported following maternal exposure to fumes during house renovations.[52] This is also apparent for pregnant women exposed during the first trimester to dyes, lacquers and paints at work (OR 2.9).[53] Similarly, women employed as painters were more likely to have offspring with malformation of the circulatory system (OR 2.03).[54] Leukaemia (ALL) in children was also associated with maternal exposure to paint fumes, a meta-analysis giving an OR of 1.23[31] suggesting a general deleterious effect of volatile solvents on the bone marrow and on tissue development.

19.2.5 CONCLUSION

It is unknown which solvents are more likely to cause damage although toluene is probably a major candidate. In general, lipophilic molecules appear to be guilty especially if they are halogenated. The CNS, reproductive systems and bone marrow appear to be important targets. Much more structured research is required. The evidence for solvent toxicity comes from epidemiological studies where retrospective investigations with their many attendant problems are the norm but prospective studies are ethically challenging. If there is any chance, however remotely, of damage occurring to an unborn child because the pregnant mother is exposed to solvents, either through inhalation or dermal absorption, this must be avoided. Strict controls and work practices must be put in place to safeguard the children of the future.

REFERENCES

1 Moore KL, Persaud TVN, Torchia MG. (2015). **The Developing Human: Clinically Oriented Embryology**. 10th edn. London: *W.B. Saunders Company*.

2 Sadler T.W. (2014). **Langman's Medical Embryology**. 13th edn. Philadelphia: *Wolters Kluwer Health*.

3 Khattak S, Moghtader GK, McMartin K, Barrera M, Kennedy D, Koren G. (1999). Pregnacy outcomes following gestational exposure to organic solvents: a prospective controlled study. *J Am Med Assoc.,* **281** (12): 1106-1109.

4 Lindbohm ML, Taskinen H, Sallman M, Hemminki K. (1990). Spontaneous abortions among women exposed to organic solvents. *Am J Indust Med.,* **17** (4): 449-463.

5 McMartin KL, Chu M, Kopecky E, Einarson TR, Koren G. (1998). Pregnancy outcome following maternal solvent exposure: A meta-analysis of epidemiological studies. *Am J Indust Med.,* **34** (3): 288-292.

6 Garlantezec R, Chevrier C, Coiffec I, Celebi C, Cordier S. (2012). Combined effect of prenatal solvent exposure and GSTT1 or GSTM1 polymorphisms in the risk of birth defects. *Birth Defects Research*, **94** (6): 481-485.

7 Qin X, Wu Y, Wang W, Liu T, Wang L, Hu Y, Chen D. (2008). Low organic solvent exposure and combined maternal-infant gene polymorphisms affect gestational age. *Occup Environ Medicine,* **65** (7): 482-7

8 Holmberg PC. (1979). Central nervous system defects in children born to mothers exposed to organic solvents during pregnancy: A case controlled study. *Lancet,* **2**, 177-179.

9 Kurppa K, Holmberg PC, Hernberg S, Rantala K, Riala R, Nurminen T. (1983) Screening for occupational exposures and congenital malformations. Preliminary results from a nationwide case-referent study. *Scan J Work Environ Health,* **9**, 89-93.

10 Eskenazi B, Gaylord L, Bracken MB, Brown D. (1988). In utero exposure to organic solvents and human neurodevelopment. *Developmental Medicine and Child Neurology,* **30**, 492-501.

11 Pelé F, Muckle G, Costet N, Garlantézec R, Monfort C, Multigner L, Rouget F, Cordier S. (2013). Occupational exposure during pregnancy and child behaviour at age 2. *Occup Environ Med.,* **70**(2): 114-119.

12 Siambana C. (2000). Maternal occupational exposure to organic solvents during pregnancy and subsequent visual and cognitive development in the child: A prospective controlled pilot study. MA Thesis, University of Toronto.

13 Logman JF, de Vries LE, Hemels ME, Khattak S, Einarson TR. (2005). Paternal organic solvent exposure and adverse pregnancy outcomes: a meta-analysis. *Am J Indust Medicine*, **47** (1): 37-44.

14 Wennborg H, Bodin L, Vainio H, Axelsson G. (2001) Solvent use and time to pregnancy among female personnel in biomedical laboratories in Sweden. *Occup Environ Medicine*, **58** (4): 225-231.

15 Sallmen M, Neto M, Mayan ON. (2008.) Reduced fertility among shoe manufacturing workers. *Occup Environ Medicine*, **65** (8): 518-524.

16 Desrosiers TA, Lawson CC, Meyer RE, Stewart PA, Waters MA, Correa A, Olshan AF. (2015). Assessed occupational exposure to chlorinated, aromatic and Stoddard solvents during pregnancy and risk of fetal growth restriction. *Occup Env Medicine*, **72** (8): 587-593

17 Doyle P, Roman E, Beral V, Brookes M. (1997). Spontaneous abortion in dry cleaning workers potentially exposed to perchloroethylene. *Occupat Environ Medicine*, **54** (12) 848-853.

18 Agnesi R, Valentini F, Mastrangelo G. (1997). Risk of spontaneous abortion and maternal exposure to organic solvents in the shoe industry. *Int Arch Occup Environ Health*, **69** (5): 311-316.

19 Hewitt JB Tellier L. (1998). Risk of adverse outcomes in pregnant women exposed to solvents. *J Obs Gyn Neonat Nursing*, **27** (5): 521-531.

20 Casas L, Zock JP, Carsin AE, Fernandez-Somoano A, Esplugues A, Santa-Marina L, Tardon A, Ballester F, Basterrechea M, Sunyer J. (2013). The use of household cleaning products during pregnancy and lower respiratory tract infections and wheezing during early life. *Int J Public Health*, **58** (5):757-764.

21 Till C, Westall CA, Koren G, Nulman I, Rovet JF. (2005) Vision abnormalities in young children exposed prenatally to organic solvents. *Neurotoxicol*., **26** (4): 599-613.

22 Perrin MC, Opler Mg, Harlap S, Harkavy-Friedman J, Kleinhaus K, Nahon D, Fennig S, Susser ES, Malaspina D. (2007). Tetrachloroethylene exposure and risk of schizophrenia: offspring of dry cleaners in a population birth cohort, preliminary findings. *Scizophrenia Res*., **90** (1-3): 251-254.

23 Daughtrey WC, Neeper-Bradley T, Duffy J, Haddock L, Keenan T, Kirwin C, Soiefer A. (1994). Two-generation reproduction study on commercial hexane solvent. *J Appl Toxicol*., **14**, 387-393.

24 Barone-Adesi F, Miligi L, Benvenuti A, Mattioli S, Salvan A, Tozzi GA, Ranucci A, Legittimo P, Rondelli R, Bisanti L, Zambon P, Cannizzaro S, Kirchmayer U, Cocco P, Celentano E, Assennato G,

Merlo DF, Mosciatti P, Minelli L, Cuttini M, Torregrossa V, Lagorio S, Haupt R, Risica S, Polichetti A, SETIL working group, Magnani C. Risk of childhood leukaemia and non-Hodgkin's lymphoma after parental occupational exposure to solvents and other agents. *Occup Environ Medicine*, **70** (9): 648-655.

25 Le Cornet C, Fervers B, Pukkala E, Tynes T, Feychting M, Hansen J, Togawa K, Nordby KC, Oksbjerg Dalton S, Uuksulainen S, Wiebert P, Woldbaek T Skakkebaek NE, Olsson A, Schuz J. (2017) Parental occupational exposure to organic solvents and testicular germ cell tumors in their offspring. *Env Health Perspect,* **125** (6) 067023.

26 Costa LG, Guizzetti M, Burry M, Oberdoester J. (2002.) Developmental neurotoxicity: do similar phenotypes indicate a common mode of action? A comparison of fetal alcohol syndrome, toluene embryopathy and maternal phenylketonuria. *Toxicol Lett.,* **127**(1-3): 197-205.

27 Lin HM, Liu CY, Jow GM, Tang CY. (2009) Toluene disrupts synaptogenesis in cultured hippocampal neurons. *Toxicol Lett.,* **184** (2): 90-96.

28 Stoltenberg-Didinger G, Altenkirch H, Wagner M. (1990). Neurotoxicity of organic solvent mixtures: Embryotoxicity and fetotoxicity. *Neurotoxicol Teratol*., **12**, 585-589.

29 Hannigan JH, Bowen SE. (2010). Reproductive toxicology and teratology of abused toluene. *Systems Biology in Reproductive Medicine*, **56** (2): 184-200.

30 Wilkins-Haug L, Gabow PA. (1991). Toluene abuse during pregnancy: obstetric complications and perinatal outcomes. *Obstetrics and Gynecology,* **77** (4): 504-509.

31 Zhou Y, Zhang S, Li Z, Zhu J, Bi Y, Bai Y, Wang H. (2014). Maternal benzene exposure during pregnancy and risk of childhood acute lymphoblastic leukemia: a meta-analysis of epidemiologic studies. *PLoS ONE* **9** (10): e110466.

32 Peters S, Glass DC, Greenop KR, Armstrong BK, Kirby M, Milne E, Fritschi L. Childhood brain tumors: associations with parental occupational exposure to solvents. *Brit J Cancer*, **111** (5): 998-1003.

33 Wennborg H Magnusson LL, Bonde JP, Olsen J. (2005) Congenital malformations related to maternal exposure to specific agents in biomedical research laboratories. *J Occupat Environ Medicine*, **47** (1): 11-19.

34 Katakura Y, Kishi R. (2005) Significance of laboratory studies of neurobehavioural and developmental toxicities- transgenerational effects of styrene exposure. *Japan J Hygiene,* **60** (4): 411-417.

35 Aschengrau A, Weinberg JM, Janulewicz PA, Romano ME, Gallagher LG, Winter MR, Martin BR, Vieira VM, Webster TF, White RF, Ozonoff DM. (2012) Occurrence of mental illness following prenatal and early childhood exposure to tetrachloroethylene (PCE)-contaminated drinking water: a retrospective cohort study. *Env Health,* **11**, 2 Jan 20.

36 Aschengrau A, Weinberg JM, Janulewicz PA, Romano ME, Gallagher LG, Winter MR, Martin BR, Vieira VM, Webster TF, White RF, Ozonoff DM. (2011) Affinity for risky behaviours following prenatal and early childhood exposure to tetrachloroethylene (PCE)- contaminated drinking water: a retrospective cohort study. *Env Health,* **10**, 102 Dec 02.

37 Aschengrau A, Winter MR, Veiria VM, Webster TF, Janulewicz PA, Gallagher LG, Weinberg J, Ozonoff DM. (2015) Long-term health effects of early life exposure to tetrachloroethylene (PCE)-contaminated drinking water: a retrospective cohort study. *Env Health*, **14**:36 April 12.

38 Desrosiers TA, Lawson CC, Meyer RE, Richardson DB, Daniels JL, Waters MA, van Wijngaarden E, Langlois PH, Romitti PA. (2012) Maternal occupational exposure to organic solvents during early pregnancy and risks of neural tube defects and orofacial clefts. *Occup Env Medicine,* **69**, (7): 493-499.

39 Gilboa SM, Desrosiers TA, Lawson C, Lupo PJ, Riehle-Colarusso TJ, Stewart PA, van Wijngaarden E, Waters MA, Correa A. (2012). Association between maternal occupational exposure to organic solvents and congenital heart defects, National Birth Defects Prevention Study 1997-2002. *Occup Environ Medicine,* **69** (9) 628-35.

40 Bagchi G, Waxman DJ. (2008). Toxicity of ethylene glycol monomethyl ether: impact on testicular gene expression. *Int J Androl.,* **31** (2): 269-274.

41 Cordier S, Garlantezec R, Labat L, Rouget F, Monfort C, Bonvallot N, Roig B, Pulkkinen J, Chevrier C, Multigner L. (2012). Exposure during pregnancy to glycol ethers and chlorinated solvents and the risk of congenital malformations . *Epidemiology*, **23** (6): 806-812.

42 Garlantezec R, Multigner L, Labat L, Bonvallot N, Pulkkinen J, Dananche B, Monfort C, Rouget F, Cordier S. (2012). Urinary biomarkers of exposure to glycol ethers and chlorinated solvents during pregnancy: determinants of exposure and comparison with indirect methods of exposure assessment. *Occup Env Medicine*, **69** (1): 62-70.

43 Chevrier C, Dananche B, Bahuau M, Nelva A, Herman C, Francannet C, Robert-Gnansia E, Cordier S. (2006) Occupational exposure to organic solvent mixtures during pregnancy and the risk of non-syndromic oral clefts. *Occup Env Medicine*, **63** (9): 617-623.

44 Riley EP, Infante MA, Warren KR. (2011). Fetal alcohol spectrum disorders: an overview.

Neuropsychology Review, **21** (2): 73-80.
45 Seleverstov O, Tobiasz A, Jackson JS, Sullivan R, Ma D, Sullivan JO, Davison S Akkhawattanangkul Y, Tate DL, Costello T, Barnett S Li W, Mari G, Dopico AM, Bukiya AN.(2017) Maternal alcohol exposure during mid-pregnancy dilates fetal cerebral arteries via endocannabinoid receptors. *Alcohol*, **61**, 51-61.
46 Ba A. (2017) Alcohol and thiamine deficiency trigger differential mitochondrial transition pore opening mediating cellular death. *Apoptosis*, **22** (6), 741-752.
47 Reid A, Glass DC, Bailey HD, Milne E, Armstrong Bk, Alvaro F, Fritschi L. (2011). Parental occupational exposure to exhausts, solvents, glues and paints and risk of childhood leukemia. *Cancer Causes and Control*, **22** (11); 1575-1585.
48 Hunter AGW, Thompson D, Evans JA. (1979). Is there a fetal gasoline syndrome? *Teratology,* **20**, 75-79.
49 Dejmek J, Selevan S, Beneš I, Solanský I, Šrám R. (1999). Fetal growth and maternal exposure to particulate matter during pregnancy. *Environmental Health Perspectives*, **107**, (6), 475-480.
50 Wilhelm M, Ritz B. (2003). Residential proximity to traffic and adverse birth outcomes in Los Angeles county, California, 1994-1996. *Environ Health Perspect,* **111**(2): 207-216.
51 Hjorteberg D, Anderson AMN, Grane E, Raaschou-Nielsen O, Sørensen M. (2012) Non-occupational exposure to paint fumes during pregnancy and risk of congenital anomalies: a cohort study. *Environmental Health,* **11**, 54. Online journal 7pp.
52 Lui Z, Li X, Li N, Li S, Dang K, Lin Y, Chen X, You F, Li J, Mu D, Wang Y, Zhu J. (2013). Association between maternal exposure to housing renovation and offspring with congenital heart disease: A multi-hospital case-control study. *Environ Health,* **12** (25) 1-9. http://www.ehjournal.net/content/12/1/25.
53 Tikkanen J, Heinonen OP. (1988). Cardiovascular malformations and organic solvent exposure during pregnancy in Finland. *Am J Indust Med*., **14** (1): 1-8. Tikkanen J, Heinonen OP. (1992). Risk factors for conal malformations of the heart. *Eur J Epidemiol.,* **8** (1): 48-57.
54 Vaktskold A, Talykova LV, Nieboer E. (2011). Congenital anomalies in newborns to women employed in jobs with frequent exposure to organic solvents - a register-based prospective study. *BMC Pregnancy Childbirth,* **11**, 83 Oct 27.

19.3 NEPHROTOXICITY OF INDUSTRIAL SOLVENTS

Nachman Brautbar*+ and Michael P. Wu*
+University of Southern California, Keck School of Medicine, Department of Medicine, Clinical Professor Emeritus of Medicine
***Nachman Brautbar, M.D., Inc., Los Angeles, CA, USA**

19.3.1 INTRODUCTION

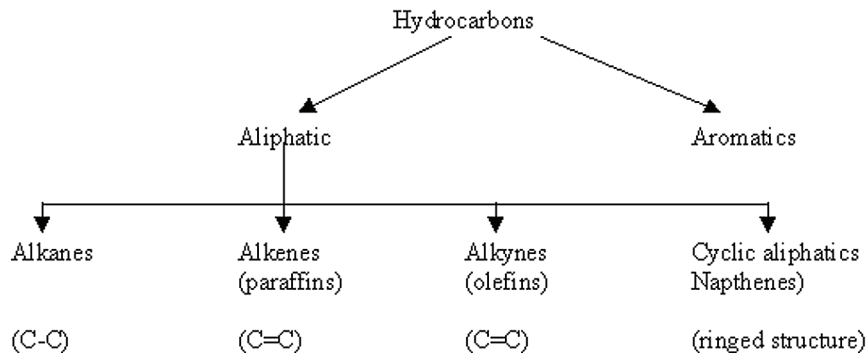


Figure 19.3.1. General classification of hydrocarbons based on general structure.[Adapted, by permission, from A.T. Roy, *Nephron*, **58**, 385, 1991.]

Industrial solvents are used extensively in the industry, as well as in modern living. The various types of commonly used hydrocarbons are presented in Figure 19.3.1.

Solvents are absorbed into the human body through several routes including: 1) inhalation through the lungs; 2) absorption through the skin; and 3) ingestion (in rare cases). The main route of absorption is commonly pulmonary, the lung, and this depends on several factors including the frequency of breathing, diffusion of solvent vapors across the alveolar membrane, partial pressure of solvent vapor in inspired air and blood, and solubility of the solvent in blood as the result of air partition coefficient, and blood flow through the lungs.[2-4] Once in the circulation, 25% of the cardiac output which is about 1200 cubic centimeter of blood per minute passes through the kidneys. Therefore, it is no surprise that with this amount of blood passing through the kidney and carrying solvents (from either industrial inhalation, skin absorption and/or on rare occasions ingestion) the effects of solvents on the kidney has become a practical clinical concern.

Inhaled hydrocarbons are readily absorbed into the bloodstream, become lipophilic and readily pass across the lipid membranes. In addition to reaching the kidney, solvents may target the brain (most notably, ethanol) and enter the blood-brain barrier in high concentration.

Skin absorption is the second most important route for solvent entry into the body and at times is much more significant than inhalation. Absorption of organic solvent vapors by inhalation at the threshold limit value is less than 2%.[4] In contrast, solvents may

be absorbed through the skin in significant amounts even at below the threshold limit value.[4] Factors that affect skin absorption of solvents include the composition of the skin, whether the skin is healthy or not (there is increased absorption if the skin has reduced cellular membrane), and the lipid solubility of the solvent.

The gastrointestinal tract is not commonly a significant route of absorption. Solvents absorbed *via* the gastrointestinal tract are removed immediately by the liver through the first-pass metabolism. If the amount of solvents and quantity of solvents ingested is increased significantly and exceeds the capacity of the liver to metabolize the solvents, then the gastrointestinal tract route will become significant.[5-7]

The distribution of an organic solvent in the human body depends upon its partial pressure in the arterial blood, the solubility of the solvent in the tissue, as well as the blood flow rate through the tissue.[8] Data on tissue distribution of various solvents are limited at best.

The metabolism of solvents depends on its composition. Alcohols are metabolized *via* alcohol dehydrogenase, whereas other organic solvents are mainly metabolized by the Cytochrome P450 dependent enzymes. These enzymes may be found in the liver, kidneys, lungs, gastrointestinal tract, gonads, adrenal cortex, and other body organ tissues. The metabolism of solvents has been described extensively,[9,10] and the reader is referred to those writings.

The metabolites of the organic solvents are eliminated *via* the kidneys through urine excretion and to some extent, by exhalation of the unchanged original solvent. Commonly, the parent solvent is eliminated by the kidneys, and this amounts to less than 1%. The metabolites are the main source of excretion of the metabolized parent solvent. The metabolites of solvents may also play important roles in nephrotoxicity and kidney carcinogenicity.

In the last several decades, there have been several studies in experimental animals, case reports in humans, case studies in humans, and epidemiological studies in humans on the effects of solvents on the kidney, both acutely and chronically. The scope of this chapter is the clinical chronic effects of solvents on the kidney (chronic nephrotoxicology).

19.3.2 EXPERIMENTAL ANIMAL STUDIES

The toxic effects of organic solvents on the kidneys have been studied in several experimental species, especially mice and rats due to its similarities in metabolic pathways. Damage to the kidney has been shown in these experimental animals in the form of acute damage to various parts of the nephron, especially the tubules. This has usually been described as tubular degeneration with regenerative epithelium, deposits of mineral crystals and intralobular proteins, and interstitial inflammation.[9,11-16] Several studies have shown glomerular damage in experimental animal,[17,18] and it has been suggested that long-term solvent exposure alters the immune system, which leads to the glomerulopathy with mesangial IgA deposits.

While the exact mechanism is not known and various mechanisms have been postulated, it is reasonable to accept a mechanistic approach which takes into account genetic, environmental, susceptibility (such as pre-existing diseases including hypertensive kidney

disease and diabetes), direct tubular toxicity, permeability changes, and immunosuppression.

Immune-mediated mechanisms play a major role in the pathogenesis of the glomerular disease, in general. In the vast majority of the cases, antigen-antibody reaction and immune complexes form in the kidney, mainly around the glomerular capillary wall and mesangium. Cellular antigens, both endogenous such as DNA and tumor antigens, as well as exogenous such as viral antigen hepatitis B and C, drugs, and bacteria have been shown to be causative factors in human glomerular immune-mediated diseases. The most common pathological process described in association with solvent exposure and chronic glomerular nephritis has been that of IgA nephropathy, Good Pasture's syndrome, and proliferative glomerulonephritis.

Unlike acute renal failure caused by hydrocarbons, where the renal damage is secondary to the nephrotoxins and mainly cause damage of the proximal tubule acute renal failure, glomerular chronic renal failure appears to be immunologically mediated. Among others, genetic factors may be involved in the pathogenesis of hydrocarbon induced nephropathy. It has been suggested that the propensity to develop this autoimmune disease depends on a combination of a genetic component and predilection and environmental component.[19] Individuals susceptible to glomerular or tubular injury by hydrocarbons may develop chronic kidney disease through three possible mechanisms. The first mechanism is direct tubular toxicity which is commonly the cause of acute renal failure. While it is true that the initial injury of acute renal failure is directed toward the tubule of the nephron, glomerulonephritis may be the result of an autoimmune reaction to the tubulotoxins.[20,21] The second mechanism mainly involves immunosuppression. Ravnskov,[20] in a review of the pathogenesis of hydrocarbon associated glomerulonephritis, suggested that hydrocarbons are immunosuppressive and this effect is noted in several locations in the immunological cascade. This includes leukocyte mobility and phagocytosis suppression such as shown in the benzene effects in mice.[22] This suppression of the normal immune response by hydrocarbons may play a role in the pathogenesis of immune-mediated glomerular lesions. The third mechanism involves an alteration in membrane permeability. Good Pasture's syndrome is mediated by antibodies reactive with the glomerular and alveolar basement membranes. Antibodies in experimental models can usually bind to alveolar basement membranes in vitro by indirect immunofluorescence. Experimental studies suggested that hydrocarbons alter the permeability of pulmonary capillaries, thereby allowing antiglomerular basement membranes to bind to the alveolar basement membranes.[23] This etiology is further supported by the observation that differential sensitivity to exposures due to genetic factors since DR3 and DR4 antigens are more frequent in patients with toxic nephritis than in the general population.[24,25] The study by Zimmerman *et al*.[26] have shown that 6 of eight patients with Good Pasture's syndrome had extensive occupational exposure to solvents ranging from 4 months to 10 years. The results of this study suggest the interaction between the inhaled hydrocarbons and the lung and kidney basement membranes could induce autoantibodies to these membranes. Goyer[27] suggested an autoimmune mechanisms responsible for glomerular lesions following chronic exposure to solvents. Based on the case studies and case reports, it is proposed that chronic exposure

to low levels of solvents in susceptible individuals induces an initial cell injury sufficient to damage cell membranes and to provide the antigen triggering the immune response, accelerating a cascade of a reaction ending with glomerulonephritis.

Effect of solvents and drugs on kidney damage and the damage mechanisms are discussed in the recent review.[28]

19.3.3 SOLVENTS AND KIDNEY DISEASES

The earlier documentation of chronic renal disease and hydrocarbon exposure consists of case reports, and this data was summarized by Churchill *et al*.[29] describing Good Pasture's syndrome in 15 adults, epimembranous glomerulonephritis in 5 adults, and subacute proliferative glomerulonephritis in one adult. The hydrocarbon exposures were for solvents in 12 patients, gasoline in 4, gasoline-based paint in 3, jet fuel, mineral turpentine and unspecified in 1 case report. These case reports were previously summarized[1] and are represented in Table 19.3.1.

Table 19.3.1. Case series report of glomerulonephritis and hydrocarbon exposure.

Study	# of cases	Diagnosis*	Agent
Sperace[30]	2	Goodpasture's	Gasoline
Heale *et al*.[31]	1	Goodpasture's	Gasoline
Klavis and Drommer[32]	1	Goodpasture's	Gasoline
Beirne and Brennan[33]	5 1	Goodpasture's RPGN	Degreasing & paint Solvents & jet fuel
D'Apice *et al*.[19]	2	Goodpasture's	Gasoline mineral turpentine
Kleinknecht *et al*.[34]	2	Anti-GBM nephritis	Organic solvent vapors
Daniell *et al*.[35]	1	Anti-GBM nephritis	Stoddard solvent
Von Scheele *et al*.[36]	1	Subacute GN	Paint solvent
Ehrenreicht *et al*.[37]	4	Epimembranous GN	Solvents
Cagnoli *et al*.[38]	1	Epimembranous GN	?

*GBM = Glomerular basement membrane; RPGN = Rapidly progressive glomerulonephritis; GN = Glomerulonephritis

In the case of human exposure to ethylene glycol, oxalic acid was found to be the end-product of metabolism.[39] It precipitated to crystals of calcium oxalate monohydrate in the tubular lumen, causing acute kidney injury with extensive intracellular intraluminal crystal depositions, and subsequently acute oxalate nephropathy.

While these studies represent case reports, they suggest an association between exposure and the development of kidney disease, such as chronic glomerular disease.

Several case-control studies have examined the role of organic solvent exposure in a population of patients with glomerulonephritis. A total of 14 case-control studies examining human exposure to solvents and glomerulonephritis have been conducted and are documented here in Table 19.3.2.

Table 19.3.2. Glomerulonephritis and organic solvents: Case-control studies summarized.

Study	Risk factor	Study	Risk factor
Lagrue *et al.*[41,42]	4.9*, 5.2*	Yaqoob, *et al.*[48]	increased
Bell *et al.*[43]	increased	Nuyts *et al.*[49]	1.1*
Ravnskov *et al.*[44]	3.9*	Zimmerman *et al.*[26]	increased
Ravnskov *et al.*[45]	2.8*	Ravnskov[50]	increased
Porro *et al.*[46]	3.9*	Finn *et al.*[51]	3.6*, 3.2*
Yaqoob *et al.*[47]	Aliphatic, 15.5 Halogenated, 5.3 Aromatic-oxygenated, 2.0	Van der Laan[52]	1.1
		Harrison *et al.*[53]	8.9*

* $P < 0.05$, statistically significant.

The study by Lagure *et al.*[41,42] showed a significantly increased risk of solvent-related glomerulonephritis of 4.9. That this increased risk of glomerulonephritis follows a dose-response relationship was shown in multiple studies examined by Bell *et al.*,[43] Ravnskov *et al.*,[44,45] Porro *et al.*,[46] Yaqoob *et al.*,[47,48] and Nuyts *et al.*,[49] demonstrating: 1) temporal relationship between exposure to solvents and the development of kidney disease; and 2) a dose-response relationship, strongly showing the causal link between solvent exposure and glomerulonephritis. The study by Nuyts *et al.*,[49] examined a large population of 272 patients with chronic renal failure and assessed several occupational exposures, among those, were hydrocarbons. The increased risk of chronic kidney disease in the form of renal failure in patients exposed to solvents was 5.45. The study of Askergren *et al.*[54] looked into kidney functions in patients exposed to various organic solvents, specifically excretion of red blood cells in the urine in 101 patients exposed to solvents as compared to 39 non-exposed controls. Those who were exposed to organic solvents significantly excreted more cells than the ones who were not exposed. These studies show the role of organic solvent exposure in the development of damage to the glomeruli since excretion of red blood cells represents damage to the glomeruli rather than tubules. That exposure to solvents is associated with glomerular damage rather than tubular damage fits with the various case reports and case-control studies and further suggests a plausible causal connection between exposure to industrial solvents and glomerular damage leading later to chronic glomerulonephritis. The study by Bell *et al.*[43] studied 50 patients who had organic solvent exposure and biopsy-proven proliferative glomerulonephritis. These researchers found that none of the patients had evidence of any other systemic disease or preexisting infection, compared those with 100 control subjects matched for age, sex, and social class. This study is important since exposure assessment was done and showed significantly greater exposure scores in patients with glomerulonephritis compared to control subjects. Furthermore, the degree of exposure was significantly higher in those patients who have more severe glomerulonephritis than those who have less severe glomerulonephritis, further indicative of a dose-response relationship. The relevance of the study is a

significantly statistical association and dose-response relationship between solvent exposure and kidney damage in the form of the glomerular lesion and end-stage glomerulonephritis, ranging from mild to severe chronic glomerulonephritis. The study by Daniell *et al.*[35] evaluated the risk of developing glomerular lesion associated with hydrocarbon exposure and showed a dose-response relationship and variations in disease severity in relation to the exposure intensity. These investigators found an increased risk of developing glomerular nephritis, ranging from 2.8 to 8.9-fold increase as compared to the non-exposed population. The clear temporal relationship between the exposure, absence of any other causes, a dose-response relationship which further validated the observations of Bell *et al*.,[43] further supports that intense or long-term exposure (low-level but long-term or short-term and high levels) to commonly used industrial solvents play a causal role in the development of glomerular damage and chronic glomerulonephritis.

Yaqoob *et al*.[55] conducted a population study that looked into 3 groups of healthy men working in 3 different areas of a major car manufacturing plant. They have studied 3 groups: Group 1 included 112 paint sprayers exposed to a paint-based mixture of solvents; Group 2 comprised of 101 transmission shop workers with exposure to petroleum-based mineral oils; and Group 3 comprised of 92 automated press operators with minimal background exposure to lubricating oils and who acted as internal controls. The 3 groups studied were comparable in age, duration of employment, duration of hydrocarbon exposure, and other factors. The cumulative exposure to hydrocarbons was evaluated. The hydrocarbon exposure scores were significantly higher in Groups 1 and 2, as compared to Group 3 (which served as an internal control and epidemiologically was a good working population control group, since this method took into account the healthy workers). The principal hydrocarbons used throughout the period of time of the study were toluene, xylene, and n-butyl alcohol in paints and various petroleum fractions in the mineral oils. The study evaluated markers of kidney dysfunction in the subjects chronically exposed to hydrocarbons at the described work site. The authors concluded that the long-term exposure to paints was associated with renal impairment and micro-proteinuria without elevation in serum creatinine (which indicates that the kidney functions from a creatinine clearance point of view are still intact, and are less sensitive as a biological marker of glomerular damage). The investigators also reported significant urinary excretion of protein which also indicated early glomerular damage in susceptible individuals. The authors concluded from these studies that chronic hydrocarbon exposure can be associated with renal impairment. They further concluded that the early markers of renal damage could predict progressive deterioration in renal functions. These data are consistent with findings from various studies indicating that chronic hydrocarbon exposure may be associated with early and subclinical renal dysfunction leading to a chronic glomerulonephritis and end-stage renal disease.[56,57]

Porro *et al*.[46] performed a case-referent study that looked into a group of 60 patients with chronic glomerulonephritis established by biopsy, with no evidence of any other systemic diseases. They compared the cases to 120 control subjects who were not exposed to solvent vapors. Exposure assessment was based on scores from questionnaires. The results indicated that exposure was significantly higher in the case group than in the reference

control group for both total and occupational solvent exposure. They reported the odds ratio of chronic glomerulonephritis for patient's occupationally exposed to solvents was 3.9. Using a logistic regression model, they showed a dose-response effect of occupational exposure to solvents and glomerulonephritis. Histological studies of the 60 patients with chronic glomerulonephritis ruled out other systemic disease and demonstrated the whole spectrum of glomerular diseases, the most common one was IgA nephropathy. When the subgroup of patients with IgA nephropathy and their matched controls were separately examined, the cases appeared to be significantly more exposed than the patients with other non-glomerular diseases such as kidney stones. The investigators concluded that their results are in agreement with the hypothesis that the onset of glomerulonephritis could be related to a non-acute exposure to solvents even of light intensity.

De Broe *et al.*[58] conducted a study that examined the relationship between occupational renal diseases and solvent exposure. They found that the relationship between hydrocarbon exposure and glomerulonephritis seems to be well-defined from an epidemiological point of view. It was reported in a case-control study of a group of patients with diabetic nephropathy that hydrocarbon exposure was found in 39% of the patients with that particular form of kidney disease. They found that this was in agreement with findings by Yaqoob *et al.*[47] who found higher levels of hydrocarbon exposure in patients with incipient and overt diabetic nephropathy than in diabetic patients without clinical evidence of nephropathy. These data indicate a particular sensitivity of patients with diabetic kidney toward the damaging effects of the hydrocarbons. The findings of these investigators are in agreement with the study of Goyer,[27] who showed that existing renal diseases, particularly hypertensive and diabetic nephropathies, are clear risk factors predisposing to abnormal accumulation and excess blood levels of any nephrotoxic drugs and chemicals, as well as solvents. Indeed, this observation makes scientific and clinical sense, since it is known that the ability of the kidney to excrete the breakdown metabolites of various materials, including industrial solvents, is reduced with an incremental reduction of kidney function. There would certainly be more accumulation of these breakdown products, as well as the parental solvents in the kidney tissue, and as such, these individuals with underlying kidney disease (e.g., hypertensive kidney disease, diabetic kidney disease, or interstitial kidney disease which may not yet be clinically overt) are at a significantly increased risk of developing chronic kidney disease as a result of the documented damaging effects of solvents on the kidney.

The epidemiological diagnostic criteria for most cases of end-stage kidney disease is deficient since no etiologic information is available in the majority of the cases. Fewer than 10% of the end-stage renal disease cases are characterized etiologically.[59] Clinically, many patients are classified histologically such as glomerulonephritis, but little effort is made to look for toxic factors. Indeed, the majority of the clinicians seeing patients with end-stage kidney disease are not trained to look into occupational, environmental, or toxicological issues in relation to end-stage renal disease. Many patients are listed as having hypertensive end-stage kidney disease and are presumed therefore to be “idiopathic” in origin; however, these cases may very well be the result of other industrial and/or environmental factors, among them, solvent exposure. Many problems in the epidemiological

analysis result from a great reserve capacity of the kidney that can function relatively adequately despite slowly progressive damage. End-stage kidney disease is typically not diagnosed until considerable kidney damage has already occurred at the time when the patient seeks clinical attention. Furthermore, kidney biopsy and post-mortem examination, almost always find small kidneys, inadequate to help in the histopathological assessment, and therefore the etiology is either missed or is misclassified as "idiopathic" or "unknown".

The study by Stengel *et al*.[60] looked at organic solvent exposure and the risk of IgA nephropathy. These investigators have shown that the risk of IgA nephropathy is highest among the most exposed group to oxygenated solvents. The study by Yaqoob *et al*.[47] showed an increased risk factor of 15.5 for development of glomerulonephritis in patients exposed to aliphatic hydrocarbons and a risk factor of 5.3 in patients exposed to halogenated hydrocarbons. These epidemiological data further support observations made in the case reports, case studies, and experimental animal studies. The epidemiological studies by Steenland *et al*.[61] had evaluated the risks and causes of end-stage kidney disease and concluded that regular exposure to industrial solvents played a significant role in the development of chronic end-stage kidney disease. Radican *et al*.[62] conducted a retrospective cohort study to examine the risk of end-stage renal disease among aircraft workers exposed to hydrocarbons. Multivariable Cox regression analysis indicated a statistically increased risk of end-stage renal disease among workers exposed to trichloroethylene, 1,1,1-trichloroethane and JP4 gasoline compared to unexposed subjects ($P < 0.05$). Jacob *et al*.[57] reported on a cohort study of 269 patients with biopsy-proven IgA nephropathy and membranous nephropathy and the association with various types of solvents. The researchers found that any solvent exposure as associated with a significantly increased risk of end-stage renal disease. The hydrocarbons with the statistically elevated risk were ketones (hazard ratio (HR) = 13.3), gasoline, fuel and gas-oil (HR = 8.6), toluene and xylene (HR = 5.1) ($p < 0.05$).

Based on the current literature from experimental animal studies, case reports, case-control studies, and epidemiological studies, one can conclude that the studies show:

1. Biological plausibility.
2. A temporal relationship between exposure to industrial solvents and the development of chronic kidney disease (glomerulonephritis).
3. A dose-response relationship.
4. The consistency of association.
5. Statistical association in the majority of the studies. These criteria fulfill the Bradford-Hill criteria,[63] and establish the basic criteria required for causation.

19.3.3 SOLVENTS AND KIDNEY CANCER

Epidemiologic studies have investigated the relationship between occupational exposure to solvents and kidney cancer. The studies on organic solvents (non-halogenated) and occupational studies on petroleum workers are important, since the common denominator is benzene content of industrial solvents.[64] Several of these studies have separately evaluated kidney cancer associations for organic solvents and halogenated solvents.

In 1981, Gottlieb and Carr[65] published the results of a study in which they investigated cancer to determine whether there was a cancer excess in Louisiana parishes along

the Mississippi River, which is heavily industrialized with petroleum refining, chemical, and petrochemical industries. The investigators surveyed death certificates for cancer deaths occurring from 1960 to 1975. They found 351 kidney cancer deaths from kidney cancer among workers in the chemical industry, which constituted a 6-fold excess, which was not statistically significant (OR = 6.06, 95% CI = 0.73 – 279.6). Among workers in the petroleum or petrochemical industry, they found 22 kidney cancer deaths, which constituted a 2 ¼ fold increase which was statistically significant (OR = 2.27, 95% CI = 1.01 – 5.43). They also found a greater than 2 ½ fold excess of kidney cancer deaths in the combined petroleum and chemical industries, which was highly statistically significant (OR = 2.66, $p < 0.01$). The investigators concluded that the workers' occupational petrochemical exposures were most likely contributors to the etiology of their kidney cancers.

McLaughlin *et al*.[66] evaluated 495 cases of kidney cancer and 697 controls and found a significant association for exposure to petroleum, tar, and pitch products among 36 cases and 29 controls, with age- and smoking-adjusted odds ratio of 1.7 (95% CI 1.0-2.9; $p < 0.05$). The risk increased with duration of employment: employment less than 20 years (OR = 1.1; 95% CI 0.5 – 2.5); employment more than 20 years (OR = 2.6, 95% CT 1.2 – 5.7). The investigators concluded: "The significant association for exposure to petroleum, tar, and pitch products is consistent with the elevated risk of renal cancer (based on small numbers) reported for workers in the petroleum industry."

Siematycki *et al*.[67] reported increased kidney cancer for various different types of petroleum products: automotive gasoline (OR = 2.6, 95% CI = 1.2 – 5.8); aviation gasoline (OR = 2.6, 95% CI = 1.2 – 5.8); mineral spirits (OR = 1.1, 95% CI = 0.8 – 1.4); kerosene (OR = 1.3, 95% CI = 0.8 – 1.6); jet fuel (OR = 2.5, 95% CI = 1.1 – 5.4); diesel fuel (OR = 1.4, 95% CI = 0.8 – 2.3).

Asal *et al*.[68] reported a 7-fold increased risk of kidney cancer was found among those employed in petroleum refining, which increase was statistically significant (OR = 7.2, 95% CI = 1.7 – 10.9). This increase was reduced but still significantly elevated (OR = 4.3) after adjustment for age, weight, and smoking. Risks were also increased for other petroleum-related occupations and remained so after adjustment for age, weight and smoking: Chemical manufacturing (OR = 3.3 [1.9], 95% CI = 0.6 – 5.8), machining (OR = 2.1 [1.7], 95% CI = 0.7 – 4.3), and metal degreasing/cleaning (OR = 1.9 [1.7], 95% CI = 0.7 – 3.8). The investigators concluded that "the increased risk associated with petroleum refining and distributing confirm the finding of other studies and reflects the carcinogen potential of hydrocarbon exposure." They also found positive associations for dry cleaning in women, which they concluded, "confirms results from several proportionate mortality studies and is consistent with the petroleum finding in that the predominant solvent used in dry cleaning in Oklahoma is Stoddard compound, a petroleum derivative."

In 1988, the Missouri Department of Health[69] published the results of a case-control study of kidney cancer in Missouri. The study evaluated 326 cases and 978 age and sex-matched controls. Excess kidney cancers (which were not statistically significant perhaps due to the small size of the study) were found in automobile mechanics (OR = 1.8, 95% CI = 0.4 – 2.0), and machinists (OR = 2.2, 95% CI = 0.5 – 10.3).

Jensen *et al*.[70] conducted a case-control study of 96 patients with the renal pelvis and ureter cancer. The data indicated a statistically significant 4-fold excess of kidney cancer in petrochemical workers, after controlling for age and smoking (OR = 4.0, 95% CI 1.6 – 9.8). Additionally, the use of chemicals and vapors carried elevated risk (OR = 5.0, 95% CI = 1.8–13.9; OR = 5.6, 95% CI = 1.9 – 16.5, respectively).

Harrington *et al*.,[71] in a case-control study of 54 cases of kidney cancer, found an excess of kidney cancer among those occupationally exposed to solvents, which was not statistically significant, clearly because of the small number of cases (OR = 1.30, 95% CI = 0.31 – 8.50), with the risk increasing with greater exposure (OR = 1.54, 95% CI = 0.69 – 4.10).

In 1989, researchers from Oklahoma published the results of a case-control study in which they studied 210 cases and 210 age, sex and frequency-matched population controls to evaluate the association between occupational hydrocarbon exposure and risk of kidney cancer.[72] Kadamani *et al.* found an increased risk for males exposed to petroleum hydrocarbon products which was not statistically significant (OR = 1.6, 95% CI = 0.3 – 3.2). However, the risk was greater for those moderate exposed and was statistically significant (OR = 2.7, 95% CI = 1.2 – 6.5).

In 1990, researchers from New Zealand published the results of a study assessing cancer risk in painters based on data from the New Zealand Cancer Registry.[73] Bethwaite *et al*. found an increased risk for kidney and other urothelial cancers (OR = 1.45, 95% CI = 0.85 – 2.50), which was not statistically significant.

Partanan *et al*.[74] examined in a case-control study of occupational risk factors for kidney cancer. The researchers found a four-fold increased risk of kidney cancers for petrochemical exposure, which adjusted for age and smoking, was statistically significant (OR = 4.19, 95% CI = 1.90 - 16.1). Partanan *et al*. reported that, "gasoline exposure was consistently related to kidney cancer risk." The increased risk persisted after controlling for obesity, smoking, coffee consumption, concomitant diesel fuel exposure, social status, and farming occupations. An exposure-response relation was observed for the level of exposure to gasoline." These researchers noted that some of the exposed workers (e.g., printing press operators) used gasoline as a cleaning solvent.

McCredie *et al*.,[75] in a case-control study of kidney cancer in New South Wales, evaluated occupational associations for 489 cases of renal cell cancer and 147 cases of renal pelvic cancer. These investigators noted excesses of kidney cancer for various petroleum products, most of which were statistically significant: solvent exposure (OR = 1.54, 95% CI = 1.11 – 2.14); gasoline exposure (OR = 1.23, 95% CI = 0.81 – 1.86); oil and mist exposure (OR = 1.99, 95% CI = 1.23 – 3.23); and exposure to other petroleum products (OR = 1.96, 95% CI = 1.23 – 3.23); and exposure to other petroleum products (OR = 1.96, 95% CI = 1.28 – 2.99).

Mellemgaard *et al*.[76] published the results of a case-control study for occupational risk factors for kidney cancer. Controlling for age and smoking, these investigators reported increased risks for exposure to petrochemical products, which were all of borderline statistical significance; gasoline exposure (OR = 2.1, 95% CI = 1.1 – 4.1); solvent exposure (OR = 1.5, 95% CI = 0.9 – 2.4); and cutting oils (OR = 2.1, 95% CI = 1.0 – 4.3).

A case-control study based on the New Zealand Cancer Registry assessed occupational risks among the 1,060 kidney cancer cases.[77] Delahunt *et al*. reported increased risks for such occupations as photographers (OR = 2.08, 95% CI = 0.75 – 5.71); firefighters (OR = 3.51, 95% CI = 2.09 – 5.92); chemical processors (OR = 2.61, 95% CI = 1.00 – 2.43). Stratification of data by smoking history and age yielded a higher and statistically significant association for painters (OR = 1.79, 95% CI = 1.31 – 3.44).

Schlehofer *et al*.[78] conducted a case-control study examining kidney cancer in which they investigated occupation, smoking and demographic factors as risk factors. After controlling for age and smoking, these investigators found excesses of kidney cancer among those occupationally exposed to petroleum products, although the excess was not statistically significant (OR = 1.27, 95% CI = 0.83 – 1.93).

That gasoline (containing benzene) and solvents are statistically associated with increased kidney cancer risk was demonstrated by Mandel *et al.*[79] In this case-control study of 1,732 kidney cancer cases and 2,309 controls were studied, the investigators reported increased risks of kidney cancer for workers in oil refining (OR = 1.3, 95% CI = 0.6 – 2.4), printing or graphics (OR = 1.3, 95% CI = 0.8 – 2.0), and as a gas station attendant (OR = 1.3, 95% CI 0.9–1.9), controlling for the critical confounding variables of age, smoking and weight. The study reported statistically significant increased risks of kidney cancer for workers exposed to gasoline (OR = 1.6, 95% CI = 1.2 – 2.0) and other petroleum products (OR = 1.6, 95% CI = 1.3 – 2.1). Risk for exposure to petroleum products increased with duration of exposure: 1-9 years (OR = 1.5, 95% CI = 1.0 – 2.2), 10-24 years (OR = 1.6. 95% CI = 1.1 – 2.3), and 25-60 years (OR = 1.9, 95% CI = 1.8 – 2.7).

Pesch *et al*.[80] in a case-control study assessing risks of specific jobs and chemicals for kidney cancer in Germany, noted increased risks for jobs involving petrochemical exposure after controlling for smoking and age; which were highest for male workers with very long duration of exposure: chemical workers (OR = 3.1, 95% CI = 1.2 – 7.9); rubber workers (OR = 4.3, 95% CI = 1.1 – 17.4); printers (OR = 3.5, 95% CI = 1.1 – 11.2); and painters (OR = 2.3, 95% CI = 0.8 – 6.8). Notably, risk of kidney cancer was increased among males working in metal cleaning and degreasing: medium duration of exposure (OR = 1.3, 95% CI = 0.9 – 1.9), long duration of exposure (OR = 1.1, 95% CI = 0.8 – 1.6), and very long duration of exposure (OR = 1.3, 95% CI = 0.7 – 2.3). The investigators also reported that workers who were considered as "substantially exposed to organic solvents" showed a significant excess risk of kidney cancer: males (OR = 1.6, 95% CI = 1.1 – 2.3); females (OR = 2.1, 95% CI = 1.0 – 4.4).

Hu *et al*.[81] published a case-control study designed to assess the effect of occupational exposure to specific chemicals on kidney cancer. The study evaluated 1,279 cases and 5,370 population controls in eight Canadian provinces between 1994 and 1997. The study controlled for multiple confounding variables, including age, education, weight, smoking, alcohol, and meat consumption. With respect to petroleum products, the study revealed the following associations for men after adjustment for confounders: benzene (OR = 1.8, 95% CI = 1.2 – 2.6); coal tar, soot, pitch, creosote, asphalt (OR = 1.4, 95% CI = 1.1 – 1.8); and mineral, cutting or lubricating oil (OR = 1.3, 95% CI = 1.1 – 1.7). A highly significant statistical trend for increasing exposure for benzene was observed

before and after adjustment for confounding variables ($p = 0.001$). The adjusted values for years of exposure were: 0 years (OR = 1.0); 1-5 years (OR = 1.1, 95% CI = 0.6 – 2.4); > 6 years (OR = 2.1, 95% CI = 1.3–3.2). The authors concluded that "the present study showed a significant association with a dose-response relationship between RRC (renal cell carcinoma) and benzene exposure; the results provide further evidence that occupational exposure to benzene may be related to RCC risk."

Paganini-Hill *et al*.[82] reported a mortality study of 1,361 newspaper web pressmen who were members of the Los Angeles Pressmen's Union for at least one year between 1949 and 1965. This study is pertinent because newspaper web pressmen use large quantities of organic solvents to clean inks from huge presses. Using the general population as a comparison group, the investigators found a statistically significant excess of kidney cancer among the pressman (5 observed vs. 1.6 expected, SMR = 303, $p < 0.05$). Although the study design could not control for confounding variables, a statistically significant excess of leukemia was also found (7 observed vs. 2.8 expected) SMR 247, $p < 0.05$), which indicates that the significant kidney cancer excess was due to organic solvent exposure, because organic solvents exposure is a known cause of human leukemia due to the benzene content of organic solvents.

A series of cohort studies of refinery workers in the United States found increased incidences of kidney cancer in petroleum refinery workers. However, due to small numbers, the studies lacked sufficient statistical power to detect statistically significant increases in kidney cancer: refinery operators, mechanics, and laborers.[83-87]

Bertazzi *et al*.[88] published the results of a mortality study of 1595 male workers employed in one of the largest Italian refineries for the period 1949 to 1982. The investigators found a statistically significant 7½-fold increase in kidney cancer in the refinery workers (SMR = 750, 95% CI = 293 – 5781).

Researchers from the International Agency for Research on Cancer (IARC) published the results of a mortality study of cancer in two shoe manufacturing cohorts.[89] This study is relevant to the association between solvents and kidney cancer, because shoe manufacturing workers use petroleum-based adhesives and solvents to make shoes, and such workers have experienced significant excesses of leukemia from benzene in adhesives and solvents. The study revealed a 3 to 4-fold excess in kidney cancer deaths among exposed workers, which increased with exposure: probable solvent exposure (SMR = 353, 95% CI = 73 – 10310; high solvent exposure (SMR = 400; 95% CI = 83 – 1169). An excess of leukemia supported the conclusion that the kidney cancer excess among the shoe worker cohorts was due to solvent exposure.

Lynge *et al*.[90] published the results of a cancer incidence study in a cohort of 19,000 service station workers. A borderline statistically significant excess of kidney cancer was found in this cohort (SIR = 1.3, 95% CI = 1.0 – 1.7).

Pukkala *et al*.[91] conducted a study to examine the cancer incidence study among Finnish oil refinery workers. The cohort consisted of 7,412 men and 1,942 women who had been employed for at least 3 months in a Finnish refinery. Using national incidence rates for comparison, the investigator found an approximately 2-fold statistically signifi-

cant excess of kidney cancer among the refinery workers (SIR = 1.97, 95% CI = 1.29 – 2.88).

While not specifically addressing benzene, clearly refinery workers, and workers exposed to solvents are exposed to benzene, since industrial solvents contain benzene (halogenated industrial solvents).[64] Furthermore, the studies in regard to chlorinated solvents, such as perchloroethylene and trichloroethylene, further support an increased risk of kidney cancer and a causative nexus in patients exposed to chlorinated solvents. A number of epidemiologic studies have reported significantly increased risks of renal cell carcinoma in persons exposed to chlorinated solvents.[78,79,92,93]

19.3.4 PERCHLOROETHYLENE AND KIDNEY CANCER

Perchloroethylene is a colorless chlorinated solvent (also called tetrachloroethylene and tetrachloroethene) used as a dry cleaning agent, chemical intermediate and metal degreasing agent. Perchloroethylene has also been used as an insulating fluid and cooling gas in electrical transformers, in paint removers, printing inks, adhesives, paper coating, and leather treatment; in aerosol formulations, as an extractant for pharmaceuticals, to remove soot from industrial boilers, and as an antihelminthic agent. Perchloroethylene is a volatile liquid, as such when it is released to surface water or surface soil, it tends to volatilize quickly. Perchloroethylene is also mobile in soil and has the potential to leach below the soil surface and contaminate groundwater. Perchloroethylene can also biodegrade to trichloroethylene, dichloroethylene, vinyl chloride, and ethene through reductive dechlorination; therefore the exposed population can also be exposed to the degradation product, trichloroethylene – a known human carcinogen, which is often found as a contaminant in products with perchloroethylene.[94]

Several agencies that assess carcinogenic risk of chemicals have reported on the evidence of human cancer risk from perchloroethylene exposure. The U.S. Environmental Protection Agency (EPA) has identified perchloroethylene as likely to be carcinogenic in humans by all routes of exposure.[95] The National Toxicology Program[96] categorizes perchloroethylene as reasonably anticipated to be a human carcinogen. The IARC[97] lists perchloroethylene as Group 2A – probably carcinogenic to humans. The IARC found that "There is sufficient evidence in experimental animals for the carcinogenicity of tetrachloroethylene." Specifically, the IARC referenced an association with health outcomes in the kidney, as well as evidence from experimental animal studies that indicate kidney as a target organ. To date, existing research indicates sufficient evidence to establishes perchloroethylene and its metabolites as genotoxic and mutagenic, whereby exposure to perchloroethylene can lead to DNA damage and initiate carcinogenic processes.[98-101]

The IARC Working Group reviewed experimental animal studies that evaluated the carcinogenicity of perchloroethylene. It is evident that perchloroethylene can increase cancer risks in humans and is carcinogenic in animals as well. Perchloroethylene produces renal tubular cell karyomegaly in male and female rats, renal tubular cell hyperplasia in male rats, and renal tubular cell adenomas or adenocarcinomas (combined) in male rats.[102] In a study of mice given perchloroethylene by gavage in corn oil on 5 days per week for 78 weeks, mortality was significantly increased in treated mice compared with controls.[103] Exposure to perchloroethylene was observed to cause toxic nephropathy (characterized by

degenerative changes in the proximal convoluted tubules at the junction of the cortex and medulla, with cloudy swelling, fatty degeneration, and necrosis of the tubular epithelium) in treated mice. A rare renal tubular cell carcinoma was observed in a male at the lower dose.

Numerous epidemiologic studies have evaluated risks of kidney cancer from exposure to perchloroethylene. There are several case-control studies indicating a potential association between perchloroethylene exposure and kidney cancer in humans, particularly among dry cleaning industry workers: McCredie *et al.*[75] (renal pelvic cancer, OR = 4.68, 95% CI = 1.32 – 16.56); Mandel *et al.*[79] (renal cell cancer, OR = 1.4, 95% CI = 1.1 – 1.7); and Karami *et al.*[104] (renal cell carcinoma, OR = 3.0, 95% CI = 1.2 – 7.4; with a significant P-trend = 0.031 for duration). Pesch *et al.*[82] conducted a case-control study that analyzed agent-specific risks for renal cell carcinoma. Using conditional logistic regression analysis, the researchers found male renal cell carcinoma cases had a significantly higher risk when exposed to perchloroethylene (OR = 1.4, 95% CI = 1.1 – 1.7, for medium exposure). A case-control study by Purdue *et al.*[105] examined the risk of kidney cancer from exposure to six chlorinated solvents. These investigators showed that jobs with high exposure intensity, high cumulative hours exposed to perchloroethylene was associated with statistically significant increased risk of kidney cancer (OR = 3.1, 95% CI = 1.7 – 7.4).

There are also several cohort studies that found significantly elevated occurrence of kidney cancer in dry cleaning workers and laundry workers: Katz *et al.*[106] (PMR = 257, $p \leq 0.05$, using all occupations as control); Duh *et al.*[107] (SMOR = 3.8, 95% CI = 1.9 – 7.6); and Ji *et al.*[108] (SIR = 1.36, 95% CI = 1.20 – 1.54 in men; and SIR = 1.26, 95% CI = 1.07 – 1.47 in women).

Ecological studies are also important in examining the risk of kidney cancer due to perchloroethylene exposure. Ma *et al.*[109] conducted a study that matched the diagnosis of kidney cancer from hospital discharges to the density of dry cleaners using perchloroethylene in New York City. They found a significant association between the density of perchloroethylene dry cleaners and the rate of hospital discharges that include the diagnosis of kidney cancer among persons 45 years of age and older living in New York City. The rate ration increased by 10 to 27% for the populations in zip codes with a higher density of perchloroethylene drycleaners.

Based on the weight of scientific evidence presented, it is evident that perchloroethylene is likely to cause tumor formation in humans. Since perchloroethylene is a genotoxic/mutagenic carcinogen, there may not be any level of exposure to perchloroethylene that is without an increased cancer risk over a lifetime of exposure in humans. In addition, the peer-reviewed scientific literature shows that increased dose levels of exposure to perchloroethylene over extended periods of time increases the human cancer risk in a significant manner. Based the available data, we conclude that there is a reasonable association between perchloroethylene exposure and increased risk of kidney cancer in humans.

19.3.5 TRICHLOROETHYLENE AND KIDNEY CANCER

Trichloroethylene is used as a man-made, chlorinated solvent with a sweet odor and a sweet, burning taste. Automotive manufacturers and the metal industry use it for metal-

degreasing operations. The textile industry uses trichloroethylene as an extraction solvent for greases, oils, fats, waxes, and tars on wool, cotton, and other fabrics. Trichloroethylene is utilized in dyeing and finishing operations. It is also used as a chemical intermediate in the production of pharmaceuticals compounds, polychlorinated aliphatics compounds, flame retardant chemicals, and insecticides. Trichloroethylene can be used for low-temperature heat transfer in refrigerants and for flushing liquid oxygen in the aerospace industry. It can also be found in some household products, including typewriter correction fluid, paint removers, adhesives, lubricants, paints, paint strippers, pesticides, varnishes, and spot removers. Due to its volatility, trichloroethylene is the ubiquitous environmental pollutant that can easily evaporate into the air and may be found and remain in the soil and groundwater for long periods of time.[110]

Trichloroethylene is also recognized as a human carcinogen by the U.S. EPA[111] and National Toxicology Program[112] has recognized trichloroethylene as known to be a human carcinogen. The IARC[113] has classified trichloroethylene as Group 1 – carcinogenic to humans. There is sufficient evidence in experimental animals of trichloroethylene carcinogenicity. In humans, the scientific literature supports a causal relationship between trichloroethylene and kidney cancer. The U.S. EPA has recently concluded that trichloroethylene is carcinogenic to humans by all routes of exposure based on convincing evidence of a causal association due to trichloroethylene exposure in humans.[114]

There is sufficient evidence from the scientific literature cited above that establishes trichloroethylene and its metabolites as genotoxic and mutagenic, whereby exposure to trichloroethylene can lead to DNA damage and initiate carcinogenic processes. Experimental studies also demonstrate trichloroethylene, following metabolism, has the potential to be genotoxic.[99,115,116] Data from human epidemiological studies support the possible mutagenic effect of trichloroethylene leading to gene damage and subsequent occurrence of renal cell carcinoma. Association of increased mutation frequency in trichloroethylene-exposed renal cell carcinoma cases has been observed.[117-119]

The IARC Working Group reviewed experimental animal studies that evaluated the carcinogenicity of trichloroethylene. In three studies in three different strains of rats, treatment with trichloroethylene by gavage increased the incidences of adenoma or carcinoma (combined) of the kidney in males or females, with the incidence of kidney carcinoma also increased in one of these studies.[120,121] Overall, nine studies of exposure by gavage or inhalation in several different strains reported rare kidney adenoma or carcinoma in at least one or more rats treated with trichloroethylene per study.

There is strong evidence that trichloroethylene can cause kidney cancer in people. Lifetime exposure to trichloroethylene resulted in increased kidney cancer in rats at relatively high exposure levels. The IARC and the U.S. EPA determined that there is convincing evidence that trichloroethylene exposure can cause kidney cancer in humans. Epidemiological studies found that occupational exposure to trichloroethylene was associated with an excess incidence of kidney cancer. Many of these studies are based on a small number of exposed workers and may have been confounded by exposure to other solvents. In case-control studies, results were estimated from exposure to solvents in general. These

studies typically reported higher cancer rates for tissue sites similar to those observed in the cohort studies.

In 1998, researchers published the findings of a hospital-based case-control study that evaluated with the risk of renal cell cancer and occupational exposure to trichloroethylene.[122] The study consisted of 58 renal cell cancer cases and a control group of 84 patients from the accident wards of three general hospitals. The mean latency period between first exposure and time of diagnosis was 33 years. After adjusting for age, gender, smoking, body mass index (BMI), blood pressure, and intake of diuretics, the study found a statistically significant increased risk of renal cancers with exposure to trichloroethylene (OR = 10.80, 95% CI = 3.36 – 34.75).

A population-based case-control study was conducted to analyze the risk of renal cell carcinoma and occupational exposures to organic solvents.[123] The study included 438 renal cell cancer cases from the Minnesota Cancer Surveillance System Registry and 687 population-based controls. The results indicated a significantly elevated relative risk among women with renal cell carcinoma exposed trichloroethylene (RR = 1.96, 95% CI = 1.0 – 4.0). The analysis adjusted for risk factors of age, smoking, hypertension and/or use of diuretics and/or anti-hypertension drugs and body mass index.

In 2000, German researchers published the results of a case-control study assessing risks of kidney cancer for specific jobs and chemicals.[80] After controlling for age, study center and smoking, the increased risk was noted for job tasks involving trichloroethylene exposure in men (medium exposure group OR = 1.6, 95% CI 1.0 – 1.8).

In 2003, researchers published the results of a hospital-based case-control study that evaluated the renal cell cancer risk from occupational exposure to trichloroethylene.[124] The study consisted of 134 renal cell cancer cases and 401 controls. Logistic regression analysis found the significantly elevated risk for renal cell cancer and trichloroethylene exposure (OR = 2.47, 95% CI = 1.36 – 4.49). The result was adjusted for age, gender and smoking. The risk remained elevated for exposure to trichloroethylene less than 10 years (OR = 3.78, 95% CI = 1.54 – 9.28). Bruning *et al*. examined the lag periods (defined as the time period between the first exposure and year of the interview) on the development of renal cell cancer. They reported a significantly elevated risk of renal cell cancer and 20 or more years after first exposure (OR = 2.86, 95% CI = 1.49 – 5.49). These results provide additional evidence to support the human nephrocarcinogenicity of trichloroethylene.

In 2006, French researchers published the results of a case-control study of a region with a high frequency of renal cell cancer and a high degree of trichloroethylene exposure.[125] The study was based on 86 renal cell cancer cases and 316 age and gender-matched controls. Charbotel *et al*. reported the results of a logistic regression analysis, which matched for sex, age, tobacco smoking, and BMI. The data indicated a significantly higher risk of renal cell cancer cases and high cumulative dose (OR = 3.34, 95% CI = 1.27 – 8.74) and high cumulative dose and peak exposure (OR = 3.80, 95% CI = 1.27 – 111.40) to trichloroethylene. The findings support the association between high levels of trichloroethylene exposure and increased risk of renal cell cancers.

A hospital-based case-control study of renal cell cancer was conducted to evaluate the risk of renal carcinoma from occupational exposure to trichloroethylene.[126] The study

population comprised of 1,097 cases and 1,476 controls from seven centers in four countries of Central and Eastern Europe. The researchers found renal cell cancer cases were significantly more associated with probable or certain trichloroethylene exposure (OR = 2.23, 95% CI = 1.13 – 3.73), with cumulative exposure ≥1.58 ppm-years (OR = 2.23, 95% CI = 1.07 – 4.64), and with average intensity of exposure ≥0.076 ppm (OR = 2.41, 95% CI = 1.05 – 5.56). The study provides strong support that trichloroethylene exposure is associated with elevated risk of renal cell cancers.

In 1995, German researchers published the results of a cohort study of cardboard workers exposed to trichloroethylene.[127] The study consisted of 169 men who had been exposed to trichloroethylene for at least one year. Seven cases of renal cancers were found with a latency period ranging from 18 to 37 years (average 28.1 years). The incidence of renal cancers in this cohort was significantly higher when compared to Cancer Registry of Denmark (SIR = 11.15, 95% CI = 5.44 – 27.89) and Cancer Registry of the former German Democratic Republic (SIR = 9.66, 95% CI = 3.14 – 22.55). The findings support that exposure to high levels of trichloroethylene over prolonged periods of time may cause kidney cancer in humans.

In 2003, the Danish group published the cancer risk findings of a cohort of workers in Danish companies with documented trichloroethylene use.[128] The cohort consisted of the 40,049 blue-collar workers. Fifty-three renal cell carcinoma cases were identified in a subcohort with expected higher trichloroethylene exposure levels. Within this subcohort, the results showed a significantly higher incidence of renal cell carcinoma with latency period ≥20 years between first exposure and the start of follow up for cancer (SIR = 1.6, 95% CI = 1.0 – 2.3).

In 2005, Zhao *et al.*[129] analyzed the cancer incidence of a cohort of aerospace workers. The cohort comprised of 6,107 male workers employed at a California aerospace company between 1950 and 1993. The researchers reported a statistically significant higher incidence of kidney cancer in this cohort (rate ratio = 4.90, 95% CI = 1.23 – 19.6).

In 2014, the Agency for Toxic Substances and Disease Registry (ATSDR) published the findings of Camp Lejeune mortality study.[130] The study consisted of Marine and Naval personnel who began service during 1975 to 1985 and were stationed at Camp Lejeune (n = 154,932) or Camp Pendleton (n = 154,969). The two drinking water systems at U.S. Marine Corps Base Camp Lejeune, North Carolina were contaminated with solvents, notably perchloroethylene, trichloroethylene, vinyl chloride, and benzene. Camp Pendleton's drinking water system was not contaminated. Compared to Camp Pendleton, Camp Lejeune cohort had higher mortality hazard ratio for kidney cancer (HR = 1.35, 95% CI = 0.84 – 2.16). Since less than 6% of the cohort had died, the authors caution that long-term follow-up is necessary to thoroughly assess the effects of drinking water exposures at Camp Lejeune.

Wartenberg *et al.*[131] reviewed 28 cohort studies on the cancer epidemiology of trichloroethylene exposure. The meta-analysis divided the reviewed cohort studies into three tiers. Tier I cohort studies defined trichloroethylene exposure using urinary biomarkers, job exposure matrices, and job histories. These are generally high-quality studies. The standardized incidence ratio reported for Tier I cohort studies was significantly elevated

for kidney cancer (SIR = 1.7, 95% CI = 1.1 – 2.7). Tier II cohort studies assessed the mortality rates of workers exposed to trichloroethylene based on job titles and other general information. Tier II cohort studies reported significantly elevated standardized incidence ratio for kidney cancer (SIR = 3.7, 95% CI = 1.7 – 8.1). Tier III cohort studies consisted of cancer mortality among drycleaners and laundry workers. Tier III cohort studies also reported a statistically significant higher standardized mortality ratio for kidney cancer (SMR = 2.3, 95% CI = 1.5 – 3.5). Overall, the results of this meta-analysis provide additional evidence in support for a strong association between kidney cancer and exposure to trichloroethylene.

Kelsh et al.[132] conducted a meta-analysis of 16 cohorts and 7 case-control studies that reported on the relationship between trichloroethylene-exposed workers and kidney cancer. The risk of kidney cancer across all studies was significantly elevated (RR = 1.42, 95% CI = 1.17 – 1.77). Within the Group I cohort studies (cohort studies where trichloroethylene was specifically identified as a workplace exposure), the risk for kidney cancer was significantly higher for kidney cancer (RR = 1.34, 95% CI = 1.07 – 1.67). Among the case-control studies, the risk was significantly increased for kidney cancer (RR = 1.57, 95% CI = 1.06 – 2.30). The authors reported positive associations across various study groups and suggest that occupational exposure to trichloroethylene is linked to kidney cancer.

In 2011, researchers from the U.S. EPA published the results of a systematic and quantitative review of trichloroethylene and cancer.[133] The meta-analysis included 15 studies that reported on the kidney cancer epidemiology of trichloroethylene exposure. The summary relative risk estimate for kidney cancer from the random effects model was 1.27 (95% CI = 1.13 – 1.43). For the highest exposure groups, the summary relative risk estimate was 1.58 (95% CI = 1.28 – 1.96). The authors conclude that the findings provide strong support for a causal association between kidney cancer and exposure to trichloroethylene.

Karami *et al.*[134] reported on their findings of a meta-analysis of occupational trichloroethylene exposure and kidney cancer risk. The study incorporated 15 cohort studies and 13 case-control studies. The analysis of cohort studies indicated a significantly elevated risk for kidney cancer (RR = 1.26, 95% CI = 1.02 – 1.56). For case-control studies, the study reported a statistically significant increased risk for kidney cancer (RR = 1.35, 95% CI = 1.17 – 1.57). For cohort and case-control studies combined, the relative risk was 1.32 (95% CI = 1.17 – 1.50). Regardless of the study design, the authors found the results confirm the association between kidney cancer and occupational exposure to trichloroethylene.

There is convincing evidence for an association between exposure to human exposure to trichloroethylene and kidney cancer. From a biological perspective, kidney tumors observed in humans may be related to trichloroethylene exposure because the metabolites derived from trichloroethylene are identical in humans and experimental animals.[113,135]

Chiu *et al.*[136] summarized and discussed key findings from the U.S. EPA Integrated Risk Information System's toxicological review of trichloroethylene. For trichloroethylene exposure, the authors found the epidemiological data convincingly support a causal asso-

ciation for kidney cancer in humans. Mutagenicity studies also provided key evidence in support for establishing mechanisms in trichloroethylene-induced kidney carcinogenicity. Lastly, the authors state that trichloroethylene is "carcinogenic to humans by all routes of exposure".

In 2009, the IARC expert panel met to review the classification of trichloroethylene as a carcinogen.[137] In determining the research needed to change the classification, an expert panel of scientists used a systematic approach to review the monograph and literature published since the last monograph to determine if potential research gaps and needs still existed. The IARC's 1995 monograph[138] listed trichloroethylene as probably carcinogenic to humans (Group 2A) based on limited evidence in humans for carcinogenicity of trichloroethylene and sufficient evidence in experimental animals for the carcinogenicity of trichloroethylene. In its most recent review, the expert panel found the available mechanistic data do not suggest a lack of human carcinogenic hazard from trichloroethylene exposure. Additionally, it was found that "Overall, the body of literature provides convincing evidence of a causal association between trichloroethylene exposure in humans and site-specific cancers, particularly in the kidney." Based on the expert panel's review, the current research warranted the reclassification of trichloroethylene as carcinogenic to humans (Group 1). In 2014, the IARC[113] published an updated monograph for trichloroethylene, which states, "There is sufficient evidence in humans for the carcinogenicity of trichloroethylene. Trichloroethylene causes cancer of the kidney."

In summary, trichloroethylene is a genotoxic/mutagenic carcinogen. As such, there may not be any level of exposure to trichloroethylene that is without an increased cancer risk over a lifetime of exposure in humans. In addition, the peer-reviewed scientific literature indicates that increased dose levels of exposure to trichloroethylene over extended periods of time increases the human cancer risk in a significant manner. The scientific literature clearly describes a toxicological link between trichloroethylene exposure and kidney cancer. Therefore, based on the weight of scientific evidence presented above, it is evident that trichloroethylene causes kidney tumor formation in humans.

*Disclosure: Some of the materials in this chapter have been added from court declarations of Dr. Brautbar.

REFERENCES

1 Roy AT, Brautbar N and Lee DB, *Nephron*, **58**, 385-392 (1991).
2 Morrison, RR and Boyd RN, **Organic Chemistry**, 5th Edition, Morrison RT, Boyd RN, Eds, *Allyn & Bacon*, Boston (1987).
3 Domask, WG, **Renal Effects Of Petroleum Hydrocarbons**, Mehlman MA, Hemstreet GP III, Thorpe JJ, Weaver NK, Eds, *Princeton Scientific Publishers*, Princeton, 1-25 (1984).
4 Pederen LM, *Pharmacol Toxicol*, **61** Suppl 3, 1-38 (1987).
5 Ervin ME, **Clinical Management of Poisoning and Drug Overdose**, Addad LM, Winchester JF, Eds, *Saunders*, Philadelphia, 771 (1983).
6 Wolfsdorf J and Paed D, *J Pediatr*, **88**, 1037 (1976).
7 Janssen S, *et al*., *Intensive Care Med*, **14**, 238-240 (1988).
8 Smith TC and Wollman H, **The Pharmacological Basis of Therapeutics**, Goodman A, Gilman L, Eds, *MacMillan*, New York, 260-275 (1985).
9 Clayton GD and Clayton EE (Eds), **Patty's Industrial Hygiene and Toxicology**, *Wiley*, New York, 2A (1981) and 2C (1982).
10 World Health Organization and Nordic Council of Ministers, Organic Solvents and the Central Nervous System, Environmental Health 5, Copenhagen and Oslo, 1-135 (1985).

11 Browning E, **Toxicity & Metabolism of Industrial Solvents**, *Elsevier Publishing Company*, Amsterdam-London-New York (1965).
12 Mehlman MA, *et al*., **Series: Advances in Modern Environmental Toxicology: Volume VII-Renal Effects of Petroleum Hydrocarbons**, *Princeton Scientific Publishers*, Princeton (1984).
13 Carpenter CP, *et al*., *Toxicol Appl Pharmacol*, **41**, 251-260 (1977).
14 Gibson JE and Bus JS, *Ann NY Acad Sci*, **534**, 481-485 (1988).
15 Thomas FB, *et al*., **Renal Heterogeneity and Target Cell Toxicity**, Back PH, Lock EA, Eds., *John Wiley & Sons Inc*., Chichester, 477-480 (1985).
16 Halder CA, *et al*., *Am Ind Hyg Assoc J*, **47**, 164-172 (1986).
17 Coppor, R, *Am J Kidney Disease*, **12**, 420-424 (1988).
18 Emancipator SN, *Kidney Int*, **38**, 1216-1229 (1990).
19 D'Apice AJF, *et al*., *Ann Intern Med*, **88**, 61-62 (1980).
20 Ravnskov U, *Clin Nephrol*, **23**, 294-298 (1985).
21 Tubbs RR, *et al*., *Am J Clin Pathol*, **77**, 409 (1982).
22 Horiguchi S, Okada H and Horiuchi K, *Osaka City Med J*, **18**, 1 (1972).
23 Yamamoto T and Wilson CB, *Am J Pathol,* **126**, 497-505 (1987).
24 Emery P, *et al*., *J Rheumatol*, **11**, 626-632 (1984).
25 Batchelor JR, *et al*., *Lancet*, 1107-1109 (1980).
26 Zimmerman SW, Groehler K and Beirne GJ, *Lancet*, 199-201 (1975).
27 Goyer RA, *Med Clin of North America*, **74**, 2, 377-389 (1990).
28 Howse ML and Bell GM, *Medicine*, **39**, 356-361 (2011).
29 Churchill DN, Fina A and Gault MH, *Nephron*, **33**, 169-172 (1983).
30 Sperace GA, *Am Rev Resp In Dis*, **88**, 330-337 (1963).
31 Hele WF, Matthisson AM, and Niall JF, *Med J Aust*, 355-357 (1969).
32 Klavis G and Drommer W, *Arch Toxicol*, **26**, 40-50 (1970).
33 Beirne GJ and Brennan JT, *Arch Environ Health*, **25**, 365-369 (1972).
34 Kleinknecht D, *et al*., *Arch Intern Med*, **140**, 230-232 (1980).
35 Daniell WE, Couser WG and Rosenstock L, *JAMA*, **259**, 2280-2283 (1988).
36 Von Scheele C, *et al*., *Acta Med Scan*, **200**, 427-429 (1976).
37 Ehrenreicht T, Yunis SL and Churg, *J, Environ Res*, **24**, 35-45 (1977).
38 Cagnoli L, *et al*., *Lancet*, 1068-1069 (1980).
39 Seo JW, *et al*., *Kidney Res Clin Pract*, **31**, 249-252 (2012).
40 Brautbar N and Barnett A, *Environ Epidem Tox*, **1**, 163-166 (1999).
41 Lagrue G, *et al*., *J Urol Nephrol,* **4-5**, 323-329 (1977).
42 Lagrue G, *et al*., *Nouv Presse Med*, **6**, 3609-3613 (1977).
43 Bell GM, *et al*., *Nephron*, **40**, 161-165 (1985).
44 Ravnskov U, Forsbergg B and Skerfving S, *Acta Med Scand*, **205**, 575-579 (1979).
45 Ravnskov U, Lundstrom S and Norden A, *Lancet*, 1214-1216 (1983).
46 Porro A, *et al*., *Br J Ind Med*, **49**, 738-742 (1992).
47 Yaqoob M, *et al*., *Q J Med*, **301**, 409-418 (1992).
48 Yaqoob M, *et al*., *Diabet Med*, **11**, 789-793 (1994).
49 Nuyts GD, *et al*., *Lancet*, **346**, 7-11 (1994).
50 Ravnskov U, *Acta Med Scand*, **203**, 351-356 (1978).
51 Finn R, Fennerty RG and Ahmad R, *Clin Nephrol*, **14**, 173-175 (1980).
52 Van der Laan G, *Int Arch Occup Envion Health*, **47**, 1-8 (1980).
53 Harrison DJ, Thompson D and MacDonald MK, *J Clin Pathol*, **39**, 167-171 (1986).
54 Askergren A, *Acta Med Scand*, **210**, 103-106 (1981).
55 Yaqoob M, *et al*., *Q J Med*, **86**, 165-174 (1993).
56 Ravnskov U, *Am J Ind Med*, **37**, 599-606 (2000).
57 Jacob S, *et al*., J Am Soc *Nephrol*, **18**, 274-81 (2007).
58 De Broe ME, *et al., Curr Opin Nephrol Hypertens*, **5**, 114-121 (1996).
59 Landrigan P, *et al*., *Arch Environ Health*, **39**, 3, 225-230 (1984).
60 Stengels B, *et al*., *Int J Epidemiol,* **24**, 427-434 (1995).
61 Steenland NK, *et al*., *Am J Public Health*, **80**, 2, 153-156 (1990).
62 Radican L, *et al*., *J Occup Environ Med*, **48**, 1-12 (2006).
63 Hill AB, *Proc Royal Soc Med*, **9**, 295-300 (1965).
64 Mehlman MA, *Eur J Oncol*, **9**, 15-36 (2004).
65 Gottlieb MS and Carr JK, **Banbury Report 9: Quantification of Occupational Cancer**, Peto R

and Scheiderman, eds. *Cold Spring Harbor Laboratory*, 195-204 (1981).
66 McLaughlin JK, *et al*., *J Natl Cancer Inst*, **72**, 275-298 (1984).
67 Siematycki J, *et al*., *Scand J Work Environ Health*, **13**, 493-504 (1987).
68 Asal NR, *et al*., *Cancer Detect Prev*, **13**, 263-279 (1988).
69 Brownson RC, *Arch Environ Health*, **43**, 238-241 (1998).
70 Jensen OM, *et al*., *Int J Cancer*, **41**, 557-561 (1988).
71 Harrington JM, *et al*., *Br J Ind Med*, **46**, 643-650 (1989).
72 Kadamani S, Asal NR and Nelson RY, *Am J Ind Med*, **15**, 131-141 (1989).
73 Bethwaite PB, Pearce N and Fraser J, *Br J Ind Med*, **47**, 742-746 (1990).
74 Partanan T *et al*., *Scand J Work Environ Health*, **17**, 231-239 (1991).
75 McCredie M and Stewart JH, *Br J Ind Med*, **50**, 349-354 (1993).
76 Mellemgaard A, *et al*., *Scand J Work Environ Health*, **20**, 160-165 (1994).
77 Delahunt B, Bethwaite PB and Nacey JN, *Br J Urol*, **75**, 578-582 (1995).
78 Schlehofer B, *et al*., *Int J Epidemiol*, **24**, 51-57 (1995)
79 Mandel JS, *et al*., *Int J Cancer*, **61**, 601-605 (1995).
80 Pesch B, *et al*., *Int J Epidemiol*, **29**, 1014-1024 (2000).
81 Hu J, Mao Y and White K, *Occup Med (Lond)*, **53**, 157-164 (2002).
82 Paganini-Hill A, *et al*., *J Occup Med*, **22**, 542-544 (1980).
83 Hanis, NM, *et al*., *J Occup Med*, **24**, 203-212 (1982).
84 Thomas TL, *et al*., *J Occup Med*, **24**, 135-140 (1982).
85 Wen CP, *et al*., *Am J Epidemiol*, **118**, 526-542 (1983).
86 Hanis NM, *et al.*, *J Occup Med*, **27**, 361-369 (1985).
87 Wen CP, *et al*., *Am J Ind Med,* **9**, 171-180 (1986).
88 Bertazzi PA, *et al*., *Int Arch Occup Environ Health*, **61**, 261-270 (1989).
89 Fu H, *et al*., *Occup Environ Med*, **53**, 394-398 (1996).
90 Lynge E, *et al*., *Am J Epidemiol*, **145**, 449-458 (1997).
91 Pukkala E, *J Occup Environ Med*, **40**, 675-679 (1998).
92 Sinks T, *et al*., *Epidemiology*, **3**, 483-489 (1992).
93 Buzio L, *et al*., *Med Lav*, **93**, 303-9 (2002).
94 Agency for Toxic Substances and Disease Registry (ATSDR), Draft Toxicological Profile for Perchloroethylene, Atlanta, GA (2014).
95 U.S. Environmental Protection Agency (EPA), Tetrachloroethylene (Perchloroethylene) (CASRN 127-18-4), Integrated Risk Information System (IRIS), (2012).
96 National Toxicology Program (NTP), *Tetrachloroethylene, Rep Carcinog*, **14**, 1-3 (2016).
97 International Agency for Research on Cancer (IARC), *IARC Monogr Eval Carcinog Risks Hum*, **106**, 229-350 (2014).
98 Mazzullo M, *et al*., *Res Commun Chem Pathol Pharmacol*, **58**, 215-235 (1987).
99 Walles SA, *Toxicol Lett,* **31**, 31-35 (1986).
100 Vamvakas S, Dekant W and Henschler D, *Toxicol In Vitro*, **3**, 151-156 (1989).
101 Vamvakas S, *et al*., *J Biochem Toxicol*, **4**, 21-27 (1989).
102 National Toxicology Program (NTP), Natl Toxicol Program Tech Rep Ser, 311, 1-197 (1986)
103 National Cancer Institute, Bioassay of tetrachlorethylene for possible carcinogenicity, Bethesda, MD (USA): National Toxicology Program Technical Report, TR-013, 77-813 (1977).
104 Karami S, *et al*. BMC *Cancer*, **12**, 344 (2012).
105 Purdue MP, *et al.*, *Occup Environ Med*, **74**, 268-274 (2017).
106 Katz RM and Jowett D, *Am J Public Health*, **71**, 305-307 (1981).
107 Duh RW and Asal NR, *Am J Public Health*, **74**, 1278-1280 (1984).
108 Ji J, Grandstrom C and Hemminki K, *World J Urol*, **23**, 271-278 (2005).
109 Ma J, *et al*., *J Environ Public Health*, **2009**, 183920 (2009).
110 Agency for Toxic Substances and Disease Registry (ATSDR), Draft Toxicological Profile for Trichloroethylene (TCE), Atlanta, GA (2014).
111 U.S. Environmental Protection Agency (EPA), Toxicological Review of Trichloroethylene, Washington, DC, EPA/635/R-09/011F (2011).
112 National Toxicology Program (NTP), Trichloroethylene, *Rep Carcinog*, **14**:1-4 (2016).
113 International Agency for Research on Cancer (IARC), *IARC Monogr Eval Carcinog Risks Hum*, **106**, 35-217 (2014).
114 U.S. Environmental Protection Agency (EPA), Trichloroethylene (CASRN 79-01-6), Integrated Risk Information System (IRIS), Washington, DC (2011).

115 Robbiano L, *et al*., *Toxicology*, **204**, 187-195 (2004).
116 Robbiano L, *et al*., *Mutat Res*, **413**, 1-6 (1998).
117 Brauch H, *et al*., *Toxicol Lett*, **151**, 301-310 (2004).
118 Brauch H, *et al*., *J Natl Cancer Inst*, **91**, 854-861 (1999).
119 Bruning T, *et al*., *Arch Toxicol*, **71**, 332-325 (1997).
120 National Toxicology Program (NTP), *Natl Toxicol Program Tech Rep Ser*, **243**, 1-174 (1990).
121 National Toxicology Program (NTP), *Natl Toxicol Program Tech Rep Ser*, **273**, 1-299 (1988).
122 Vamvakas S, *et al*., *J Cancer Res Clin Oncol*, **124**, 374-382 (1998).
123 Dosemeci M, Cocco P and Chow WH, *Am J Ind Med*, **36**, 54-59 (1999).
124 Bruning T, *et al*., *Am J Ind Med*, **43**, 274-285 (2003).
125 Charbotel B, *et al*., *Ann Occup Hyg*, **50**, 777-787 (2006).
126 Moore LE, *et al.*, *Cancer Res*, **70**, 6527-6536 (2010).
127 Henschler D, *et al*., *Arch Toxicol*, **69**, 291-299 (1995).
128 Raaschou-Nielsen O, *et al*., *Am J Epidemiol,* **158**, 1182-1192 (2003).
129 Zhao Y, *et al*., *Am J Ind Med*, **48**, 249-258 (2005).
130 Bove FJ, *et al, Environ Health*, **13**, 10 (2014).
131 Wartenberg D, Reyner D and Scott CS, *Environ Health Perspect*, **108** Suppl 2, 161-176 (2000).
132 Kelsh MA, *et al*., *Epidemiology*, **21**, 95-102 (2010).
133 Scott CS and Jinot J, *Int J Environ Res Public Health*, **8**, 4238-4272 (2011).
134 Karami S, *et al.*, *Occup Environ Med*, **69**, 858-867 (2012).
135 Birner G, *et al*., *Environ Health Perspect*, **99**, 281-284 (1993).
136 Chiu WA, *et al*., *Environ Health Perspect*, **121**, 303-311 (2013).
137 International Agency for Research on Cancer (IARC), A Collaboration Project between International Agency for Research on Cancer (IARC) and National Occupational Research Agenda (NORA). IARC Technical Publication No. 42. Identification of research needs to resolve the carcinogenicity of high priority IARC carcinogens. Trichloroethylene. Views and Expert opinions of an IARC/NORA expert group meeting. Lyon, France, (2009)
138 International Agency for Research on Cancer (IARC), *IARC Monogr Eval Carcinog Risks Hum*, **63**, 75 (1995).

19.4 LYMPHOHEMATOPOIETIC MALIGNANCIES AMONG WORKERS EXPOSED TO BENZENE INCLUDING LEUKEMIA, LYMPHOMA, AND MULTIPLE MYELOMA

Nachman Brautbar[+]*, Michael P. Wu*, and Alexandra E. Rieders*
[+]University of Southern California, School of Medicine, Department of Medicine, Clinical Professor Emeritus of Medicine
***Nachman Brautbar, M.D., Inc., Los Angeles, CA, USA**

19.4.1 INTRODUCTION

Benzene is an aromatic hydrocarbon. Historically, it has been produced during the process of coal tar distillation and coke production, but today benzene is produced mainly by the petrochemical industry. Based on the National Institute of Occupational Safety and Health (NIOSH), in the United States, it has been estimated that in 1976 two million Americans were exposed occupationally to benzene.[1] According to Agency for Toxic Substances and Disease Registry (ATSDR), 238,000 people may have been occupationally exposed to benzene in the United States in 2007.[2] Worldwide production of benzene is approximately 15 million tons.[3] Global benzene demand increased to 29 million tons in 2010.[4] Much of the increase in demand for benzene came from the Asia-Pacific region and the same trend is expected to continue in the future.[4] Asia-Pacific is expected to account for 61.6% of the global benzene demand in 2020 which is expected to grow to reach to 42 million tons in 2020.[4] The production in the United States was estimated to be increasing at least 3% annually, approaching 6 million tons of benzene produced in the United States in 1990 and 6.36 million tons produced in 1993.[2] Production of benzene in U.S. in 2010 was 6.1 million tons.[5] Major U.S. benzene producers include BP, ExxonMobil, Flint Hills resources, LyondellBasell, Shell, and Total.[5] In 2009, 104 companies contributed to world market of benzene.[6] Current use of benzene is for synthesis of other compounds (not as solvent anymore); the main product is ethylbenzene (about 50% of total benzene use).

Benzene has been described as a clear, colorless, non-corrosive, and flammable liquid with a strong odor. Benzene was used as an excellent solvent and degreasing agent, and as a basic aromatic unit in the synthetic process of other chemicals.[7] Exposure to benzene in the occupational setting most commonly occurred in past in the chemical, printing, rubber, paint, and petroleum industry. Among other sources of exposure to benzene, non-occupational exposures occur in the form of cigarette smoking and exposure to gasoline and its vapors during fueling motor vehicles.[8]

19.4.2 ROUTES OF EXPOSURE

The major route of exposure to benzene is inhalation of benzene vapors through the lungs; however, skin absorption of benzene has been shown to be significant depending on the circumstances of the exposure, such as time of contact between the benzene and the skin.[1,9] Benzene, as with other solvents, absorbs through the skin and is enhanced if the skin condition is altered by either disease, loss of skin, or cracking of the skin.[7] The dermal absorption of benzene deserves much more attention than previously described in var-

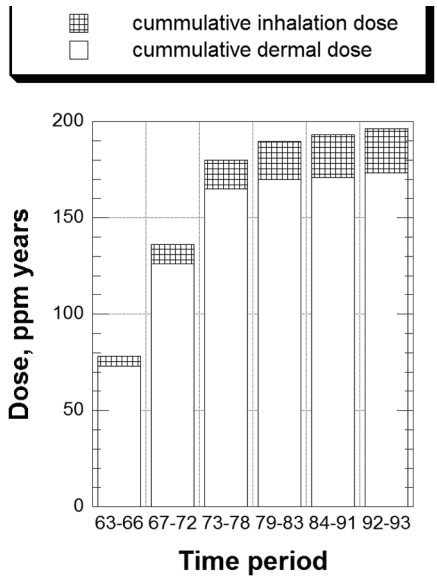


Figure 19.4.1. Cumulative dose of benzene over 30 years. [Adapted, by permission, from D. Brenner, *Eur. J. Oncol.*, **3**(4), 399-405, 1998.]

ious texts of toxicology and occupational medicine, as well as environmental and industrial health. Dermal absorption of benzene in workers who use either toluene containing benzene or other solvents containing benzene, is a significant factor in calculating dosimetry and absorption of benzene, and can be calculated utilizing standard accepted methodology. A study by Brenner *et al*.[9] described chronic myelogenous leukemia due to skin absorption of benzene as a contaminant of other solvents. The investigators of the study concluded that the total benzene absorbed dose *via* skin and inhalation was equivalent to an accumulated vapor exposure of 196.4 + 42 ppm-years (Figure 19.4.1). Dermal exposure accounted for 97% of the total absorbed dose of benzene. Inhalation of benzene from occupational, smoking and ambient non-occupational sources accounted for only 3% of the benzene dose. The authors presented the reports of dermal absorption of benzene in the Table 19.4.1.

Table 19.4.1. Summary of benzene dose expressed as equivalent ppm-years
[Adapted, by permission, from Brenner D, *et al.*, *Eur J Oncol*, **3**, 399-405, (1998).]

Case	Solvent	Dermal	Occup. inhalation	Cigarette smoke	Ambient inhalation	Total
1997	Toluene, MEK, acetone	170.4	19.2	0.05*	0.29	189.9
1998/1	Mineral spirits	41.1	17.8	0.1*	0.23	59.3
1998/2	Refinery process streams	19.0	4.6	1.4	0.4	196.4

*Second-hand cigarette smoke

Therefore, workers who are exposed to solvents containing benzene should be evaluated by skin absorption dosimetry, in addition to other sources such as inhalation, to address the range of levels of exposure.

Therefore, dermal absorption of benzene, especially in connection with benzene as a by-product in other solvents, is of extreme importance in dosimetry analysis.

Once benzene reaches the blood, it is metabolized mainly in the liver. The metabolic products are excreted in the urine within 48 hours from absorption. Several metabolites have been found in the urine after benzene exposure; among those are phenol, quinone,

hydroquinone, and muconic acid.[10] The liver utilizes the cytochrome P450 and oxidization system for the metabolism of benzene.[11,12]

Specific cellular toxic effects from benzene have been described, including the central nervous system (doses of over 100 ppm), liver, kidney, skin, immunological, and carcinogenic effects. The various toxicological effects of benzene will not be discussed in this chapter since the scope of this chapter is the hematopoietic effects; the reader is referred to other sources.[2]

19.4.3 HEMATOPOIETIC EFFECTS OF BENZENE

Benzene is a proven human carcinogen. The toxicity of benzene has been known since the 19th century when aplastic anemia was first reported.[7,13] Indeed, the causal link between benzene and bone marrow toxicity in the form of hematoxicity and bone marrow suppression was described already in 1897.[14] In 1928, Delore *et al.* described leukemia as a result of benzene exposure.[15] In 1932, Lignac[16] reported lymphoblastoma in association with benzene exposure. Several studies have reported the association between exposure to benzene and hematopoietic toxicity and leukemia.[17,18] Acute myeloid leukemia has been the most frequent form of leukemia found to be related to benzene exposure. Other forms of leukemia, such as erythroleukemia, thrombocytopenia, chronic myeloid leukemia, myelodysplastic syndrome, acute lymphoblastic leukemia, chronic lymphocytic leukemia, as well as Hodgkin's and non-Hodgkin's lymphoma have all been described to have an association with benzene exposure. As a result of the high toxicity of benzene, the American Petroleum Institute published a paper in 1948 concluding that the only safe level of exposure to benzene is *no exposure at all*.[19] The language utilized was as follows, “In as much as the body develops no tolerance to benzene, and as there is a wide variation in individual susceptibility, it is generally considered that the only absolutely safe concentration for benzene is zero.”

The following hematological conditions have been described in association with benzene.[20-42]

1. Acute myeloid leukemia.
2. Erythroleukemia.
3. Aplastic anemia.
4. Acute monocytic leukemia.
5. Chronic myeloid leukemia.
6. Myelofibrosis and myeloid metaplasia.
7. Thrombocythemia.
8. Acute lymphoblastic leukemia.
9. Chronic lymphocytic leukemia.
10. Lymphomas and related disorders.
11. Multiple myeloma
12. Myelodysplastic syndrome.

19.4.4 BENZENE'S CLASSIFICATION AS A HUMAN CARCINOGEN

Benzene is recognized as a human carcinogen by all organizations that evaluate the carcinogenicity of chemicals and governmental agencies that classify chemicals as carcinogens.

The U.S. Environmental Protection Agency (EPA) classifies benzene as a "human carcinogen," i.e., a chemical for which there is sufficient evidence from epidemiologic studies to support a causal association between exposure and cancer.[43]

The International Agency for Research on Cancer (IARC) classifies benzene as "carcinogenic to humans."[44]

The National Institute for Occupational Safety and Health lists benzene as a "potential occupational carcinogen," i.e., "any substance, or combination or mixture of substances, which causes an increased incidence of benign and/or malignant neoplasms, or a substantial decrease in the latency period between exposure and onset of neoplasms in humans or in one or more experimental mammalian species as the result of any oral, respiratory or dermal exposure, or any other exposure which results in the induction of tumors at a site other than the site of administration." This definition also includes any substance, "which is metabolized into one or more potential occupational carcinogens by mammals."[45]

The National Toxicology Program (NTP) classifies benzene as a "known carcinogen."[46]

The Occupational Safety and Health Administration (OSHA) categorizes benzene as a carcinogen based on the classification of IARC and the NTP.[47]

Several well conducted epidemiological scientific studies and data have provided the epidemiological basis for benzene as a hematopoietic and lymphopoietic cancer. Mehlman described a wide range of the hematotoxicity of benzene.[48] Nilsson *et al*.[49] described leukemia, lymphoma, and multiple myeloma in seamen exposed to benzene in tankers. In this study, an increased incidence of lymphatic and hematopoietic malignancies was described and while it is true that the cargo vapors from gasoline and other light petroleum products and chemicals have been shown to be carcinogenic, benzene exposure during loading, unloading, and tank cleaning operations were concluded to be the likely source of the carcinogenic exposure. Rinsky *et al*.[28] described various hematological malignancies in their study of benzene exposure and showed that the overall standardized mortality ratio for leukemia and multiple myeloma were increased significantly. The investigators of this study concluded that there is a quantitative association between benzene exposure and development of leukemia. Wong[50] evaluated a mortality study of chemical workers occupationally exposed to benzene and found a significantly increased risk for lymphohematopoietic malignancies. Linet *et al*.[51] studied hematopoietic malignancies and related disorders among benzene exposed workers in China and showed a wide spectrum of hematopoietic malignancies.

Yin *et al*.[52] in a cohort study of cancer among benzene exposed workers in China, studied workers employed in a variety of occupations and showed a statistically significant increased deaths among benzene exposed subjects for leukemia, malignant lymphoma, neoplastic diseases of the blood, and other malignancies. The rates were significantly elevated for the incidence of lymphohematopoietic malignancies (risk ratio of 2.6), malignant lymphoma (risk ratio of 3.5), and acute leukemia (risk ratio of 2.6). A significant excess risk was also found for aplastic anemia and myelodysplastic syndrome. These investigators concluded that employment in benzene exposure occupations is asso-

ciated with a wide spectrum of myelogenous and lymphatic malignant diseases and related disorders of the hematopoietic lymphatic system.

Hayes *et al.*[53] in one of the largest epidemiological studies on benzene exposure, showed a wide spectrum of hematological neoplasms and their related disorders in humans. The risk for these conditions is elevated at average benzene exposure levels of less than 10 ppm. These investigators further concluded that the pattern of benzene exposure appears to be important in determining the risk of developing specific diseases.

Wong[54] studied a cohort of 7,676 male chemical workers from seven plants who were occupationally exposed continuously or intermittently to benzene for at least 6 months, and compared them to a group of male chemical workers from the same plant who had been employed for at least 6 months during the same period but were never occupationally exposed to benzene and showed a significantly increased risk of lymphohematopoietic malignancies.

In experimental animals, benzene has been shown to be associated, in rats, with cancers of zymbal gland, oral cavity, nasal cavities, skin, forestomach, mammary gland, Harderian gland, preputial glands, ovary, uterus, angiosarcoma of liver, hemolymphoreticular neoplasia, lung cancers, and leukemia.[55] The ability of benzene metabolites to affect lymphocytic growth and function *in vitro* is shown to correlate with the oxidation capacity and concentration of the metabolites at the target site. Benzene also affects macrophages, as well as lymphocytes.[38,56,57] Kalf and Smith[58,59] have shown that benzene exposure reduces the ability of marrow stromal cells to support normal stem cell differentiation. From these experimental animal studies, and *in vitro* studies a wide range of bone marrow effects of benzene metabolites is shown. It has been concluded that the hematotoxicity of benzene depends on the breakdown metabolites and can affect the stem cell at any point in time, for instance myeloid, erythroid, macrophages, and lymphocytic stem cells. Therefore, benzene has been named as a pleural potential stem cell toxicant.[60]

In addition to carcinogenic effects, animal studies have shown the effects of benzene exposure on the immune system. Reid *et al.*[61] showed a significant decrease in splenic cell proliferation in mice exposed to benzene for 14 days. Experimental animal studies also reported reduced circulating white blood cells, as well as changes in spleen morphology and weight in various experimental animal studies.[60] These experimental animal studies further support the observation from 1913 by Winternits and Hirschfelder that rabbits exposed to benzene showed an increased susceptibility to pneumonia and tuberculosis.[62]

The experimental animal data and the epidemiological studies clearly show that:

1. benzene is a carcinogen for the lymphohematopoietic system;
2. benzene has a direct effect on the immune system;
3. benzene has a direct effect on the early development of the blood cells; and
4. benzene is a pluripotent hematological carcinogen.

19.4.5 RISK ASSESSMENT ESTIMATES

The U.S. EPA has used several databases in their estimates for benzene exposure and risk.[43] The data utilized by the EPA to assess the risk included the study by Rinsky *et al.*[63] where the duration of exposure was at least 24 years and exposure levels were between 10 to 100 ppm (8 hour TWA) with a statistically significant increased incidence of leukemia. The study of Ott *et al.*[64] showed levels of anywhere from 2 to 25 ppm (8 hour TWA) with

increased incidence of leukemia; and Wong *et al*.,[54] where the exposure was at least 6 months, levels were from 1 ppm to 50 ppm, and there was a statistically significant increase in the incidence of leukemia, lymphatic and hematopoietic cancers.

The International Agency for Research on Cancer (IARC) has classified benzene as a Group 1 carcinogen.[26] A Group 1 carcinogen is defined as an agent that is carcinogenic to humans. This classification is based on sufficient evidence for carcinogenicity in humans. IARC based this conclusion on the fact that numerous case reports and follow-up studies have suggested a relationship between exposure to benzene and the occurrence of various types of leukemia. In addition, IARC considers the evidence for carcinogenicity to animals to be sufficient.

The regulatory agencies in estimating the increased risk of benzene related cancers rely mainly on the study by Rinsky,[28] which concluded that the mean annual cumulative exposure level of less than 1 ppm accumulated over 40 years working life-time would not be associated with increased death from leukemia. This epidemiological study showed an exponential decrease in the risk of death from leukemia which could be achieved by lowering occupational exposure to benzene. According to the model derived in this study, a worker occupationally exposed to benzene at an average exposure level of 10 ppm for 40 years would have an increased risk of death from leukemia of 3.37. If the average exposure was lowered to 1 ppm, that excess risk would decrease to 1.7. At 0.1 ppm times 40 years cumulative exposure the risk be virtually equivalent to background risk.[28] Infante *et al.*[65] have shown a relative risk of 5.6 with an estimated cohort exposure of 10 to 100 ppm over 8.5 years average. Vigliani *et al*.[66] showed a relative risk of 20 estimated cohort exposure to 200 to 500 ppm over 9 years average. Aksoy showed a relative risk of 25 with an estimated cohort exposure of 150 to 210 ppm over 8.7 years average.[22] These studies clearly show that the risk of developing lymphohematopoietic cancers is significant, and that benzene is carcinogenic from an epidemiological point of view at very low levels of 0.1 ppm.

19.4.6 LEVELS OF EXPOSURE

19.4.6.1 Dose metrics

While dose is important in toxicology in determining the toxic effects of a chemical, it is important to consider the metric by which dose is quantified. Several different dose metrics can be used for toxicology and risk assessment. These include average or mean intensity of exposure, 8-hour time weighted average exposures, short-term (15 minute) average exposures, peak exposures, and cumulative exposure. Historically, most epidemiologic studies of benzene exposed workers have used only one dose metric: cumulative exposure, expressed in units of parts per million years (ppmy). (One ppmy equals the total amount of benzene inhaled by a worker over the course of one year if the worker is, on average, exposed daily to 1 ppm benzene.) While cumulative exposure has often been used in occupational epidemiology, it has not been validated as the valid dose metric for assessing the risk of leukemia from benzene exposure.

There is no evidence that cumulative dose has been validated as the proper metric for assessing whether benzene causes leukemia. While epidemiological studies show that workers with high cumulative exposures to benzene do develop acute myeloid leukemia,

they do not establish that it is the cumulative benzene dose that does so. To the contrary, experimental studies investigating the mechanisms by which benzene causes toxicity to the bone marrow show that average intensity and peak exposures to benzene, rather than cumulative benzene dose, present the greatest risk of genetic damage, bone marrow aplasia, and cancer in animals.[67]

Regulatory levels of exposure to various chemicals, among them solvents and benzene, have been a subject for constant pressure from industry manufacturers on one hand, and regulatory agencies, health care, and patients on the other hand. The most common question asked is, "Is there a safe level of exposure to benzene?" The answer to that question has been given by the American Petroleum Institute in their paper on benzene, 1948,[19] and their statement was that the only safe level of exposure to benzene is *no exposure at all*. Rightly so, the paper based that opinion on the fact that the body develops no tolerance to benzene and there is wide variation in individual susceptibility and therefore the only absolutely safe concentration for benzene is zero. This approach has been confirmed from a point of view of epidemiological studies and experimental animal studies showing benzene to cause cancer in experimental animals, along with case reports and epidemiological studies in humans. Based on epidemiological studies and extrapolation from experimental animal studies, IARC's position is that a linear regression line should be applied for the dose-response crossing the zero point for low level exposure of benzene. The U.S. EPA concurred that at low levels of exposure (since no epidemiological studies are available at low levels of exposure) linear dose-response is indicated. The modalities of exponential dose-response relationship for low levels is not applicable here based on the most recent U.S. EPA and IARC positions.[43,44] This linear, non-threshold model assumes that every increment of dose is accompanied by a commensurate increment in the excess cancer risk. The use of this toxicological model allows extrapolation of risks from relatively high dose levels, where cancer responses can be measured, to relatively low dose levels, where such risks are too small to be measure directly through epidemiological studies.[68] Figures 19.4.2 and 19.4.3 demonstrate the extrapolation from high levels of exposure to low levels of exposure utilizing the linear modality.

The U.S. EPA[68] further supports that approach and the panel members who evaluated the data felt that for the leukemogenic effects of benzene the linear model is consistent with the spirit of the proposed cancer risk assessment guidelines.

19.4.6.2 Benzene exposure limits and recommendations

Several organizations and governmental agencies prepare regulations or recommendations limiting exposure to toxic chemicals. The regulations and recommendations for limiting benzene exposure are summarized below.

Occupational Safety and Health Administration (OSHA) defines the Permissible Exposure Limit to be 1 ppm (8 hour time weighted average) and Short Term Exposure Limit to be 5 ppm (15 minute average). These limits have the effect of law and represent maximum allowable exposures in the workplace.

The National Institute for Occupational Safety and Health (NIOSH) has adopted a Recommended Exposure Limit for benzene of 0.1 ppm (8 hour time-weighted average) and a Short Term Exposure Limit of 1 ppm (15 minutes).[70]

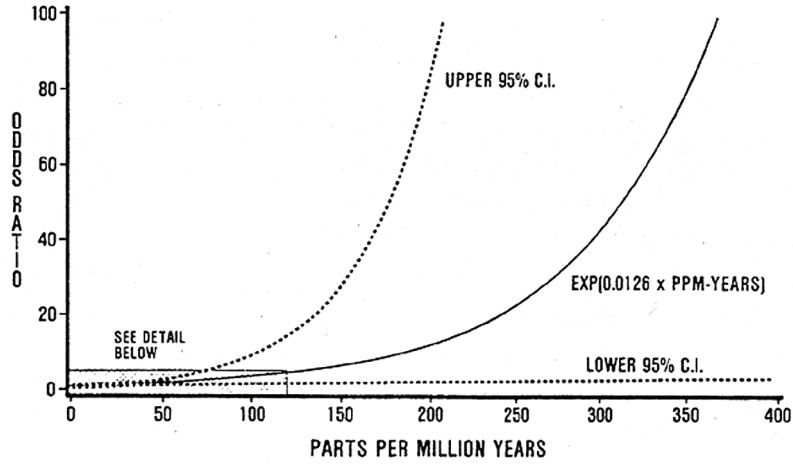


Figure 19.4.2. Extrapolations of levels of exposure to benzene. [Adapted, by permission, from R.A. Rinsky, *New England J. Med.*, **316**, 1044-1050 (1987).]

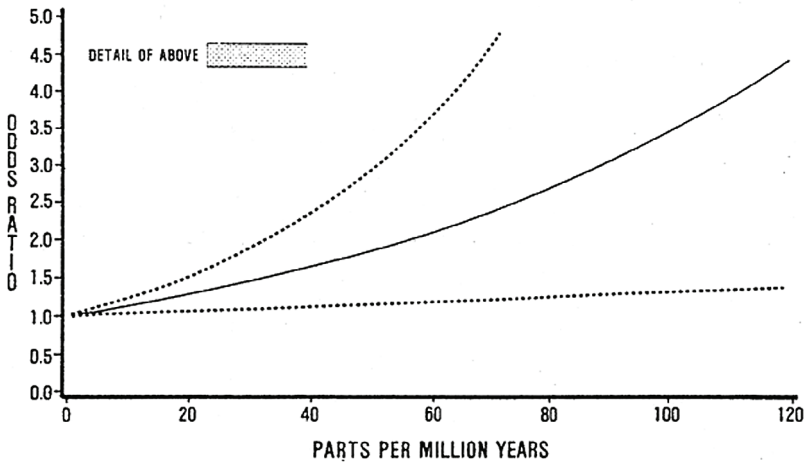


Figure 19.4.3. Extrapolations of levels of exposure to benzene. [Adapted, by permission, from R.A. Rinsky, *New England J. Med.*, **316**, 1044-1050 (1987).]

The Agency for Toxic Substances Disease Registry (ATSDR) has derived an Acute Inhalation Minimal Risk Level (MRL) of 0.05 ppm for benzene based on a Lowest Observed Adverse Effect Level (LOAEL) for immunological effects in mice.[71] The ATSDR has derived an Intermediate Inhalation MRL of 0.004 ppm for benzene based on a LOAEL for neurological effects in mice.[72]

The American Conference of Governmental Industrial Hygienists (ACGIH) has adopted a Threshold Limit Value (TLV) of 0.5 ppm (8 hour time-weighted average) and a

Short Term Exposure Limit (STEL) of 2.5 ppm (15 minute time-weighted average). These are recommendations for breathing zone concentrations, which should not be exceeded in the workplace. As recommendations for industry, they do not have the force or effect of law.[73]

The California Environmental Protection Agency (Cal/EPA) has adopted a No Significant Risk Level (NSRL) of benzene of 13 µg/day by inhalation. This represents the maximum amount of benzene that the State of California has determined a person may be exposed daily that poses no significant risk of cancer.[74]

The Collegium Ramazzini has recommended a Threshold Limit Value (TLV) for benzene of 0.1 ppm.[75] However, recently, the Collegium Ramazzini issued a Statement calling for reduction of benzene exposure to the lowest level possible.[76]

The World Health Organization (WHO) has concluded that "no safe level of exposure can be recommended."[77]

Even the American Petroleum Institute (API) recognizes that there is no safe level of exposure to benzene.[19] As early as 1948, the API published a Toxicological Review on Benzene, which acknowledged that "as much as the body develops no tolerance to benzene, and as there is a wide variation in individual susceptibility, it is generally considered that the only absolutely safe concentration for benzene is zero."

19.4.7 CELL TYPES: HEMATOLYMPHOPROLIFERATIVE EFFECTS OF BENZENE

The hematopoietic cell type toxicity from benzene has been described in animal data, case reports, case studies, animal data, and epidemiological data. Essentially, Wong in his OSHA testimony[78] concludes that for the continuously exposed group, the lymphohematopoietic cancer risk ratio was 3.2 with a statistical significance of $p < 0.05$ and the risk ratio for non-Hodgkin's and other lymphopoietic cancer, i.e. all lymphopoietic cancers minus Hodgkin's disease, for the continuously exposed group was 3.77. The data demonstrated a statistical significant dose-response relationship between cumulative exposure to benzene and mortality from all lymphopoietic cancer combined with leukemia. Wong further stated that it would be appropriate to combine lymphoma and leukemia in some of the analyses. This approach has also been recommended recently by other investigators,[79] and therefore the agency conducting the hearing felt that the analysis based on the revised grouping of lymphopoietic cancers with Hodgkin's disease separated out was appropriate.[78] In the documents submitted to the OSHA hearing, Wong concluded that a dose-response relationship for all lymphatic and hematopoietic cancers has been demonstrated.

Based on the case reports, case studies, and epidemiological studies, the sub-classification to cell types is indicated from a medical point of view to treat various hematopoietic diseases and cancers with the various appropriate treatments per each type of cell injured; however, the data from the experimental data and clinical analysis of benzene cases clearly show that benzene causes damage to the stem cell and therefore it is a pluripotent toxin, causing a wide range of lymphohematopoietic malignancies.

19.4.7.1 Classification of leukemia

There are four major types of leukemia, categorized by cell lineage (myeloid or lymphoid) and presentation (acute or chronic). The four major types of leukemia are acute myeloid

leukemia (AML), acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML), and chronic lymphocytic leukemia (CLL).

AML has been classified according to the French-American-British (FAB) classification, by the degree of differentiation and the extent of cell maturation.[80] There are eight subtypes of AML:

- Acute Myeloblastic Leukemia with Minimal Differentiation
- Acute Myeloblastic Leukemia without Maturation
- Acute Myeloblastic Leukemia with Granulocytic Maturation
- Acute Promyelocytic Leukemia
- Acute Myelomonocytic Leukemia
- Acute Monocytic Leukemia
- Acute Erythroid Leukemia
- Acute Megakaryoblastic Leukemia

Most experts agree that all eight subtypes of AML can be caused by benzene. Recent epidemiologic study[81] evaluating the subtypes of AML supports the causation nexus between benzene, AML and AML subtypes.

19.4.7.2 Classification of lymphoma

Lymphoma is a group of blood malignancies, the source of which is lymphocytes. Various classification systems have been devised for categorizing the different human blood cells and malignancies developing in them. Historically, leukemias have been classified according to four major types, based upon cell of origin and manifestation of disease: acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphocytic leukemia (ALL) and chronic lymphocytic leukemia (CLL). Historically, lymphomas have been classified according to two basic types: Hodgkin's lymphoma and non-Hodgkin's lymphoma. Hodgkin's lymphoma (also known as Hodgkin's disease) is a common type of lymphoma that was first described by Thomas Hodgkin in 1832 and is characterized by pathognomonic giant cells, which were first identified by Reed and Sternberg (so-called “Reed-Sternberg” cells). All other malignancies manifesting in lymphatic tissue have, by default, been classified as non-Hodgkin's lymphomas. A subtype of non-Hodgkin's lymphoma has been recognized for those malignancies manifesting at extramedullary sites in plasma cells – the disease commonly called multiple myeloma.[82]

The WHO published a classification of lymphomas. Essentially there are five groups that have been described.[83]

1. Mature B cell neoplasms
2. Mature T cell and natural killer (NK) cell neoplasms
3. Precursor lymphoid neoplasms
4. Hodgkin lymphoma
5. Immunodeficiency-associated lymphoproliferative disorders

19.4.8 EPIDEMIOLOGICAL STUDIES

Wong[54] studied a cohort of 7,676 male chemical workers from seven plants who were occupationally exposed continuously or intermittently to benzene for at least 6 months, and compared them to a group of male chemical workers from the same plant who had been employed for at least 6 months during the same period but were never occupationally

exposed to benzene. When the group with no occupational exposure was used for direct comparison, the continuously exposed group experienced a relative risk from lymphohematopoietic cancer of 3.2 with a statistical significance of $p < 0.05$. That paper further concluded that the medical problems are replete with reports documenting the transition from certain lymphomas and multiple myelomas to leukemias. It was concluded that the transitions or progressions from lymphoma to leukemia are further complicated by the historical changes in nomenclature and in diagnostic overlap between the 2 disorders. It was felt, based on the work of others, that the major clone in chronic myelocytic leukemia affected cells capable of becoming lymphocyte, granulocyte, and erythrocyte differentiations, leading to the conclusion that transformation events occur at an early multipotent stem cell level.

Nilsson *et al.*[49] investigated Swedish seamen, 20-64 years of age, who had been exposed to cargo vapors for at least 1 month on chemical or product tankers, had an increased risk of lymphatic and hematopoietic malignancies (odds ratio (OR) of 2.6 with 95% confidence interval (CI) of 1.1 to 5.9), with a significant exposure-response relation. The odds ratio was significantly increased for non-Hodgkin's lymphoma (OR =3.3 with 95% CI = 1.1 – 10.6).

Rinsky *et al.*[28] studied a cohort of 11,065 white men with at least 1 ppm per day of cumulative exposure to benzene. The investigators demonstrated a statistical significant increase in death from all lymphatic and hematopoietic neoplasms: 15 observed deaths versus 6.6 expected deaths with a standard mortality ratio of 227 (95% CI = 127 – 376) further providing evidence that benzene is toxic to all cell types.

Hayes *et al.*[53] studied a cohort of 74,821 benzene exposed and 35,805 unexposed workers from 1972 until 1987 in 12 cities in China. This is the largest and most significant cohort of benzene workers studied and published. The investigators found that: 1) benzene exposure is associated with a spectrum of hematological neoplasms; 2) workers with 10 or more years of benzene exposure had a risk ratio of developing non-Hodgkin's lymphoma of 4.2 (95% CI = 1.1 – 15.9), and the development of this neoplasm was linked most strongly to exposure that had occurred at least 10 years before the diagnosis; and 3) the risk for the combination of acute non-lymphocytic leukemia and related myelodysplastic syndromes was significantly increased among those with more recent benzene exposure. These studies confirm the previous studies proving that the damage from benzene is to all cell types.

Linet *et al.*[51] studied hematopoietic malignancies and related disorders among benzene-exposed workers in China and showed a wide range of hematopoietic malignancies.

Yin *et al.*[52] examined a large cohort of benzene workers and concluded that benzene-exposed workers have a statistically significant excess death due to leukemia, with a risk ratio of 2.3 (95% CI = 1.5 – 5.0); malignant lymphoma, with a risk ratio of 4.5 (95% CI = 1.3 – 28.4).

Goldstein observed that because benzene is a known cause of human leukemia, there has been little reason for organizations such as IARC or the National Toxicology Program to perform standard hazard identification of benzene as a cause of other cancers such as lymphocytic neoplasms.[84] Goldstein applied the standard weight of evidence approaches

used by these organizations to assess whether an environmental chemical causes human diseases. It clearly shows that there is sufficient evidence to identify benzene as a cause of human lymphocytic tumors. He noted that lymphomas were long ago reported in laboratory animals subjected to long-term benzene exposure. Goldstein concluded that the epidemiological studies by themselves reached the level of evidence required to be seen as sufficient. He further noted that even if one were to discount the strength of the epidemiological evidence, there was sufficient mechanistic evidence to judge that benzene should be considered to be a cause of human lymphoproliferative neoplasms. Goldstein pointed out two reasons for this conclusion. First, the criteria for assigning overall sufficiency of evidence for carcinogenicity have changed to allow greater scope for mechanistic evidence. IARC permits classification in Group I when there is less than sufficient evidence in humans but sufficient evidence in animals and "strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity." The presence in the lymphocytes of benzene-exposed workers of chromosomal abnormalities has been well documented, as has the role of chromosomal effects in carcinogenesis. Second, modern molecular biological approaches have demonstrated that the morphological distinctions that are made among hematological disease often have little to do with basic issues of causality. The early hematopoietic stem cell, which can be a target of benzene in causing myeloid cancers, can also become a lymphocytic cell line. Furthermore, the classification of lymphomas has evolved so that non-Hodgkin's lymphoma now includes such formerly distinct disorders as chronic lymphocytic leukemia and multiple myeloma. Goldstein therefore concluded that, "Based upon the evidence in humans supporting a biologically plausible mechanism of carcinogenesis, on the current understanding of the effects of benzene on early bone marrow stem cells, on the further recognition of the molecular biology of lymphomas, on the insights provided by the evolving classification of human lymphomas, and on the existing epidemiological data, benzene should be considered a cause of human lymphoproliferative disorders."

In summary, these epidemiological studies published in the peer-reviewed scientific literature and relied on by scientific and governmental agencies clearly show that: 1) significant statistical association between benzene exposure and lymphohematopoietic cancers of all cell types; 2) an increased risk and/or increased standard mortality rate over a factor of 2 in patients exposed to benzene with the development of non-Hodgkin's lymphoma, leukemias, and other lymphohematopoietic malignancies; and 3) benzene is carcinogenic with a linear dose-response demonstrating no threshold.

19.4.9 SOLVENTS AND BENZENE

Solvents commonly used in the industry have been shown to contain benzene. Elkins *et al.*[85] found that from time to time analyzed solvents for benzene content showed anywhere from 1% to 2% benzene. In that paper, which was published in 1956, the authors stated that the threshold limit value (TLV) from a regulatory point of view, at that time, was 35 ppm compared with 100 ppm previously. According to their calculations, they found that a benzene content below 3.5% will be necessary, for instance in solvents containing naphtha, hexane, and toluene, otherwise the permissible level for benzene vapor will be exceeded over 35 ppm, which we now know is extremely and significantly higher than the

standard allowed today from a regulatory point of view. At the request of the petrochemical companies, the authors decided to reevaluate the content of benzene in solvents and for this purpose a total of 8 samples of low boiling petroleum naphtha were obtained. After utilizing methodology which included, among others, mass spectrometry for benzene content, the authors concluded that, in general, the benzene content of solvents ranged from 1% to 4% in volume. They have further shown that in the air of one plant where hexane with a relatively low benzene content (1.5%) was used as a solvent in a fabric-spreading operation, a benzene vapor concentration of 1 ppm was found. Since exposure to benzene is cumulative, if a worker is exposed to hexane containing 1.5% benzene, with both inhalation and skin contact, the cumulative exposure over a certain period of time increases the risk of developing benzene-related cancers as described by the Rinsky model. The study by Pagnotto[86] looked at and analyzed 32 naphtha solvents. The benzene concentration ranged from 1.5% to 9.3% by weight. Excessive benzene exposure was found at 3 out of 4 plants during their operations on a daily basis. On one occasion, the concentration of benzene vapor was as high as 125 ppm (extremely high), and the urinary phenol excretion of the workers in these 3 plants were the highest that these investigators reported, ranging from 370 to 917 mg per liter of urine. These studies indicate that solvents that contain benzene, even at levels of 1.5% per volume, can be associated with significant atmospheric exposure to benzene, shown as causing human exposure with significant excretion of phenol in the urine, indicative of heavy benzene exposure. The investigators recommended additional ventilation, and on a follow-up visit the benzene exposure was found to have been reduced to about 70 ppm with urinary phenols of less than 70 mg/L, still significantly elevated and considered a significant risk. These investigators also looked at blood examinations of 47 men at these plants. Five employees showed lower hemoglobin. One man showed a low hemoglobin at the age of 28, having been employed for 3 years in the environment preparing mixes for the saturating machine. While leukemia was suspected due to bone marrow disease, the patient was treated with iron and recovered. The authors conclude that excessive benzene exposures are consistently found on saturators using naphtha containing more than 3% benzene. This study further shows the importance of assessing benzene concentration is other solvents, from a dosimetry point of view.

NIOSH[87] recommended standards to be applied to occupational exposure of workers to the following refinery petroleum solvents: petroleum ether, rubber solvent, varnish maker's and painter's naphtha, mineral spirits, Stoddard solvents, and kerosene are all included in the term refined petroleum solvents. According to these standards: petroleum ether, rubber solvents would contain 1.5% benzene, varnish maker's and painter's naphtha would contain 1.5% benzene, mineral spirits would contain 13-19% aromatics, Stoddard solvents would contain 0.1% benzene, and 140 Flash Aliphatic Solvent would contain 0.7% benzene. NIOSH indicated that some of the refined petroleum solvents contain aromatic hydrocarbons including, in some cases, benzene. Standards were applied to reduce the benzene exposure. Among others, the use of respirators and skin protective devices were required to protect from the effects of the solvents, as well as the benzene component.[87] In his testimony in front of the Occupational Safety and Health Administration, Proctor testified that, among others, refining operations are continuously changing.[88]

Many refineries obtain crude of differing characteristics from various producing areas which sometimes must be processed individually due to crude incompatibility and produce requirements. This means the operation of a crude fractionating unit is altered frequently; a single crude run may be as short as two days. Consequently, the crude tankage, crude fractionation units, and all downstream processing units frequently contain benzene. Proctor further stated that it should be clear by now that benzene is a naturally occurring compound in crude oil and is also found in the catalytic and cracking process, and therefore will always be a contaminant of these solvents. Benzene levels in gasoline today are about 1.1% on average across the nation, but some individual samples may reach 4%. Reduction of benzene levels in gasoline is technically possible through employment of a number of physical processing schemes to the various gasoline component streams. He further testified that any attempt of physical separation of hydrocarbons, such as distillation, solvent extraction, or adsorption, the separation will not be 100% complete; some residuals of benzene will always be present in the remaining fraction. Therefore, he recommended that benzene should be converted to cyclohexane by hydrogenation, which would require an expensive catalyst, expensive high pressure reaction vessels, and consumption of valuable hydrogen. The testimony further indicates that it is almost physically impossible to reduce these streams below 0.1% benzene. The 1978, OSHA indicated that "The record establishes that there is a wide variation in the benzene content of petroleum solvents used in the rubber, paints, coatings, adhesives, sealants, and other downstream industries.[87] As reported by Smith, reporting on behalf of MCA,[89] the benzene content of petroleum solvents of all types generally range from under 0.1% to 4%. Data submitted by downstream industries confirms that benzene is present in virtually all petroleum solvents, at levels which approach and even exceed 3.5% in some cases." It was stated that in the rubber industry, solvent benzene content appears to range from 0.1% to 0.7%, or slightly higher. Similarly, solvents used by adhesive manufacturers show broad variations from less than 0.1% to 3.5%.[87] Representatives of the paint industry report variations from under 0.1% to as high as 3.7%.[85] Smith in his testimony emphasized that solvent benzene content is likely to vary substantially among supplies, among different plants of the same supplier, and among deliveries from the same plant. Because refinery processes are not designed to precisely control benzene content, variations will inevitably occur. Solvents used to degrease parts contain high to very high concentration of benzene, as has been demonstrated by several investigators in peer reviewed journals.[90-92]

Kopstein[93] analyzed benzene levels in industrial solvents in preparation of the IARC working group meeting in 2017. Kopstein concluded, among others, that benzene levels in solvents is in certain industries elevated and recommended prudence in reference to industry evaluation of occupational benzene exposure.

These data clearly show that benzene contents in solvents are difficult to control and vary depending on the sources, processes and therefore solvent exposure must take into account the level of benzene concentration in these solvents.

One must remember the importance of benzene exposure through the use of solvents produced through the petrochemical refining processes.

**Disclosure: Some of the materials in this chapter have been added from court declarations of Dr. Brautbar.*

REFERENCES

1 National Institute of Occupational Safety and Health (NIOSH), Occupational safety and health guideline for benzene. Potential human carcinogen. Cincinnati, OH, *DHEW Publications*, (1988).
2 Agency for Toxic Substances and Disease Registry (ATSDR), Toxicological profile for benzene, U.S. Department of Health & Human Services, Atlanta, Georgia (2007).
3 Fishbein L, *Scan J Work Environ Health*, **8 Supp 1**, 5-16 (1992).
4 Benzene Global Market to 2020 - Driven by the Styrene Monomer Market, Asian Consumption Will Continue to Dominate. *GBI Research*, 2011.
5 U.S. benzene production rises 19% in 2010. *ICIS News*, February 2011.
6 World Benzene Market. *Reportlinker*, 2009.
7 Browning E, Toxicity and Metabolism of Industrial Solvents, Amsterdam, *Elsevier Publishing*, Chapter 1 (1965).
8 Wallace LA, *Environ Health Perspect*, **82**, 165-169 (1999).
9 Brenner D, *et al*., *Eur J Oncol*, **3**, 399-405 (1998).
10 Henderson RF, *et al*., *Environ Health Perspect*, **82**, 9-17 (1989).
11 Snyder CA, *et al.*, *Toxicol Appl Pharmacol,* **54**, 323-331 (1980).
12 Snyder R, *et al., Environ Health Perspect*, **8**, 31-35 (1989).
13 Goldstein BD, *Adv Mod Environ Toxicol*, **4**, 51-61 (1983).
14 Santesson CG, *Archiv fur Hygiene*, **31**, 336-349 (1897).
15 Delore P and Borgomano C, *J Med Lyon*, **9**, 227-233 (1928).
16 Lignac GOE, *Krankeitsforsch*, **9**, 426-453 (1932).
17 Vigliani EC, and Saita G, *N Engl J Med*, **271**, 872-876 (1974).
18 Aksoy M, Erdem S, and Dincol G, *Blood*, **44**, 837-841 (1974).
19 America Petroleum Institute (API), Toxicological Review on Benzene, September, (1948).
20 Maltoni C, Myths and Facts in the History of Benzene Carcinogenicity: in Advances in Modern Environmental Toxicology, Volume IV, M. Mehlman (Ed). *Princeton Scientific Publishing Company*, Princeton, 1-15 (1983).
21 National Institute of Occupational Safety and Health (NIOSH), Criteria for a Recommended Standard. Occupational Exposure to Benzene. *U.S. Department of Health, Education and Welfare, Public Health Service, Center for Disease Control*, Cincinnati, OH, Pub. No.74-137 (1974).
22 Aksoy M, *Environ Res*, **23**, 181-190, (1980).
23 Aksoy M, *Environ Health Perspect*, **82**, 1931-198 (1989).
24 U.S. Environmental Protection Agency (EPA), Ambient Water Quality Criteria for Benzene, Environmental Criteria and Assessment Office, Cincinnati, OH, EPA 440/5-80-018, NTIS PB81-117293 (1980).
25 Goldstein BD and Snyder CA, *Environ Sci Res*, **25**, 277-289 (1982).
26 International Agency for Research on Cancer (IARC). Volume 100, Review of Human Carcinogens, IARC, Lyon, France, (2012).
27 Aksoy M, *et al., Br J Ind Med*, **44**, 785-787 (1987).
28 Rinksy RA, *et al., N Engl J Med*, **316**, 1044-1050 (1987).
29 Goldstein BD, Benzene Toxicity, In: Occupational Medicine: State of the Art Reviews, 3(3), 541-554, NK Weaver (ed), *Hanley and Belfus, Inc*., Philadelphia PA (1988).
30 Paci E, *et al., Scand J Work Environ Health*, **15**, 313-318 (1989).
31 Rinksy RA, *Environ Health Perspect*, **82**, 189-192 (1989).
32 Ciranni R, Barale R, and Adler ID, *Mutagenesis*, **6**, 417-421 (1991).
33 Cox LA, *Risk Anal*, **11**, 453-464 (1991).
34 Ruis MA, Vassallo J, and Desouza CA, *J Occup Med*, **33**, 83 (1991).
35 Midzenski MA, *et al., Am J Ind Med*, **22**, 553-565 (1992).
36 Medinsky MA, Schlosser PM and Bond JA, Environ Health Perspect, **102 Suppl 9**, 119-124 (1994).
37 Travis LB, *et al, Leuk Lymphoma*, **14**, 92-102 (1994).
38 Niculescu R and Kalf GF, *Arch Toxicol,* **69**, 141-148 (1995).
39 Wintrobe MM, Lee GR and Boggs DR, Wintrobe's Clinical Hematology, 554, *Lea and Febiger*, Philadelphia, PA (1981).
40 Schottenfeld D and Fraaumeni JF Jr, Cancer: Epidemiology and Prevention. Saunders, Philadelphia, PA

(1982).
41 Zoloth SR, *et al., J Natl Cancer Inst*, **76**, 1047-1051 (1986).
42 Mehlman MA (ed.) Advanced in Modern Environmental Toxicology, Volume IV, *Princeton Scientific Publishing Company*, Princeton, NJ (1983).
43 U.S. Environmental Protection Agency (EPA), Carcinogenic Effects of Benzene: An Update. *National Center for Environmental Assessment-Washington Office. Office of Research and Development*. EPA/600/P-97/001F (1998).
44 International Agency for Research on Cancer (IARC), Benzene, *IARC Monogr Eval Carcinog Risks Hum*, 100F (2012).
45 National Institute for Occupational Safety and Health (NIOSH). NIOSH Pocket Guide to Chemical Hazards. (2005).
46 National Toxicology Program (NTP), Benzene, *Rep Carcinog*, 14, 1-3 (2016).
47 U.S. Department of Labor. Occupational Safety and Health Administration (OSHA). Chemical Sampling Information: Benzene. (2005).
48 Mehlman MA, *Am J Ind Med*, **20**, 707-711 (1991).
49 Nilsson RI, *et al., Occup Environ Med*, **55**, 517-521 (1998).
50 Wong O, *Br J Ind Med*, **44**, 382-395 (1987).
51 Linet MS, *et al., Environ Health Perspect*, 104 Suppl 6, 1353-1364 (1996).
52 Yin SN, *et al., Am J Ind Med*, **29**, 227-235 (1996).
53 Hayes RB, *et al., J Natl Cancer Inst*, **89**, 1065-1071 (1997).
54 Wong O, *Br J Ind Med*, **44**, 365-381 (1987).
55 Huff JE, *et al., Environ Health Perspect,* **82**, 125-163 (1989).
56 Lewis JG, Odom B and Adams DO, *Toxicol Appl Pharmacol,* **92**, 246-254 (1988).
57 Thomas DJ, Reasor MJ and Wierda D, *Toxicol Appl Pharmacol*, **97**, 440-453 (1989).
58 Kalf GF, *Crit Rev Toxicol,* **18**, 141-159 (1987).
59 Smith MT, *et al., Environ Health Perspect*, **82**, 23-29 (1989).
60 Gist GL and Burg JR, *Toxicol and Health*, **13**, 661-714 (1997).
61 Reid LL, *et al., Drug Chem Toxicol*, **17**, 1-14 (1994).
62 Winternitz MC and Hirschfelder AD, *J Exp Med*, **17**, 657-664 (1913).
63 Rinsky RA, *et al., Am J Ind Med*, **2**, 217-45 (1981).
64 Ott MG, *et al., Arch Environ Health*, **33**, 3-10 (1978).
65 Infante PF, *et al., Lancet*, **2**, 76-78, (1977).
66 Vigliani EC and Saita G, *N Engl J Med*, **271**, 872-876 (1964).
67 Infante PF, *Appl Occup Environ Hygiene*, **7**, 253-262 (1992).
68 Fishbein L and AJ McMichael, *IARC Sci Publ*, **85**, 3-8 (1988).
69 U.S. Environmental Protection Agency (EPA). Integrated Risk Information System (IRIS). Attachment to IRIS file for Benzene, October 14, 1998. Response to The Peer-Review. Draft Carcinogenic Effects of Benzene: An Update (1998).
70 National Institute for Occupational Safety and Health (NIOSH). NIOSH recommendations for occupational safety and health. Compendium of Policy Documents and Statements. DHHS (NIOSH) Publication No. 92-100 (1992).
71 Rozen MG, Snyder CA and RE Albert RE, *Toxicol Lett*, **20**, 343-349 (1984).
72 Li L, *et al., Biomed Environ Sci*, **5**, 349-354 (1992).
73 American Conference of Governmental Industrial Hygienists (ACGIH), 2004 TLVs and BEIs: Based on the documentation of the threshold limit values for chemicals and physical agents & biological exposure indices, Cincinnati, OH (2004).
74 California Environmental Protection Agency (Cal/EPA), 22 California Code of Regulations, 12701.
75 Collegium Ramazzini. American Conference of Governmental Industrial Hygienists, Threshold Limit Value Committee. (Call for a reduction of exposure to benzene to the lowest possible level) (1993).
76 Collegium Ramazzini. 8th Collegium Ramazzini Statement. Call for a Reduction of Exposure to Benzene to the Lowest Possible Level (2004).
77 World Health Organization (WHO), Regional Office for Europe. Air Quality Guidelines - Second Edition. Chapter 5.2 Benzene. Air Quality Guidelines - Second Edition. *WHO Regional Office for Europe*, Copenhagen, Denmark (2000).
78 Statement Submitted to the OSHA Benzene Hearing by Otto Wong, ScD., FACE., Environmental Health Associates, Inc., 3/4/1986.
79 Decoufle P, Blattner WA and Blair A, *Environ Res*, **30**, 16-25 (1983).
80 Bennett JM, Catovsky D, Daniel MT, *Br. J. Haematol*, **33**, 451-458 (1976).

81 Wong O, *et al., Chem. Biol. Interact*, **184**, 112-128 (2010).
82 National Cancer Institute (NCI). Adult Non-Hodgkin Lymphoma Treatment (PDQ). Bethesda, MD (2018).
83 Swerdlow SH, *et al., Blood*, **127**, 2375-2390 (2016).
84 Goldstein BD, *Chem Biol Interact*, **184**, 147-150 (2010).
85 Elkins HB, and Pagnotto LD, *Arch Ind Health*, **13**, 51-54 (1956).
86 Pagnotto LD, *et al., Ind Hyg J,* 417-421 (December 1961).
87 National Institute for Occupational Safety and Health (NIOSH). A Recommended Standard for Occupational Exposure to Refined Petroleum Solvents from the U.S. Department of Health, Education and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health (July 1977).
88 Testimony of RS Proctor in regards to Proposed Revised Permanent Standard for Occupational Exposure to Benzene, OSHA Docket No. H-059A, (July 11, 1977).
89 Post-Hearing Comments and Records Designations in OSHA Docket H-059 In re: Proposed Amendment to the Permanent Standard for Occupational Exposure to Benzene (June 12, 1978).
90 Mehlman MA, *Eur J Oncol*, **9**, 15-36 (2004).
91 Fedoruk MJ, Bronstein R and BD Kerger, *Appl Occup Environ Hyg*, **18**, 764-771 (2003).
92 Kopstein M, *J Occup Environ Hyg*, **3**, 1-8 (2006).
93 Kopstein M, *New Solut*, **28**, 10-23 (2018).

19.5 GENOTOXICITY OF BENZENE

Nachman Brautbar[+]*, Michael P. Wu*, Alexandra E. Rieders*
[+]University of Southern California, School of Medicine,
Department of Medicine, Clinical Professor Emeritus of Medicine
*Nachman Brautbar, M.D., Inc., Los Angeles, CA, USA

Benzene and its metabolites have long been known to cause chromosomal aberrations of various types of cell cultures of exposed humans. While it is true that genetic changes have been described and that these frequently affect chromosomes 5 and 7, along with others, there is no scientific evidence that these are required for the diagnosis of benzene exposure-related cancers. Specifically, many cases of patients who have been exposed to benzene and have developed hematopoietic malignancies do not have changes in chromosomes, and therefore the chromosomal changes cannot be used as a "genetic fingerprint." Indeed, Irons[1] concluded that the significance of these chromosomal alterations with respect to bone marrow damage or leukemogenesis of benzene is unclear. It is not possible today to determine whether leukemia is caused by benzene based on changes in chromosomes, specifically chromosomes 5 and 7. Smith,[2] a leading authority in the biological markers of benzene exposure, opined that the data, which supposedly suggest that one must have changes in chromosomes 5 and 7 to assume benzene causation, is unreliable and obsolete. As such, while it is true benzene and related products have been described in association with changes in chromosomes, DNA adducts and cell cycle, by no means can these genetic markers be used as a diagnostic tool to address benzene causation.

Several technologies have been developed in the last 10 years to look at chromosomal changes and DNA changes caused by environmental exposures, as well as to serve as markers of environmental exposures. The use of chromosomal translocation as a biological marker of exposure in humans has become an important tool in the research. Several methodologies have utilized and include structural chromosomal aberrations, sister chromatid exchanges (SCEs) and micronuclear changes. These are markers of changes in the cellular genetic materials, and represent damage induced by chemicals. These methodologies are viewed as cytogenetic assays, and by themselves cannot provide a diagnosis, but they complement other methodologies, including gene mutation analysis and DNA changes. Among the important uses of cytogenetics as a biomarker is the relationship between chromosomal aberrations secondary to chemicals and carcinogenesis. Since the scope of this chapter is not addressing mechanisms of carcinogenesis, the reader is referred to other sources.[3]

Studies in patients with acute non-lymphocytic leukemia whose bone marrow analyzed for chromosomal changes have shown that 50% of them had changes in chromosomes 5, 7, 8 and 21.[4] Mitelman *et al*.[5] have looked at patients with acute non-lymphocytic leukemia and looked at the occupational history. They studied a group of 56 patients. Twenty-three out of the 56 patients had a history of exposure to chemical solvents, insecticides, and petroleum products. It was further shown that in males with acute non-lymphocytic leukemia, the frequency of exposure to petroleum products was as high as 36%. A striking difference was observed between the chromosomal findings in non-

exposed versus exposed groups. In the non-exposed group, only 24.2% of the patients had chromosomal aberrations in their bone marrow cells, while 82.6% of the exposed patients had chromosomal aberrations. The authors concluded based on these studies, the difference between the exposed and non-exposed group strongly indicates that the karyotypic pattern of the leukemic cells were, in fact, influenced by the exposure. The authors further suggested that the prognosis in those patients with normal chromosomes was significantly better than those with abnormal chromosomes, something which has been suggested by previous investigators.[6-8] Based on their observations along with others,[9-13] the authors suggested that certain chromosomal regions are possibly vulnerable to the chromosome-damaging actions of different chemical carcinogens. Indeed, the changes of chromosomes 5, 7, 8 and 21 in workers exposed to different chemical solvents, among them also petrol and pesticides, supports this hypothesis.

Studies in cultured lymphocytes from 73 workers in chemical laboratories and the printing industry were found to have a significantly increased frequency of chromatid and sister chromatid breaks in comparison to 49 control subjects.[14] Funes-Cravioto *et al.* suggested that the observed cytogenetic changes are reasonably assumed to be the result of strong factors in the working environment, which induced chromosome breaks and sister chromatid exchange. The considerable variation in cytogenetic changes between subjects suggested varying degrees of exposure to mutagenic agents.

Brandt *et al.*[15] studied the effects of exposure to organic solvents and chromosomal aberrations. Ten patients had a history of daily handling of organic solvents for at least one year preceding the diagnoses of non-Hodgkin's lymphoma. All have been exposed to a variety of solvents to include aromatic and aliphatic compounds. Forty-four patients for only a shorter period of time worked with organic solvents, and therefore served as the control group. There was a statistically significant increase in chromosomal changes in the exposed group compared to the non-exposed group. Based on their results, the authors suggested non-Hodgkin's lymphoma patients with a history of significant occupational exposure to organic solvents tend to have a larger number of chromosomal aberrations in the lymphoma cells. Furthermore, certain aberrations may be characteristic for the exposed patients. It was concluded that the overrepresentation of certain chromosome aberrations in non-Hodgkin's lymphoma patients occupationally exposed to organic solvents supports the concept that these exposures may be relevant for the subsequent development of non-Hodgkin's lymphoma. Their data are in agreement with the studies published previously, indicating that workers handling organic solvents and other petroleum products have an increased frequency of chromosomal aberrations in lymphocytes.[14,16-18] Indeed, the association between exposure to solvents and other chromosomal changes in the cells have been studied by other investigators, describing chromosomal changes in acute non-lymphocytic leukemia.[5,19-21]

In cultured cells, Koizumi *et al*.[22] examined the effects of benzene on DNA syntheses in chromosomes of cultured human lymphocytes. These investigators showed increased incidents of chromatid gaps and breaks in cultures treated with benzene, compared to those who were untreated with benzene. They also showed changes in DNA metabolism in the form of inhibition of syntheses in those samples that were treated with

benzene. This observation was confirmed by other investigators[23] who have also demonstrated increased chromosomal aberrations in cultured human leukocytes exposed to benzene.

In *in vivo* and *in vitro* experimental animal studies, rats treated with benzene have been found to have increased chromosomal changes taken from the bone marrow as compared to the non-treated animals.[24] It is of interest that the degree of chromosomal changes induced by benzene were similar to that induced by toluene[25] (probably secondary to the benzene in toluene). Experimental rabbits treated with benzene have also shown a significant amount of bone marrow chromosomal changes persisting up to 60 days after the end dosing with benzene.[26]

Pollini *et al*.[27] reported on a patient who has developed aplastic anemia after exposure to benzene. The patient was shown to have significant chromatid fragments.

Forni *et al*.[28] carried out a cytogenetic study on a patient who developed leukemia after 22 years of continuous exposure to a high concentration of benzene and showed that later in the process there were changes in 47 chromosomes in the bone marrow.

Sellyei *et al*.[29] studied patients who developed pancytopenia after having been exposed for 18 months to benzene. Significant chromosomal changes were detected even 7 years after remission from the anemia and the presentation of leukemia.

In line with these changes, Forni *et al*.[30] studied 25 subjects with a history of hematopoietic abnormalities and benzene exposure, and compared these to 25 matched controls. These investigators reported increased chromosomal aberrations in the exposed group as compared to the control group 18 years after clinical and hematological symptoms.

Tough *et al*.[31] studied chromosomes of workers exposed to benzene for periods varying from 1 to 18 years. They demonstrated a small but significant increase in chromosomal changes compared to a control group. The same investigators looked at workers exposed to benzene levels from 25 to 120 ppm, and found that they had significant chromosomal aberrations as compared to the normal population (which has a general background exposure to benzene levels).

The study of Forni *et al*.[16] showed significant chromosomal aberrations in those patients who were exposed mainly to benzene, and not to those who were exposed to toluene only.

Hartwich *et al*.[32] looked at 9 healthy refinery workers who were exposed to low levels of benzene, and also found significantly increased chromosomal changes compared to the control group.

The National Research Council Advisory Center and Toxicology Study[33] concluded that close correlation between occupational exposure to benzene and persistence of chromosomal aberrations can be discussed only when there is an association between benzene induced hematopoietic disease and chromosomal aberrations; however, the absence of chromosomal changes cannot be a determinant in the temporal relationship between exposure to benzene and hematopoietic diseases.

While some studies suggested that the chromosomal changes require heavy exposure to benzene, the study by Picciano[34] looked at chromosomal changes in 52 workers exposed to a mean benzene concentration of less than 10 ppm compared to non-exposed

controls. A significant increase in chromosomal aberrations was observed with exposure to benzene concentrations as low as less than 10 ppm. Furthermore, these same investigators[35] reported a dose-response increase in the aberrations when the exposed workers were divided into smaller groups by the exposure levels (less than 1 ppm, 1-2.5 ppm, and 2.5-10 ppm).

Fredga *et al.*[17] examined the chromosomal changes in drivers of petrol tankers and crew members of gasoline tankers, ships and petrol station attendants. The degree of exposure to benzene of the three groups was estimated to be at a mean of 0.4 ppm, and the crew members were estimated to be at 6.56 ppm while engaging in handling of gasoline. The frequency of chromosomal and chromatid aberrations in the petrol tanker drivers was significantly greater than in those of petrol attendants and the crew members. The effects of long-term benzene exposure from the incidents of chromosomal changes were studied in 16 female workers who were exposed to a maximum of 40 ppm benzene between 1-20 years.[36] The cytogenetic study was conducted 6 months after benzene was eliminated from the work environment, and they found no significant increase in chromosomal changes.

Clare *et al*.[37] investigated chromosomal changes in the peripheral lymphocytes of workers after a single shift following a large spillage of benzene. Exposure levels were described as high after a spillage of a large amount of benzene during the loading of a ship. Three months after the incident, chromosomal analysis showed no significant abnormalities. The authors concluded that there was no evidence of lasting chromosomal damage in the peripheral blood lymphocytes of these exposed workers.

Golomb *et al*.[20] reviewed the literature and reported the results in regards to exposure to benzene and chromosomal changes. They studied exposure data on 74 patients with acute leukemia. It was described that 75% of the exposed patients had an abnormal karyotype, whereas only 43% of the patients characterized as non-exposed had an abnormal karyotype. While it is true that these findings are in agreement with previous studies,[20] they still could not explain the 43% of the patients who were not exposed and still had abnormal chromosomal changes. This is a very important observation, since some investigators in the field claimed that the "absence of chromosomal changes" in benzene exposed individuals negates the clinical causative diagnosis of benzene-induced hematopoietic disease. Essentially, all of the above studies show benzene can cause chromosomal changes, but that it may not be observed in all patients. The absence of chromosomal changes cannot and does not rule out the exposure to benzene as a causative factor. In this same report, Golomb *et al.*[20] looked at the chromosomal changes of patients treated with chemotherapeutic agents for other malignancies, essentially, secondary leukemia developing as a result of alkylating agents. The authors proposed that losses of part or all of chromosomes numbers 5 and 7 are the specific changes resulting from mutagenesis, leukemogenesis associated with exposure to various chemicals, including insecticides, petroleum products and alkylating agents.

Jakab *et al*. examined formaldehyde-exposed women from four pathology departments in Hungary.[38] The study included 16 exposed to formaldehyde and various organic solvents, and 21 exposed mainly to formaldehyde. Measures of genotoxicity included the

determination of the frequencies of chromosomal aberrations and sister-chromatid exchange. In both formaldehyde-exposed groups, the apoptotic activity and the chromosomal aberrations levels in peripheral blood lymphocytes were significantly higher than in controls. The chromosomal aberrations included mostly breaks of the chromatid type. In the second group, which was mainly exposed to formaldehyde, chromosomal aberrations were slightly lower in comparison with the group exposed to formaldehyde and solvents, and may be attributed to a different rate of elimination of damaged lymphocytes as a consequence of formaldehyde induced apoptotic activity.

While this interpretation is compatible with the various animal studies, as well as observations in patients, there is certainly a lack of scientific connection between the benzene exposed chromosomal changes, and the chromosomal changes reported in patients treated with alkylating agents.

In a recent paper, Smith[39] suggested that oxidation of benzene to multiple metabolites plays a role in producing benzene induced toxicity of DNA damage in bone marrow and adds further weight to the hypothesis that multiple metabolites are involved in benzene toxicity. They also described DNA changes that have been shown to be cause point mutation. The investigators measured mutation frequency in 24 workers heavily exposed to benzene, and 23 matched controls. They found that benzene caused a highly significant increase in one variant of mutation, suggesting that benzene produces gene duplicating mutations, but no gene inactivating ones. It is suggested that the most likely consequence of aberrant recombination caused by benzene metabolites is the production of stable chromosomal translocation. Indeed, there are several chromosomal abnormalities shown in leukemic cells. This includes Philadelphia chromosome, which results from reciprocal translocation between chromosome 9 and 22, and has been associated with chronic myeloid leukemia, and reciprocal translocation between chromosomes 8 and 21. From these studies, it is concluded that benzene is a genotoxic carcinogen, but that other genetic phenomena may mediate benzene-induced hematopoietic toxicity. Based on the available data up to date, it is proposed that benzene is a carcinogen that does not produce cancer through simple gene mutations, but rather through a separate class of carcinogens (metabolites of benzene) that act by a similar mechanism.

Inhibition of topoisomerase II (topoII) by benzene and its metabolites represents a potential mechanism by which benzene could induce its chromosome-altering and leukemogenic effects. Figure 19.5.1 includes proposed mechanism. The inhibition of enzymatic activity at the closed clamp and other stages of the catalytic cycle in bone marrow cells would likely result in DNA breakage, the formation of chromosomal aberrations, and could potentially result in leukemia-associated chromosomal translocations.

The studies showing that benzene and its metabolites induce chromosomal aberrations *in vitro* and the studies showing that benzene increases chromosomal aberrations in lymphocytes of exposed workers are important, because several well-conducted studies show that increased chromosomal aberrations in peripheral blood lymphocytes increase the risk of cancer in humans.[40-45]

In a recent review, Eastmond *et al.*[46] examined the cellular origin and changes induced by benzene, leading to leukemias and lymphomas. Most adult leukemias originate

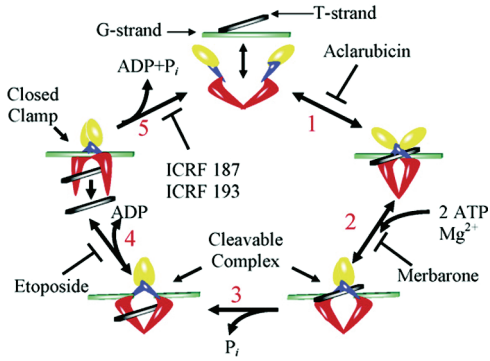


Fig. 19.5.1. The catalytic cycle of topoisomerase II, topoII. A description of the catalytic cycle of topoisomerase II is illustrated as well as the sites of inhibition of various topoII inhibitors. (1) The binding of topoII to two segments of double stranded DNA, the gate segment (G-segment) and the transport segment (T-segment). These two segments may be from the same or two different double helices. The binding of topoII to DNA promotes the closure of the N-terminal clamp. This step can be inhibited by aclarubicin. (2) The binding of 2 ATP molecules promotes the dimerization of the ATPase domains and the production of a transient double strand break in the G-segment of DNA resulting in a stabilized DNA enzyme complex known as the cleavable complex. Merbarone has been reported to inhibit this step of the cycle. (3) The hydrolysis of one ATP and release of the hydrolyzed phosphate induces the passage of the T-segment of DNA through the G-segment. (4) The release of the ADP promotes the religation of the G-segment and release of the T-segment through the C-terminal gate of the enzyme resulting in the formation of the topoII enzyme in the closed clamp configuration. This step can be inhibited by etoposide and other topoII poisons. (5) The hydrolysis and release of ADP+ P_i causes the disassociation of the ATPase domains and the opening of the N-terminal gate to allow the release of the G-segment and the return of topoII to its native state. This last step can be inhibited by the bisdioxopiperazine class of drugs such as ICRF 187 and 193, and bioactivated hydroquinone, BAHQ, which is benzene metabolite. [Adapted, by permission, from Mondrala S, Eastmond, *Chemico-Biological Interactions*, **184**, 259-68 (2010).]

at the pluropotent stem cell. On the other hand, many lymphomas and myelomas originate in mature lymphoid cells. The authors state that among the 100+ agents that the International Agency for Research on Cancer (IARC) evaluate as Group 1 (known human carcinogens), approximately 25% have been established as causing lymphatic and hematopoietic cancers. In experimental animal studies, benzene has been shown to cause structural chromosomal aberrations and numerical aberrations.[47,48] Zhang, *et al*.[49] described chromosomal aberrations in humans exposed to benzene.

In summary, the studies in experimental animals, *in vivo* and *in vitro*, and observations of solvent-exposed patients show that benzene and a wide range of organic solvents are associated with changes in chromosomes and DNA adducts. While these changes may be helpful in epidemiological studies, the absence or presence of genetic changes or DNA adducts cannot be used in a specific case to rule out or establish causation. The biomarkers described in this chapter, in the form of specific genetic changes, can be helpful in identifying individual susceptibility and, in some cases, understanding of the mechanism of the disease process; however it must also be understood that there are significant limitations to its application, including measurements, errors, and confounding factors.

**Disclosure: Some of the materials in this chapter have been added from court declarations of Dr. Brautbar.*

REFERENCES

1 Irons R, *J Toxicol Environ Health*, **16**, 673-678 (1985).
2 Kathleen Lavender, *et al*., v Bayer Corporation, *et al*., Civil Action No. 93-C-226K, in the Circuit Court of Marshall County, West Virginia.
3 **Biomarkers: Medical and Workplace Applications**, Medelson ML, Moor LC, and Peeters JP (eds), *John Henry Press*, Washington, D.C. (1998).

4 Rowley JD and Potter D, *Blood*, **47**, 705-721 (1976).
5 Mitelman F, Brandt L, and Nilsson PG, *Blood*, **52**, 1229-1237 (1978).
6 First International Workshop on Chromosomes in Leukaemia: Chromosomes in acute non-lymphocytic leukaemia. *Br J Haematol*, **39**, 311-316 (1978).
7 Golomb HM, Vardiman J and Rowley JD, *Blood*, **48**, 9-21 (1976).
8 Nilsson PG, Brandt L and Mitelman R, *Leukemia Res*, **1**, 31-34 (1977).
9 Mitelman F, *et al., Science,* **176**, 1340-1341 (1972).
10 Mitelman F, **The Rous sarcoma virus story: Cytogenetics of Tumors induced by RSV** in German J (ed): Chromosomes and Cancer, New York, *Wiley*, page 675 (1974).
11 Levan G and Levan A, *Hereditas*, **79**, 156-160 (1975).
12 Levan G and Mitelman F, *Hereditas*, **82**, 167-174 (1976).
13 Sugiyama T, *et al., J Natl Cancer Inst*, **60**, 1399-1404 (1978).
14 Funes-Cravioto F, *et al., Lance*t, **2**, 322-325 (1977).
15 Brandt L, *et al., Eur J Haematol*, **42**, 298-302 (1989).
16 Forni A, Pacifico E, and Limonta A, *Arch Environ Health*, **22**, 373-378 (1971).
17 Fredga K, Reitalu J, and Berlin M, *Chromosome studies in workers exposed to benzene*. In: Berg K (ed), Genetic Damage in Man Caused by Environmental Agents, New York, *Academic Press*, 187-203, (1979).
18 Hogstedt B, et al., *Hereditas*, 94, 179-184 (1981).
19 Mitelman F, *et al., Cancer Genet Cytogenet*, **4**, 194-214 (1981).
20 Golomb HM, *et al., Blood*, **60**, 404-411 (1982).
21 Fourth International Workshop on Chromosomes in Leukemia, *Cancer Genet Cytogenet*, **11**, 326-331 (1984).
22 Koizumi A, *et al., Jap J Ind Health*, **12**, 23-29 (1974).
23 Morimoto K, *Jap J Ind Health*, **17**, 106-107 (1975).
24 Philip P and Jensen MK, *Acta Pathol Microbiol Scand, Section A*, **78**, 489-490 (1970).
25 Dobrokhotov VB, *Gig Sanit,* **37**, 36-39 (1972).
26 Kissling M and Speck B, *Helv Med Acta*, **36**, 59-66 (1971).
27 Pollini G and Colombi R, *Med Lav*, **55**, 244-255 (1964).
28 Forni A and Moreo L, *Eur J Cancer,* **3**, 251-255 (1967).
29 Sellyei M and Kelemen E, *Eur J Cancer*, **7**, 83-85 (1971).
30 Forni AM, *et al., Arch Environ Health*, **23**, 385-391 (1971).
31 Tough IM and Court Brown WM, *Lancet*, **1**, 684 (1965).
32 Hartwich G and Schwanitc G, *Dtsch Med Wochenschr*, **97**, 45-49 (1972).
33 National Research Council Advisory Centre on Toxicology, Washington D.C., Health Effects of Benzene: A Review. Prepared for the Environmental Protection Agency. Report No. NAS/ACT/P-829, (June, 1976).
34 Picciano DJ, Environ Res, 19, 33-38 (1979).
35 Picciano DJ, **Monitoring Industrial Populations by Cytogenetic Procedures**. In: Infante PF and Legator MS (eds). Proceedings of the Workshop on Methodology for Assessing Reproductive Hazards in the Workplace, *U.S. Government Printing Office*, Washington DC, pages 293-306 (1980).
36 Watanabe T, *et al., Environ Health*, **46**, 31-41 (1980).
37 Clare MG, *et al., Br J Ind Med*, **41**, 249-253 (1984).
38 Jakab MG, *et al., Mutation Res*, **698**, 111-17 (2010).
39 Smith MT, *Environ Health Perspect*, **104**, 1219-1225 (1996).
40 Rossner P, *et al., Environ Health Perspect*, **113**, 517-20 (2005).
41 Bonassi S, *et al., Cytogenet Genome Res*, **104**, 376-82 (2004).
42 Bonassi S, *et al., Cancer Res*, **60**, 1619-1625 (2000).
43 Liou SH, *et al., Cancer Res*, **59**, 1481-1484 (1999).
44 Hagmar L, *et al., Cancer Res*, **58**, 4117-4121 (1998).
45 Bonassi S, *et al., Cancer Genet Cytogenet*, **79**, 133-135 (1995).
46 Eastmond, D.A., Keshava N and Sonawane B, *Mutat Res*, **761**, 40-64 (2014).
47 International Agency for Research on Cancer, A review of human carcinogens - Part F: Chemical agents and related occupations. *World Health Organzation*, Lyon, France, 2012.
48 Eastmond, D.A., *et al., Res. Rep. Health Effects Inst*, 102, 1-68 (2001).
49 Zhang, L., *et al*., *Crit. Rev. Toxicol,* **32**, 1-42 (2002).

19.6 CHROMOSOMAL ABERRATIONS AND SISTER CHROMATOID EXCHANGES

NACHMAN BRAUTBAR
University of Southern California, Keck School of Medicine,
Department of Medicine, Clinical Professor Emeritus of Medicine
Nachman Brautbar, M.D., Inc. Los Angeles, CA, USA

Several technologies have been developed in the last 10 years to look at chromosomal changes and DNA changes caused by environmental exposures, as well as a marker of environmental exposures. The use of chromosomal translocation as a biological marker of exposure in humans have become an important tool in the research, as well as, in some instance, a marker of exposure. Several methodologies have been utilized and included structural chromosomal aberrations, sister chromatoid exchanges (SCEs) and micronuclear changes. These are markers of changes in the cellular genetic materials, and represent damage induced by chemicals. These methodologies are viewed as cytogenetic assays, and by themselves cannot provide a diagnosis, but they complement other methodologies which include gene mutation analysis, and DNA changes. Among the important uses of cytogenetics as a biomarker is the relationship between chromosomal aberrations secondary to chemicals and carcinogeneses. Since the scope of this chapter is not addressing mechanisms of carcinogeneses, the reader is referred to other sources.[1]

Studies in patients with acute non-lymphocytic leukemia whose bone marrow analyzed for chromosomal changes have shown that 50% of them had changes in chromosomes 5, 7, 8 and 21.[2] Mitelman *et al*.[3] have looked at patients with acute non-lymphocytic leukemia and looked at the occupational history. They have studied a group of 56 patients. Twenty-three out of the 56 patients had a history of exposure to solvents, insecticides and petroleum products. They have further shown that in males with acute non-lymphocytic leukemia the frequency of exposure to petroleum products was as high as 36%. In their study, Mitelman *et al*.[3] found a striking differences between the chromosomal findings in non-exposed versus exposed groups. In the non-exposed group only 24.2% of the patients had chromosomal aberrations in their bone marrow cells, while 82.6% of the exposed patients had chromosomal aberrations. The authors concluded, based on these studies that the difference between the exposed and non-exposed group strongly indicates that the karyotypic pattern of the leukemic cells was, in fact, influenced by the exposure. The authors further suggested that the prognosis in patients with normal chromosomes was significantly better than for those with abnormal chromosomes, something which has been suggested by previous investigators.[4-6] Based on their observations and others,[7-11] the authors suggested that certain chromosomal regions are potentially vulnerable to the chromosome damaging actions of different chemicals which are carcinogens. Indeed, the changes of chromosomes 5, 7, 8 and 21 in workers exposed to different chemical solvents, and also gasoline and pesticides, supports this hypothesis. Studies in cultured lymphocytes from 73 workers in chemical laboratories and the printing industry were found to have a significantly increased frequency of chromatoid and sister-chroma-

toid breaks in comparison to 49 control subjects.[12] The authors suggested that the observed cytogenetic changes are reasonably assumed to be the result of strong factors in the working environment which induced chromosome breaks and sister-chromatoid exchange. The considerable variation in cytogenic changes between subjects suggested varying degrees of exposure to mutagenic agents. Brandt *et al.*[13] studied the effects of exposure to organic solvents and chromosomal aberrations. Ten patients had a history of daily handling of organic solvents for at least one year preceding the diagnoses of non-Hodgkin's lymphoma. All have been exposed to a variety of solvents to include aromatic and aliphatic compounds. Forty-four patients for only a shorter period of time worked with organic solvents, and therefore served as the control group. There was a statistically significant increase in chromosomal changes in the exposed group compared to the non-exposed group. The authors suggested based on their results, that at diagnosis of non-Hodgkin's lymphoma, patients with a history of significant occupational exposure to organic solvents tends to have a larger number of chromosomal aberrations in the lymphoma cells. Furthermore, certain aberrations may be characteristic for the exposed patients. They have concluded that the over representation of certain chromosome aberrations in non-Hodgkin's lymphoma patients occupationally exposed to organic solvents supports the concept that these exposures may be relevant to the subsequent development of non-Hodgkin's lymphoma. Their data are in agreement with the studies published previously, indicating that workers handling organic solvents and other petroleum products have an increased frequency of chromosomal aberrations in lymphocytes.[12,14-16] Indeed, association between exposure to solvents and other chromosomal changes in the cells have been studied by other investigators, describing chromosomal changes in acute non-lymphocytic leukemia.[3,17-19] In cultured cells, Koizumi[20] examined the effects of benzene on DNA syntheses in chromosomes of cultured human lymphocytes. They have shown an increased incidents of chromatoid gaps and breaks in cultures treated with benzene, compared to those who were untreated with benzene. They also have shown changes in DNA metabolism in the form of inhibition of syntheses in those samples which were treated with benzene. This observation was confirmed by other investigators[21] who have shown an increased chromosomal aberrations in cultured human leukocytes exposed to benzene. From the *in vitro* to the *in vivo* experimental animals, it was shown that rats treated with benzene, were found to have increased chromosomal changes taken from the bone marrow as compared to the non-treated animals.[22] It was of interest that the degree of chromosomal changes that were induced by benzene, were similar to that induced by toluene[23] (probably secondary to the benzene in toluene). Experimental rabbits treated with benzene also showed a significant amount of bone marrow chromosomal changes persisting up to 60 days after the end of dosing with benzene.[24]

A patient who has developed aplastic anemia after exposure to benzene, was shown to have significant chromatoid fragments.[25] A cytogenic study, which was carried out later,[26] on a patient who developed leukemia after 22 years of continuous exposure to a high concentration of benzene, have shown that, later in the process, there were changes in 47 chromosomes in the bone marrow. Sellyei *et al.*[27] studied patients who developed pancytopenia after having been exposed for 18 months to benzene. Significant chromosomal

changes were detected even 7 years after remission from the anemia and the presentation of leukemia. In line with these changes, Forni *et al.*[28] have studied 25 subjects with a history of hematopoietic abnormalities and benzene exposure, and compared these to 25 matched controls. They have shown that 18 years after clinical and hematological symptoms, chromosomal aberrations were increased as compared to the control group. In 1965, Tough *et al.*[29] have studied chromosomes of workers exposed to benzene for periods varying from 1 to 18 years. They have also shown a small but significant increase in chromosomal changes compared to a control group. These same investigators looked at workers exposed to benzene levels from 25 to 120 ppm, and found that they had significant chromosomal aberrations as compared to the normal population (which has a general background exposure to benzene levels). The study of Forni *et al.*[14] have shown significant chromosomal aberrations in patients who were exposed mainly to benzene, and not to those who were exposed to toluene only. Hartwich *et al*.[30] looked at 9 healthy refinery workers who were exposed to low levels of benzene, and also found significantly increased chromosomal changes compared to the control group. The National Research Council Advisory Center and Toxicology Study[31] concluded that close correlation between occupational exposure to benzene and persistence of chromosomal aberrations can be discussed only when there is an association between benzene induced hematopoietic disease and chromosomal aberrations, however, the absence of chromosomal changes, cannot be a determinant in the temporal relationship between exposure to benzene and hematopoietic diseases.[31] While some studies suggested that the chromosomal changes require heavy exposure to benzene, the study by Picciano, 1979,[32] looked at chromosomal changes in 52 workers exposed to a mean benzene concentration of less than 10 ppm compared to non-exposed controls. There was a statistically significant increase in chromosomal aberrations on exposure to as low as less than 10 ppm. Furthermore, these same investigators[33] reported a dose response increase in the aberrations when the exposed workers were divided into smaller groups by the exposure levels (less than 1 ppm, 1-2.5 ppm, and 2.5-10 ppm). Drivers of petroleum tankers and crew members of gasoline tankers, ships and gas station attendants were studied for chromosomal changes.[15] The degree of exposure to benzene of the three groups was estimated to be at a mean of 0.4 ppm, and the crew members were estimated to be at 6.56 ppm while engaging in handling of gasoline. The frequency of chromosomal and chromatoid aberrations in the gas tanker drivers was significantly greater than in those of gas station attendants and the crew members. The effects of long-term benzene exposure from the incidents of chromosomal changes were studied in 16 female workers who were exposed to a maximum of 40 ppm benzene for 1-20 years.[34] The cytogenetic study was conducted 6 months after benzene was eliminated from the work environment, and they have found no significant increase in chromosomal changes. Clare *et al.*[35] looked at chromosomal changes in the peripheral lymphocytes of workers after a single exposure to benzene. Exposure levels were described as high after a spillage of a large amount of benzene during the loading of a ship. Three months after the incident, chromosomal analysis have shown no significant abnormalities. The authors concluded that there was no evidence of lasting chromosomal damage in the peripheral blood lymphocytes of these exposed workers. Golomb *et al*.[18]

reviewed the literature and reported the results in regards to exposure to benzene and chromosomal changes. They have stated that they studied exposure data on 74 patients with acute leukemia. They describe that 75% of the exposed patients had an abnormal karyotype, whereas only 43% of the patients characterized as non-exposed had an abnormal karyotype. While it is true that these findings are in agreement with previous studies[18] they still could not explain the 43% patients who were not exposed, and still had abnormal chromosomal changes. This is a very important observation, since some investigators in the field claimed that the "absence of chromosomal changes" in benzene exposed individuals negates the clinical causative diagnosis of benzene induced hematopoietic disease. Essentially, all studies show that benzene can cause chromosomal changes, but does not cause it in all the patients, and the absence of chromosomal changes cannot and does not rule out the exposure to benzene as a causative factor. In this same paper, Golomb *et al.*[18] looked at the chromosomal changes of patients treated with chemotherapeutic agents for other malignancies. Essentially, they looked at a secondary leukemia developing as a result of contact with alkylating agents. For some reasons, they have proposed that losses of part or all of chromosomes numbers 5 and 7 are the specific change resulting from mutagenesis, leukemogenesis associated with various chemicals including insecticides, petroleum products and alkylating agents.

Formaldehyde-exposed women from four pathology departments in Hungary, included 16 exposed to formaldehyde and various organic solvents, and 21 exposed mainly to formaldehyde.[36] Measures of genotoxicity included the determination of the frequencies of chromosomal aberrations and sister-chromatid exchange.[36] In both formaldehyde-exposed groups, the apoptotic activity and the chromosomal aberrations levels in peripheral blood lymphocytes were significantly higher than in controls.[36] The chromosomal aberrations included mostly breaks of the chromatid type.[36] In the second group, which was mainly exposed to formaldehyde, chromosomal aberrations were slightly lower in comparison with the group exposed to formaldehyde and solvents, which may be attributed to a different rate of elimination of damaged lymphocytes as a consequence of formaldehyde induced apoptotic activity.[36]

While this interpretation is compatible with the various animal studies, as well as observations in patients, there is certainly a lack of scientific connection between the benzene exposed chromosomal changes, and the chromosomal changes reported in patients exposed to alkylating agents.

Smith, in a recent paper[37] suggested that oxidation of benzene to multiple metabolites plays a role in producing benzene induced toxicity of DNA damage in bone marrow, and adds further weight to the hypothesis that multiple metabolites are involved in benzene toxicity. They also described DNA changes which have been shown to be cause-point mutation. The investigators measured mutation frequency in 24 workers heavily exposed to benzene, and 23 matched controls. They found that benzene caused a highly significant increase in one variant of mutation, suggesting that benzene produces gene duplicating mutations, but no gene inactivating ones. They suggested that the most-likely consequence of aberrant recombination caused by benzene metabolites is the production of stable chromosomal translocation. Indeed, there are several chromosomal abnormalities

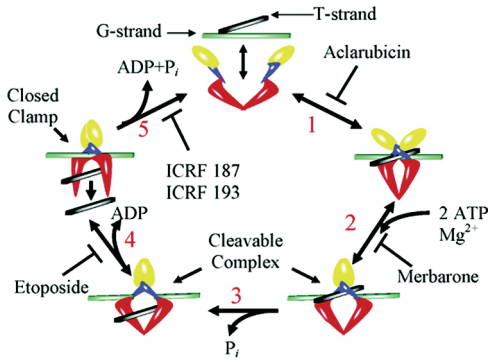


Fig. 19.5.1. The catalytic cycle of topoisomerase II, topoII. A description of the catalytic cycle of topoisomerase II is illustrated as well as the sites of inhibition of various topoII inhibitors. (1) The binding of topoII to two segments of double stranded DNA, the gate segment (G-segment) and the transport segment (T-segment). These two segments may be from the same or two different double helices. The binding of topoII to DNA promotes the closure of the N-terminal clamp. This step can be inhibited by aclarubicin. (2) The binding of 2 ATP molecules promotes the dimerization of the ATPase domains and the production of a transient double strand break in the G-segment of DNA resulting in a stabilized DNA enzyme complex known as the cleavable complex. Merbarone has been reported to inhibit this step of the cycle. (3) The hydrolysis of one ATP and release of the hydrolyzed phosphate induces the passage of the T-segment of DNA through the G-segment. (4) The release of the ADP promotes the religation of the G-segment and release of the T-segment through the C-terminal gate of the enzyme resulting in the formation of the topoII enzyme in the closed clamp configuration. This step can be inhibited by etoposide and other topoII poisons. (5) The hydrolysis and release of ADP+ P_i causes the disassociation of the ATPase domains and the opening of the N-terminal gate to allow the release of the G-segment and the return of topoII to its native state. This last step can be inhibited by the bisdioxopiperazine class of drugs such as ICRF 187 and 193, and bioactivated hydroquinone, BAHQ, which is benzene metabolite. [Adapted, by permission, from Mondrala S, Eastmond, *Chemico-Biological Interactions*, **184**, 259-68 (2010).]

shown in leukemic cells. This includes Philadelphia chromosome which results from reciprocal translocation between chromosome 9 and 22, and has been associated with chronic myeloid leukemia, and reciprocal translocation between chromosomes 8 and 21. From these studies it is concluded that benzene is a genotoxic carcinogen, but that other genetic phenomena may mediate benzene induced hematopoietic toxicity. Based on the available data up to date, it is proposed[36] that benzene is a carcinogen that does not produce cancer through simple gene mutations, but rather through a separate class of carcinogens (metabolites of benzene) that act by a similar mechanism.

Inhibition of topoisomerase II (topoII) by benzene and its metabolites represents a potential mechanism by which benzene could induce its chromosome-altering and leukemogenic effects.[38] Figure 19.5.1 includes proposed mechanism.[38] The inhibition of enzymatic activity at the closed clamp and other stages of the catalytic cycle in bone marrow cells would likely result in DNA breakage, the formation of chromosomal aberrations, and could potentially result in leukemia-associated chromosomal translocations.[38]

In summary, the studies in experimental animals, *in vitro*, and patients show that benzene and a wide range of organic solvents are associated with changes in chromosomes and DNA adducts. While these changes may be helpful in epidemiological studies, the absence or presence of genetic changes or DNA adducts, cannot be used in a specific case to rule out or establish causation. The biomarkers described in this chapter in the form of genetic biomarkers, can be helpful in identifying individual susceptibility, and in some cases understanding of the mechanism of the disease process. They have a significant number of limitations, and these include measurements, errors and confounding factors.

REFERENCES

1 **Biomarkers: Medical and Workplace Applications**, Medelson ML, Moor LC and Peeters JP (eds), *John Henry Press*, Washington, D.C., (1998).
2 Rowley JD and Potter D, *Blood*, **47**:705, (1976).
3 Mitelman F, Brandt L and Nilsson PG, Blood, **52**(6):1229-1237, (December 1978).
4 First International Workshop on Chromosomes in Leukaemia: Chromosomes in acute non-lymphocytic leukaemia. *Br J Haematol*, 39:311, (1978).
5 Golomb HM, Vardiman J and Rowley JD, *Blood*, **48**:9, (1976).
6 Nilsson PG, Brandt L and Mitelman R, *Leukemia Res*, **1**:31, (1977).
7 Mitelman F, *et al., Science*, **176**:1340, (1972).
8 Mitelman F, **The Rous sarcoma virus story: Cytogenetics of Tumors induced by RSV** in German J (ed): Chromosomes and Cancer, New York, *Wiley*, page 675, (1974).
9 Levan G and Levan A, *Hereditas*, **79**:161, (1975).
10 Levan G and Mitelman F, *Hereditas*, **84**:1, (1976).
11 Sugiyama T, *et al., J Natl Cancer Inst*, **60**:153 (1978).
12 Funes-Cravioto F, *et al., The Lancet*, 322-325, (August 13, 1977).
13 Brandt L, *et al., Eur J Haematol,* **42**:298-302, (1989).
14 Forni A, Pacifico E, and Limonta A, *Arch Environ Health*, **22**:373-378, (1971).
15 Fredga K, Reitalu J, and Berlin M, **Chromosome studies in workers exposed to benzene.** In: Berg K (ed), Genetic Damage in Man Caused by Environmental Agents, New York, *Academic Press*, 187-203, (1979).
16 Hogstedt B, *et al., Hereditas*, **94**:179-184, (1981).
17 Mitelman F, *et al., Cancer Genet Cytogenet*, **4**:194-214, (1981).
18 Golomb HM, *et al., Blood*, **60**(2):404-411, (1982).
19 Fourth International Workshop on Chromosomes in Leukemia, 1982: The correlation of karyotype and occupational exposure to potential mutagenic/carcinogenic agents in acute nonlymphocytic leukemia. *Cancer Genet Cytogenet,* **11**:326-331, (1984).
20 Koizumi A, *et al., Jap J Ind Health*, **12**:23-29, (1974).
21 Morimoto K, *Jap J Ind Health*, **17**:106-107, (1975).
22 Philip P and Jensen MK, *Acta Pathol Microbiol Scand, Section A*, **78**:489-490, (1970).
23 Dobrokhotov VB, *Gig Sanit,* **37**:36-39, (1972).
24 Kissling M and Speck B, *Helv Med Acta*, **36**:59-66, (1971).
25 Pollini G and Colombi R, *Med Lav*, **55**:244-255, (1964).
26 Forni A and Moreo L, *Eur J Cancer,* **3**:251-255, (1967).
27 Sellyei M and Kelemen E, *Eur J Cancer*, **7**:83-85, (1971).
28 Forni AM, *et al., Arch Environ Health*, **23**:385-391, (1971).
29 Tough IM and Court Brown WM, *Lancet*, **I**, 684, (1965).
30 Hartwich G and Schwanitc G, *Dtsch. Med. Wschr*, **87**:45-49, (1972).
31 National Research Council Advisory Centre on Toxicology, Washington D.C., **Health Effects of Benzene: A Review.** Prepared for the *Environmental Protection Agency*. Report No. NAS/ACT/P-829, (June, 1976).
32 Picciano DJ, *Environ Res*, **19**:33-38, (1979).
33 Picciano DJ, **Monitoring Industrial Populations by Cytogenetic Procedures**. In: Infante PF and Legator MS (eds). Proceedings of the Workshop on Methodology for Assessing Reproductive Hazards in the Workplace, *U.S. Government Printing Office*, Washington DC, pages 293-306, (1980).
34 Watanabe T, *et al., Environ Health*, **46**:31-41, (1980).
35 Clare MG, *et al., Br J Ind Med*, **41**:249-253, (1984).
36 Jakab MG, Klupp T, Besenyei K, Biro A, Major J, Tompa A, *Mutation Res*., **698**, 111-17 (2010).
37 Smith MT, *Environ Health Persp*, **104**(6):1219-1225, (December 1996).
38 Mondrala S, Eastmond, *Chemico-Biological Interactions*, **184**, 259-68 (2010).

19.7 HEPATOTOXICITY OF INDUSTRIAL SOLVENTS

Nachman Brautbar*+ and Michael P. Wu*
+University of Southern California, Keck School of Medicine, Department of Medicine, Clinical Professor Emeritus of Medicine
***Nachman Brautbar, M.D., Inc., Los Angeles, CA, USA**

19.7.1 INTRODUCTION

Solvent inhaled, absorbed by skin and enter blood circulation, or at times ingested are largely metabolized by the liver. The liver has a complex mechanism composed of the cytochrome P450 enzyme, and other enzymes related to conjugation pathways, such as glutathione conjugation. This is represented schematically in Figure 19.7.1.

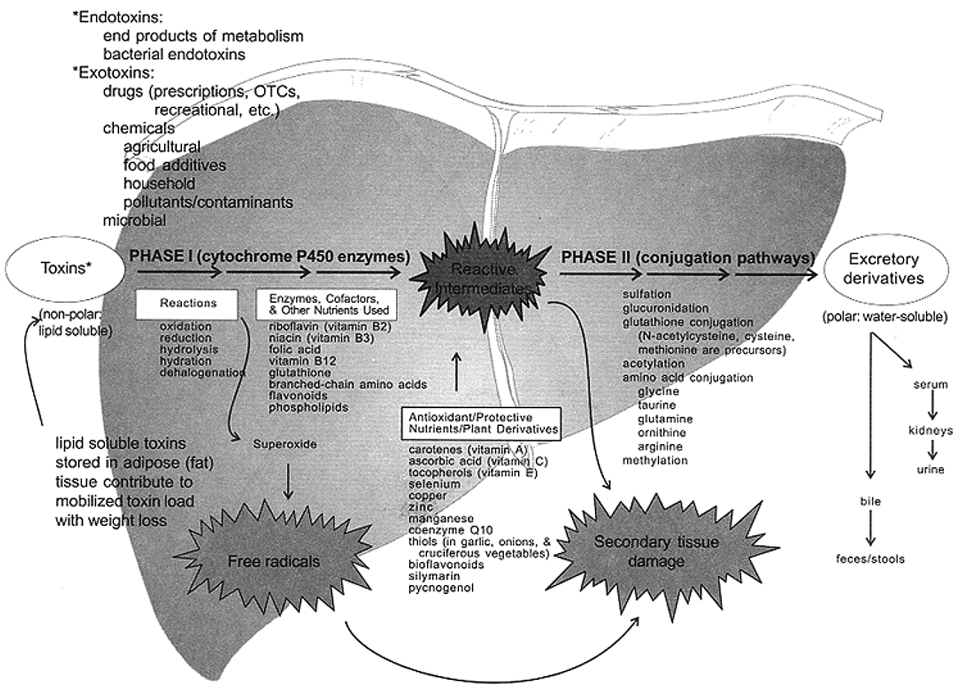


Figure 19.7.1. The phases of detoxification. [Adapted, by permission, from DS Jones, **Detoxification: A Clinical Monograph**. *Institute for Functional Medicine, Inc*., 1999].

It is therefore no surprise that in the occupational setting as well as non-occupational setting, liver damage anywhere from transient to subacute to chronic, and, at times, terminal liver damage has been described.

The circumstances of exposure to hepatotoxic agents are divided to:

1. Occupational: Either through a routine daily inhalation or skin absorption of solvents which have been shown to be toxic to the liver (accidental exposure).
2. Domestic during either accidental or intentional suicidal exposure, ingestion in foods or as a toxic contaminant of food, exposure to toxic agents such as in the form of glue sniffing.
3. Environmental, most commonly exposure through contaminated water with solvents (drinking water contamination) or through atmospheric pollution such as release to the environment from plants utilizing solvents.

Historically, the first cases attributing chloroform to liver toxicity were described in 1887, 1889 and 1904.[2,3,4] The role of carbon tetrachloride and liver injury has been originally described in 1967 and 1973.[5,6] In general, the understanding of hepatotoxicity is extremely complex, and the reader is referred to the outstanding text by Hyman J. Zimmerman.[7] A typical example of how metabolism and toxicity of a water takes place is the aromatic chemical such as benzene attached to bromine. The effect on the liver has been originally studied by Mitchell in 1975[8] who have shown that a change in the rate of the metabolism of this compound is required to create its toxic products. While bromobenzene and carbon tetrachloride share a similar place of metabolism in the liver, the toxicity of bromobenzene and carbon tetrachloride are different, since the bromobenzene toxicity is related to the metabolic capacity of the liver, while that of carbon tetrachloride is not.

Several factors contribute to the handling of the solvents by the liver and affect the final toxicity, including species differences. For instance, rats are vulnerable to a wide variety of toxic agents such as carbon tetrachloride and bromobenzene due to the ability of the liver to convert these agents to their respective toxic metabolites.[6,9] Among other mechanisms responsible for the species differences are liver blood flow, protein binding, and the points of binding intracellularly. Genetic factors in humans are of extreme importance. Genetic factors are most-likely responsible for the various levels of adverse effects of alcohol in different individuals due to induced activity of detoxification enzymes in the liver in some and lack of those or reduced activity in others. Another important factor is age. The effect of age on the susceptibility has been shown in experimental animals. For instance, the neonatal rats are less susceptible to carbon tetrachloride and bromobenzene toxicity as compared to adult animals.[9] In humans, liver necrosis after the administration of Halothane was rare in children, but more common in more elderly patients. Factors such as sex and endocrine status had also influence and different toxic effects of solvents in this case. Nutritional status is a major factor in the effects of solvents on the liver. For instance, protein malnutrition leads to reduced activity of cytochrome P450. Increasing the percentage of fat in the liver has been shown to increase the susceptibility of toxicity to such agents as carbon tetrachloride. Several studies have looked into the histopathological injury of some solvents and solvent-like agents and the liver, and are shown in Table 19.7.1.

Table 19.7.1. Partial list of agents that produce hepatic necrosis in experimental animals. [Adapted, by permission, from HJ Zimmerman, Hepatotoxicity, 1978]

	Site of necrosis				
	Centrizonal	**Midzonal**	**Peripheral Zone**	**Massive**	**Steatosis**
Bromobenzene	+				
Bromotrichloromethane	+				+
CCl_4	+				+
Chlorobenzenes	+				
Chloroform	+				+
Dichloropropane	+				+
Dinitrobenzene	+			(+)	+
Dinitrotoluene	+			(+)	+
Ethylene dichloride	+				+
Methylene chloride	(+)			(+)	(+)
Naphthalene	+				+

The specific mechanism of hepatotoxicity of many solvents are unknown, however, the knowledge have been gathered from experimental studies now available for the reader for review.[10-13]

Due to the lack of specific information for many solvents, this chapter will focus solvents that have been used in the past heavily, or are used currently.

Table 19.7.2. Some occupational solvents that produce acute and chronic liver disease.

Carbon tetrachloride	Halothane	Ethyl alcohol
Chloroform	Trichlorodiphenyl	A mixture of solvents such as toluene and xylene
Trichloroethylene	Trichloroethene	Dichloromethane
Tetrachloroethylene	Trinitrotoluene	Dinitrobenzene

Tables 19.7.3 and 19.7.4 describe two major phases in the liver metabolism and detoxification of drugs, foreign agents, and solvents.

Table 19.7.3. Phase I reactions. [Adapted, by permission, from Zimmerman HJ, **Hepatotoxicity: The Adverse Effects of Drugs and Other Chemicals on the Liver**, *Appleton-Century-Crofts*, New York, 1978].

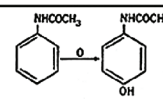
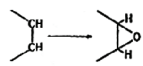
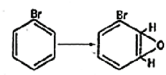
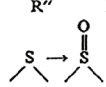
I. OXIDATIONS	
A. MFO-dependent	
Aromatic hydroxylations	
Aliphatic hydroxylations	
Primary alcohol	$RCH_2CH_2CH_3 \xrightarrow{O} RCH_2CH_2CH_2OH$
Secondary alcohol	$RCH_2CH_2CH_3 \xrightarrow{O} RCH_2CH(OH)CH_3$
Tertiary alcohol	$RCH_2CH(R')CH_3 \xrightarrow{O} R-CH_2-C(R')(OH)CH_3$
Epoxidation	
Arene oxide formation	
Oxidative dealkylation	
N—dealkylation	$R-NH-CH_3 \longrightarrow [R-NH-CH_2OH] \longrightarrow RNH_2 + HCHO$
O—dealkylation	$R-O-CH_3 \longrightarrow [R-O-CH_2OH] \longrightarrow ROH + HCHO$
S—dealkylation	$R-S-CH_3 \longrightarrow [R-S-CH_2OH] \longrightarrow RSH + HCHO$
N—Oxidation	
Primary amine	$RNH_2 \longrightarrow RNHOH$
Secondary amine	$R_2NH \longrightarrow R_2NOH$
Tertiary amine	$R-N(R')(R'') \longrightarrow R-N(R')(R'')=O$
S—oxidation	
Deamination	$RCH(NH_2)-CH_3 \longrightarrow [R-C(OH)(NH_2)-CH_3] \longrightarrow R-C(=O)-CH_3 + NH_3$
Desulfuration	$RSH \longrightarrow ROH$
Dechlorination	$CCl_4 \longrightarrow [CCl_3] \longrightarrow CHCl_3$
B. Amine oxidase	$RCH_2-NH_2 \longrightarrow RCHO + NH_3$
C. Dehydrogenation	
Alcohols and aldehydes	$CH_3CH_2OH \longrightarrow CH_3CHO \longrightarrow CH_3COOH \longrightarrow CO_2 + H_2O$
II. REDUCTION REACTIONS	
Azo reductions	$RN=NR' \longrightarrow RNH-NHR' \longrightarrow RNH_2 + R'NH_2$
Nitro reductions	$RNO_2 \longrightarrow RNO \longrightarrow RNHOH \longrightarrow RNH_2$
Carbonyl reductions	$RC(=O)-R' \longrightarrow RCH(OH)-R'$
III. HYDROLYSIS REACTIONS	
Esters	$RCOOR' \longrightarrow RCOOH + R'OH$
Amides	$RCONH_2 \longrightarrow RCOOH + NH_3$

Table 19.7.4. Phase II (conjugation) reactions. [Adapted, by permission, from Zimmerman HJ, **Hepatotoxicity: The Adverse Effects of Drugs and Other Chemicals on the Liver**, *Appleton-Century-Crofts*, New York, 1978].

Type of conjugation	Endogenous substance	Transferring enzyme and location	Type of xenobiotics & metabolites conjugated
Glucuronidation	UDP-glucuronic acid	UDPG-transferase (microsomes)	Phenols; alcohols; carboxylic acids; primary amines; hydroxylamines; sulfonamides, etc.
Dihydrodiol formation	Water	(Epoxide) hydrase (cytosol)	Epoxides and arene oxides
GSH conjugation	GSH	GSH-S-transferase (cytosol)	Epoxides; arene oxides; halides; nitro-groups; hydroxylamines, etc.
Glycine conjugation	Glycine	Acyl CoA-glycine transferase (mitochondria)	CoA derivatives of carboxylic acids
Sulfate conjugation	PAP-sulfate	Sulfotransferase (cytosol)	Phenols; alcohols; aromatic amines
Methylation	S-adenosyl-methionine	Transmethylase (cytosol)	Catechols; phenols; amines; histamine

19.7.2 INDIVIDUAL VARIABILITY AND HEPATOTOXICITY OF SOLVENTS

The issue of individual variability based on various factors as described above is important, especially in medical monitoring and risk assessment in occupationally exposed patients. The fact that workers in industrial environments are not the same and are subject to differences such as body build, underlying kidney function differences (genetic or acquired), exposure to other solvents or other liver toxicants may affect the results. A study by Droz *et al.*[14] evaluated a population response to solvent exposure. These investigators showed that body fat is the most important body compartment for fat-soluble solvents. Body fluids and physical work load affect the blood flow, alveoli ventilation, and therefore will affect the amount of solvent inhaled as well as absorbed through the blood and delivered to the liver. A physiological model has been developed that takes into account variability in the form of exposure, physical overload, body build, liver function and renal function. Other factors to take into account are solubility in blood and tissue. Investigators suggested that such a model should be useful in improving our understanding of the complex and multifactorial system, to generate a hypothesis and improve our assessment of occupational exposure. This has significance from a clinical toxicology point of view. A patient who has an increased body fat will be at a higher risk of solvent toxicity. If this same patient also has a habit of heavy alcohol consumption the risk for solvent liver toxicity is significantly increased. Epidemiological studies are commonly not designed to evaluate the individual hepatotoxicity of solvents, and therefore the issue of cause and effect must be viewed taking into account individual variability, other risk factors and medical common sense, following the well-established criteria by practitioners of medicine.

19.7.3 CARBON TETRACHLORIDE

Carbon tetrachloride is a colorless organic solvent with a sweet odor. It does not occur naturally and has been manufactured for use as a dry cleaning solvent, degreasing agent, refrigerant, fumigant, in fire extinguishers and for lacquers and varnishes. It has found to cause liver injury in man and in experimental animals.[15] Carbon tetrachloride is a known and potent liver toxicant, and therefore has been studied extensively in experimental animals. Recknagel *et al*.[6] and Reynolds[16] showed that single doses will lead to areas of necrosis in the liver within a few minutes. This has been shown to be associated with changes in liver enzymes that are known to indicate liver damages.[10,11] Prolonged exposure to carbon tetrachloride has been shown to lead to liver cirrhosis and to liver cancers. In order to become toxic, carbon tetrachloride has to undergo metabolic changes in the liver.[6,17] The lesions described initially in animals have been shown in humans poisoned with carbon tetrachloride.[15,18] It has also been shown that alcohol enhances the susceptibility to carbon chloride toxicity.[19] Several factors play a role in the susceptibility to toxicity by carbon tetrachloride, among them are sex, age, diet, underlying preexisting liver dysfunction and alcoholism. Over the years in clinical and experimental studies and observations, it has been shown that carbon tetrachloride-induced liver damage is divided to fatty metamorphosis, and independently liver necrosis. Fat starts to accumulate in experimental animals as early as one hour after administration of a high dose of carbon tetrachloride. Liver necrosis occurs as early as 6 to 12 hours, and a maximum of 24 to 36 hours.

The concept of steatosis (fat accumulation in the liver) is a common one for looking at the effect of solvents (those that are known to be toxic to the liver). Fat accumulation is the result of abnormal transport of lipids and as a result, accumulation of lipids in the liver. Therefore, industrial exposure to hepatotoxic solvents is associated with liver steatosis, among others.

Necrosis is the second most common effect of liver damage of solvents toxic to the liver, and is the result of destruction of the cell architecture as well as biochemical pathways. It has been shown in many experimental studies that the toxicity of carbon tetrachloride (and some of the other solvents that are toxic to the liver and other organs, such as benzene on the hematopoietic system) requires several reactions in order to produce the toxic metabolites that cause damage. Most studies point to the responsibility of cytochrome P450 system.[6] The metabolite responsible for the hepatotoxic effect of carbon tetrachloride is a trichloromethyl free radical (Cl_3C) which is formed from carbon tetrachloride.[6,20] There is, however, also information that non-metabolized carbon tetrachloride contributes to the injury, especially on the cell membrane, something that is logical since solvents can cause mechanistic injury to various tissues through the effects on the cell membrane, either dissolved or damaged by the solvent.[21,22] A consolidation of the data available examining the hepatotoxic effects of carbon tetrachloride has been eloquently described by Zimmerman.[7]

The carcinogenic effect of carbon tetrachloride will not be discussed in this chapter, and the reader is referred to other texts.[23]

19.7.4 CHLOROFORM

Chloroform is another haloalkane that has been typically used as an example to understand and study the toxic effects on the liver. Studies in experimental animals as early as 1866 showed that the chloroform causes liver toxicity.[24] In 1923, Meyer *et al.*[15] showed the hepatotoxic effects of chloroform in humans. Chloroform was used years ago as an anesthetic, and has been used successfully, however, due to its toxicity its use been abandoned. Acute exposure and toxicity has been associated with liver necrosis and liver steatosis. Chronic exposure has been associated with liver cirrhosis. The mechanism of injury most-likely is the result of metabolic changes of chloroform by the liver. Different effects and level of toxicity between carbon tetrachloride and chloroform is most-likely the result of the solubility in lipid and water, and the mechanisms by which these two agents are metabolized and then cause liver toxicity. Table 19.7.5 summarizes liver damage described in the literature as a result of halogenated aliphatic hydrocarbons.

Table 19.7.5. Lesions produced by halogenated aliphatic hydrocarbons. [Adapted, by permission, from Zimmerman HJ, **Hepatotoxicity: The Adverse Effects of Drugs and Other Chemicals on the Liver**, *Appleton-Century-Crofts*, New York, 1978].

Steatosis and centrizonal necrosis	Steatosis only	Slight steatosis or no injury
CCl_4	CH_2ClBr	CH_3Cl
CI_4	CH_2Cl_2	CH_3Br
CCl_3Br	CHCl=CHCl (*cis*)	CH_3I
$CHCl_3$	$CCl_2=CCl_2$	CCl_2F_2
CHI_3	$CH_3CH_2CHClCH_3$	CHCl=CHCl (*trans*)
$CHBr_3$		CH_3CH_2Cl
$CHCl_2CHCl_2$		CH_3CH_2I
CH2ClCH2Cl		CH_3CH_2Br
CH_2BrCH_2Br		$CH_3CH_2CH_2CH_2Cl$
CH_3CCl_3		
$CHCl_2CCl_3$		
$CHCl=CCl_2$		
$CH_3CHClCH_3$		
$CH_3CHClCH_2Cl$		

19.7.5 TRICHLOROETHYLENE

Trichloroethylene is used as a chlorinated solvent for metal-degreasing operations. Automotive manufacturers and the metal industry use trichloroethylene for vapor degreasing metal parts. The textile industry uses trichloroethylene as an extraction solvent for greases, oils, fats, waxes and tars on wool, cotton, and other fabrics. Trichloroethylene is utilized in dyeing and finishing operations. Trichloroethylene is used as a chemical intermediate in the production of pharmaceuticals compounds, polychlorinated aliphatics compounds, flame retardant chemicals and insecticides. Trichloroethylene can be used for low-temperature heat transfer in refrigerants and for flushing liquid oxygen in the aerospace industry. It can also be found in some household products, including typewriter cor-

rection fluid, paint removers, adhesives, lubricants, paints, paint strippers, pesticides, varnishes and spot removers. Trichloroethylene has a sweet odor and a sweet, burning taste.[25]

Trichloroethylene is readily absorbed into the blood from the lungs. Once in the bloodstream, trichloroethylene is rapidly transported to various tissues in the body. Major sites of distribution are the liver and body fat.[26] The liver is a target organ toxicity for trichloroethylene in experimental animals. Data for humans are limited.[27] Case reports describe trichloroethylene induced hepatitis and liver necrosis.[28] Guzelian *et al*. described both hepatic necrosis and fatty metamorphosis.[29] As early as in 1962, the hepatotoxicity of trichloroethylene has been studied in humans. Trichloroethylene has been found to cause liver damage after both acute and chronic exposures.[30-34] Several studies reported a history of pathological changes including individual or focal necrosis after treatment of experimental animals with trichloroethylene.[35] In addition to these histopathological changes, Berman also found a dose-response relationship to the histopathological changes. Since trichloroethylene is commonly present as a contaminant in ground water (from degreasing, paint thinning and plastic metal processes), Barton has evaluated risks assessment of trichloroethylene and liver toxicity, and showed that exposure was associated with continuous response in the form of liver toxicity.[36] There was a connection between increased liver weight over body weight and liver toxicity, this effect also appears to be a sensitive indicator of liver toxicity. The authors concluded that trichloroethylene is toxic to the liver, based on their analysis of their findings, and that the use of liver enzymes by themselves may miss the early signs of toxicity to the liver by trichloroethylene. From these studies on trichloroethylene, and the studies on solvent mixtures described above, it is reasonable to conclude that the early and therefore subclinical stages of solvent hepatotoxicity are clinical tools commonly missed. When patients present to the doctor they will already be in more advanced stages such as liver steatosis and/or chronic hepatitis, and at times liver fibrosis.

The toxicity of trichloroethylene depends on metabolism and induction of cytochrome P450. Trichloroethylene is metabolized through chloral hydrate to compounds including trichloroacetic acid and dichloroacetic acid which alter intercellular communication, induce peroxisome proliferation and may promote tumor production. Significant variability in trichloroethylene metabolism in 23 human haptic microsomal samples was reported by Lipscomb *et al*.[37] It was also demonstrated that the trichloroethylene metabolism depended on enzymatic activities of the cytochrome system. Their data indicated humans were not uniform in their capacity for CPY dependent metabolism of trichloroethylene and increased activity might increase susceptibility to trichloroethylene-induced toxicity in humans. These observations are compatible with the variability reaction that depends on nutritional factors, enzyme induction factors, hormonal factors and interaction with other environmental chemicals, prescription medications and general health conditions, and explains the variable reports regarding trichloroethylene and level of liver toxicity in individuals studied. In a predisposed individual (for example, a patient who is on medications or alcohol), it is highly likely that exposure to trichloroethylene will trigger or add onto the genesis of a wide variety of liver diseases.

The International Agency for Research on Cancer (IARC) Working Group reviewed experimental animal studies that evaluated the carcinogenicity of trichloroethylene.[38] In four studies in B6C3F1 mice, treatment with trichloroethylene by gavage increased the incidence of hepatocellular adenoma and hepatocellular carcinoma in males and/or females. In one study in Swiss mice treated by inhalation, there was an increase in the incidence of malignant hepatoma in males. The evaluation of trichloroethylene carcinogenicity took into account toxicokinetic data for trichloroethylene and trichloroethylene metabolites, which were consistent qualitatively, for absorption, distribution, metabolism, and excretion across species and routes of exposure.[39] Mice, rats, and humans all metabolize trichloroethylene *via* similar pathways. As a result, it is evident that toxicokinetic data support the biological plausibility of trichloroethylene carcinogenicity in humans. This is because humans and laboratory animals have similar mixtures of trichloroethylene and trichloroethylene metabolites in target tissues known to cause cancer.

Epidemiological studies found that occupational exposure to trichloroethylene was associated with an excess incidence of liver cancer. Several cohort studies and meta-analyses have been reported in support of significant association between trichloroethylene exposure and excess liver cancers in humans. Raaschou-Nielsen *et al*.[40] reported a statistically significant increased risk of liver cancer among trichloroethylene-exposed workers (RR = 1.35, 95% CI = 1.02 - 1.75). Likewise, Griffith et al.[41] reported increased risk of liver cancer among female workers exposed to trichloroethylene (PIR = 4.04, p value = 0.039). Additional cohort studies that report statistically significant increased risk of liver cancer among trichloroethylene-exposed groups include Hansen *et al*.[42] (RR = 1.93, 95% CI = 1.19 - 2.95), Ritz (RR = 12.1, 95% CI = 1.03 - 144, with 15-year lag rate), and Dubrow *et al*.[44] (PMR = 297, $p \leq 0.05$). Wartenberg *et al*.[45] reviewed over 80 published papers and letters on the cancer epidemiology of people exposed to trichloroethylene. Evidence for excess cancer incidence among occupational cohorts was found for liver cancer (RR = 1.9, 95% CI = 1.0 - 3.4). More recently, a meta-analysis conducted by the U.S. Environmental Protection Agency found the risk of liver cancer was significantly elevated in studies with high potential for trichloroethylene exposure (RR = 1.29, 95% CI = 1.07 - 1.56).[46]

As of 2014, the IARC has classified trichloroethylene as Group 1 – carcinogenic to humans. IARC has concluded that, "There is sufficient evidence in humans for the carcinogenicity of trichloroethylene. Trichloroethylene causes cancer of the kidney. A positive association has been observed between exposure to trichloroethylene and non-Hodgkin lymphoma and liver cancer. There is sufficient evidence in experimental animals for the carcinogenicity of trichloroethylene."[47]

These findings add to the societal increased risk of liver cancer, among other causes such as hepatitis C virus, liver cirrhosis and fatty liver infiltration. It is unclear on whether patients with underlying liver disease has a substantially increased risk after short-term exposure to very high levels of solvents, such as trichloroethylene. It is of interest that trichloroethylene and its metabolites increase glucagon and bile acid production. Furthermore, questions remain whether medications that alter the liver P450 enzymes activity may play a role in conjunction with other intracellular enzymes. Although some experi-

mental animal studies and in vitro studies have been conducted, human data is scarce at this point.

19.7.6 PERCHLOROETHYLENE

Perchloroethylene is a colorless liquid (also called tetrachloroethylene or tetrachloroethene) used as a dry cleaning agent, chemical intermediate and metal degreasing agent. Perchloroethylene has also been used as an insulating fluid and cooling gas in electrical transformers, in paint removers, printing inks, adhesives, paper coating and leather treatment; in aerosol formulations, as an extractant for pharmaceuticals, to remove soot from industrial boilers, and as an antihelminthic agent. Perchloroethylene is a volatile liquid, as such when it is released to surface water or surface soil, it tends to volatilize quickly. Perchloroethylene is also mobile in soil and has the potential to leach below the soil surface and contaminate groundwater. Perchloroethylene can also biodegrade to trichloroethylene, dichloroethylene, vinyl chloride, and ethene through reductive dechlorination, therefore the exposed population can also be exposed to the degradation product, trichloroethylene, which is often found as a contaminant in products with perchloroethylene. The liver is the target organ in humans, mainly in reports of accidental exposure to a high concentration. Meckler *et.al*.[48] described liver damage in a woman exposed occupationally to perchloroethylene fumes documented by a liver biopsy. Other investigators have shown that exposure to perchloroethylene is associated with elevation of liver enzymes, jaundice, and enlarged liver.[49,50] Experimental animal studies also have shown liver damage by inhalation of perchloroethylene.[51-54] Liver necrosis occurred in experimental mice exposed to 100 and 200 ppm of perchloroethylene for 103 weeks.[55] Experimental animals exposed orally to perchloroethylene have been shown to develop liver changes similar to those produced by inhalation studies, and mice are more sensitive than rats to perchloroethylene induced liver toxicity. Humans exposed by oral routes to perchloroethylene except for heavy doses commonly have not shown significant changes other than obstructive jaundice and enlarged liver reported in an infant exposed to perchloroethylene via breast milk.[56] It is highly likely that perchloroethylene is a hepatotoxic agent at high doses, and probably at low doses as well in susceptible individuals with other environmental exposures, are taking prescription medications, have alcoholism, nutritional and/or genetic factors, or preexisting disease of the liver.

The IARC Working Group reviewed experimental animal studies that evaluated the carcinogenicity of perchloroethylene. In mice given perchloroethylene in corn oil by gavage, there were increases in the trend and in the incidence of hepatocellular carcinoma in males and females.[57,58] In two separate studies in mice of two different strains exposed by inhalation, significant increases in the incidence of hepatocellular adenoma, carcinoma, and adenoma or carcinoma (combined) were observed in males and females.[59,60]

There are numerous cancer studies in humans examining the risk from exposure to perchloroethylene. It is evident that perchloroethylene can increase cancer risks in humans and is carcinogenic in animals as well. There are epidemiological studies that link exposure to perchloroethylene and increased risk of liver cancer in humans. A case-control study Lynge and Thygesen[61] reported an increased liver cancer incidence in Danish female dry cleaning and laundry workers with a follow-up study by Lynge[62] finding that

the increased liver cancer incidence in the female Danish workers was associated with the laundry workers (SIR = 3.4, 95% CI = 1.4 - 7.0). In a report by Hernberg *et al*.[63] a survey among 377 exposed people to various solvents including perchloroethylene compared to 385 unexposed controls indicated an increased incidence of liver cancer in females.

The National Toxicology Program has categorized perchloroethylene as reasonably anticipated to be a human carcinogen.[64] The IARC has listed PCE as Group 2A – probably carcinogenic to humans. The IARC found that, "Positive associations have been observed for cancer of the bladder. There is sufficient evidence in experimental animals for the carcinogenicity of perchloroethylene."[65] Epidemiologic data suggest a possible increased incidence of liver in humans, but data are limited.

19.7.7 DICHLOROMETHANE

Dichloromethane is a colorless liquid that has a mild sweet odor. It is used widely in the industry as a solvent and a paint stripper. It is commonly found in spray painting operations, automotive degreasing, in cleaners and in household products. Stewart *et al*.[66] found no changes in liver enzymes in patients exposed for a period of 6 weeks to levels of dichloromethane *via* inhalation from 50 to 500 ppm. On the other hand, Ott *et al*.[67] showed an elevation in bilirubin in workers exposed to dichloromethane up to 475 ppm. In experimental animals, dichloromethane exposure has been associated with fatty changes of the liver and elevated liver enzymes. Norpoth *et al*.[68] showed hepatic microsomal enzyme elevation at 500 ppm of dichloromethane exposure for 10 days, and others have shown significant fatty changes of the liver upon exposure of mice and rats for 100 days to 75-100 ppm of trichloroethylene.[69-71] When exposure to dichloromethane continued for 2 years, there was increased evidence of pathological changes and fatty liver changes.[72-74] The overall weight of the data supports a hepatotoxic effect of dichloromethane on the liver.

19.7.8 1,2-DICHLOROPROPANE

1,2-Dichloropropane is a man-made, colorless liquid with a chloroform-like odor. It is primarily used as a chemical intermediate in the production of other organic chemicals, such as propylene, carbon tetrachloride and tetrachloroethylene. Other uses for 1,2-dichloropropane include paint stripping, furniture finishes, greasers, cleaning products, glues and adhesives, and insecticides. Wang *et al*.[75] found that 1,2-dichloropropane exposure caused significant liver necrosis in mice. It was hypothesized that 1,2-dichloropropane inhibited the mitochondrial respiratory chain complex I-IV activities, resulting in mitochondrial dysfunction and extreme ATP consumption. Additionally, 1,2-dichloropropane impaired mitochondrial defense ability by inhibiting the mitochondrial glutathione S-transferase 1 (MGST1) activity, causing additional liver damage. A 13-week study of mice exposed to 1,2-dichloropropane *via* inhalation showed significant swelling, necrosis, fatty changes, vacuole change and mineralization of centrilobular hepatocytes.[76] Dose-dependent increases in incidence of hepatic necrosis and hepatomegaly were observed in long-term bioassays in mice exposed to 1,2-dichloropropane by savage for 2 years.[77] There have been several case reports of workers exposed to 1,2-dichloropropane found to have severe liver damage and elevated liver enzymes.[78,79] Kumagai *et al*.[80] reviewed the occupational

and medical history of ten patients diagnosed with cholangiocarcinoma and had worked proof-printing workers. These workers were exposed to 1,2-dichloropropane for 6 to 17 years. AST and ALT levels were elevated in exposed workers. For six patients, levels of γ-glutamyl transpeptidase (γ-GTP) were found to have exceeded the normal range during the exposure period. Two of these six patients were diagnosed with cholangiocarcinoma during the exposure. The other four patients were diagnosed 1-9 years after exposure ended. The remaining four patients had γ-GTP levels that were within the standard range during the exposure period, but had increased γ-GTP levels thereafter, subsequently diagnosed with cholangiocarcinoma 4-10 years after termination of exposure. A follow-up study found an exposure-response relationship between cumulative exposure to 1,2-dichloropropane and increased incidence of cholangiocarcinoma among proof-printing workers.[81] Cholangiocarcinoma is a rare cancer and substantial human reporting of workers exposed to 1,2-dichloropropane is likely missed, secondary to not obtaining occupational history.

On the basis of experimental and epidemiological findings, the IARC has classified trichloroethylene as Group 1 – carcinogenic to humans. IARC has concluded that, "There is sufficient evidence in humans for the carcinogenicity of 1,2-dichloropropane. 1,2-Dichloropropane causes cancer of the biliary tract (confirmed as cholangiocarcinoma)."[82]

19.7.9 1,1,1-TRICHLOROETHANE

1,1,1,-Trichloroethane is a colorless solvent which is man-made. It is produced by industry and is used in commercial products as a solvent. It is heavily used in glue and paint, as well as a degreaser and metal parts manufacturing. It is also used in some household products such as spot cleaners, glues and aerosol sprays. 1,1,1,-Trichloroethane is commonly found in soil and water as a contaminant. Brief single exposures to very high levels of 1,1,1-trichloroethane and a moderate high concentration have been shown to cause elevation of urobilinogen in patients.[83] This type of finding indicates reduced bile excretion and some intrinsic liver damage. Stewart *et al*.[84] showed in patients accidentally exposed to a high concentration of 1,1,1-trichloroethane increased levels of urinary urobilinogen for approximately 4 days following the exposure. While looking at enzyme levels in the blood after exposure to 1,1,1-trichloroethane, there was no evidence of elevated serum enzyme levels.[83-87] Case studies of people exposed to a high concentration of 1,1,1-trichloroethane did not show elevated liver enzymes.[84,88] Histopathological examination of the liver of patients who died following inhalation of a high concentration of 1,1,1-trichloroethane showed minimal changes, mainly those of mild fatty changes of the liver.[89,90] Kramer *et al*.[91] studied humans at low levels of exposure and found minor changes in liver enzymes. Experimental animal studies showed mild histopathological changes and effects on liver enzymes.[92,93] Truffert *et al*.[94] showed that intermittent duration and intermittent exposure to a low concentration of 1,1,1-trichloroethane produced a 67% increase in the synthesis of DNA of the livers of exposed rats, and concluded that the DNA synthesis measurements may be a more sensitive indicator of liver damage than just measurements of liver enzymes. McNutt *et al*.[95] showed histological damage following exposure to 1,1,1-trichloroethane with hepatocyte necrosis. The most commonly reported effects of 1,1,1-trichloroethane on the liver in experimental animals increased fat accumulation.[96-98] The

function of duration of exposure played an important role in experimental rats, and was seen in those who were exposed for 7 hours, but was not seen in those exposed for 2 hours to high levels. Savolainen *et al*.[99] showed that exposure to a moderate concentration in experimental animals caused decreased microsomal cytochrome P450 enzyme activity. Overall, the animal studies and human studies suggest an effect of 1,1,1-trichloroethane on the liver, but the severity appears to be related to the dose and duration of the exposure.

19.7.10 STODDARD SOLVENT

Stoddard solvent is a widely used synthetic, organic solvent that comes from the refining of crude oil. It is a petroleum mixture made from distilled alkanes, cycloalkanes (naphthenes), and aromatic compounds. It also goes by other names such as Varsol 1, TexSolve S and others. It is commonly used as a paint thinner, as solvents in some types of photocopier toners, printing inks, adhesives, dry cleaning and as a general cleaner and degreaser. Dossing *et al*.[100] described painters who were exposed to non-specified levels of Stoddard solvents and other chemicals for chronic periods, and elevated levels of serum alanine aminotransferase, but other functions were normal and normal liver biopsies. Twelve men exposed to 610 mg per cubic meter of vaporized Stoddard solvents for a period of 6 hours had no changes in serum glucose, triglycerides, cholesterol or urate.[101] Flodin *et al*.[102] has studied a group of patients exposed to a variety of solvents, including Stoddard solvents and showed normal liver function tests, but an elevated γ-glutamyl transferase. Hane *et al*.[103] showed that a group of painters exposed to Stoddard solvents had no significant abnormality of liver enzymes. Studies in experimental animals showed minimal fatty changes of the liver.[104-107] The data from experimental animals and humans suggests a potential hepatotoxic effect of Stoddard solvents, but additional studies and a case by case evaluation is required.

19.7.11 NON-HALOGENATED SOLVENTS

While the halogenated hydrocarbons discussed here include carbon tetrachloride, chloroform, trichloroethylene, perchloroethylene, dichloromethane, 1,2-dichloropropane, 1,1,1-trichloroethene and Stoddard solvent as significantly hepatotoxic, the literature on the toxicity of the non-halogenated hydrocarbons yielded a combination of positive and negative studies. Several studies looking into the hepatotoxicity of both aliphatic solvents such as kerosene, hexane and aromatics such as xylene, toluene and styrene have reported mixed results. Xylene is an aromatic hydrocarbon which is used heavily in the industry, as well as medical technology as a solvent.

19.7.12 XYLENE

Xylene commonly has been reported as an impurity, along with ethylbenzene, phenol, benzene and toluene, in varying amounts in organic solvents.[108] To evaluate the effects of xylene in experimental animals, Toftgard *et al*.[109] studied rats which were exposed for three days by inhalation to xylene and to a mix of xylene isomers. Hepatic cytochrome P450 concentration increased as well as C reductase activity, and NADPH cytochrome C reductase activity. Furthermore, xylene and its isomers were able to modify the metabolism of other potentially toxic substances. In addition to these biochemical changes, the investigators found that xylene increased liver body weight, most-likely secondary to pro-

liferation of the endoplastic reticulum. These studies show that at these levels, xylene induced cytochrome P450 activity and NADPH cytochrome C reductase activity, but was not associated with significant pathological abnormalities. On the other hand, these same investigators, concluded that the capacity of xylene and xylene isomers to induce hepatic cytochrome P450 suggests the possibility of synergistic toxic effects from simultaneous exposure to xylene and substances metabolically activated by these cytochromes P450. Therefore, exposure to a mixture of solvents which also includes xylene will increase the toxicity because xylene is a synergistic liver toxicant. For instance, the formation of 2-hexanoyl a metabolic precursor of 2,5-hexanedione, which is the main metabolite found in urine of workers exposed to n-hexane, is increased following xylene treatment.[110]

19.7.13 TOLUENE

Industrial use of toluene is wide. It is commonly used in paints, paint thinners, fingernail polish, lacquers, adhesives, rubbers and in the printing industry. Toluene is extensively metabolized by the liver; however, the liver does not appear to be a primary target for toluene toxicity. A study of printing factory workers who were exposed to toluene at a concentration of less than 200 ppm, showed minimal changes of liver enzymes.[111] The cohorts included 289 men, of which 8 showed elevated liver enzymes, and 6 of them had enlarged livers. Seven of those patients had liver biopsies that showed some centrally lobular and periportal fat accumulation, and Kupffer cell hyperplasia. The study by Svensson *et al*.[112] has looked at 47 rotogravure workers occupationally exposed to toluene at a concentration of 80 ppm for 3-39 years, and showed a significant elevation of liver enzymes, finding of chemical hepatitis. Seiji *et al*.[113] has examined a group of 157 female shoemakers who were exposed to toluene at levels of 7-324 ppm from 2-14 months, and showed no significant elevation of commonly measured liver functions. Another study that looked at 47 Swedish paint industry workers who were exposed for more than a 10 year period of time to organic solvents which included xylene, toluene, isobutanol, n-butanol, mineral spirits, methyl acetates, dichloromethane, methyl ethyl ketone and isopropanol did not show any changes in liver enzymes.[114] However, this study was constrained by a small cohort size, along with exposures to multiple solvents, and therefore limiting the power to detect the effects of toluene on the liver of exposed workers. Experimental animals exposed to toluene at concentrations of 533 to 800 ppm for 7 days showed increased liver weights, but no significant morphological changes by microscopy. Electron microscopical examination revealed ultrastructural changes which were compatible with changes in the cytochrome P-450 concentrations. Others have shown no effect on liver size or liver functions.[115-118] Overall the data seems to suggest that toluene may cause liver damage in certain industries, and especially in synergism with other solvents. It is highly likely that toluene can cause liver damage from chemical hepatitis to necrosis and fibrosis, especially in predisposed individuals.

19.7.14 SOLVENT MIXTURES

Various solvent mixtures have been reported as hepatotoxic, Fischbein *et al*.[119,120] reported abnormal liver functions in chemical workers exposed to a mixture of solvents. It was suggested that bile acids as indicators of hepatic function will be utilized as markers of injury.

Franco *et al.*[121] examined a group of workers exposed to organic solvents, and used the criteria addressing exposure to solvent mixtures for over two years, daily ethanol consumption less than 50 grams, no history of hepatic disease, no drug intake in the previous three months. Workers were exposed to between 6 and 9 solvents, mostly toluene, xylene, acetone, methyl acetate, and butanol ethyl acetate. The mean levels of liver enzyme activities in the exposed and the control group were similar. The mean serum bile acid contents were statistically and significantly increased in the exposed group compared to the controlled group. The authors concluded that the observation of higher serum bile acid levels in the group of workers currently exposed to organic solvents might be explained by a change in hepatocyte function, and that the commonly followed parameters of liver enzymes may be insensitive to these preliminary initial changes in liver function. Conventional liver function tests seem to be rather insensitive to early detect liver damage from solvents exposure. Early detection is crucial but is probably missed since the standard liver functions tests are not sensitive enough to detect early liver damage from solvents. What that means is by the time the patient is seen by the doctor with liver fibrosis or necrosis and solvent toxicity, it is already in advanced stages.

Chen *et al.*[122] evaluated the effects of solvents exposure on liver functions, specifically looking at γ-glutamyl transferase activity. They have studied the effects of xylene and toluene. The median air concentration was evaluated in the exposed workers who used mixed solvents in the process of spray booth car painting. These investigators showed that γ-glutamyl transferase activities increased independently with both an increased consumption of alcohol and exposure to a mixture of solvents. The investigators concluded that an increase in γ-glutamyl transferase activity may be a form of enzyme induction rather than a marker for cellular damage.

Kurpper *et al.*[123] examined the effect of mixed organic solvents on liver enzymes activity in car painters and found that at the exposure level of that study (at that time was 1/2 the level recommended by the regulatory agencies) the liver enzyme activities of car painters were not affected by exposure to mixed solvents. A follow-up study by Franco *et al.*[124] examined serum bile acid concentrations as a marker of liver functions in a group of workers exposed to organic solvents. They showed a significant increase in concentration of serum bile acids with normal liver enzymes. These researchers concluded that this indicated a very sensitive and early marker of liver function abnormality in patients exposed to mixed solvents and might be explained as an early sign of liver dysfunction. While it was not possible to state which solvent caused what type of abnormality, the authors concluded that conventional liver function tests seem to be rather insensitive for early liver disease detection, and normal measurement does not rule out the existence of subclinical disease. Therefore, an elevation of serum bile acid indicates early potential hepatotoxicity from mixed organic solvents. From a clinical point of view, this study suggests that exposure to mixture of solvents in an industrial setting may cause liver damage that is subclinical and initially undetected, unless liver enzymes and bile acids are measured. It seems likely that the initial stage of liver damage in patients exposed to solvent mixtures is commonly missed.

Lindbohm *et al*.[125] conducted a cohort study to examine the risk of liver cancer and exposure to organic solvents. Using the national Finnish Cancer Registry, the investigators identified 1691 male and 783 female cases of liver cancer. The results suggested an increased risk of liver cancer with these types of solvent mixtures (aromatic hydrocarbons and chlorinated hydrocarbons).

Synergistic hepatotoxicity of N,N-dimethylformamide (DMF) and carbon tetrachloride was examined.[126] Treatment of rats with either DMF or CCl_4 resulted in small increase in plasma transaminases and lactate dehydrogenase activities, but combined treatment with both solvents markedly increased blood biochemical changes. Single dose of CCl_4 enhances liver toxicity of DMF.

The hepatotoxic effects of co-exposure to 1,2-dichloropropane and dichloromethane, which occurs frequently among printing workers, has been studied.[75] Wang *et al*. found that co-exposure of dichloromethane enhanced the hepatotoxicity of 1,2-dichloropropane in mice. When exposed to both solvents, they observed delays in increase of serum AST and ALT levels and drastically reduced ATP content in mice when compared with 1,2-dichloropropane exposure alone.

19.7.15 SUMMARY

In summary, from the available data, it is clear that exposure to solvents and hepatotoxicity must be evaluated in context of the individual variability, exposure to mixture of solvents, and synergistic toxicity.

*Disclosure: Some of the materials in this chapter have been added from court declarations of Dr. Brautbar.

REFERENCES

1 Jones DS, ed, Detoxification: **A Clinical Monograph**, *Institute for Functional Medicine, Inc*., 1999.
2 Ungar, *Viertelsjarisch f. gericht. Med*., **47**:98 (1887).
3 Ostertag R, *Virchows Arch.*, **118**:250 (1889).
4 Stiles HJ and McDonald S, *Scott Med Surg J*, **15**:97 (1904).
5 Recknagal RO, Pharmacol Rev, **19**:145 (1967).
6 Recknagel RO and Glinde EA, *CRC Crit Rev Toxicol*, **2**:263 (1973).
7 Zimmerman HJ, **Hepatotoxicity: The Adverse Effects of Drugs and Other Chemicals on the Liver**, *Appleton-Century-Crofts*, New York, 1978.
8 Mitchell JR, et al. In **Concepts in Biochemical Pharmacology,** Part 3, JR Gillette, JR Mitchell and PS Randall (eds), *Springer-Verlag,* Berlin, 383-419 (1975).
9 Mitchell JR, *et al., Drug Met Disp*, **1**:418 (1973).
10 Rouiller CH, In **The Liver**, Volume II, CH Rouiller (ed), *Academic Press*, New York, 335-476 (1964).
11 Von Oettingen WF, **The Halogenated Hydrocarbons of Industrial and Toxicological Importance**, Elsevier, Amsterdam (1964).
12 Browning E, **Toxicology and Metabolism of Industrial Solvents**, *Elsevier*, Amerstdam (1965).
13 Von Oettingen WF, The **Halogenated Aliphatic, Olephinic Cyclic, Aromatic and Aliphatic-Aromatic Hydrocarbons Including the Halogenated Insecticides. Their Toxicity and Potential Dangers**. *U.S. Dept. HEW, U.S. Govt Printing Office*, Washington, D.C. (1955)
14 Droz PO, *et al*., *Br J Ind Med*, **46**(7):447-460 (1989).
15 Meyer J and Pessoa SB, *Am J Trop Med*, **3**:177 (1923).
16 Reynolds ES, *Biochem Pharmacol*, **21**:2255 (1972).
17 Slater TF, *Nature* (Lond), **209**:36 (1966).
18 Jennings RB, *Arch Pathol*, **55**:269 (1955).
19 Klatskin G, **Toxic and Drug Induced Hepatitis. In Diseases of the liver**, 4th Ed, L Schiff (ed), *JB Lippincott,* Philadelphia, 604-710 (1975).

20 Slater TF, Free Radical Mechanisms in Tissue Injury, *JW Arrowsmith, Ltd*, Bristol, 118-163 (1972).
21 Le Page RN and Dorling PR, *Aust J Exp Biol*, **49**:345 (1971).
22 Rufeger U and Frimmer M, *Arch Pharmacol*, **293**:187 (1976).
23 Agency for Toxic Substances and Disease Registry (ATSDR), Toxicological Profile for Carbon Tetrachloride, ATSDR, Atlanta, Georgia (2005).
24 Nothnagel, *Berlin Klin Wchnschr*, **3**:31 (1866).
25 Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological Profile for Trichloroethylene (TCE), ATSDR, Atlanta, Georgia (2014).
26 McConnell G, Ferguson DM and Pearson CR. *Endeavour*, **34**:13-8 (1975).
27 Davidson IW and Beliles RP, *Drug Metabolism Rev*, **23**:493-599 (1991).
28 Bond GR, *Clinical Toxicology*, **34**(4):461-466 (1996).
29 Guzelian PS, Disorders of the Liver, **In Principles and Practice of Environmental Medicine**, Aylce Bezman Tacher (eds), *Plenum Medical Book Company*, New York, 319-333, (1992).
30 Baerg RD and Kimberg DV, *Annals of Internal Medicine*, **73**:713-720 (1970).
31 Clearfield HS, *Digestive Digest*, **15**:851-856 (1970).
32 Fielder RJ, Loweing RK and Shillaker RO, *Toxic Rev*, **6**:1-70 (1982).
33 Litt I and Cohen M, *New England Journal of Medicine*, **281**:543-544 (1969).
34 Sax N, **Dangerous Properties of Industrial Chemicals**, 4th Edition, *Van Nostrand Reinhold Co*, Toronto, Canada, 1186 (1975).
35 Berman E, *et al*., *J Tox Environ Health*, **45**(2):127-143 (1995).
36 Barton HA and Das S, *Regul Toxicol Pharmacol*, **24**:269-285 (1986).
37 Lipscomb JC, Garrett CM and Snawder JE., *Toxicol Appl Pharmacol*, **142**:311-318 (1997).
38 Maltoni C, *et al*., *Ann N Y Acad Sci*, **534**:316-42 (1988).
39 Lash LH, *et al*., *Environ Health Perspect*, **108** Suppl 2:177-200 (2000).
40 Raaschou-Nielsen O, *et al.*, *Am J Epidemiol*, **158**:1182-92 (2003).
41 Griffith WT, *et al*., **Occupational Health Study of Former View-Master Workers Exposed to Trichloroethylene (TCE)**. *Pacific University*, (2011)
42 Hansen J, *et al*., *J Natl Cancer Inst*, **105**:869-77 (2013).
43 Ritz B, *J Occup Environ Med*, **41**:556-66 (1999).
44 Dubrow R and Gute DM, *Am J Ind Med*, **12**:579-93 (1987).
45 Wartenberg D, Reyner D and Scott CS, *Environ Health Perspect*, **108** Suppl 2:161-76 (2000).
46 Scott CS and Jinot J, *Int J Environ Res Public Health*, **8**:4238-72 (2011).
47 International Agency for Research on Cancer (IARC). Trichloroethylene, tetrachloroethylene, and some chlorinated agents. *IARC Monogr Eval Carcinog Risks Hum*, **106** (2014).
48 Meckler LC and Phelps PK, *J Am Med Assoc*, 197:662-663 (1966).
49 Coler HR and Rossmiller HR, *AMA Arch Ind Hyg Occup Med*, **8**:227-233 (1953).
50 Hake CL and Stewart RD, *Environ Health Perspect*, **21**:231-238 (1977).
51 Kyline B, *et al.*, *Acta Pharmacol Toxicol*, **20**:16-26 (1963).
52 Kyline B, Sumegi I and Yllner S, *Acta Pharmacol Toxicol*, **22**:379-385 (1965).
53 Carpenter CP, *J Ind Hyg Toxicol*, **19**:323-336 (1937).
54 Rowe VK, *et al*., *AMA Arch Ind Hyg Occup Med*, **5**:566-579 (1952).
55 National Toxicology Program (NTP), *Natl Toxicol Program Tech Rep Ser*, **311**:1-197 (1986).
56 Bagnell PC and Ellenberger HA, *Can Med Assoc J*, **117**:1047-1048 (1977).
57 National Toxicology Program (NTP), *Natl Cancer Inst Carcinog Tech Rep Ser*, **13**:1-83 (1977).
58 Weisburger EK, *Environ Health Perspect*, **21**:7-16 (1977).
59 National Toxicology Program (NTP), *Natl Toxicol Program Tech Rep Ser.,* **311**:1-197 (1986).
60 Japan Industrial Safety Association (JISA). **Carcinogenicity study of tetrachloroethylene by inhalation in rats and mice**. *Hadano*, Japan (1993).
61 Lynge E and Thygesen L, *Scand J Work Environ Health*, **16**:108-12 (1990).
62 Lynge E, *J Occup Med*, **36**:1169-73 (1994).
63 Hernberg S, *et al*., *Scand J Work Environ Health*, **14**:356-65 (1988).
64 National Toxicology Program (NTP). Tetrachloroethylene. Rep Carcinog. 2016;14:1-3
65 International Agency for Research on Cancer (IARC). Tetrachloroethylene. *IARC Monogr Eval Carcinog Risks Hum*, **106** (2014).
66 Stewart RD, *et al.,* Methylene Chloride: Development of Biologic Standard for the Industrial Worker by Breath Analysis. Report of the National Institute of Occupational Safety and Health, Cincinnati, OH, by the Medical College of Wisconsin, Milwaukee, Wisconsin, NTIS No. PB83-245860 (1974).
67 Ott MG, *et al.*, *Scand J Work Environ Health,* **9**(Suppl 1):17-25 (1983).

68 Norpoth K, *et al*., *Int Arch Arbeitsmed*, **33**:315-321 (1974).
69 Haun CC, *et al*., Continuous Animal Exposure to Low Levels of Dichloromethane. In: Proceedings of the Third Annual Conference on Environmental Toxicology. Wright Patterson Air Force Base, OH: Aerospace Medical Research Laboratory, 199-208, AMRL-TR-72-130, (1982).
70 Kjellstrand P, *et al*., *Acta Pharmacol Toxicol* (Copenh), **59**:73-79 (1986).
71 Weinstein RS and Diamond SS, Hepatotoxicity of dichloromethane (methylene chloride) with continuous inhalation exposure at a low dose level. In: Proceedings of the Third Annual Conference on Environmental Toxicology. Wright Patterson Air Force Base, OH: Aerospace Medical Research Laboratory, 209-220, AMRL-TR-72-130, (1972).
72 Burek JD, *et al*., *Fund Appl Toxicol*, **4**:30-47 (1984).
73 Nitschke KD, *et al*., *Fundam Appl Toxicol*, **11**:48-59 (1988).
74 National Toxicology Program (NTP), *Natl Toxicol Program Tech Rep Ser*., **306**:1-208 (1986).
75 Wang H, *et al*., *J Appl Toxicol*, 1-11 (2018).
76 Matsumoto M, *et al*., *Inhal Toxicol*, **25**:435-443 (2013).
77 National Toxicology Program (NTP), *Natl Toxicol Program Tech Rep Ser*, **263**:1-182 (1986).
78 Lucantoni C, Grottoli S and Gaetti R. *Toxicol Appl Pharmacol*, 117:133 (1992).
79 Pozzi C, *et al*., *Br J Ind Med,* **42**:770-772 (1985).
80 Kumagai S, *et al*., *J Occup Health*, **56**:279-284 (2014).
81 Kumagai S, *et al*., *Occup Environ Med*, **73**:545-552 (2016).
82 International Agency for Research on Cancer (IARC). 1,2-Dichloropropane. *IARC Monogr Eval Carcinog Risks Hum*, **110** (2017).
83 Stewart RD, *et al*., *Am Ind Hygn Assoc J*, **22**: 252-262 (1961).
84 Stewart RD, *J Am Med Assoc*, **215**:1789-1792 (1971).
85 Stewart RD, *et al*., *Arch Environ Health*, **19**:467-472 (1969).
86 Dornette WH and Jones JP, *Anesth Analg*, **39**:249-252 (1960).
87 Torkelson TR, *et al.*, *Am Ind Hygn Assoc J*, **19**:353-362 (1958).
88 Wright MF and Strobl DJ, *J Am Osteopath Assoc*, **84**:285-288 (1984).
89 Caplan YH, Backer RC and Whitaker JQ, *Clin Toxicol*, **9**:69-74 (1976).
90 Hall FB and Hine CH, *J Forensic Sci*, **11**:404-413 (1966).
91 Kramer CG, *et al*., *Arch Environ Health*, **33**:331-342 (1978).
92 Carlson GP, *Lif Sci* (United States), **13**:67-73 (1973).
93 Gehring PJ, *Toxicol Appl Pharmacol*, **13**:287-298 (1968).
94 Truffert L, *et al*., *Arch Mal Prof Med Trav Secur Soc*, **38**:261-263 (1977).
95 McNutt NS, *et al.*, *Lab Invest*, **32**:642-654 (1975).
96 Takahara K, Okayama *Igakkai Zasshi*, **98**:1099-1110 (1986).
97 Adams EM, *et al.*, *Am Med Assoc Arch Ind Hyg Occup Med*, **1**:225-236 (1950)
98 Herd PA, Lipsky M and Martin HF, *Arch Environ Health*, **28**:227-3 (1974).
99 Savolainen H, *et al*., *Arch Toxicol*, **38**:229-237 (1977).
100 Dossing M, Arlien-Soborg P and Petersen LM, *Eur J Clin Invest*, **13**:151-158 (1983).
101 Pederson LM and Cohr KH, *Acta Pharmacol Toxicol*, **55**:317-324 (1984).
102 Flodin U, Edling C and Axelson O, *Am J Ind Med*, **5**:287-295 (1984).
103 Hane M, *et al*., *Scand J Work Environ Health*, **3**:91-99 (1977).
104 Jenkins LJ, *et al.*, *Toxicol Appl Pharmacol*, **18**:53-59 (1971).
105 Carpenter CP, *et al*., *Toxicol Appl Pharmacol*, **32**:246-262 (1975).
106 Carpenter CP, *et al*., *Toxicol Appl Pharmacol*, **32**:282-297 (1975)
107 Phillips RD and Egan GF, *Fundam Appl Toxicol*, **4**:808-818 (1984).
108 International Agency for Research on Cancer (IARC), *Monographs on the Evaluation of Carcinogenic Risks to Humans*, Volumed 47:125-156; IARC, Lyon, France Volumes **43-48** (1987-1990).
109 Toftgard R and Nilsen OG, *Toxicology*, **23**(2-3):197-212 (1982).
110 Frommer U, Ullrich V and Orrenius S, *FEBS Lett*, **41**(1):14-16 (1974).
111 Guzelian P, Mills S and Fallon HJ, *J Occup Med*, **30**:791-796 (1988).
112 Svensson BG, *et a*l., *Br J Ind Med*, **49**:402-408 (1992).
113 Seiji K, *et al*., *Ind Health*, **25**:163-168 (1987).
114 Lundberg I and Hakansson M, *Br J Ind Med*, **42**:596-600 (1985).
115 Bruckner JV and Peterson RG, *Toxicol Appl Pharmacol*, **61**:27-38 (1981).
116 Bruckner JV and Peterson RG, *Toxicol Appl Pharmacol*, **61**:302-312 (1981).
117 Kjellstrand P, *et al.*, *Acta Pharmacol Toxicol*, **57**:242-249 (1985).
118 National Toxicology Program (NTP), *Natl Toxicol Program Tech Rep Ser*, **371**:1-253 (1990).

119 Sotaniemi EA, *et al*., *Acta Med Scand*, **212**:207-215 (1982).
120 Fischbein A, Ross RR and Lerman Y, *Lancet*, **1**:129 (1983).
121 Franco G, *et al.*, *Br J Ind Med*, **46**:141-142 (1989).
122 Chen JD, *et al*., *Brit J Ind Med*, **48**:696-701 (1991).
123 Kurppa K and Husman K, *Scand J Work Environ Health*, **8**:137-140 (1982).
124 Franco G, *et al*., *Int Arch Occup Environ Health*, **58**:157-164 (1986).
125 Lindbohm ML, *et al*., *Int J Cancer,* **124**:2954-2559 (2009).
126 Kim TH, *et al*., *Chem Biol Interact*, **184**:492-501 (2010).

19.8 TOXICITY OF ENVIRONMENTAL SOLVENT EXPOSURE FOR BRAIN, LUNG AND HEART

Kaye H. Kilburn
School of Medicine, University of Southern California Los Angeles, CA, USA

This chapter considers the neurobehavioral effects of environmental exposures to organic solvents. Much information applicable to environmental or community exposures usually at home came from animal experiments, brief human exposures in chambers and prolonged workplace exposures. The mode of entry of solvent chemicals into the body is almost always by inhalation not by contact or ingestion.[1] While inhalational exposures to single chemicals occur, their mixtures are usual, making measurements more complex. Effects from animal experiments, and human exposures in chambers, and workplace exposures are usually consistent and help predict environmental effects. The major categories of environmental exposures to solvents are from petroleum refining to consumer use indoors, Table 19.8.1. Sometimes adverse human effects are from surprisingly small environmental doses, an order of magnitude or two lower than those needed for workplace effects. One possible explanation is the greater sensitivity of measurements but many of the methods were adapted from studies of workers.[2]

Table 19.8.1. Sources of environmental exposure to solvents.

Processes	Chemicals	Media	Example
Losses during refining and chemical production	MTBE	air	Seymour, IN, Santa Maria, CA
Losses from use in industry	TCE + toluene	water surface, groundwater, air, water	Phoenix, AZ, Motorola, Printers, Baton Rouge, LA, Abuse-gluesniffers
Leaks and spills during transportation (pipeline, truck, rail, ship)	toluene, xylene, PAH	air	Avila Beach, CA, Livington Parish, LA
Combustion: a. Fires as incidents, b. Incineration of fuel air pollution c. Incineration of garbage	hydrocarbon particles	air	Wilmington, CA, San Bernardino, CA, Los Angeles, Houston, TX, Mexico City Oak Ridge, TN, Walker, LA
Contaminated sites	TCE	water, groundwater	800 national hazardous acid pits
Outgassing indoors of forest products-like particle board, carpets, drapes, adhesives	TCA	air	Indoor air incidents, Sick building syndrome

+ – other chlorinated solvents; TCA – trichloroethane; MTBE – methyl tert-butyl ether, additive in gasoline; PAH – polyaromatic hydrocarbons, example benzo(a)pyrene

Table 19.8.2. Differences in environmental and occupational toxicology.

	Occupational	Environmental
Subjects health age, years selection positive	 healthy 18-60 selected for employment attenuated by losses of sick	 chronic illness 0-100 unselected sick collect
Duration in a week total	 40 hours years	 168 hours lifetime
Source	raw materials processes	leaks and spills (gasoline) outgassing of consumer goods fuel combustion
Chemical exposure	one or few	many
Monitoring exposure	area or personal	rarely possible
Environmental transformation of agents	unusual	frequent

Differences between exposure at work and in the community are important, Table 19.8.2. Most worker groups were younger and healthier, met job-entry criteria, have more reserve function so are less likely to manifest damage. Workers have had selective attrition of affected or less fit people to accentuate the difference.[3] In contrast, community people are unselected and include more susceptible groups: infants, children, the aged and the unwell.[1] Some differences in exposure are obvious, work exposure is rarely longer than 40 of the weeks 168 hours. This time away allows work acquired body burdens of chemicals (and their effects) to diminish or disappear while workers are at home. In contrast, home exposures may be continuous or nearly so.[4] At work the time that elapsed between exposure and effect is short, making a measurement of the dose of a toxic agent easy. It is less obvious what should be measured in community exposures.

Good detective work is needed to specify the chemicals to search for and measure in air, water, or soil. Community effects may take years to be recognized as a problem. Opportunities for pertinent environmental measurements were overlooked and have disappeared with time, often simply evaporated. Thus measurement of relevant doses are seldom possible and dose-response curves can rarely be constructed. The logical surrogates for dose such as distance and direction from a chemical source and duration are rarely satisfactory.[1] Thus plausible estimates of dose are needed to focus the association of measured effects and the chemicals that are probably responsible.

The realistic starting place is people's symptoms-complaints that indicate perception of irritation from chemicals.[3] These serve as sentinels to alert one to a problem but cannot be interpreted as impairment or damage without measurements of brain functions. The inability to characterize exposure should not postpone or prevent adequate investigation for adverse human health effects. It is intuitive and ethical to suggest that absent of adverse human effects should be the only reason for stopping the inquiry. People's com-

plaints and upset moods (anxiety, depression, anger, confusion, and fatigue) frequently reflect or parallel impairment. The question then becomes how to measure effects on the brain to decide whether it is damaged and if so how much, Table 19.8.3.

Table 19.8.3. Useful tests of evaluation of brain damage from solvents

Test	Part of brain measured
Simple reaction time & visual two-choice reaction time	retina, optic nerve and cortex integrative radiation to the motor cortex
Sway-balance	inputs: ascending proprioceptive tracts, vestibular division 8th cranial nerve, cerebellum, vision, visual integrative and motor tracts
Blink reflex latency	sensory upper division trigeminal nerves (V), pons, facial nerves (VII)
Color confusion index	center macular area of the retina, with optic cones, optic nerve, optic occipital cortex
Visual fields	retina-optic nerve-optic cortex occipital lobe
Hearing	auditory division of the 8th cranial nerve
Verbal recall memory	limbic system of the temporal lobe, smell brain
Problem-solving culture fair & digit symbol	cerebral cortex: opticoccipital and parietal lobe cortex
Vocabulary	long-term memory, frontal lobes
Information, picture completion & similarities	long-term memory, frontal lobes
Pegboard performance	optic cortex to motor cortex
Trail making A&B	(eye-hand coordination)
Fingertip number writing	parietal lobe, the sensory area of the pre-Rolandic fissure
Profile of mood states	limbic system for emotional memory

The effects of ethyl alcohol are familiar to most people so I will start with this best studied of mind-altering solvents. Measurements of alcoholic patients in the mid-twentieth century at New York's Bellevue Hospital helped David Wechsler formulate his adult intelligence scale, including 11 tests that measure attention, problem-solving, concept juggling and memory including vocabulary.[5] Many other tests were devised to estimate intelligence, how the mind works as defined by Luria and others.[6] Ward Halstead assembled and created function tests to measure the effects of traumatic damage to the brain by wartime missiles and by neurosurgery, prefrontal lobotomy.[7] Application of these tests, by Reitan,[8] helped differentiate the organic brain disorders from schizophrenia and other mental illnesses. Thus the starting place for testing became brain diseases recognized by the neurologist using simple bedside qualitative tests. The tests were not used to detect impairment before it was clinically recognized. The first steps were Benjamin Franklin's recollections of his own brain poisoning by lead while he was a printer and Lewis Carroll's mad hatter, from mercury used in felting beaver hair. The next steps were taken in Nordic countries in the 1960's.[9]

Carbon disulfide was the first solvent studied that had adverse effects observed by Delpech in 1863. Neuropsychiatric abnormalities were described 13 years later by Eulenberg in workers in the rubber and viscose rayon industries.[2] A Finnish psychologist, Helen Hanninen tested 100 carbon disulfide exposed workers in 1970 (50 were poisoned and 50 exposed) and compared them to 50 unexposed.[10] She found that intelligence, tasks of attention, motor skill vigilance, and memory were impaired in clinically poisoned and exposed men compared to unexposed. Digit symbol substitution from the Wechsler's scale[5] showed the most effect of exposure. Additional studies of spray painters in the 1970's were included computer augmented tomography (CT) scans of the brain and function tests. Symptomatic painters after 20 years or more of exposure had brain atrophy associated with impairment.[11-14]

The key to progress in this field was sensitive tests to measure brain function, Table 19.8.3. Fortunately, the Finnish, Danish and Swedish occupational-environmental health centers units included cooperative neurologists, neurophysiologists, and psychologists who did not defend disciplines to limit activities. The obvious reality that the nervous system regulates and controls many essential functions helped select measurements to assess vision, hearing, vibration, odor perception, balance, reaction time including automatic responses that are measured as blink reflex latency,[15,16] heart rate variation[17] and peripheral nerve conduction and Hoffmann's (H) reflex.[18] Tests must be sensitive and reliable, easily understood, and economical of time, taking 3 to 4 hours with rest periods.

Sensitivity's main dimensions are time and mapping. For example, balance is measured using the classic Romberg stance (1850) standing feet together with eyes ahead open and then closed and using a force (displacement) platform or even simpler the position of the head from a sound emitter secured to a headband and recorded by two microphones to inscribe the distance swayed and the speed, in centimeters per second.[19] From three performances for 20 seconds with the eyes closed alternating with the eyes open the minimal speed of sway is selected. The inscribed path, the map, may provide more information but how to interpret this is unclear.

Eye-hand choice reaction time is tested as the speed to cancel by tapping a keypad, a 4-inch letter that appears on the screen of a laptop computer.[20] Twenty trials repeated twice and the median time of the last 7 trials in each run is recorded. Simple, same letter, reaction time takes 1/4 of a second, 250 ms while choice between 2 letters takes twice as long, 500 ms. Many tests are faster in women, most deteriorate with aging after 25 years and for people with more years of educational attainment scores are higher.[21]

Vision is measured by mapping for color perception which is a central retinal cone function. This consists of placing 15 pale colors in a spectral array, the Lanthony desaturated hue test. Retinal rod function which is light perception was mapped for the central 30° of each visual field at 80 points using an automated perimeter recording to a laptop computer.[22] This standardized and speeded up the fields that had been done by the tangent screen and a skilled operator for 100 years.

It was logical to consider the 12 nerves of the head, cranial nerves as the scaffold for organizing tests and for reviewing brain functions that are adversely affected by chemicals. Smell (Nerve I, olfactory), is tested by recognition of familiar odors and of threshold

concentration for detecting them. Smell disorders include loss and disturbed perception. Nerve II, the optic was described above. Nerves III, IV and VI move the eyes and rarely show effects of chemicals. An exception is the optokinetic effects of styrene. In contrast, the faces sensory nerve, the trigeminal, number V and motor nerve, the facial, number VII are needed to blink and are tested by blink reflex latency which is measured electromyographically in milliseconds (10 to 15 ms) after stimulation by a tap, that is mechanical or an electrical impulse. Blink is slowed by exposures to chlorinated solvents like trichloroethylene (TCE), by chlorine and by arsenic. Nerve VIII has hearing and vestibular (balance) divisions which are tested by audiometry and by sway speed for balance. Nerve IX, the glossopharyngeal innervates the throat is needed for the gag reflex and baroreceptor. Nerve X, the vagus X is evaluated by recording variations of heart rate with breathing. Nerves XI, the spinal accessory is tested as the strength of neck muscles and XII tongue's hypoglossal nerve by speech.

Using these tests implies comparing scores observed to a standard, an expected value. Ideally, that would be to the same subject which is rarely possible, although it works for before and after exposures of workers. The next best comparisons are to suitable unexposed normal subjects who can be called controls.[21] We developed over several years a national sample of unexposed people, tested their performance and calculated expected values using prediction equations with coefficients for age, sex, education and other factors such as height and weight that affected some tests. Thus individual observed values for each subject are compared to predicted values (observed/predicted x 100) equal percent predicted. Frequently, we needed to be sure that comparison groups of apparently unexposed control people were normal because adverse effects are widespread. Next, from the standard deviations of the mean, each tests confidence intervals were developed that included 95% of values, excluded as abnormal approximately 5% of unexposed subjects on each test that defined abnormal precisely. For these tests, they were values outside the mean plus 1.5 x standard deviations that defined normal. The next concern was the best summary for each subject. The number of abnormalities was best adjusting balance and vision above other tests and given grip strength, blink reflex and color discrimination 0.5 for right and left sides of the body.

The attributes of plausible association leading to attribution of effect include temporal order, strength of association, exposure intensity and duration, specificity, consistency of findings and coherence and plausibility.[1] As noted earlier the fact of exposure or suspected exposure may be the only certainty about exposure so its plausibility is important based on chemical properties, experiments, and studies of workers. The consistency of results of occupational exposures and animal experiments is helpful. Koch's 4 postulates developed to judge causation of infectious agents (1, an organism present in every case; 2, grown in pure culture; 3, produces the disease when inoculated and 4, recovery and growth in pure culture) are usually inapplicable. This reality is discomforting to some interpreters of the new observations.

The next section reviews, the neurobehavioral effects of solvents found in the environment in the order of importance.[2,4] We begin with trichloroethylene (TCE) and related short-chain chlorinated agents.[22] Next are aromatic compounds such as toluene including

related xylene and styrene with comments on creosols or phenols. The chlorinated aromatic compounds follow: dichlorophenol and polychlorinated biphenyls and their highly neurotoxic derivatives, the dibenzofurans. Straight chain solvents include n-hexane and white spirit (paint thinner), and solvent mixtures.

Before studies of effects of TCE on many brain functions came the measurement of blink reflex latency in 22 people exposed at home to solvents rich in TCE at Woburn, MA. They showed a significant delay of blink but no other functions were measured.[16] In France about this time workers exposed to TCE had similar delays of blink.[24] Earlier experimental exposure of 12 subjects to TCE at 1,000 parts per million (ppm) for 2 hours in a chamber had produced rapid flickering eye movements when following figures on a rotating drum (optokinetic nystagmus), a lowered fusion limit.[22] Thus TCE induced dysfunction of several cranial nerves VI (with III, IV) and V and VII. Nystagmus normalized after a washout and recovery time. Blink is the easier and quicker measurement.[16]

A community within Tucson, AZ of over 10,000 people who depended on well-water for drinking and bathing had developed many complaints and had excesses of birth defects and cancers that associated with TCE in their water. The source was metal cleaning that included stripping off protective plastic coatings, from demothballing aircraft stored in the desert with TCE. This had dumped vast quantities of TCE on the porous, desert floor that drained into the shallow Santa Cruz River aquifer. Testing 544 people from this water exposure zone showed increased blink reflex latency, impaired balance, slowed simple and choice reaction times, reduced recall, poor color discrimination, and impaired problem solving in making designs with blocks, digit symbol substitution and Culture Fair (consisting of 4 subtests: selection of designs for serial order, for difference, for pattern completion and refining defined relationships).[25,26] Also peg placement in a slotted board and trail making A (connecting 25 numbers in ascending sequence and B connecting numbers alternating with letters).[27] TCE concentrations at the wellheads and distribution pipes to homes were measured to calculate with duration of exposure, lifetime peak levels, lifetime averages, and cumulative exposure. Possible relationships of neurobehavioral test scores to these surrogates for dose were searched by regression analysis. No relationships were found for these dose surrogates which was disappointing.

TCE dominated the mixture of chlorinated aliphatic solvents in air and water of north-east Phoenix around two Motorola microchip manufacturing plants that began production in 1957. Neighbor's complaints of adverse health effects started amelioration effects in 1983. An underwater TCE solvent plume spread west and south of the plants in the Salt River aquifer. Test wells showed concentrations of TCE from 50 ppm to 1.4%. Also, air dispersal was important for direct exposure as TCE escaped into the air from the plant. It drained into dry wells, sewers and into a canal running northwest through the neighborhood. In 1993, 236 exposed adults were compared to 161 unexposed ones from a town 80 km northwest across the mountains at a higher elevation. The exposed group showed delayed blink reflex, faster sway speed, slowed reaction time, impaired color discrimination and reduced cognitive function and perceptual motor speed and reduced recall. Airway obstruction was shown by pulmonary function testing. Adverse mood state scores and frequencies of 32 symptoms were also increased.[4,28]

Remedial efforts directed at dumping and groundwater had not reduced the effect suggesting either these were ineffective or impairment was permanent and had developed after 1983. Additional groups of subjects on plume but not in the lawsuit were not different from clients so there was no client bias. Phoenix residents off the plume had only abnormal slowing of blink interpreted as due to TCE and abnormal airway obstruction compared to the unexposed population of Wickenburg, AZ. Airway obstruction was attributed to Phoenix wide air pollution. Proximity within 1.6 km seemed to increase impairment.

In 1998 retesting of 26 people from original groups showed improvement with faster blink reflexes but worse airway obstruction that had persisted (ref. 4 and unpublished). The improvement to normal in blink paralleled that seen in chlorine exposed people 3 years after exposure and first evaluations that were abnormal.[4] The perceptual-motor tests, trail making A and B and peg placement were improved, as were cognitive function measured as Culture Fair and verbal recall. We deduced that diminished TCE releases from Motorola after 1993 allowed recovery of cranial nerves V and VII so blink latency decreased, accompanied by some improvement in vigilance and tracking for the better scores. A possible reversal of effect is so important that these observations should be verified in other groups.

Workers welding and grinding on jet engines in a repair shop were an unusual way to focus attention on the Gerber-Wellington aquifer in Oklahoma.[28] Our attention was temporarily on metals in alloys but when testing of 154 workers showed impaired balance, slowed choice reaction times, and impaired color discrimination compared to 112 unexposed subjects, the priority became effects on the brain. These worker's cognitive function, perceptual motor, and recall were all abnormal using the same tests as in Phoenix. We probed for their exposures after observing these effects and found that these workers had used TCE, trichloroethane, methanol and Freon FC-113 in metal cleaning. The 112 control subjects had not worked with solvents or TCE, but many people, both workers and control groups, lived on and drew well water from the Gerber-Wellington aquifer that is contaminated with TCE. Mapping the blink reflex latencies in the control group showed the people with normal blink lived outside the aquifer. The aquifer was TCE contaminated (national priority list 1990). Thus here we had an example of a probable environmental exposure to TCE with a superimposed occupational one.[4]

TCE leakage had produced these same effects in Joplin, MO neighbors of a company manufacturing ball bearings and cleaning with this solvent. The companies decision to clean and reuse TCE rather than dump it ameliorated the effects.[4] In San Gabriel and San Fernando Valleys in California, similar observations confirm adverse effects from TCE contamination of groundwater and air. Clearly, the observations were replicated and each time TCE was associated with reasonable timing and proximity. More than half of the federal Superfund sites in the US are contaminated with TCE suggesting 800 potential replications.[29] Experience with several patients have shown me that the effects of dichloroethylene and of 1,1,1-trichloroethane are indistinguishable from those of TCE.

Toluene is the most toxic and best studied of the aromatic compound solvents. Both acute and chronic effects were observed by 1961 from inhaling “huffing” toluene[30,31] or

lacquer thinner,[32] especially in children sniffing airplane glue.[30] Chronic impairment was shown in case of shoemakers[33] and rotogravure printing workers[34] using neurobehavioral testing. Toluene exposed experimental animals, mainly rats and mice showed enhanced motor activity, abnormal movements, altered sleep patterns and electroencephalograph (EEG) changes from an integrative brain loop, the hippocampus.[2] Occupational exposures produced memory disturbances, poorer performance on block design assembly, embedded figures, visual memory and eye-hand coordination. CT scans showed some generalized brain swelling[34] that correlated with impaired psychological functions.[35] Women working in the electronic assembly had environmental air levels of toluene of 88 ppm compared to 13 ppm for controls and comparable differences in blood levels. These workers were less apt at placing pegs in a grooved board, at trail making, digit symbol, visual retention and reproduction and verbal memory.[36] They were tested during the day after being away from exposure for at least 16 hours.

Protracted sniffing of solvents alone or in glue has produced intention tremor and titubating gait[30] consistent with cerebellar degeneration which continued after 5 years with ataxia, EEG slowing and cerebral atrophy.[31] Polyneuropathy was observed in 2 glue sniffers in Japan whose exposures were to n-hexane and toluene.[37] Many such descriptions[2] outweigh one epidemiological study that found no differences in performance when comparing 12 glue sniffing boys, ages 11 to 15, mean 13.8 years and 21 controls, ages 11 to 15, mean 12.6 years. Four non-standard tests and the Benton visual retention and design reproduction test were used but the exposed group was 1.2 years older and should have outperformed younger controls whose skills were less developed.[38]

Some published data are difficult to interpret. For example, 26 men were exposed in tanks and holds of two merchant vessels being painted (solvents) and sprayed with malathion 20% and pyrethrin 1.5%, with piperonyl butoxide in toluene. They showed losses of concentration, unawareness of danger and unconsciousness at toluene levels estimated as 10,000 to 12,000 ppm and up to 30,000 ppm below waist level.[39] Additive effects of the neurotoxic insecticides were not discussed.

Effects of toluene in 52 men and paint solvents in 44 men were contrasted with unexposed men. Painters had impaired reading scores, trails B, visual search, block design, grooved pegboard, simple reaction time and verbal memory.[40] Toluene exposed men had only abnormal reading scores reduced significantly, although scores on all tests were lower. Levels of toluene were less than 200 ppm for 4 years prior to this study, although above 500 ppm earlier.

The axiom that environmental exposures are “never” to pure chemicals is matched by another that the mixtures are frequently so complex as to defy description. The few observations suggest that effects seen from mixtures may be due to one or two specific neurotoxic agents. Judgment must be exercised to curb bias and accept the most plausible attribution as the above studies illustrate.

Studies of a population exposed in Louisiana to toluene-rich solvents and other chemicals distilled from a site for 17 years were contrasted to unexposed people living 55 km to the east.[41] The combustion site accepted 9 million gallons of used motor oil in 1975-1976 and 3 to 4 million gallons from 177 to 1983. Tons of liquid chemical waste from

over 100 chemical factories was consigned to this site including toluene, xylene, styrene and benzene, many chlorinated aliphatics solvents like TCE and chlorinated aromatics including PCBs and dibenzofurans. Lead, cadmium, mercury and other metals were present in samples of sludge in ponds after the site closed in 1983 but they were rich in toluene, benzene, and other aromatics. Modeling based on toluene and benzene and using standard Environmental Protection Agency assumptions and a windrose showed symmetrical spread eastward. Excesses of leukemia in school children, cancers and neurobehavioral symptoms in the about 5,000 neighbors of the site led to neurobehavioral testing for impairment in 131 adult subjects within 2 km of the site and 66 adult controls from voter registration rolls of a town 50 km east. The exposed group-matched controls for age but were 1.4 years less educated.

There were adverse effects from exposures while living within 2 km from the site for 4 to 17 years.[41] that were shown by slowed simple and choice reaction times and abnormal sway speeds. Cognitive function in Culture Fair and block design was decreased and pegboard and trail making A and B were diminished, as was a recall of stories. Profile of mood states (POMS) scores were 2.5 fold increased with low vigor and high depression, tension, confusion, anger, and fatigue. Thirty of 32 symptoms inquiring about chest complaints, irritation, nausea and appetite associated, balance, mood, sleep, memory and limbic brain were significantly more frequent in exposed people and the other two were rare in both groups. When differences were adjusted for age, color discrimination and similarities became abnormal were added and trail making A became normal.

The second study was designed to answer how large an area-population was affected, was direction important and were abnormalities related to the duration of exposure.[42] I examined 408 subjects selected to fill 3 distances outward to 1.6, 3.2 and 4.8 km in 8 compass octants, thus 24 sectors. The same tests were given by the same staff and results replicated the earlier study. Regression analysis of each test against distance showed no significant coefficient and comparison of inner and other sectors found no differences, thus there was no evidence of a diminished effect from distance. There were no effects of direction. A possible lessening of effect for duration of exposure of less the 3 years was seen only for peg placement and trail making B scores. Distance, direction, and duration as surrogates for exposure did not influence impairment as measured.

We concluded that the periphery of effect was beyond 4.8 km meaning a health impact area larger than 75 km^2. There was no gradient of effect from the distilling plant outward suggesting airborne spread and mixing had produced even dosing from a large "cloud".[4] Peoples migration inside the exposure zone did not influence effects. The bias of examiners was unlikely. Was the control group suitable? Their average measurements and the distribution were like three other groups in different parts of the country. The possibility of confounding exposures was considered from two sites that were beyond 4.8 km and to the south. Unfortunately, the resources were unavailable to extend testing beyond 4.8 km to find the rim of combustion's effect on people and detect effects of other nearby sites.

Xylene is a solvent for paints, lacquers, and adhesives and is a component of gasoline. In human volunteers in exposure chambers xylene at 70 ppm for 2 hours had no effect on reaction time or recall memory but levels of 100 to 400 ppm for 2 hours impaired

body balance, memory span, critical flicker fusion and caused eye irritation.[43-45] Alcohol and 1,1,1-trichloroethane had adverse effects on balance that showed synergism with xylene[46] and increased the latencies for visual and auditory evoked potentials.[47] Occupational studies have focused on psychiatric symptoms in photogravure workers who also showed headache, nausea, vomiting, and dizziness.[48] Only one study showed impairment for recall memory attributed to xylene but workers were also exposed to formaldehyde.[49]

Xylene toxicity has received less study than that of toluene but appears considerably less which supports attributing neurotoxicity to toluene and mixtures of xylene and benzene with straight chain hydrocarbons such as gasoline.

Styrene's major use is in reinforced fiberglass plastics in constructing boats and bathtubs and showers and in styrene-butadiene rubber.[2] Small amounts are used in polystyrene foam cups and packing materials. Styrene inhalation increased locomotion activity in rats and grip strength at the highest 700 to 1,400 ppm concentrations.[2] Studies of workers showed a hearing loss (increased high-frequency hearing thresholds at 16 kHz).[50] Color discrimination is also reduced.[51] Other observers found abnormal hearing and by posturography-larger sway areas and poor rotary visual suppression-inhibition or vestibular nystagmus.[52] In 25 studies of workers[2] some showed slowing reaction time, poor performance on block design, short-term memory, EEG abnormalities, and neuropathy.

These relatively mild effects made me predict less than the severe impairment than observed in 4 women from a factory making styrene-fiberglass shower-bathtubs. Two sprayed styrene and the other 2 who had developed skin and airway symptoms on initial exposure did lay-up and assembly. Five weeks after her first exposure one woman became light-headed and dizzy, felt hot and her vision blacked out. On testing, reaction times were slow, sway speed was increased. Problem-solving was impaired as was a verbal recall and POMS scores were elevated. She left work stopping exposure. Ten days later, on a trip to the mountains 4,000 feet above sea level she collapsed and became unconscious. Retesting showed constricted visual fields and worse performance of the above tests. Testing on the second woman who had developed asthma showed multiple blind spots in her visual fields, diminished problem-solving ability, grip strength, excessive fingertip writing errors and failure to recall stories after 30 minutes. A third woman also had asthma and severe airway obstruction showed abnormal balance with eyes open and closed, diminished hearing, bilaterally constricted visual fields, and decreased vibration sense.

The fourth woman had a skin rash and red welts that had kept her away from direct contact with epoxy and styrene. She had abnormal color discrimination, decreased vibration sensation, a blind spot in the retina of the left eye and decreased recall of stories. She was the least impaired although her POMS score and symptom frequencies were increased.

Air sampling was not permitted, concentrations of styrene are unknown and contributions of other chemicals to this exposure cannot be excluded. However, exposures to formaldehyde and phenol are unlikely as these workers did not “lay-up” fiberglass resin. Inhalation of sprayed styrene frequently causes the neurobehavioral impairments. The impairment exceeded that found in a review of boat building and other studies but tests

were more sensitive and the styrene levels may have been higher. We encourage more neurobehavioral evaluations of styrene spraying workers using such sensitive tests.

Polychlorinated biphenyls (PCBs), the ultimate (poly)chlorinated solvents are 2 membered ring compounds that when heated to 270° produce dibenzofurans (DBFs) that are 1,000 or more times as neurotoxic.[53] Initial evaluations were of a few PCB exposed individuals and 14 firemen exposed to DBFs who showed severe impairment measured after a medical schools power plant transformers cooked and exploded. Most of the firemen could not pass the physical, balance and truck driving requirements to return to duty and were retired on disability.[4,54]

A community study explores effects of environmental exposures. PCBs were used as pump lubricants in natural gas pipelines running north from Texas and Louisiana from 1950 to the middle 1970's. One pumping station was at Lobelville, TN and at least 16 other US communities had them.[4] Ninety-eight adult village dwellers were compared to 58 unexposed subjects from 80 km east or 35 km north. The exposed people were the most abnormal group I have studied. They had abnormal simple and choice reaction times, balance, hearing, grip strength and the visual function of color discrimination, contrast sensitivity, and visual field performance. The cognitive functions of Culture Fair, digit symbol were abnormal as were vocabulary, information, picture completion, and similarities. Story recall was diminished and peg placement and trail making A and B and fingertip number writing errors were decreased. Other possible associations were ruled out and there were no other causes of impairment. This exposure had caused the most severe neurobehavioral impairment for these people that I have observed.[4] It exceeded that from distilling chemical waste rich in toluene, from TCE and from other solvents.

n-Hexane by inhalational or through the skin causes peripheral nerves to die-back. Glue sniffing exposure frequently combines n-hexane and toluene. Twenty-five percent of workers using glue in shoes and leather goods with n-hexane, 40 to 99.5% had symptomatic polyneuropathy, slowed nerve conduction and neurological signs.[55] Abnormal findings increased with age and duration of exposure and were accompanied by lower limb weakness and pain, abnormal sensations (parenthesis) in the hands and muscles spasm. In another shoe plant exposure group, upper extremity nerve conduction was slowed, frequently after 5 years of exposure.[56] Sensorimotor distal neuropathy characterized 98 of 654 workers in the Italian shoe industry, 47 had decreased motor conduction velocity with a headache, insomnia, nausea and vomiting irritability and epigastric pain.[57] Most workers improved when removed from exposure.[56] In Japan beginning in 1964, several studies found polyneuropathy in polyethylene laminating printers[58] and makers of sandals and slippers.[59] A major metabolite of n-hexane and of methyl butyl ketone is 2,5-hexanedione that is more neurotoxic than these precursors causing swelling of nerve axons and accumulations of neurofilaments in mid-portions of peripheral nerves.[60] Methyl ethyl ketone studied in workers lengthened choice reaction time and motor nerve conduction and decreased vibration sensation signs of neuropathy. These effects were also seen in glue sniffers.[2]

The focus on polyneuropathy in 14 studies[2] has usurped studies of central nervous system (CNS) functions except for one showing increased latencies of visual and auditory

evoked potentials.[61] Neurophysiological and psychological assessments[62] show narcotic effects that match those in animals.[2] Until restricted from foods n-hexane was used to extract oil from soybean meal and exposed US workers. They had a headache, dysesthesia, insomnia, somnolence and memory loss but testing for appraising brain damage was not done.

Gasoline is a mixture of aliphatic straight and branched chains and aromatic hydrocarbons with toxicity attributable to toluene, xylene and perhaps hexane and additives including methyl tert-butyl ether and tri-ortho-cresyl phosphate.[63]

Effects on the lungs by inhaled solvents simplify to the consideration of agents affecting airway cells that include n-hexane and PCBs. Both cause proliferation and transformation of distal airway lining cells to produce mucus and obstruct airways[64-66] and cause inflammatory cells to pour into the lungs distal alveolar spaces interfering with for gas exchange.

Cardiac effects of solvents are of three types A, alterations in rhythm B, cardiomyopathy and C, hypertension directly and *via* renal changes as in interstitial nephritis, glomerulonephritis and Goodpasture's syndrome.[67]

Alterations in heart rhythm have been attributed to anesthesia with TCE and were serious, especially when administered in soda lime CO_2 absorbing anesthesia machines to stop the use of TCE for anesthesia in the 1960's.[4] Rhythm disturbances have also been observed in some groups of workers exposed to TCE. Knowing this we did electrocardiograms (ECG's) on the Tucson TCE exposed population and found no arrhythmias. A loss of respiratory variation in heart rate has been associated with exposure to organic solvents, including carbon disulfide, acrylamide and alcohol but not toluene and with diabetes mellitus and syndromes of autonomic nervous system dysfunction.[17,68,69] Later freons, volatile chlorofluorocarbons were associated with arrhythmias and withdrawn from use to propel therapeutic aerosols used for asthma.[70] Cardiomyopathy, heart muscle dysfunction and enlargement have been associated with alcohol ingestion. Two epidemics were ascribed to cobalt used to color beer.[9] But in the most common cardiac muscle disorder from alcohol, cobalt is not incriminated.

Hypertension has been associated with solvent exposure in workers, an association that needs further study. Associations with hypertension were absent in the author's studies of TCE, toluene rich waste and PCBs discussed earlier.

Workers who used methylene chloride in making acetate film had sleepiness and fatigue and decreased digit symbol substitution scores and lengthened reaction time.[71] Use of methylene chloride in closed spaces has been fatal with brain edema, elevated blood levels of carboxyhemoglobin and caused temporary right hemispheric paralysis and/or unconsciousness.[2] Chronic exposure has been associated with dementia, headache, dizziness and disturbed gait.[72]

Chloromethane exposures from foam production caused tremor and decreased attention and ability to do arithmetic.[73] Environmental exposures from leaks in refrigerating systems[2] caused deaths, convulsions, myoclonus and personality changes. One fishing boat exposure of 15 men left profound neurological residuals, fatigue, depression and alcohol intolerance.[2] The effects resemble those of methyl bromide poisoning.

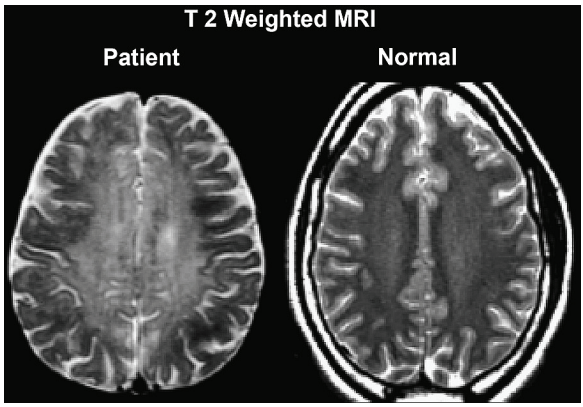


Figure 19.8.1. Axial T2 weighted MRI of a chronic toluene abuser and a normal individual. The scan on the left shows diffuse hyperintensity of the cerebral white matter consistent with widespread myelin injury. [Adapted, by permission, from Arciniegas DB, Anderson CA, Filley CM. **Behavioral neurology & neuropsychiatry**. New York: *Cambridge University Press*; 2013. p. 425.]

Methanol has profound and specific toxic effects on the optic nerve and vision causing central blind spots and ingestion of methanol for the intoxicating effects of ethanol has caused blindness.[74] Its metabolism to formic acid suggests the possibility that of other central nervous system effects.

White spirit is a mixture of straight and branched chain paraffins, naphthalenes and alkyl aromatic hydrocarbons, which is widely used as a paint solvent. Ten studies of painters, mostly in Nordic countries, have shown increased neurobehavioral symptoms and several showed decreased performance on psychological tests.[11-14] Longitudinal studies showed an almost doubled risk for a neuropsychiatric disability pension in painters compared to construction workers. Several such studies support the concept of neuropsychiatric impairment and disability linked to the painting trade in many countries.[75-78] Several women in my consulting practice had profound neurobehavioral impairment after entering their homes during spray painting including unconsciousness which suggest there may be a considerable problem from environmental exposures.

Many industrial painters exposures are to solvent mixtures. Those painting airplanes where dust and hence fume exposure is limited by strict cleanliness, which means good air hygiene for the workers, have little trouble compared to symptoms, impairment, disability and brain atrophy with dementia in car and refrigerator painters. These groups supplied the clear evidence of solvent effects in workers in Nordic countries that established how to assess human subject's neurobehavioral status and detect impairment that was discussed early in this chapter. Many cross-sectional studies showed adverse effects, excessive neuropsychiatric symptoms and several longitudinal studies show greatly increased the likelihood of receiving a pension for neuropsychiatric disability.[2,78-80]

Toxic leukoencephalopathy is a structural alteration of white matter following exposure to a variety of agents, including environmental toxins, radiation, or therapeutic drugs.[81] Lacquer thinner contains a mixture of organic solvents, including toluene, the main component, acetone, xylene, and other hydrocarbons.[81] Toluene is the main component responsible for neurotoxicity.[81] 3 years of exposure is the minimum duration to have MRI evidence of white matter changes.[81] A lacquer thinner explosion may expose patients to an extraordinarily high level of toluene, as happened to a person analyzed in this research.[81] This person’s MRI showed target-like lesions with rings of restricted water dif-

fusion and contrast enhancement, findings indicating cytotoxic edema and disruption of the blood-brain barrier.[81]

Toluene is rapidly absorbed through the lungs after inhalation and quickly crosses the blood-brain barrier to reach the lipid-rich central nervous system, sparing the peripheral nervous system.[82] Loss of gray-white matter differentiation and the appearance of periventricular white matter hyperintensity are a typical result of toluene abuse (Figure 19.8.1).[82]

REFERENCES

1 K Kilburn, and R Warshaw, **Epidemiology of adverse health effect from environmental chemicals**, *Princeton Scientific Publishing Co*., 1995, pp 33-53.
2 P Arlien-Soberg, **Solvent Neurotoxicity**, *CRC Press*, Boca Raton, 1992.
3 J Angerer, Scan. *J. Work. Environ. Hlth.*, **11** (Suppl 1), 45 (1985).
4 K Kilburn, **Chemical Brain Injury**, *John Wiley & Sons*, New York, 1998.
5 D Wechsler, **Adult Intelligence Scale Manual,** (revised), *The Psychological Corporation*, New York, 1981.
6 AR Luria, **Higher Cortical Function in Man**, *Travistock*, London, 1966.
7 W Halstead, **Brain and Intelligence**, *The University of Chicago Press*, Chicago, 1947.
8 R Reitan, *Percept. Motor Skills*, **8**, 271 (1958).
9 D Hunter, **Diseases of Occupations**, 4th Edition, *Little Brown*, Boston, 1969.
10 H Hanninen, *Brit. J. Indust. Med.*, **28**, 374 (1971).
11 B Knave, B Kolmodin-Hedman, H Persson, and J Goldberg, *Work Environ, Health*, **11**, 49 (1974).
12 S Elofsson, F Gamberale, T Hindmarsh, *et al., Scand. J. Work Environ. Health*, **6**, 239 (1980).
13 O Axelson, M Hane, and C Hogstedt, *Scand. J. Work Environ. Health*, **2**, 14 (1976).
14 P Arlien-Soberg, P Bruhm, C Gyldensted, and B Melgaard, *Acta Neurol. Scand*., **60**, 149 (1979).
15 R Feldman, J Chirico-Post, and S Proctor, *Arch. Environ. Health*, **43**, 143 (1988).
16 K Kilburn, J Thornton, and B Hanscom, *Electromyograph Clin. Neurophysiol*., **38**, 25 (1998).
17 E Matikainen, and J Juntunen, **Neurobehavioral Methods in Occupational and Environmental Health**. *World Health Organization*, Copenhagen, 1985, pp. 57-60.
18 S Oh, **Clinical Electromyography; nerve conduction studies**, 2nd Edition, *Wilkins and Wilkins*, Baltimore, 1993, pp.89.
19 K Kilburn, and R Warshaw, *Occup. Environ. Med*., **51**, 381 (1994).
20 J Miller, G Cohen, R Warshaw, J Thornton, and K Kilburn, *Am. J. Indust. Med*., **15**, 687 (1989).
21 K Kilburn, J Thornton, and B Hanscom, *Arch. Environ. Health*. **53**, 257 (1998).
22 B Kylin, K Axell, H Samuel, and A Lindborg, *Arch. Environ. Health*, **15**, 48 (1967).
23 K Kilburn, *Neurotoxicology*, **21**, (2000).
24 L Barrett, S Garrel, V Danel, and J Debru, *Arch. Environ. Health*, **42**, 297 (1987).
25 R Cattell, S Feingold, and S Sarason, *J. Educational Psych*., **32**, 81 (1941).
26 R Cattell, *J. Consulting Psych.*, **15**, 154(1951).
27 K Kilburn, and R Warshaw, *J Toxicol. Environ. Health*, **39**, 483 (1993).
28 K Kilburn, *Environ. Res.*, **80**, 244 (1999).
29 National Research Council, Public Health and Hazardous Waste, Environ. Epid., *National Academy Press*, Washington DC, 1991.
30 D Grabski, *Am. J. Psychiatry*, **118**, 461 (1961).
31 J Knox, and J Nelson, *New Eng. J. Med.*, **275**, 1494 (1966).
32 L Prockop, M Alt, and J Tison, *JAMA*, **229**, 1083 (1974).
33 T Matsushita, Y Arimatsu, A Ueda, K Satoh, and S Nomura, *Ind. Health*, **13**, 115 (1975).
34 J Juntunen, E Matikaninen, M Antti-Poika, H Suouanta, and M Valle, *Acta Neurol. Scand*., **72**, 512 (1985).
35 H Hanninen, M Antti-Poika, and P Savolainen, *Int. Arch. Occup. Environ. Health*, **59**, 475 (1987).
36 S Foo, J Jeyaratnam and D Koh, *Brit. J. Indust. Med*., **47**, 480 (1990).
37 T Shirabe, T Tsuda, A Terao, and S Araki, *J. Neurol. Sci*., **21**, 101 (1974).
38 J Dodds, and S Santostefano, *J. Pediatr*., **64**, 565 (1964).
39 E Longley, A Jones, R Welch, and Lomaev, *Arch. Environ. Hlth*., **14**, 481 (1967).
40 N Cherry, H Hutchins, T Pace, and H Waldron, *Brit. J. Indust. Med.*, **42**, 291 (1985).
41 K Kilburn, and R Warshaw, *Neurotoxicol. Terato.*, **17**, 89 (1995).
42 K Kilburn, *Environ. Res.*, **81**, 92 (1999).

43 C Carpenter, E Kinkead, D Geary Jr, L Sullivan, and J King, *Toxicol. Appl. Pharmacol*., **33**, 543 (1976).
44 K Savolainen, V Riihimaki, and M Linnoila, *Int. Arch. Occup. Environ. Hlth*., **44**, 201 (1979).
45 K Savolainen, V Riihimaki, Omuona, and J Kekoni, A Laine, *Arch. Toxicol., Suppl.*, **5**, 96 (1982).
46 K Savolainen, V Riihimaki, O Muona, J Kekoni, R Luukkonen, and A Laine, *Acta Pharmacol. Toxicol*., **57**, 67 (1985).
47 A Seppalainen, K Savolainen, and T Kovala, *Electroencephalo. Clin. Neurophysiol.*, **51**, 148 (1981).
48 D Klaucke, M Johansen, and R Vogt, *Am. J. Induct. Med.*, **3**, 173 (1982).
49 K Kilburn, R Warshaw, and J Thornton, *Arch. Environ. Health*, **42**, 117 (1987).
50 H Muijser, E Hoogendijk, and J Hooisma, *Toxicol*., **49**, 331 (1988).
51 F Gobba, and A Cavalleri, In: **Butadiene and Styrene: Assessment of Health Hazards**, *IARC Scientific Publications* No. 127, Lyon, France, 1993.
52 C Moller, L Odkvist, B Larsby, R Tham, T Ledin, and L Bergholtz, *Scand. J. Work. Environ. Hlth.*, **16**, 189 (1990).
53 O Hutzinger, G Choudhry, B Chittim, and L Johnston, *Environ. Health Perspect*., **60**, 3 (1985).
54 K Kilburn, R Warshaw, and M Shields, *Arch. Environ. Health*, **44**, 345 (1989).
55 E Buiatti, S Cecchini, O Ronchi, P Dolara, and G Bulgarelli, *Brit. J. Ind. Med.*, **35**, 168 (1978).
56 I Aiello, G Rosati, G Serra, and M Manca, *Acta Neurol.,* **35**, 285 (1980).
57 S Passero, N Battistini, R Cioni, F Giannini, C Paradiso, F Battista, F Carboncini, and E Sartorelli, *Ital. J. Neurol. Sci.*, **4**, 463 (1983).
58 S Yamada, *Jpn. J. Ind. Health*, **6**, 192 (1964).
59 Y Yamamura, *Folia Psychiatr. Neurol. Jpn.,* **23**, 45(1969).
60 P Spencer, and H Schaumburg, *J. Neurol. Neurosurg. Psychiatr*., **38**, 771 (1975).
61 A Seppalainen, C Raitta, and M Huuskonen, *Electroencephalogr. Clin. Neurophysiol.*, **47**, 492 (1979).
62 S Sanagi, Y Seki, K Sugimoto, and M Hirata, *Int. Arch. Occup. Environ. Health,* **47**, 69 (1980).
63 T Burbacher, *Environ. Hlth. Perspect.*, **101**(Suppl 6),133 (1993).
64 R Warshaw, A Fischbein, J Thornton, A Miller, and I Selikoff, *Ann. NY Acad. Sci*., **320**, 277 (1979).
65 P Houch, D Nebel, and S Milham Jr, *Am. J. Indust. Med*., **22**, 109 (1992).
66 N Shigematsu, S Ishimaru, and R Saito, *Environ. Res*., **16**, 92 (1978).
67 N Benowitz, **Cardiotoxicity in the workplace**, Occup. Med., Vol 7, No. 3, *Hanley & Belfus, Inc*., Philadelphia, 1992.
68 Y Kuriowa, Y Shimada, and Y Toyokura, *Neurology*, **33**, 463-467 (1983).
69 K Murata, S Araki, K Yokoyama, K Yamashita, F Okajima, and K Nakaaki, *NeuroToxicol*., **15**, 867-876 (1994).
70 W Harris, *Arch. Intern. Med*., **131**, 1621 (1973).
71 N Cherry, H Venables, H Waldron, and G Wells, *Brit. J. Ind. Med*., **38**, 351 (1981).
72 B Friedlander, T Hearne, and S Hall, *J. Occup. Med.*, **20**, 657 (1978).
73 J Repko, P Jones, L Garcia, E Schneider, E Roseman, and C Corum, **Behavioral and neurological effects of methyl chloride**, CDC-99-74-20, *National Institute for Occupational Safety and Health*, 1976.
74 W Grant, **Toxicology of the Eye**, *Charles C Thomas Publisher*, Springfield, Illinois, 1974.
75 S Mikkelsen, *Scand. J. Soc. Med*., (Suppl. 16), 34, (1980).
76 H Rasmussen, J Olsen, and J Lauritsen, *J. Occup. Med.*, **27**, 561 (1985).
77 K Lindstrom, *Scand. J. Work Environ. Health*, **7** (Suppl. 4), 48 (1981).
78 J Olsen, and S Sabroe, *Scand. J. Soc. Med.*, **44** (Suppl. 16), 44, (1980).
79 K Lindstrom, H Riihimaki, and K Hanninen, *Scand. J. Work Environ. Health*, **10**, 321 (1984).
80 T Riise, and B Moen, *Acta Neurol. Scand.*, 77 (Suppl. 116), **104** (1988).
Note: **New general source for neurotoxicity for solvents**. R Feldman, Occupational and Environmental Neurotoxicology, *Leppincott-Raven*, Hagerstown, Maryland, 1999.
81 H-W Kao, L Pare, R Kim, AN Hasso, *J. Clin. Neurosci.*, in press, 2013.
82 C Filley, *Psychiatr Clin N Am*, **36**, 293–302 (2013).

20

Substitution of Solvents by Safer Products

20.1 SUPERCRITICAL SOLVENTS

Aydin K. Sunol, Sermin G. Sunol, and Kyle Cogswell
Department of Chemical Engineering, University of South Florida, Tampa, FL, USA

20.1.1 INTRODUCTION

Significant and steady inroads towards wider and more effective utilization of supercritical fluids have been made over the last four decades, especially for high value-added differentiated products. The new wave of the second-generation supercritical technologies

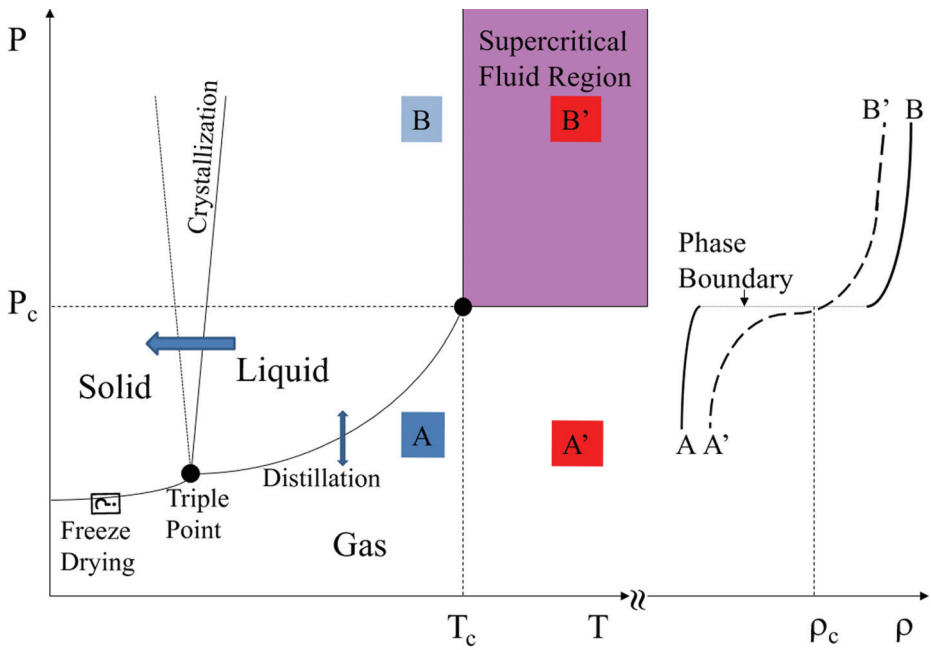


Figure 20.1.1. Pressure-temperature and pressure-density behavior of matter.

emerged later, bringing forth new roles for dense gases as a processing media, particularly in material synthesis. The renewed interest in energy conversion, particularly renewable, switched processing media from nonrenewable to renewable hydrocarbon sources such as coal to biomass. The motivation of this chapter is to assess the current status of the technology in an effort to extricate the challenges both in the current practice of processing with supercritical fluids and potential areas into which we have as yet to venture. The foundations including transport phenomena, reactions and thermodynamics as well as generic processing principles will be highlighted.

"Supercritical" refers to the state of the matter where the temperature and pressure of a single component fluid is above the critical point at which the phase boundaries diminish. A portfolio of chemical and physical operations carried out in the vicinity of this region defines Supercritical Fluid Technology (SFT). The pressure-temperature-volume (PVT) behavior of a substance can be best depicted by pressure-temperature and pressure-density (volume) projections, as shown in Figure 20.1.1. Pressure-temperature diagram identifies the supercritical fluid region, alternative separation techniques that involve phase transition including the associated phase boundaries, and the fact that an isotherm below critical (AB) involves phase transition while one above (A'B') does not. Pressure density projections illustrate tunability of the solvent density at supercritical conditions (A'B') and again the continuity of the isotherm that does not encounter any phase transition. The aforementioned behavior is for a pure component, solvent. The critical properties of various organic and inorganic substances are shown in Table 20.1.1.

Table 20.1.1. The critical properties of solvents.

Solvents	Critical temperature, ^{o}C	Critical pressure, atm
Critical conditions for various inorganic supercritical solvents		
Ammonia	132.5	112.5
Carbon dioxide	31.0	72.9
Carbonyl sulfide	104.8	65.0
Nitric oxide	–93.0	64.0
Nitrous oxide	36.5	71.7
Chlorotrifluoro silane	34.5	34.2
Silane	–3.46	47.8
Xenon	16.6	58.0
Water	374.1	218.3
Critical conditions for various organic supercritical solvents		
Acetone	235.5	47.0
Ethane	32.3	48.2
Ethanol	243.0	63.0
Ethylene	9.3	49.7
Propane	96.7	41.9

Table 20.1.1. The critical properties of solvents.

Solvents	Critical temperature, ^{o}C	Critical pressure, atm
Propylene	91.9	45.6
Cyclohexane	280.3	40.2
Isopropanol	235.2	47.0
Benzene	289.0	48.3
Toluene	318.6	40.6
p-Xylene	343.1	34.7
Chlorofluoromethane	28.9	38.7
Trichlorofluoromethane	198.1	43.5

20.1.1.1 A promising path to green chemistry

One of significant paradigm shifts in chemical processing for the new millennium is the increased use of environmentally benign technologies. The effectiveness of green solvents such as supercritical water and supercritical carbon dioxide for carrying out reactions, difficult separations, and materials processing is naturally very promising. Introduction of supercritical fluids into other processing fluids such as ionic liquids to tune the processing further diversify the utility of these fluids. The effectiveness of the supercritical solvents is related to their state, critical temperature, and pressure. Obviously, synergy between the physical characteristics of solvent and the conditions favorable for the desired chemistry is of paramount importance for the success of the application.

20.1.1.2 Unique and tunable physico-chemical properties

Supercritical fluids have the mobility of gases and the dissolving power of liquid solvents resulting in efficient penetration into porous matrices, high mass transfer rates, and high solvency. Furthermore, these properties are extremely sensitive to perturbations in temperature, pressure and composition resulting in innovative processing concepts along with control challenges. Furthermore, tailored products with tunable performance could be produced through synthesis and creative operating policies. Thus, over the last four decades, a

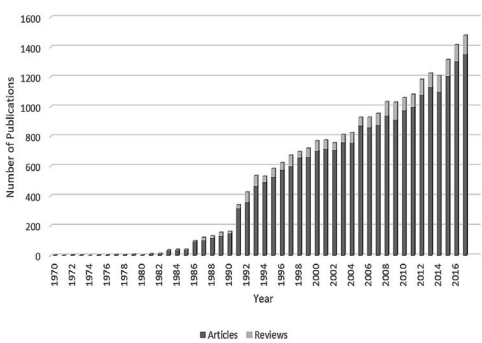


Figure 20.1.2. Annual number of publications related to supercritical fluids.

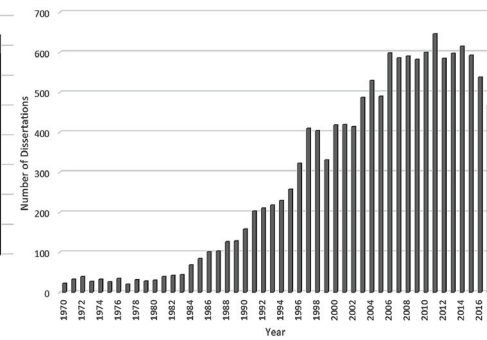


Figure 20.1.3. Annual number of dissertations related to supercritical fluids.

spate of supercritical processes have been developed particularly for manufacture of high value-added products that are superior in performance and exhibit conscious regard for a more socially responsible manufacturing practice.

20.1.1.3 Sustainable applications in many different areas

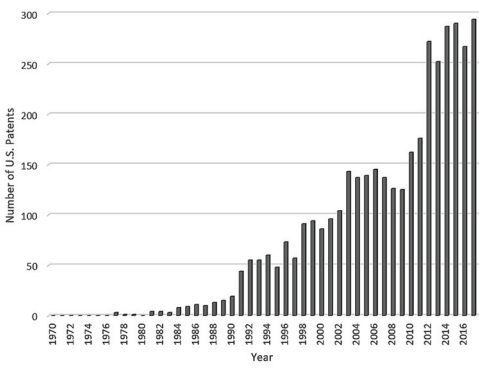


Figure 20.1.4. Annual number of patents related to supercritical fluids.

Despite the higher capital charges associated with relatively high pressures, the necessity to often add a new component into the processing environment, and operational challenges at conditions foreign to most process engineers, the interest in supercritical fluids had been growing steadily since the early eighties beyond the select number of areas. We see applications in the food and beverage industries, pharmaceutical, biomedical, microelectronic industries, textiles, forest products, petrochemicals, chemicals, environmental clean-up, synthetic fuel production, polymeric materials, ceramics, auto industry, coatings and paint industry, energetic materials, and fuels. As depicted in Figures 20.1.2-20.1.4, the number of the publications, dissertations, and patents in the area are still growing from one year to next.

20.1.2 FUNDAMENTALS

20.1.2.1 Phase behavior with supercritical solvents

The first recorded observation of supercritical fluid's ability to dissolve solids with low volatility goes back to 1879.[1] Since then, better understanding of high-pressure phase equilibrium emerged partially as a result of experiments of the last century, especially those of Timmermans,[2] Schneider,[3,4] Franck[5] on aqueous systems, McHugh[6] on polymeric systems, and more recently the Delft group in Holland.[7,8] In classification of phase diagrams, one of the most important analytic contribution is due to Scott and Van Konynenberg.[9] They demonstrated that most of the experimental observations could be described qualitatively by the van der Waals equation of state. Their analysis of critical and three phase boundaries in temperature-pressure projection of the phase behavior led to their categorization of possible fluid phase equilibrium into five classes. Rowlinson and Swinton[10] later added a sixth class that occurs in some aqueous systems but is not predicted by the van der Waals equation of state. The classes described by Scott illustrate only a few of the known types of phase equilibrium and are shown in Figure 20.1.5. This classification scheme illustrates the principal lines (degrees of freedom = 1) and end points (degrees of freedom = 0) that form the boundaries of pressure-temperature space of the surfaces that describe the equilibrium between two components.

Type I mixtures have continuous gas-liquid critical line and exhibit complete miscibility of the liquids at all temperatures. Mixtures of substances with comparable critical

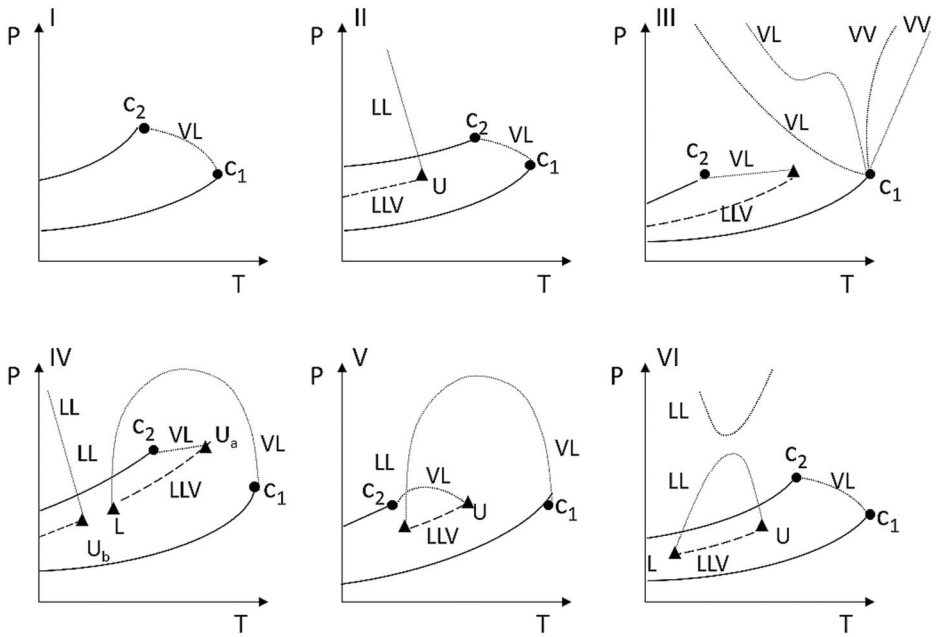


Figure 20.1.5. Classification of vapor-liquid phase behavior of binary systems. The types of boundaries are: 1. Solid lines (_____) are pure component vapor pressure curves. 2. The dashed lined (_ _ _ _ _) are for three phase lines. 3. The dotted lines (.....) are for critical lines. The types of points are: 1. The filled circles are pure component critical points, 2. The triangles are critical end points, lower (L) and upper (U).

properties or substances belonging to a homologous series form Type I unless the size difference between components is large. The critical locus could be convex upward with a maximum or concave down with a minimum. Examples of Type I mixtures are: water + 1-propanol, methane + n-butane, benzene + toluene, and carbon dioxide + n-butane.

Type II systems have liquid-liquid immiscibility at lower temperatures while locus of liquid-liquid critical point (UCST) is distinct from gas-liquid critical line. Examples include: water + phenol, water + tetralin, water + decalin, carbon dioxide + n-octane, and carbon dioxide + n-decane.

When the mutual immiscibility of two components becomes large, the locus of liquid-liquid critical solution moves to higher temperatures and it eventually interacts with gas-liquid critical curve disrupting the gas-liquid locus. This particular class is type III and some examples include: water + n-hexane, water + benzene, carbon dioxide + n-tridecane, and carbon dioxide + water.

Type IV systems have three critical curves, two of which are VLL. If the hydrocarbon mixtures differ significantly in their critical properties, they conform to type IV or V. The primary difference between Type IV and V is that type IV exhibits UCST and LCST while type V has LCST only. One important class of systems that exhibit type IV behavior is solvent-polymer mixtures such as cyclohexane + polystyrene. Other examples of type IV include carbon dioxide + nitrobenzene and methane + n-hexane while ethane with eth-

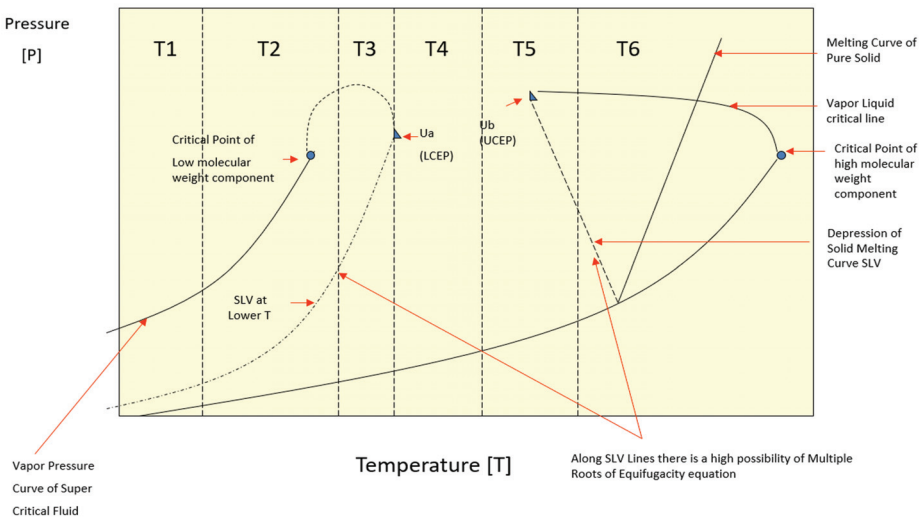


Figure 20.1.6 Binary solid – supercritical system. Phase behavior of dissimilar binary systems

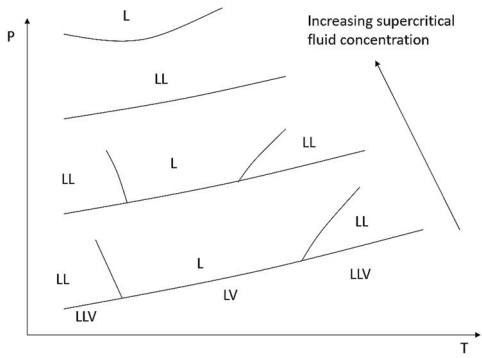


Figure 20.1.7. The effect of supercritical fluid concentration on polymer-solvent phase behavior.

anol or 1-propanol or 1-butanol exhibit type V behavior.

Type VI systems are composed of complex molecules with hydrogen bonding or other strong intermolecular forces and result in behavior where LCST and UCST are at temperatures well removed from gas-liquid critical temperature of the more volatile component.

Types IV and I are of particular interest in representing behavior exploited in supercritical extraction. There are many more possible classes and subclasses, especially where azeotropic behavior variations are involved, as discussed in the works of Rowlinson[10] and King.[11] More on the phase behavior applicable to dense gases can be found in reviews[12,13] and specialized texts[14] in this area.

Supercritical extraction often involves separation of relatively non-volatile components, often in the solid phase, through selective solubility in the supercritical gasses. Thus, the critical temperatures of the pure components are likely to be significantly different and the critical temperature of the solvent is likely to be lower than the triple point temperature of the solute. The implication is that there is no common temperature range where both components will be liquid. The phase diagram of systems with solid and supercritical fluid is shown in Figure 20.1.6.[15] The full lines are the sublimation, melting,

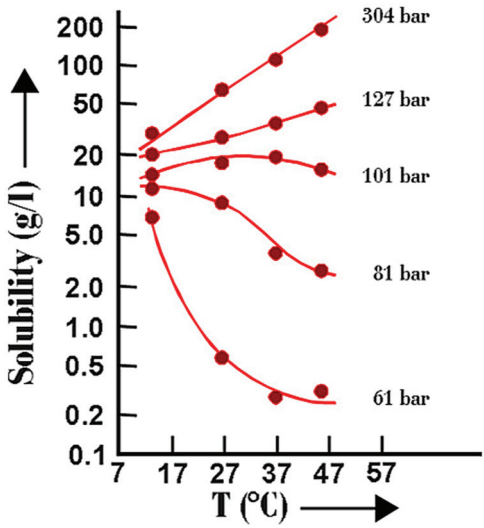


Figure 20.1.8. Solubility of naphthalene in supercritical ethylene.

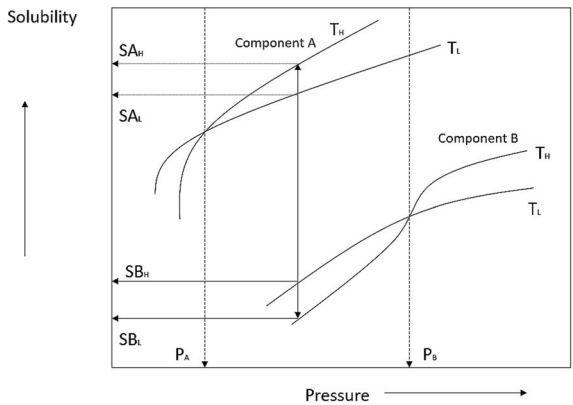


Figure 20.1.9. The crossover pressure and retrograde behavior supercritical fluid and two solutes.

and vapor pressure curves of the pure components. If the temperature of C_2 lies far below of that triple point of C_1, the three-phase region S, L, G curves upward and intersects the gas liquid line to form critical end points U_a and U_b. No liquid phase exits between the temperatures of U_a and U_b. The three-sided region is a region of gas-liquid phase separation. At temperatures between this region and U_a, the solid phase of component C_1 is in equilibrium with C_2 rich gas phase.

The polymer solution behavior is of significant importance due to large number of applications in the field. The supercritical fluids primarily follow type IV behavior. An example related to the effect of supercritical solvent on phase behavior of such systems is shown in Figure 20.1.7. More comprehensive coverage of the field can be found in texts[6] and review papers.[16]

The unique behaviors of supercritical fluids relate to solubility enhancement and how the solubility varies with operating conditions. As can be seen from Figure 20.1.8, the solubility of a solid solute is enhanced by several orders of magnitude over the ideal solubility.[17] Furthermore, the solubility decreases with increasing temperature at supercritical pressures somewhat above the critical, while at supercritical pressures above a "crossover pressure", solubility of a solute increases with temperature. The crossover pressures are different for different solutes. As depicted in Figure 20.1.9, complete fractionation of solutes solubilized in the supercritical solvent is possible by slight increase in temperature.[18] An other unique behavior, called "barotropic effect", exists when highly compressed dense gas reaches pressures higher than the incompressible liquid. In such instances, dense gas phase is below the liquid or the second gas phase.

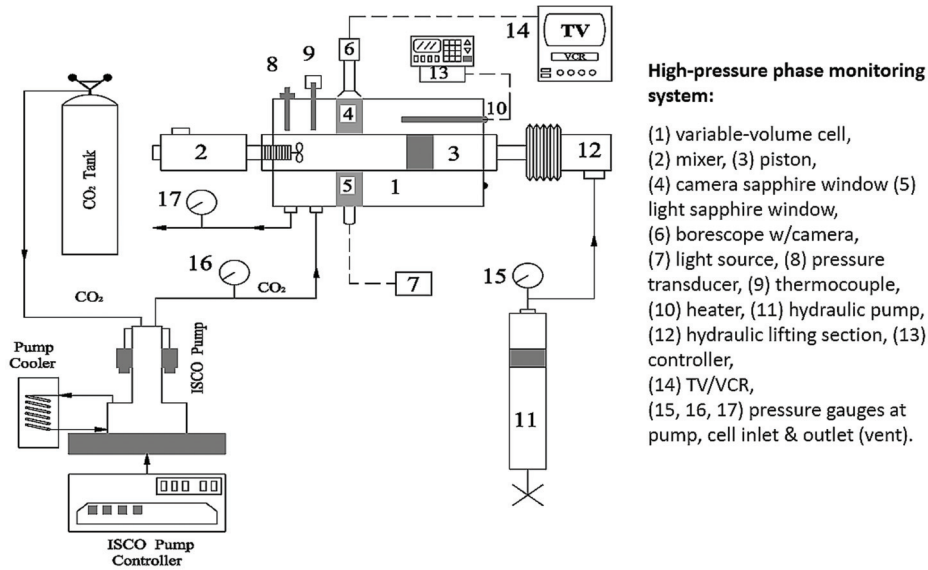


Figure 20.1.10. A phase analyzer system for synthetic determination of phase behavior.

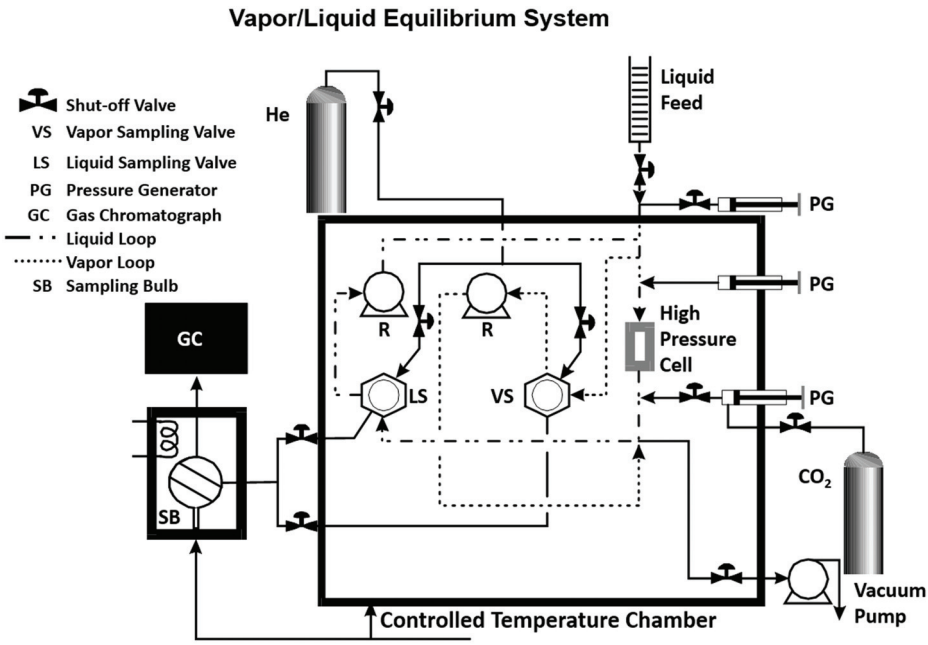


Figure 20.1.11. A high pressure fluid phase equilibrium measurement system for fluids.

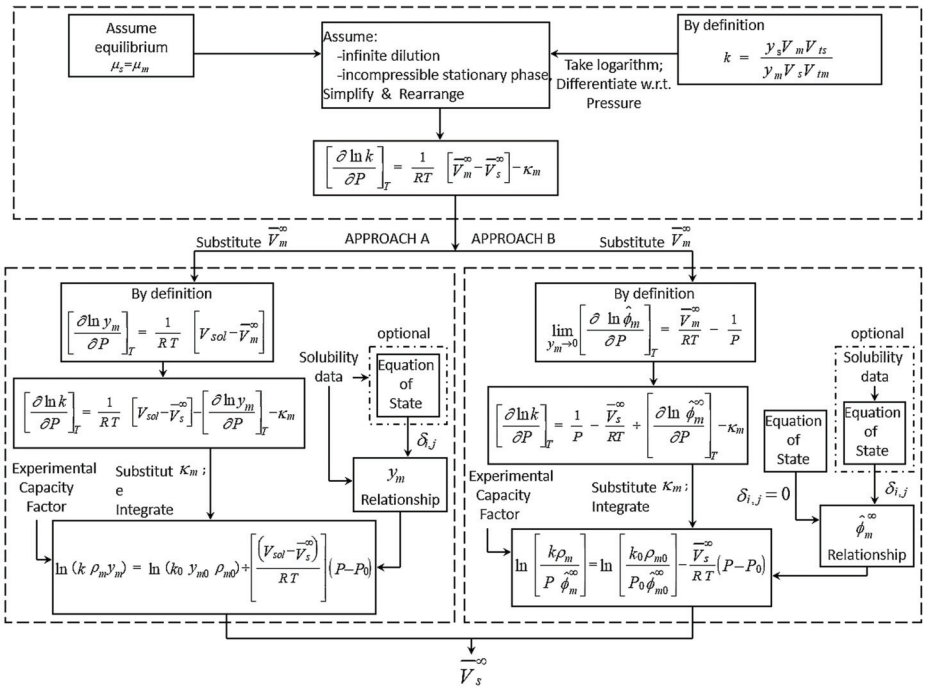


Figure 20.1.12. Estimation of solubility and partial molar volume using supercritical fluid chromatography.

There are three essential elements that make up the thermodynamic foundations of supercritical fluids. These elements are experimental and identification techniques for elucidating the phase behavior, models for dense gases, and computation methods.

20.1.2.1.1 Experimental methods

There are two basic approaches to experimental determination of the high-pressure phase behavior of a system, synthetic and analytic. In the synthetic approach, phase boundaries of a fixed (known) composition system are observed, usually visually, in a cell with sight windows, by manipulation of the system pressure and temperature.

These experimental systems, one shown as Figure 20.1.10 allow determination of cloud point, dew point, bubble point, and critical point of particular binary systems including polymers. Unlike earlier custom-designed experimental systems, such systems are readily available from commercial vendors.

In the analytical approach, the components are equilibrated and the compositions of the co-existing phases are determined either through sampling and off-line analysis or on-line spectroscopic techniques. A typical system for determination of vapor/liquid/liquid phase behavior is shown in Figure 20.1.11. The system is a double recirculation variable volume system. A dynamic variant of this method is for the determination of the solubility of solids in a supercritical fluid. The stationary solid phase is contacted with a continuous supply of supercritical fluid that is ensured to exit with an equilibrium amount of the solid.

The chromatographic and calorimetric information can also be used to infer phase behavior information. For example, solubility measurements can be performed on a Supercritical Fluid Chromatograph (SFC) where a relatively short fused silica capillary tubing system replaces the usual column. Sample is coated into this tubing using the same techniques that are used to coat a stationary phase on an analytical capillary column. Raising the solvent pressure stepwise from a selected starting point allows isothermal measurements of solubility. At each step, the ion current in the mass spectrometer, which is used as the detector, is monitored to determine the quantity of solute in solution. Also, solubility may be estimated from the last equations in Approach A and Approach B summarized in Figure 20.1.12.[20] This is true provided that the adsorbent is a solid and partial molar volume of the solute (e.g., naphthalene) in the stationary phase is equal to the solid molar volume of the solute.

It is worth noting that Supercritical Fluid Chromatography is an important experimental tool for measurement of a portfolio of physical-chemical properties as depicted in Table 20.1.2.

Table 20.1.2. Classification of physicochemical properties that can be measured by SFC.

Equilibrium properties	Kinetic and transport properties	Other properties
*Fluid phase interactions - Second virial coefficients *Solution interactions - Partial molar volumes - Solubilities *Surface interactions - Adsorption isotherms	*Diffusion coefficients *Mass transfer coefficients	* Molecular masses
	°Adsorption and desorption rate constants °Reaction rate constants	

*Properties determined by SFC; °Properties determined by GC and can be determined by SFC

However, indirect approaches and methods that involve sampling suffer from magnification of propagated error due to the high sensitivity and non-linear nature governing fundamental relations in the critical region.

Due to the inherent limitation of predictive methods, relative importance of experimental methods become very significant when compared to simple fluids at near ambient condition. Therefore, the area is a popular review[3,21] topic and is included in most texts[6,22] in the field.

20.1.2.1.2 Computation of high-pressure phase behavior

Computation and definition of critical phenomena is essential in prediction, modeling, and identification of various phases at high pressures. Gibbs presented the definition of critical state in his pioneering paper “On the Equilibrium of Heterogeneous Substances” in 1876.[23] For mixtures, mechanical and thermal stability criteria are not sufficient to describe the critical behavior. Therefore, the necessary formulations should include the

diffusional (material) stability criteria. Various investigators have transformed Gibbs' criteria to other variable sets, including Reid and Beegle[24] who developed Gibbs' criteria through Legendre transforms with suggestions to overcome indeterminacy. Works of Michelsen[25] and Heidemann[26] combine algorithms with more convenient representation of Gibbs' criteria. The most comprehensive study that coupled global algorithms and introduction of solid phase considerations into modeling of binary phase diagrams is due to Patel and Sunol[27] who also incorporated a differential approach that integrate tracing of the thermodynamic landmarks with non-zero degrees of freedom and stability.

Generation of complete phase diagrams is not a trivial task and may require utilization of either insight and heuristic guidance or global approaches coupled with Mixed Integer Non-linear Programming (MINLP) or intelligent search algorithms such as genetic algorithms and simulated annealing or global equation solving techniques such as interval methods[28] or continuation methods.[29]

The methods used in generation of phase diagrams may either employ the more popular integral approach that is suitable for design purposes or the more insightful differential approach that is preferred for generation of phase diagrams.[30] The basic elements of integral approach are the determination of fluid phase partition coefficient, K, for each component as well as stability criterion coupled with a computational algorithm.

For determination of the fluid phase partition coefficients, K, one may take a symmetric approach that uses Equation of States (EOS) for all fluid phases or an unsymmetrical approach that makes use of liquid activity models for the liquid phase retaining the equation of state models for the gas phase.

For symmetric approach:

$$K_i = \frac{\hat{\varphi}_i^{\beta}(T, P, x_i)}{\hat{\varphi}_i^{\alpha}(T, P, y_i)}$$

For the unsymmetrical approach:

$$K_i = \frac{\gamma_i^{\beta}(T, P, x_i) f_i}{\hat{\varphi}_i^{\alpha}(T, P, y_i)}$$

where:

K_i partition coefficient of component i in phases α and β
$\hat{\varphi}_i^{\beta}$ fugacity coefficient of component i in mixture for phase β
$\hat{\varphi}_i^{\alpha}$ fugacity coefficient of component i in mixture for phase α
γ_i^{β} activity coefficient of component i in mixture for phase β
f_i fugacity of pure component i

If one assumes no solvent in the solid phase, the relation for solubility of the solid in the supercritical solvent reduces to:

$$y_i = \left[\frac{p_i^{sub}(T)}{P}\right]\left[\frac{1}{\hat{\varphi}_i^{DG}}\right]\exp\left[\frac{\bar{V}_i^{s}(P - P^{sub})}{RT}\right]$$

A B C

where:

y_i mole fraction of component i in gas phase
p_i^{sub} sublimation pressure of component i
P total pressure
$\overline{V}_i^s$ partial molar volume of component i in solid phase
R universal gas constant
T absolute temperature

The first term A is for ideal gas solubility, the second term B accounts for the non-ideality, while the third term C (Poynting correction) accounts for the pressure effects. The product of the second and third terms is often referred as the Enhancement Factor (over the ideal). In the absence of data, the sublimation pressure may be approximated through extrapolation of the vapor pressure information.

20.1.2.1.3 Equation of State Models

The approaches to modeling the high pressure phase behavior follow either use of the equation of state models for fugacity coefficient determination or the treatment of the dense gas as an "expanded liquid" through an activity coefficient model, the former approach being more popular.

The macroscopic dense gas modeling approaches include van der Waals family of equation of states, virial family of equation of states, and non-classical approaches. The molecular/theoretical approaches and considerations contribute not only to more comprehensive models but also provide insight bringing forth sound parameters/terms to the macroscopic models. Computer simulation (molecular) can also be used to directly compute phase behavior with some success.[31,32] The virial family of equation of states finds limited use in supercritical applications due to the necessity for a large number of terms and their inadequacy in representing the critical point. The non-classical scaling approaches[33,34] fail when extended beyond the very narrow critical region and their combinations with equations of state (crossover EOSs) are still far from having practical applicability. Therefore, we will focus on the van der Waals family of Equation of States.[35]

These equations of states have both a repulsive and an attractive term. The most popular variants differ in how the attractive terms are modeled. The success of more recent Peng-Robinson[36] (PR) and Soave-Redlich-Kwong[37] (SRK) equation of states in phase behavior representation is due to the added parameter, acentric factor that incorporates vapor pressure information into the model. The shortcomings around the critical point are mainly due to the enhanced contribution of repulsive forces that can be modified through Perturbed Hard Chain Theory (PHCT).[38] Naturally, one other inherent difficulty is due to the instability of high molecular weight compounds at their critical point. This implies use of other parameters or pseudo-critical properties to model the compounds and their mixtures. These equations of states are better in representing molar gas volume then the liquid. The accuracy of molar liquid volume can be improved through volume translation.[39] The added terms and parameters naturally complicate the equation of state since the order of the equation increases above cubic.

Yet another essential dimension of the equation of states is their representation of mixture properties, which is achieved through mixing rules (models) that often include

adjustable binary interaction parameters determined from multicomponent, ideally binary, data. Most classical approaches fail to model mixing behavior of systems with dissimilar size components and hydrogen bonding, particularly if one expects to apply them throughout a wide pressure and temperature range that extends from very low to high pressures. Some of the empirical density dependent mixing rules such as Panagiotopoulos-Reid[40] can account for the relative size of the solute and the solvent, but have theoretical shortcomings violating one fluid model. There are also approaches that combine equation of state with activity models by forcing the mixture EOS to behave like the activity models (G_E) at liquid densities.[35] EOS-G_E models can be combined with group contribution models to make them predictive. More recently, Wong-Sandler[41] mixing rules provide an avenue to incorporate more readily available low-pressure information into the equation of states and extrapolate throughout the entire pressure range, ensuring fundamentally correct boundary conditions.[42]

Considering the difficulty associated with representing fugacity coefficients that may vary over ten orders of magnitude by mere change in temperature, pressure and composition; a simple equation of state such as Peng-Robinson, which is given below, do very well in correlating the experimental data and representing the phase behavior well.

$$P = \underbrace{\frac{RT}{V_m - b}}_{\text{repulsive term}} - \underbrace{\frac{a}{V_m(V_m + b) + b(V_m - b)}}_{\text{attractive term}}$$

where:

$$b = \Sigma_i x_i b_i$$

$$a = \Sigma_i \Sigma_j x_i x_j (a_i a_j)^{0.5} (1 - k_{ij})$$

$$b_i = 0.0778\left(\frac{RT_{ci}}{p_{ci}}\right)$$

$$a_i = \alpha_i 0.45724 (R^2 T_{ci}^2 / P_{ci})$$

$$\alpha_i [1 + m_i (1 - T_{ri}^{0.5})]^2$$

$$m_i = 0.37464 + 1.54226\omega_i - 0.26992\omega_i^2$$

where:

P	pressure
R	universal gas constant
T	absolute temperature
V_m	molar volume
b	function of T_{ci}, P_{ci} and x_i
a	function of T_{ci}, P_{ci}, x_i and k_{ij}
α_i	a function of reduced temperature T_{ri} and accentric factor, ω_i
m_i	a function of accentric factor of component i
ω_i	acentric factor of component i
k_{ij}	the interaction coefficient of the molecules i and j
T_{ci},P_{ci}	critical temperature and pressure of component i
x_i	mole fraction of component i
T_{ri}	reduced temperature T/T_{ci}

The polymer solutions[43] warrant use of a special class of lattice models such as Flory-Huggins. For correlation purposes Sanchez-Lacombe[44] method is usually sufficient, but one may also use Statistical Association Fluid Theory[45] (SAFT) models to obtain a more accurate representation and predictive power in expense of computational burden. A more comprehensive treatise of structure of the models are given by Aslam and Sunol[46] as shown in Figure 20.1.13.

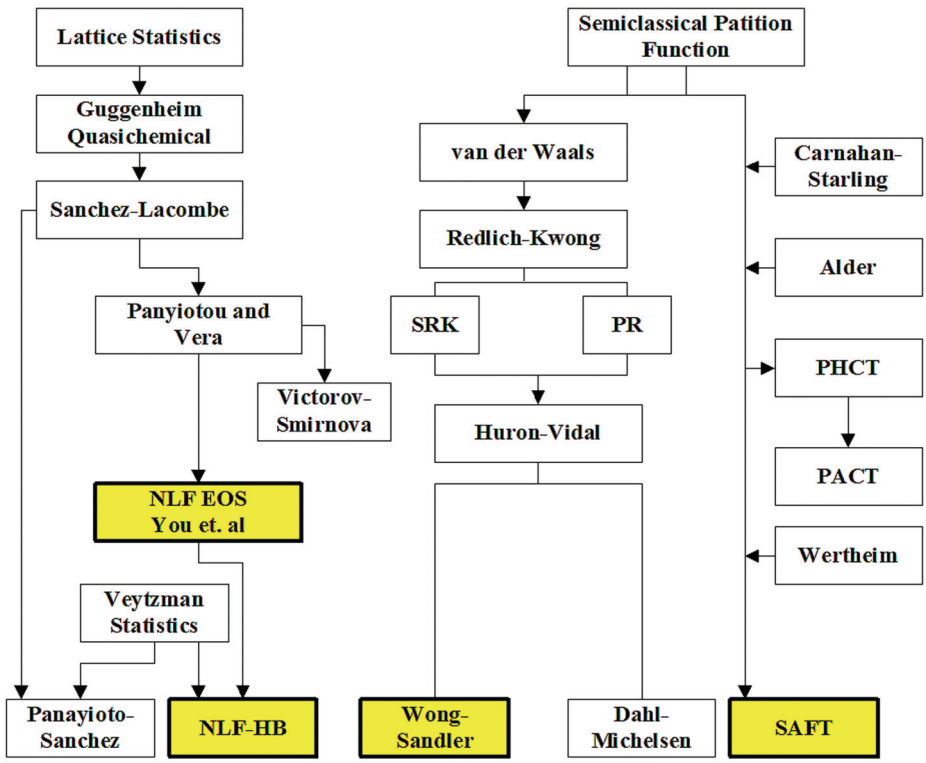


Figure 20.1.13. Different classes of equation of state models used in high pressure phase behavior representation.

20.1.2.1.4 Hildebrand Solubility Parameter at Supercritical Conditions

An empirical approach quite often used in solvent selection using the principal of "like dissolves like" is Hildebrand solubility parameter. Solutes that have similar solubility parameters to that of solvent readily solubilize within the solvent. For supercritical conditions, one can incorporate state and chemical effect to the following relation:

$$\xi_g = \text{Chemical effect x State effect}$$

where:

Chemical effect = $1.25\ Pc^{1/2}$
State effect = $PM_w/(ZRT\rho_c 2.66)$
ξ_g is the gas solubility parameter

Pc	is the critical pressure
P	is the pressure
Z	is the compressibility factor
T	is the temperature
R	is universal gas constant
ρ_c	is the critical density
M_w	is the molecular weight of the compound.

The state effect dominates for supercritical solvents and the solvent strength is adjustable.

20.1.2.2 Transport properties of supercritical solvents

The transport properties of the supercritical fluids fall somewhat in between the gas and the liquid and also depend on how removed one is from the critical point. Dense gasses have the solubilizing power of liquids and the mobility of gasses as depicted in Table 20.1.3. There are quite a few empirical correlations and theoretical models, which are primarily extensions of corresponding low-pressure liquid and gas counter parts. Similarly, some of the classical experimental methods can be used for measurement of transport properties of supercritical fluids. A rather brief overview of the methods applicable for supercritical fluids will be presented since specialized reviews in the area give a good account of the state of the art.[34,47] For engineering purposes, one can use applicable property estimation methods available in flowsheet simulators[48] such as ASPEN PLUS, PROII, G-PROMS, and CHEMCAD. These methods are discussed in a text classical in the field.[49]

Table 20.1.3. Transport properties of gases, liquids, and supercritical fluids.

State	Condition	Property		
		Density, g/cm^3	Diffusivity, cm^2/s	Viscosity, g/cm-s
Gas	1 atm, 25ºC	0.6-2 10^{-3}	1-4 10^{-1}	1-3 10^{-4}
Liquid	1 atm, 25ºC	0.6-1.6	0.2-2 10^{-5}	0.2-3 10^{-2}
SC Fluid	T_c, P_c	0.2-0.5	0.5-4 10^{-3}	1-3 10^{-4}
SC Fluid	T_c, $4P_c$	0.4-0.9	0.1-1 10^{-3}	3-9 10^{-4}

20.1.2.2.1 Viscosity

Both the capillary viscometer (providing about 0.7% accuracy), the theory of which is based on the Hagen-Poiseuille equation, and the oscillating disc viscometer (providing about 0.2% accuracy) are applicable to experimental determination of viscosity at high pressures and temperatures.

Most of the theoretically based estimation methods for viscosity of dense gases rely on modified Enskog theory. Corresponding states-based methods are also popular but should be used with care due to their empirical nature.

20.1.2.2.2 Diffusivity

The experimental techniques used to measure the diffusion are based upon chromatographic methods,[20] NMR (for self-diffusion), and photon correlation spectroscopy.[50] The so-called chromatographic method for the measurement of diffusion coefficients, strictly

speaking, is not a chromatographic method since no adsorption/desorption or retention due to partition in two phases is involved in the method. The experimental system used is however a chromatograph. Diffusion occurs in an empty, inert column on which the fluid phase is not supposed to be adsorbed. The fluid, in which the solute diffuses, flows continuously through the empty column and the solute, which is introduced into the column at one end and it is detected at the other end as effluent concentration.

The theory of diffusion in flowing fluids was first given by Taylor[51] and Aris.[52] According to Aris, a sharp band of solute, which is allowed to dissolve in a solvent flowing laminarly in an empty tube, can be described in the limit of a long column as a Gaussian distribution, the variance of which, σ^2 (in length units) is given as:

$$\sigma(x)^2 = 2D_{eff}t$$

where:

	t	time of migration of peak
	D_{eff}	effective diffusion coefficient given by, $D_{eff} = D_{12} + \frac{r^2 u^2}{48 D_{12}}$

where:

	u	average solvent velocity
	r	inner radius of the tube
	D_{12}	binary diffusion coefficient

The first term describes the longitudinal diffusion in the axial direction. The second term is called the Taylor diffusion coefficient and describes band broadening due to the parabolic flow profile and therefore radial diffusion. The height equivalent to a theoretical plate, H, is a measure of the relative peak broadening and is defined as

$$H = \sigma(x)^2 / L$$

where:

	L	length of tubing

Combining the above equations yields

$$H = \frac{2D_{12}}{u} + \frac{r^2 u}{24 D_{12}}$$

Bulk diffusivity can be calculated from the above equation.

The estimation of low-pressure diffusivity is based on the corresponding states theory. The dense gas diffusion coefficient estimation is based on the Enskog theory. The binary diffusion coefficient D_{ij}^{v} at high pressures as modeled by Dawson-Khoury-Kobayashi correlation is next given as a representative model. For a binary system, the equations are:

$$D_{ij}^{v}\rho_{m}^{v} = [1 + a_1\rho_{rm}^{v} + a_2(\rho_{rm}^{v})^2 + a_3(\rho_{rm}^{v})^3]D_{ij}^{v}(p = 0)\rho_m(p = 1\ \text{atm})$$

$$\rho_{rm}^{v} = V_{cm}/V_m^{v},\ \rho_m^{v} = 1/V_m^{v},\ V_{cm} = \frac{y_i v_{ci} + y_j v_{cj}}{y_i + y_j}$$

where:

ρ_m	molar density
ρ_{rm}	reduced molar density
a_1, a_2, a_3	constants
V_{cm}	critical molar volume
V_m	molar volume
V_{ci}	critical volume of component i
y_i	mole fraction of component i

$D_{12}^{V}(p=0)$ is the low-pressure binary diffusion coefficient obtained from the Chapman-Enskog-Wilke-Lee model. The molar volume and the molar density are calculated with an equation of state model.

20.1.2.2.3 Thermal conductivity

Transient hot-wire and co-axial cylinder methods are typically applied for measurement of the thermal conductivity of supercritical fluids.[53] The theory of thermal conductivity is based on the Enskog theory and a typical model for both vapor and liquid thermal conductivity is given by Chung-Lee-Starling. This model makes use of the PRWS (Peng-Robinson with the Wong-Sandler mixing rules) to provide a flexible and predictive equation of state. The main equation for the Chung-Lee-Starling thermal conductivity model is:

$$\lambda = \frac{312\eta(p=0)}{M} f_1 + f_2$$

where:

$f_1 = \text{fcn}(\rho_{rm}, \omega, p_r, \kappa)$
$f_2 = \text{fcn}(T_c, M, V_{cm}, \rho_{rm}, \omega, p_r, \kappa)$
$\psi = \text{fcn}(C_v, \omega, T_r)$

$\eta(p=0)$ can be calculated by the low pressure Chung-Lee-Starling model. The parameter p_r is the reduced dipole moment given by:

$$p_r = \frac{p}{V_{cm} T_c^{0.5}}$$

where:

λ	thermal conductivity
η	viscosity
M	molecular mass
ρ_{rm}	reduced molar density
ω	acentric factor
p	dipole moment
p_r	reduced dipole moment
V_{cm}	critical molar volume
V_m	molar volume
T_c, T_r	critical and reduced temperature
κ	polar parameter

For low pressures, f_1 is reduced to 1.0 and f_2 is reduced to zero. This gives the Chung-Lee-Starling expression for thermal conductivity of low-pressure gases. The molar density, ρ_{rm}, can be calculated using and equation of state model (for example, the Peng-Robinson-Wong-Sandler equation of state) where the mixing rule for b is obtained as follows. The second virial coefficient must depend quadratically on the mole fraction:

$$B(T) = \sum_i \sum_j x_i x_j B_{ij}$$

with:

$$B_{ij} = \frac{B_i + B_j}{2}(1 - k_{ij})$$

The relationships between the equation of state at low pressure and the virial coefficient are:

$$B = b - \frac{a}{RT}; \; B_{ii} = b_i - \frac{a_i}{RT}$$

Wong and Sandler have shown that the following mixing rule does satisfy the second virial coefficient equation:

$$b = \frac{\Sigma_i \Sigma_j x_i x_j B_{ij}}{1 - \frac{A_m^E(p = \infty)}{\Lambda RT} - \Sigma_i x_i B_{ij}}$$

where:

B	the second virial coefficient
k_{ij}	the interaction coefficient of the molecules i and j
b	function of T_{ci}, P_{ci} and x_i
a	function of T_{ci}, P_{ci}, x_i and k_{ij}
A_m^E	Helmholtz free energy

The pressure correction to the thermal conductivity for a pure component or mixture at low pressure is given by:

$$\lambda^v = \text{fcn}(\lambda^v(p = 0), \rho_{rm}, y_i, M_i, T_{ci}, V_{ci}, Z_{ci})$$

$$B(T)\rho_{rm} = \sum_i y_i \frac{V_{ci}}{V_m^v}$$

where:

λ^v	thermal conductivity
ρ_{rm}	reduced molar density for mixtures
y_i	mole fraction of component i
M_i	molecular mass of component i
T_{ci}	critical temperature of component i
V_{ci}	critical volume of component i
Z_{ci}	critical compressibility of component i

The vapor molar volume V_m^v can be obtained from the equation of state models as described above.

20.1.2.2.4 Surface tension

Stability of phase boundaries depends on the surface tension. Surface tension in a supercritical fluid system is of major importance for drying,[54] surfactant efficacy, and

extraction. The surface tension of a gas increases with pressure and approaches zero at the critical point while the surface tension of liquid decreases with pressure resulting in dissolution of supercritical components in the liquid phase. The methods useful in correlating surface tension include Macleod-Sugden correlation and corresponding states theory.[22]

20.1.2.3 Entrainer (co-solvent) effects with supercritical solvents

Entrainers, modifiers, and co-solvents are basically mixed solvent systems and provide another dimension to supercritical fluid extraction. The entrainers enhance the solubility of the low volatile substance in the solvent and provide selective solubility in instances with multiple solutes. Furthermore, they enhance the sensitivity of the solubility and selectivity to temperature, pressure, and composition. The entrainers may be reactive and are also useful as slurrying media. Table 20.1.4 shows representative data on the effect of entrainers on vapor-liquid systems that have been systematically studied by Brunner's group. Kurnik and Reid[55] as well as Johnston's group[56] present data for dense gas-solid systems.

Table 20.1.4. The effect of entrainers on separation factor (Adapted from Brunner[22]).

Entrainer	α	Entrainer	α
Hexadecanol(1)-octadecane(2)-entrainer -nitrous oxide (120 bar, 70°C, y_0 = 1.5 wt%, a_0 = 2, $y_{(1)+(2)}$ = 2 wt%)		Octadecane(1)-salicylic acid phenyl ester(2) -entrainer-nitrous oxide (120 bar, 70°C, y_0 = 1.5 wt%, a_0 = 2, $y_{(1)+(2)}$ = 1.7 wt%)	
acetone	3	methanol	1.65
methanol	2.4	dichloromethane	1.5
dichloromethane	2.1	benzene	1.45
benzene	2	cyclohexane	1.4
methyl acetate	2	acetone	1.4
hexane	1.9	hexane	1.3
cyclohexane	1.7	methyl acetate	1.2
Hexadecanol(1)-octadecane(2)-entrainer -ethane (120 bar, 70°C, y_0 = 15 wt%, a_0 = 2.5, $y_{(1)+(2)}$ = 30 wt%)		Hexadecanol(1)-octadecane(2)-entrainer-carbon dioxide (120 bar, 70°C, y_0 = 0.4 wt%, a_0 = 2.5, $y_{(1)+(2)}$ = 1 wt%)	
methanol	2.2	methanol	3.4
acetone	1.6	acetone	1.8
hexane	1.6	methyl acetate	1.6
(120 bar, 90°C, $y_{(1)+(2)}$ = 20 wt%)		hexane	1.4
methyl acetate	1.8		
benzene	1.2		
dichloromethane	1.1		

Although entrainers provide the aforementioned added advantages, they also bring forth more complex process flow-sheets. The fractionation of extract from entrainer and entrainer from the supercritical component are not as easy and as sharp as in the instances

without entrainer. The selection of entrainer is based on the thermodynamic, environmental, and economic considerations. The solute-entrainer and entrainer-supercritical separations are the key from the processing perspective.[57]

20.1.2.4 Reaction rate implication in supercritical solvents

Reactions in supercritical media utilize high pressures. Therefore, the effect of pressure on reaction equilibrium as well as reaction rate plays an important role in supercritical phase reactions.[58]

The kinetics of the reaction can be explained in terms of the transition-state theory. According to the theory, the reaction occurs *via* a transition state species M* and the generic elementary reaction can be written as:

$$aA + bB + \ldots \leftrightarrow M^* \rightarrow \text{Products}$$

The effect of pressure on the rate constant is given as:

$$\left[\frac{\partial \ln k_x}{\partial P}\right]_T = \left[\frac{\partial \ln K_x^*}{\partial P}\right]_T + \left[\frac{\partial \ln \kappa}{\partial P}\right]_T = \frac{\Delta \bar{V}^*}{RT} + \left[\frac{\partial \ln \kappa}{\partial P}\right]_T$$

where:

k_x	rate constant in mole fraction units
P	pressure
T	temperature
K_x^*	mole fraction based equilibrium constant for reaction involving reactants and transition state
κ_T	isothermal compressibility
$\Delta \bar{V}^*$	activation volume (difference between partial molar volumes of activated complex and reactants), $\Delta \bar{V}^* = \bar{V}^* - a\bar{V}_A - b\bar{V}_B - \ldots$
R	universal gas constant

The rate constant in the above equation is expressed in terms of pressure independent units (mole fraction). If the rate constant is expressed in terms of pressure dependent units (such as concentration), the relevant equation is:

$$\left[\frac{\partial \ln k_x}{\partial P}\right]_T = -\frac{\Delta \bar{V}^*}{RT} + \left[\frac{\partial \ln \kappa}{\partial P}\right]_T + \kappa_T(1 - a - b - \ldots)$$

If the volume of activation is positive, the reaction is hindered by pressure. However, for high negative values of the volume of activation, the pressure enhances the rate of the reaction. Therefore, supercritical fluids that exhibit very high negative activation volumes for certain reactions will improve the rate of the reaction.

The volume of reaction, rather than activation, is crucial in determining the effect of pressure on the equilibrium constant.

$$\left[\frac{\partial \ln K_x}{\partial P}\right]_{T,\,x} = -\frac{\Delta \bar{V}_f}{RT}$$

where:

$\Delta \bar{V}_f$	reaction volume (difference between partial molar volumes of products and reactants)

If the equilibrium constant is expressed in terms of pressure dependent units (such as concentration), the relevant equation is:

$$\left[\frac{\partial \ln K_x}{\partial P}\right]_{T,\,x} = -\frac{\Delta \bar{V}_f}{RT} + \kappa_T \sum v_i$$

where:

v_i stoichiometric coefficient

As the above equation implies, supercritical fluids that exhibit very high negative activation volumes for certain reactions will improve the equilibrium conversion of the reaction.

20.1.2.5 Sorption behavior of supercritical solvents

Both adsorption from a supercritical fluid to an adsorbent and desorption from an adsorbent find applications in supercritical fluid processing.[59,60] The extrapolation of classical sorption theory to supercritical conditions has merits. The supercritical conditions are believed to necessitate monolayer coverage and density dependent isotherms. Considerable success has been observed by the authors in working with an equation of state based upon the Toth isotherm.[61] It is also important to note that the retrograde behavior observed for vapor-liquid phase equilibrium is experimentally observed and predicted for sorptive systems.

20.1.2.6 Swelling with supercritical solvents

As the pressure of the gas is increased, the solubility of the supercritical gas in the solid polymer increases resulting in swelling, a phenomenon that could be advantageous in certain applications while its deleterious impact should be minimized, if not totally eliminated, in other instances.

The sorption of supercritical solvent and the resulting swelling could be very high, for example around 30% and 20% respectively for carbon dioxide in polymethylmethacrylate (PMMA). In such instances, the experimental information could be summarized using polymer equation of states such as Sanchez-Lacombe where a single mixture fitting parameter is used.[6] Likewise, an equation of state will provide some level of approximation for the level of swelling to be expected in the polymer. This is highly dependent on the original model and predictive capability of the mixing rules that include the interaction parameter (s).

Swelling can be advantageous in that it enables permeation and diffusion of the supercritical fluid into the polymer network. Fragrances, dyes, or medicinal substances loaded in the supercritical fluid can readily impregnate into the polymer and load the polymer with the aforementioned additives. Upon release of the pressure, only the supercritical fluid (i.e., carbon dioxide) flashes off. This avenue has led to a plethora of controlled (timed) release products.

Polymer impregnation described above comes with certain challenges, namely the verification of impregnation. Multiple traditional analytical techniques may be used but like any analysis must be done using the correct procedure. Microscopic analysis methods such as SEM or TEM may be used on prepared polymer slices to verify the presence of

materials which take on a defined structure within the polymer matrix. Fourier Transform Infrared Spectroscopy (FTIR) is another method that may be used on the polymer cross sections to verify that a specific solute has been successfully impregnated. Internal layers of the polymer may be dissolved in solvent and processed via a chromatographic method. However, verification of impregnation is tied directly to analysis of internal layers of the polymer matrix. Analyzing the sample as a whole may lead to the false conclusion that impregnation was carried out when only surface coating occurred.

Naturally, swelling may be undesirable in many instances as well. For example, swelling of organic polymer-based membranes decreased selectivity. Other possible deleterious effects could include malfunctions due to solubilization and swelling of sealants such as gaskets or o-rings.

20.1.2.7 Surfactants and micro-emulsions

Most highly polar and ionic species are not amenable to processing with desirable solvents such as carbon dioxide or any other solvent such as water that has a higher critical temperature well above the decomposition temperature of many solutes. In such instances, the combination of the unique properties of supercritical fluids with those of micro-emulsions can be used to increase the range of applications of supercritical fluids.[62] The resulting thermodynamically stable systems generally contain water, a surfactant and a supercritical fluid (as opposed to a non-polar liquid in liquid micro-emulsions). The possible supercritical fluids that could be used in these systems include carbon dioxide, ethylene, ethane, propane, propylene, n-butane, and n-pentane while many ionic and non-ionic surfactants can be used. The major difference between the liquid based emulsions and the supercritical ones is the effect of pressure. The pressure affects the miscibility gaps as well as the microstructure of the micro-emulsion phase.

The incorporation of the micro-emulsion phase creates interesting potential advantages for reactions as well as separations. Isolation of components from fermentation broths and garment cleaning appear to be two of the more competitive applications of these systems.

20.1.2.8 Dimensionless numbers and supercritical fluids

Dimensionless numbers are often used in engineering for capturing underlying phenomena and scale up. A thorough comparison of supercritical fluids with gases and liquids is not possible following observations highlight the major differences

- Schmitt number which is the kinematic viscosity to mass diffusivity illustrates mixing characteristics including inhomogeneities and their duration. Typical Schmitt numbers are about 1 for gases and about 10 for supercritical fluids. The implication is gases mix rapidly, liquids need stirring, and supercritical fluids mix much more rapidly than liquids.
- Prandtl number is analogous to Schmitt number but focuses on heat transfer. It is the ratio of kinematic viscosity to thermal diffusivity. Typical Prandtl numbers are about 1 for gases and about 10 for supercritical fluids. The implication thermal inhomogeneity in gases degrade rapidly, liquids need stirring, and supercritical fluids mix much more rapidly than liquids.

Archimedes number is the ratio of gravitational forces to viscous forces. The number is about 3,500 for water, 9,000 for air and 700,000 for supercritical carbon dioxide. This leads to Reynolds numbers two orders of magnitude higher at the minimum fluidization velocity and fluidized bed heights that are an order of magnitude smaller than liquids and gas counter parts.

20.1.3 SEPARATION WITH SUPERCRITICAL SOLVENTS

Supercritical fluids are effective at much lower temperatures than distillation, and their application in separation avoids degradation and decomposition of heat-labile compounds. Attractiveness of supercritical extraction processes are due to the sensitivity of responses to process variables, promise of complete and versatile regeneration of solvents, energy savings, enhanced solute volatilities, solvent selectivity, favorable transport properties for solvents, and state governed effectiveness of solvents which enables the use of low cost, non-toxic, environmentally acceptable solvents. The impact of inherent characteristics of supercritical fluids on separations is summarized in Table 20.1.5.

Table 20.1.5 The characteristics and challenges with supercritical separations.

Inherent characteristics of systems @ supercritical conditions	Resulting promise	Challenges to be met
Enhanced solubility	Effective at lower temperatures	Recovery of substances inadvertently extracted
Favorable transport properties	High mass transfer rates especially in porous media	
Inherent characteristics of systems @ supercritical conditions	Resulting promise	Challenges to be met
Sensitivity of responses to process variables	Effective recovery of solvents, and innovative fractionation possibilities	Control and optimization
High pressure		High capital cost and need for recovery of mechanical energy
Dominance of physical characteristic on solvency over chemical	Expansion of solvent spate to environmentally benign, inexpensive, and non-flammable solvents and their mixtures	

There have been many useful attempts made to classify separation technologies. Supercritical fluids are applicable to both intra-phase and inter-phase separations. Due to the ease and flexibility in which a new phase can be formed for regeneration of the solvent, intra-phase is the more common. Furthermore, material solubility and swelling problems, particularly with organic component-based membranes, limit interphase separations. This is due to the enhanced solubility of these components in supercritical solvents.

Generic steps involved in a typical chemical process are shown in Figure 20.1.14, with each separation subtask type identified. Environmental processes are usually domi-

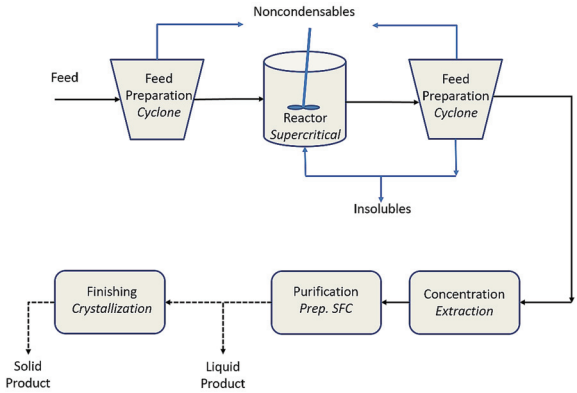


Figure 20.1.14. A generic process flow-sheet with possible supercritical steps.

nated by feed preparation tasks while biochemical processes utilize all of the four subtasks. Blending is considered a finishing task while splitting is considered a feed preparation task. The objective criteria used for the separation may vary according to the subtask. For example, in feed preparation, technical feasibility such as removal of the fines is more appropriate while the usual economic objectives subject to technical feasibility constraints become the goal for the purification and finishing stages.

The feed preparation task involves removal of insoluble components and at times non-condensable compounds. The technology selection and the scheduling of tasks are concentration and particle size distribution dependent. These processes are usually physical/mechanical in nature. The feed preparation may be carried out in a unit designed particularly for the purpose or the function may be tied to another function within a single unit. For example, the fines, either nucleated through temperature and/or pressure perturbation, or particles suspended in the supercritical fluid can be readily separated through cyclones.

Concentration (or isolation) tasks are usually necessary with streams where the product concentration is very low (dilute). Adsorption and extraction are typical technologies utilized here. Energy considerations dominate the technology selection subject to product contamination and stability constraints. Thus, the base technology depends on the availability of the mass separating agent (e.g., adsorbent or solvent) and its efficient recycle. Supercritical extraction of organic compounds from aqueous streams is a typical example of isolation step.

The candidate technologies for purification are many. Distillation, the workhorse of the chemical processes, leads the pack. Most of the synthesis effort to date has concentrated on the product purification step. This step is often the last step for liquid products especially in the chemical and petrochemical industries. The biochemical industry utilizes membrane and chromatographic processes more than the other industries due to the thermal stability and purity requirements. In the electronic industry, membrane processes are more prevalent due the ultra-purities necessary. Supercritical fractionation of alcohol water systems with the aid of a dense gas is an example of a purification step.

Crystallization, drying, and blending are typical operations necessary to polish (finish) the product to its final form. Particle nucleation from a supercritical fluid solution is an example of finishing. Each supercritical separation technique is identified on this generic process.

20.1.3.1 Leaching – generic application

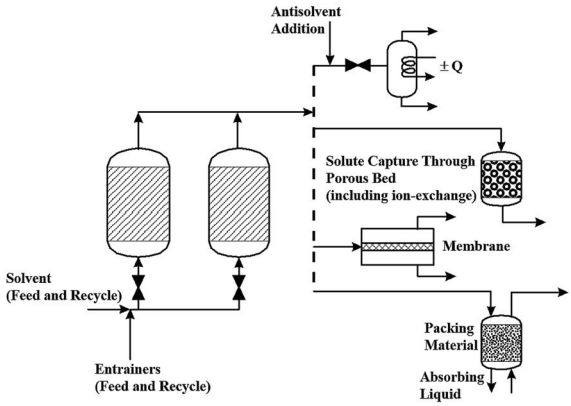


Figure 20.1.15. Supercritical leaching and options for supercritical solvent regeneration.

Leaching is usually incorrectly referred to as extraction of a solid substrate, and is commercially the most significant application of supercritical fluids. A generic flow-sheet, shown in Figure 20.1.15, illustrates the basic processing concepts. A heat labile natural substrate is usually contacted with a flowing supercritical fluid in a semi-continuous mode. The supercritical fluid may optionally be doped with an entrainer. Due to the stationary (batch) nature of the leaching stage, two or more parallel vessels loaded with the substrate may be utilized. The material leached is recovered and fractionated through pressure reduction, temperature perturbation, adsorption, membranes or through absorption. During the initial stages of leaching, the solute loading is high and may approach the equilibrium solubility limit, while at the latter stages kinetic and mass transfer limitations are responsible for relatively lower concentration of the solute. Both coffee decaffeination[63] and hops extraction[64] are popular commercial successes of this application. Further, typical applications include food processing,[65-69] environmental and parts cleaning,[22,71,72] bioactive compounds production,[66,67,73-76] and fuel processing.[67,77,78] Examples are given in Table 20.1.6.

Table 20.1.6. Leaching applications of supercritical fluids.

Application	Substrate	Supercritical solvent	Extract
Food	Meat, egg	Carbon dioxide	Cholesterol, lipid
	Carrot, tomato, potato, grape skin	Carbon dioxide	Natural color
	Citrus peal, tea	Carbon dioxide	Flavoring compound
	Algae, microalgae	Carbon dioxide	Lipid
	Cheese	Carbon dioxide	Fat
	Onion, garlic	Carbon dioxide+ethanol	Flavoring compound
	Pepper	Carbon dioxide+ethanol+ methanol	Flavoring compound

Table 20.1.6. Leaching applications of supercritical fluids.

Application	Substrate	Supercritical solvent	Extract
Pharmaceutical	Cumin	Carbon dioxide	Antimicrobial oil
	Ginger	Carbon dioxide+methanol	Antipyretic
	Cammomile	Carbon dioxide	Anti-inflammatory Antispasmodic
	Sunflower leaves	Carbon dioxide Carbon dioxide+water	Herbicide
	Rosehip, cherry, grape seed, rosemary, algae, microalgae	Carbon dioxide	Antioxidant
	Bamboo shavings	Carbon dioxide+cosolvent	Anti-fatigue
	Algae, microalgae	Carbon dioxide	Lipid, metabolites, pigments
Energy	Algae, microalgae	Carbon dioxide	Lipid, hydrocarbons, alkadines
	Coal, lignite	Toluene, water, acetone, methanol, THF, tetralin, ethanol	Liquid products
Environmental	Soil	Carbon dioxide+modifier	Polycyclic aromatic hydrocarbons, pesticides
	Treated wood, soil, sand	Carbon dioxide+chelating agent	Heavy metals
	Solid fuels	Toluene, water, acetone, methanol, THF, tetralin, ethanol	Sulfur, oxygen, nitrogen
	Soil	Nitrous oxide	Pesticides
	Soil	Water	Polycyclic aromatic hydrocarbons

20.1.3.2 Extraction – generic applications

Liquid streams containing close-boiling and heat-labile components can be fractionated with the aid of supercritical fluids or valuable components of aqueous streams could be isolated and concentrated using supercritical solvents. Entrainers could also be added to the solvent to enhance the selectivity, particularly in fractionation instances. The main reason for using entrainers for concentration purposes is to enhance solubility. One can also use membranes along with supercritical fractionation.[79] Typical applications of this process technology are given in Table 20.1.7 and Table 20.1.8 while several review papers and texts provide useful design information.[80-83]

Table 20.1.7. Extraction applications of supercritical fluids.

Purpose	Supercritical medium	Substrate
Food processing		
Food purification	CO_2	Oil purification Cholesterol removal from milk fat
Flavor extraction	CO_2	Beer, wine and fruit flavor concentrates
Fractionation of food	CO_2	Oil, milk fat
Forest products		
Extraction of lignocellulosic materials and biomass	CO_2, SO_2, N_2O, H_2O, methylamine, ethanol, ethylene	Cellulose or lignocellulosic materials from wood or wood pulp
Biochemical		
Medicinal compound	CO_2	Fermentation broth
Petrochemical		
Purifying liquid fuels	CO_2	Deasphaltation, demetallization
Environmental		
Waste water extraction[73]	CO_2+entrainer	Aqueous toxic wastes, phenol, metabolic wastes
Essential oils		
Purification of essential oils	CO_2	Terpenes from orange, citrus and bergamot peel oil

Table 20.1.8. Fractionation applications of supercritical fluids

Purpose	Supercritical medium	Substrate
Essential oils		
Fractionation[74]	CO_2	Glycerol, fatty acids, glycerides
Chemical		
Fractionation	CO_2	Xylenes, glycerides, alkanes, aromatics
Fractionation	CO_2 + entrainer	Methyl esters, fullerenes
Petrochemical		
Fractionation	Toluene, pentane, propane	Petroleum pitch, asphalt
Polymer processing		
	CO_2	Polydimethylsiloxane, fluoropolymers, polypropylene

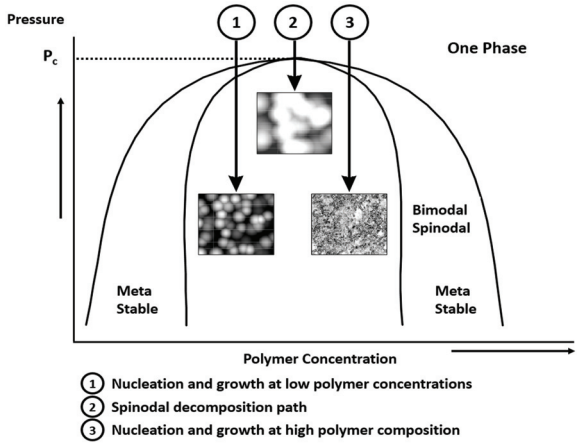


Figure 20.1.16. The pressure reduction path for nucleation of particles from supercritical fluids.

The methods useful in the design of extraction systems are the same as those traditional methods applicable to liquid and gaseous systems and include Kremser, McCabe Thiele, Panchon Savarit (including Janecke), and more rigorous rate-based as well as equilibrium based methods. Due to the highly non-linear nature of the physical and chemical properties in the critical region, great care has to be taken in representing both the properties and the solution algorithms.

20.1.3.3 Crystallization – generic applications

Particles nucleated from supercritical fluids have unique particle size, shape, and particle size distributions.[84] The means of achieving nucleation and growth are many, and include pressure reduction, temperature perturbation, and addition of anti-solvents. Time profiling and staging have profound effect on the particle characteristics. The effect of pressure reduction on the resulting nucleated material for different solute concentrations[16] is illustrated in Figure 20.1.16.

20.1.3.4 Sorption – generic applications

The sorption applications[22] include regeneration of porous beds,[85] preparative scale supercritical chromatography,[22] simulated moving beds,[22] thermal swing schemes,[86] and adsorption/desorption cycles. Although initial applications of supercritical fluids in this domain were on regeneration of porous beds, more recent emphasis on fractionation best reflects where the true potential of this technique lies. Typical examples are provided in Table 20.1.9.

Table 20.1.9. Sorption applications of supercritical fluids.[22,83]

Purpose	Supercritical medium	Substrate
Environmental		
Soil remediation	CO_2 + entrainers	Soil
Regeneration of adsorbents	CO_2	Polychlorinated biphenyls from adsorbents
Petrochemical		
Regeneration of adsorbents	CO_2	Benzene, toluene, ethyl acetate from activated carbon

Table 20.1.9. Sorption applications of supercritical fluids.[22,83]

Purpose	Supercritical medium	Substrate
Environmental		
Soil remediation	CO_2 + entrainers	
Regeneration of adsorbents	CO_2	Polychlorinated biphenyls from adsorbents
Petrochemical		
Regeneration of adsorbents	CO_2	Benzene, toluene, ethyl acetate from activated carbon
Regeneration of catalysts	CO_2, hexane, ethylbenzene, THF, benzene	Hydrocarbon, coke removal from catalysts
Chromatographic fractionation	CO_2	Coal tar, mineral oil distillate
Essential oils[78]		
Chromatographic fractionation	CO_2 + alcohol	Black pepper, clove extract
Polymer processing		
Chromatographic fractionation	CO_2, n-pentane + methanol	Styrene oligomer
Biochemical		
Chromatographic fractionation	CO_2 + alcohol	Prostaglandis
Chromatographic fractionation	CO_2 + alcohol	Vitamins, polyunsaturated fatty acids
Chromatographic chiral separation	CO_2	Optical isomers

In synthesis of supercritical sorption processes and their operating policies, the synergy between the characteristics of the supercritical fluids and the sorption needs to be captured. Naturally, the domain requires distributed process models that capture the key phenomena and solvers that can handle the numerical difficulties efficiently in addition to physical property models that accurately represent the thermophysical behavior throughout the effective operating range.

20.1.4 REACTIONS IN SUPERCRITICAL SOLVENTS

As stated in the previous sections, supercritical solvents are widely used for separation, especially for extraction of thermally labile compounds. Although the unique properties of supercritical fluids make them attractive as a reaction medium as well, the use of supercritical solvents as reaction medium has become more popular only in the recent years. The first review on reactions in supercritical fluids was presented by Subramanian and McHugh,[87] followed by a thorough review by Savage *et al.*[88] More recent reviews are on specific topics such as homogeneous catalyzed reactions,[89-93] biotransformations,[94,95] polymer reactions,[96] and heterogeneous reactions in supercritical fluids,[97-99] wastewater sludge treatment[100] as well as biofuel production such as biodiesel.[101]

Reactions in supercritical fluids, could be carried out in such a manner that separation steps are reduced or eliminated. Reactive distillation, which has been applied throughout industry, can be carried out at supercritical conditions as well. This leads to a combination of reaction and separation steps, thus resulting in a reduced capital footprint.

20.1.4.1 Motivations for carrying out reactions in supercritical fluids

The motivations for using supercritical solvents in chemical reactions are many.[102,103] In this section, the motivations will be stated and explained with examples for each type of reaction. Emphasis in this chapter will be given to more recent examples, which were not included in the previous review papers.

There are several reasons for carrying out reactions in the supercritical phase. Naturally, some of the reasons are coupled. Nevertheless, they, in general, relate to control, favorable mass transfer, and kinetic considerations.

Enhanced reaction rate

The effect of pressure on the reaction rate and equilibrium constant at high pressures is described in Section 20.1.2.4. As can be perceived from this section, supercritical fluids that exhibit very high negative activation volumes for certain reactions will improve the rate and equilibrium conversion of the reaction.

Homogenization

Reactions that otherwise would be carried out in more than one phase (heterogeneous reactions) can be transformed to homogeneous ones with the aid of supercritical fluids, so that inter-phase transport limitations are eliminated. This is realized due to enhanced solubilities of the reaction components in the supercritical fluids. Typical examples are reactions in water (supercritical water can solubilize organic compounds), homogeneous catalytic reactions, and reactions of organometallic compounds. Homogenizing one compound more than the others in a system may also affect relative rates in complex reactions and enhance the selectivity.

Enhanced mass transfer

In many instances, reaction rates are limited by diffusion in the liquid phase. The rate of these reactions can be increased if the reaction is carried out in the supercritical phase. Typical examples are enzyme catalyzed reactions as well as some very fast reactions such as certain free radical reactions. Selectivity considerations usually dominate in complex reactions. If some steps of the complex reaction are controlled by diffusion, changing the diffusivity changes the relative rates of the reaction steps and affects the selectivity.

Ease of down-stream separation

Another reason for using supercritical fluids as the reaction medium is to fractionate products, to purify the products or to remove unreacted reactants from the product stream. Supercritical fluids can be used as either a solvent or anti-solvent in these instances.

Increased catalyst activity

Some heterogeneous catalytic reactions are carried out in the supercritical phase, in order to increase catalyst activity and life through *in-situ* regeneration of surfaces with tuning of operation conditions. For example, supercritical fluids are capable of dissolving carbon that may otherwise be deposited on the catalyst in the absence of the supercritical solvent.

Tunable reaction rates through dielectric constant

Some properties of supercritical fluids can be monitored (manipulated) continuously by adjusting the density of the fluid. Dielectric constant is such a property and the solvent's dielectric constant can influence the rate of the reaction.

20.1.4.2 Homogenous reactions in supercritical solvents – examples

Homogeneous reactions carried out in supercritical fluids can be either catalytic or non-catalytic. The objective of carrying out both catalytic and non-catalytic reactions in supercritical fluids is to increase the overall rate of the reaction by eliminating the inter-phase transport effects.

20.1.4.2.1 Homogeneous catalytic reactions in supercritical solvents

Homogeneous catalysts have advantages over heterogeneous catalysts such as possibility of carrying out the reaction at milder conditions, higher activity, and selectivity, ease of spectroscopic monitoring, and controlled and tunable reaction sites.

Organic reactants and products are not soluble in water while most catalytic materials are soluble in water. Therefore, homogenization of organic systems utilize environmentally undesirable organic solvents. An alternative to environmentally unacceptable organic solvents is a supercritical solvent that has added advantages over organic solvents such as increased reaction rate, higher selectivity and easy separation of reactants and products as well as of the catalyst after the reaction. Since the properties of supercritical solvents can be adjusted by manipulating the operating conditions, reaction rate and selectivity. They are better tunable in reactions carried out in supercritical solvents.

Carbon dioxide is the supercritical solvent that is most commonly used in homogeneous catalytic reactions. In addition to being environmentally acceptable (nontoxic, nonflammable), inexpensive, and available in large quantities, carbon dioxide does not participate in most reactions. It also has an ambient critical temperature. Although, supercritical carbon dioxide is more effective in dissolution of non-polar, nonionic and low molecular mass compounds, addition of co-solvents enhances the solubility of many otherwise insoluble compounds in supercritical carbon dioxide. Homogeneous catalytic reactions under supercritical conditions are discussed in numerous reviews.[89-92,104]

When homogeneous reactions are carried out under supercritical conditions, gas/liquid interfacial transport is eliminated, which is an advantage for reactions such as hydrogenation, where diffusion of gas into the liquid may be limiting the reaction rate. In asymmetric hydrogenation reactions, hydrogen and the supercritical solvent are miscible, and this results in better enantioselectivity. In Diels-Alder reactions, the advantage of the supercritical solvent is the higher selectivity obtained rather than increased rate of the reaction due to the solvent. Most of the oxidation reactions are carried out in supercritical water. Some heterogeneously catalyzed reactions are also carried out in supercritical carbon dioxide.

Reactions in supercritical water are also well studied.[105] Despite the higher temperature and pressures required in supercritical water applications, this solvent possesses unique properties that make it attractive as a reaction medium. Supercritical water has a lower dielectric constant as compared to liquid water, and the dielectric constant of supercritical water changes significantly with the density. Also, the effect of hydrogen bonding

is less pronounced at supercritical conditions, one consequence of which is the high solubility of organics in supercritical water. The dielectric constant of water is not constant and varies with temperature and pressure. This tunable nature lends itself well to interfacing with other organics. For example, pressurized warm water may have a dielectric constant comparable to an alcohol whereas water under supercritical conditions will have a dielectric constant much more in line with a relatively non-polar organic.

The reactions in the supercritical water medium are carried out in a single phase, which implies high reactant concentration and negligible inter-phase mass transfer resistance. Also, the ion dissociation constant of water is higher in the critical region and lower as supercritical conditions are accessed. These properties also vary continuously in the supercritical region, so that they can be tuned during the reaction by changing the temperature and/or pressure. In some reactions discussed in this category, acid or base catalysts were used to enhance the rates.[91,105]

Homogeneous catalytic reactions in supercritical solvents are not limited to supercritical carbon dioxide and supercritical water. Especially, in more recent studies different solvents are employed as the supercritical media in homogeneous catalytic reactions (Table 20.1.10). Examples of homogeneous catalytic reactions carried out under supercritical conditions are summarized in Table 20.1.10.

Table 20.1.10. Homogeneous catalytic reactions in supercritical solvents.

Reaction	Supercritical solvent	Catalyst
Hydrogenation	Carbon dioxide	Ru, Rh complexes
	Water	NaOH
	CHF_3	Ru complex
Oxidation	Carbon dioxide	Fe, Mn, Rh, Pt-Ru, Mo complexes, $PdCl_2$, $CuCl_2$
	Water	Mn^{2+}, Cu^{2+}, Fe^{3+}
	C_3H_8	Fe complex
Dehydrogenation	Carbon dioxide	Rh complex
	Water	NaOH, NiO, ZrO_2
Coupling	Carbon dioxide	Pd, Ru complexes
	Water	Pd complex
Diels-Alder	Carbon dioxide	Sc, Yb, Li complexes, $AlCl_2$
	Water	NaOH
Esterification	Carbon dioxide	Yb, Pd complexes, $PdCl_2$, $CuCl_2$
	CH_2F_2	$CF_3C_6H_4SO_3H$
Alkylation	Carbon dioxide	$CF_3(CF_2)_7SO_3H$
	CHF_3	Amino alcohol, $CF_3(CF_2)_7SO_3H$
Hydroformulation	Carbon dioxide	Rh, Ru, Co complexes
Carbonation	Carbon dioxide	Re, Li, Sn, Zn, Fe complexes
Carbonylation	Carbon dioxide	Pd, Ru complexes, $PdCl_2$, $CuCl_2$

Table 20.1.10. Homogeneous catalytic reactions in supercritical solvents.

Reaction	Supercritical solvent	Catalyst
Cyclization	Carbon dioxide	Ni, Co complexes, $PdCl_2$, $CuCl_2$
Polymerization	Carbon dioxide	Pd, Rh, Co, Sn, Ti complexes
Copolymerization	Carbon dioxide	Zn, Cr, Al complexes
Epoxidation	Carbon dioxide	Mo, V, Ti complexes
Transesterification	Carbon dioxide	BF_3

20.1.4.2.2 Homogeneous non-catalytic reactions in supercritical solvents

Most non-catalytic, supercritical, homogeneous reactions are carried out in supercritical water. Hydration/dehydration, hydrolysis, decomposition and oxidation reactions are main reaction categories. No homogeneous catalyst is added in hydrolysis reactions of esters, nitriles and butyronitriles, however the reactions are autocatalytic. Biodiesel production from oils with supercritical methanol is another important reaction that has attracted increased attention in recent years as it has many benefits over traditional acid or base catalyzed biodiesel production. Decreased reactor sizes, increased reaction rate, amenability of continuous production, and variable scale are but a few of these benefits.

The use of supercritical fluids as reaction media for organometallic species has also been investigated.[106] Reactions include photochemical replacement of carbon monoxide with N_2 and H_2 in metal carbonyls, where the reaction medium is supercritical xenon. Also, photochemical activation of C–H bonds by organometallic complexes in supercritical carbon dioxide has been investigated. More recent studies on photochemical reactions also include laser flash photolysis of metal carbonyls in supercritical carbon dioxide and ethane[107] and laser flash photolysis of the hydrogen abstraction reaction of triplet benzophenone[108] in supercritical ethane and CHF_3.

Examples of non-catalytic homogeneous reactions in supercritical solvents are listed in Table 20.1.11.

Table 20.1.11. Homogeneous non-catalytic reactions in supercritical solvents.

Reaction	Supercritical solvent	Examples
C–C bond formation	Water	Alkylation
Diels-Alder	Water	Cycloaddition
Hydrogenation/ Dehydrogenation	Water	Alcohol conversion
Hydrolysis	Water	Reactions of esters, nitrites, ethers and triglycerides
Decomposition	Water	Cellulose, glucose, nitro aniline, nitrotoluene
Oxidation	Water	Phenol, alcohols, chlorinated hydrocarbons
Transesterification	Methanol	Used cooking oils to biodiesel

20.1.4.3 Heterogeneous reactions in supercritical solvents – examples

Heterogeneous reactions in supercritical fluids can be catalytic or non-catalytic. Catalytic heterogeneous reactions are reactions carried out on solid catalysts and are of great importance in the chemical process industries. As described in the next section, the advantages of carrying out these reactions in a supercritical medium include enhanced inter-phase and intra-particle mass and heat transfer and *in-situ* regeneration of catalyst. Catalytic supercritical water oxidation will also be discussed. Other heterogeneous reactions that will be described are fuels processing and treatment of biomass.

20.1.4.3.1 Heterogeneous catalytic reactions in supercritical solvents

Obviously, a solid catalyzed reaction takes place only on the active sites of the porous catalyst with the implication of some mass and heat transport steps prior to and after the reaction. The first step is the diffusion of the reactants through the film surrounding the catalyst particle to the external surface of the catalyst, followed by diffusion of the reactants into the catalyst pore to the active site in the pores. These steps are limited by the diffusivity and viscosity of the reactants. In the case of a supercritical fluid phase reaction, the diffusivity is higher than the liquid diffusivity, viscosity is less than the liquid viscosity and therefore, the rate of transfer to the active site will be higher. After the adsorption, reaction and desorption steps, the products have to diffuse out of the pore, and again through the film surrounding the particle into the bulk fluid. Rates of these steps can be accelerated utilizing a supercritical medium for the reaction. Heat transfer effects are also important in a solid catalyzed reaction. Higher thermal conductivity of supercritical fluids is an advantage as well.[105]

For two-phase reactions (typically hydrogenation and oxidation reactions), the reaction steps include the diffusion of the gas reactant to and through the gas-liquid interface and then into the bulk liquid. This mass transfer limitation is also eliminated if the reaction is carried out in a supercritical medium where the reaction takes place in a single phase.[109]

Supercritical fluids bring other benefits to the solid catalyzed reaction rate besides eliminating or minimizing mass and heat transfer resistance. Supercritical solvents have the ability to regenerate the catalyst during the course of the reaction, which increases the catalyst life and activity, since undesirable deposits on the catalyst, such as carbon deposits, are soluble in the supercritical fluids. The rate of the intrinsic reaction is increased in supercritical fluids and tuning the properties of the supercritical medium can control the selectivity.[109]

Supercritical fluids may also bring opportunities in downstream separation of the reactants and products.

Catalytic Supercritical Water Oxidation is an important class of solid catalyzed reactions that utilize advantageous solution properties of supercritical water (dielectric constant, electrolytic conductance, dissociation constant, hydrogen bonding) as well as the superior transport properties of the supercritical medium (viscosity, heat capacity, diffusion coefficient, density). The most commonly encountered oxidation reactions carried out in supercritical water are oxidation of alcohols, acetic acid, ammonia, benzene, benzoic acid, butanol, chlorophenol, dichlorobenzene, phenol, 2-propanol, (catalyzed by metal oxide catalysts such as CuO/ZnO, TiO_2, MnO_2, $KMnO_4$, V_2O_5, Cr_2O_3) and 2,4-dichloro-

phenol, MEK, and pyridine (catalyzed by supported noble metal catalysts such as supported platinum).[110]

Examples of solid catalyzed reactions in supercritical fluids are given in Table 20.1.12.[97,99, 109,111]

Table 20.1.12. Solid catalyzed reactions in supercritical solvents.

Reaction	Supercritical solvent	Catalyst
Hydrogenation	Carbon dioxide	Supported Pt, Pd, Ni, Mo catalysts
	Water	Supported Ni-Mo catalysts
	Propane	Supported Pt, Pd, catalysts
Dehydrogenation	Water	Supported Pt catalyst
Oxidation	Carbon dioxide	Supported Pt, Pd, Ni, Co, Cu, Mn, Fe catalysts
	Water	V, Mn, Ce, Cu, Zn, Co, oxide catalysts
Isomerization and rearrangement	Carbon dioxide+cosolvent	Supported Pt catalyst
	Water	Solid acid catalyst
Cracking	Carbon dioxide	Zeolite
Alkylation	Carbon dioxide	Zeolite
Esterification	Carbon dioxide	Biocatalysts, Zeolite
Hydroformulation	Carbon dioxide	Supported Rh, Fe catalysts
Coupling	Water	Supported Pt catalyst
Disproportionation	Butane	Zeolite
	Pentane	Zeolite

20.1.4.3.2 Heterogeneous non-catalytic reactions in supercritical solvents

Use of the supercritical fluids as the reaction medium in synthetic fuel processing is one of the earliest applications in the field. The advantages of the supercritical fluid as the reaction medium are again three-fold. During thermal degradation of fuels (oil shale, coal), primary pyrolysis products usually undergo secondary reactions yielding to repolymerization (coking) or cracking into gas phase. Both reactions decrease the yield of the desired product (oil). To overcome this problem, a dense (supercritical) hydrogen donor (tetralin), or non-hydrogen donor (toluene), or an inorganic (water) medium is used.[77] Also, a supercritical medium provides ease of transport in the porous coal matrix.[20] Finally, downstream processing (separation of the products) becomes an easier task when a supercritical medium is used. Kershaw[112] reviews the use of supercritical fluids in coal processing, while Sunol discusses the mechanism[113] and possible integration of these plants with supercritical fluid power cycles.[114]

The forest product applications in this category include biomass conversion[115] and delignification for pulping purposes.[116] Biomass gasification and liquefaction in supercritical water are emerging technologies for biomass conversion into gaseous and liquid fuels.[117,118] Biomass gasification principles may be applied to the reactions between super-

critical water and municipal sewage sludge. Gasification or oxidation of this sludge can produce fuels much like more traditional biomass feedstock.[100]

20.1.4.4 Biochemical reactions – examples

Due to their tunable properties, supercritical solvents provide a useful medium for enzyme catalyzed reactions.[119] The mechanism of enzyme-catalyzed reactions is similar to the mechanism described for solid catalyzed reactions. External as well as internal transport effects may limit the reaction rate. Utilizing supercritical fluids enhances external transport rate due to an increase in the diffusivity and therefore mass transfer coefficient. Internal transport rate depends on the fluid medium as well as the morphology of the enzyme. Supercritical fluids can alter both.

Water is known to be essential for the enzyme activity. Small amounts of water enhance enzyme activity, however excess water hinders the rate of some enzyme catalyzed reactions. Also, supercritical water cannot be used as the reaction medium either, because its critical temperature and pressure are too high for the enzymes used in biotransformations. The active site concentration on enzymes, hence the enzyme activity is found to be higher in the presence of hydrophobic supercritical fluids (ethane, ethylene) as compared to hydrophilic supercritical carbon dioxide.

The effect of pressure on enzyme catalyzed reactions can be explained in terms of the transition theory. Supercritical fluids that exhibit very high negative activation volumes for certain reactions are expected to improve the rate of the reaction.

Although, supercritical carbon dioxide has the advantage of being non-toxic and abundant, it is practically immiscible with water. Also, side reactions such as carbamate and carbonic acid formation can occur when carbon dioxide is employed as the supercritical fluid in enzymatic reactions. Therefore, supercritical fluids used as the reaction medium in enzyme catalyzed reactions include fluoroform, sulfur hexafluoride and ethane, while lipases are the enzymes utilized in such reactions.[120] However, ethane and propane have the disadvantages of being expensive and flammable.

20.1.4.5 Polymerization reactions – examples

Supercritical carbon dioxide is a promising green alternative to traditional solvents in polymer synthesis due to gas-like transport properties and liquid-like solubility. Supercritical carbon dioxide can be removed easily from the polymer solution by depressurization during drying of the polymer. Supercritical carbon dioxide provides easy separation of the polymer from the unreacted monomers and catalysts. Finally, supercritical carbon dioxide also exhibits Lewis acid-base interactions with electron donating functional groups of polymer chains.[116] Examples of homogeneous and heterogeneous polymerization reactions carried out in supercritical carbon dioxide are given in Table 20.1.13.

Table 20.1.13. Polymerization reactions in supercritical fluids.

Polymerization mechanism	Substrate
Homogeneous, free radical/cationic polymerization	Amorphous fluoropolymers
Precipitation, free radical polymerization	Vinyl polymer, semicrystalline fluoropolymers
Dispersion, free radical polymerization	Polyvinyl acetate and ethylene vinyl acetate copolymer
Dispersion, cationic polymerization	Isobutylene polymer
Emulsion polymerization	Acrylamide, acrylic acid, N-vinyl formaldehyde
Homogeneous/precipitation, cationic polymerization	Vinyl ether polymer
Transition metal catalyzed, ring opening methathesis polymerization	Norbornene polymer, polycarbonate
Anionic ring polymerization	Poly(ε-caprolactone)
Condensation polymerization	Polycarbonate

Butane, pentane, and propane are also used as the reaction medium in polymer synthesis.[122] Furthermore, some polymerization reactions (such as polyethylene synthesis) are carried out under supercritical conditions of the monomer.

20.1.4.6 Materials processing with supercritical solvents

The material field related applications of supercritical fluids are rapidly developing with exciting innovative developments continually emerging. The recent increase of activity in the supercritical field at large is partially due to these new horizons. Supercritical fluids are used to make highly porous materials, to aid in making uniform porous or non-porous films, and to deposit solubilized components by diffusion and permeation into porous media resulting in composites with tailored characteristics or functionalized surfaces. They are used to make particles with desired shape and particle size distribution, are used to encapsulate particles for time release applications, are used to fractionate macromolecules to desired dispersity and molecular weight distributions, and soon may be part of our household for cleaning/washing. Increased technological innovation in medicine and implants has led to a use for supercritical fluids as part of the medical system as a means for more efficient biomedical devices.[123]

What makes supercritical fluids so attractive in this domain is their sensitivity to a large number of processing variables in a region where transition from a single or multiphase system into another is rather simple through a variety of paths.

One can start with a homogeneous phase and use pressure, temperature, mass separating agents, other external fields such as electromagnetic or irradiation, to nucleate and grow, or react or fractionate, to form new material with unique performance characteristics. In the homogenization step, supercritical fluids are used to solubilize. If solubilization

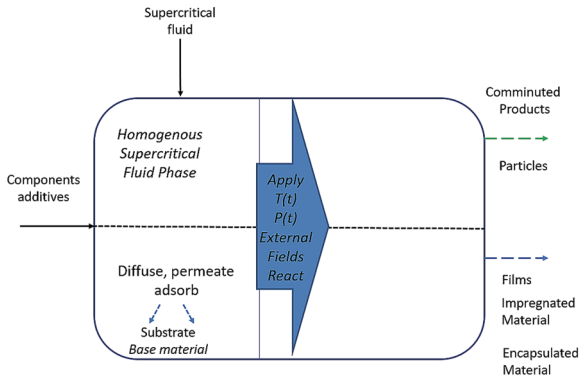


Figure 20.1.17. Homogeneous supercritical solution path to materials synthesis.

in the supercritical fluid is not possible, the supercritical fluid can be used to induce phase separation as an anti-solvent in a subsequent step.

The supercritical fluids are effective in heterogeneous environments as well. They penetrate into porous environment loaded with additives or, used as a pure supercritical fluid to clean, dry (extract), coat, impregnate and process (e.g., extrude) a low viscosity solution.

20.1.4.6.1 Particle synthesis – generic application

The routes to particle synthesis *via* supercritical fluids basically follow two paths, Rapid Expansion of Supercritical Solution (RESS) and Supercritical Anti-Solvent (SAS).[6,124] The particle nucleation through pressure reduction is the simplest is shown in Figure 20.1.16 while generic basic processing steps with various materials processing using supercritical fluids are outlined in Figure 20.1.17 and Figure 20.1.18, respectively. RESS involves homogenization of the particle's raw material in the supercritical fluid followed by rapid expansion of the solution through an expansion device such as a nozzle. Depending on the nozzle design, time-temperature and time-pressure profiles, and whether one uses entrainers or not, the particle size, shape, and particle size distribution changes. The primary particle creation mechanism is nucleation and growth. Usually the amount solubilized in the SCF is not very high for particle synthesis. For many applications such as pharmaceutical and energetic materials, the particle base material is not soluble in dense gases. In those instances, these substances are solubilized in a liquid solvent and in a subsequent stage the supercritical anti-solvent is used for synthesis of particles.

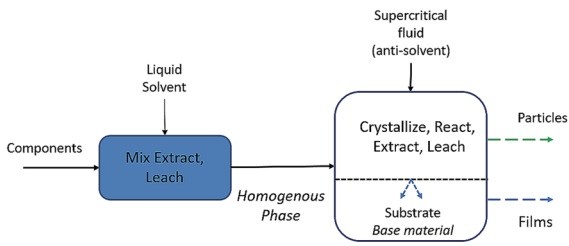


Figure 20.1.18. Anti-solvent path to materials synthesis.

20.1.4.6.2 Encapsulation – generic application

Micro-encapsulation of drug-polymer systems using the RESS (Rapid Expansion of Supercritical Fluid Solutions) techniques have been initiated with limited success due to poor understanding of the complex phenomena involved in co-nucleation of components. Not only do the particles have to be nucleated with the desired particle size and shape but also encapsulate the material simultaneously in a uniform fashion.

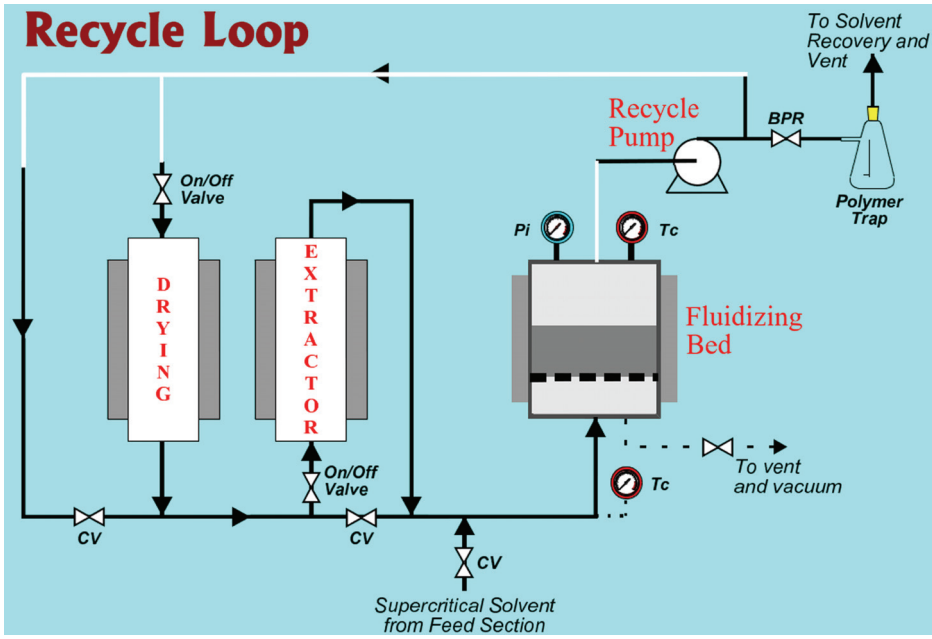


Figure 20.1.19. Microencapsulation of particles in supercritical fluid fluidized circulating beds.

An alternative approach[125,126] depicted in Figure 20.1.19 involves a sequential method where synthesized particles are coated with polymeric thin films by simultaneous nucleation of polymeric material out of a supercritical fluid, encapsulating the particles fluidized in the supercritical fluid, followed by further polymerization and binding of the encapsulating material on the particle surface. The method involves a recirculatory system that includes dissolution of the polymer in the supercritical solvent and coating the particles through a temperature swing operation in the fluidized bed that contains the particles. The particulate material coated with the tailor polymeric material possesses unique timed-release characteristics, improved stability, and often enhanced behavior. Given that all of these steps can be carried out in a single fluidized bed, the risk of cross contamination due to needing to move batches from 1 piece of equipment to the next.

20.1.4.6.3 Spraying and coating – generic application

The RESS and SAS approaches can be applied to coating and spraying applications if the inhomogenization step is exercised on a surface (a base material). These approaches can provide a more uniform surface with less risk of biological contamination, due to the properties of the supercritical fluid. However, use of this technology for coating must be balanced against the capital requirement to do so.

20.1.4.6.4 Extrusion – generic application

The addition of a supercritical fluid to a Newtonian or non-Newtonian fluid reduces the viscosity of the fluid improving its processability and end materials morphology. Supercritical fluids can aid in food and polymer extrusion.[127]

20.1.4.6.5 Perfusion (impregnation) – generic application

Excellent transport characteristics, solubilization power, and sensitivity to process variables all contribute to the success of the methodology. The generic scheme involves homogenization, impregnation, deposition, and optional post treatment steps such as curing reactions. The mechanism of transport in the porous matrix is permeation and diffusion while the primary mechanisms for deposition are pressure reduction, temperature swing, sorption, and reaction (i.e., polymerization).

This process is a simplified version of impregnation process.[128] The impregnating solvent does not contain any material to be deposited and the pressure release causes disintegration of the impregnated material.[6,83]

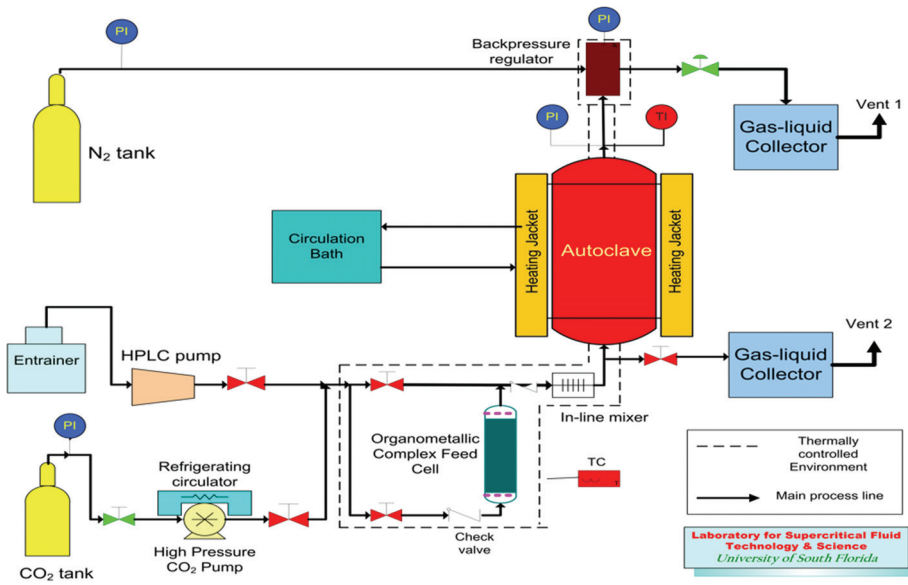


Figure 20.1.20. Supercritical fluid impregnation processes for catalyst manufacture.

One process that incorporates many of the supercritical fluid aided materials synthesis is development of aerogel photo-catalyst.[128] Templated aerogels prepared by through supercritical drying can be subsequently extracted using supercritical to remove the template material. The aerogel support than can be functionalized through impregnation of organometallic catalyst precursors.[128] Impregnation is becoming increasingly relevant in the biomed field, with the advent of drug loaded biopolymers for use in implants.[123] An experimental pilot plant for the operations is shown in Figure 20.1.20.

20.1.4.6.6 Parts cleaning – generic application

In essence, the part cleaning process is basically extraction/leaching with or without surfactants. The basic steps are shown in Figure 20.1.15. Drying in the absence of capillary forces and solvent residue-free substrate makes the technology attractive. The technology is comprehensive covered in a monograph[71] and there are many existing commercial applications.

20.1.4.6.7 Drying – generic application

A pilot plant used in drying is shown in Figures 20.1.20. The supercritical drying routes are particularly attractive in their ability to eliminate or at least minimize the capillary effect that causes non-uniformities in films as well as shrinkage and collapsing in pore structure. These supercritical avenues permit successful creation of highly porous structures such as foams, aerogels, coatings, and films.

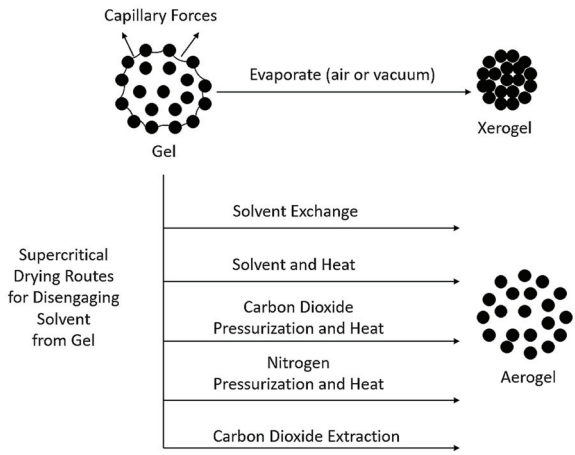


Figure 20.1.21. Sol-gel drying methods.

The solvent can be removed from the wet gel using different methods. These methods and resulting gels are shown in Figure 20.1.21. If solvent is evaporated slowly from the gel, a xerogel is obtained. During evaporation, large capillary forces are exerted as the liquid-vapor interface moves through the gel. These forces cause shrinkage of the pores within the gel. Removal of the solvent (alcohol) from the gel under supercritical conditions results in the formation of the aerogel. Since this drying procedure eliminates the liquid-vapor interface, aerogels are formed in the absence of capillary forces. Aerogels retain the morphology of the original alcogel.

There are several methods developed for removing the solvent from the gel under supercritical conditions. The first one is the one suggested in the pioneering work by Kistler,[129] in which the solvent is brought to supercritical conditions in an autoclave and evacuated under these conditions. In order to pressurize the autoclave to a pressure above the critical value for the alcohol, more alcohol is added to the autoclave. Supercritical conditions of the solvent are reached by supplying heat to the autoclave. After the pressure reaches a preselected value, which is above the critical, the temperature is raised at constant pressure. Once the temperature is also above its critical value, the supercritical fluid is vented out of the autoclave at constant temperature.[130] The P-T behavior for this procedure is shown as route A-B (1) in Figure 20.1.22.

Van Lierop and co-workers later improved this method.[131] In this improved version of the method, any boiling of the solvent was completely suppressed. This was done by

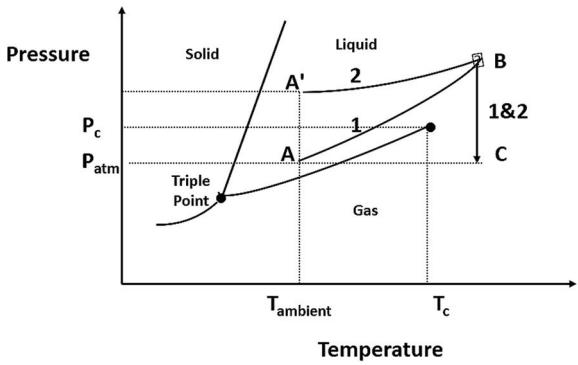


Figure 20.1.22. Pressure-temperature paths for super- critical drying.

introducing pressure of an inert gas into the autoclave prior to any heat treatment and furthermore, the autoclave was kept closed during heating until the temperature reached the predetermined value above the critical. The P-T behavior for this process is shown as route A'-B (2) in Figure 20.1.22.

In another method, developed by Jacobucci[132] and coworkers, alcohol is removed by supercritical CO_2 extraction in a semi-continuous system.

Solvent exchange is another method utilized to dry alcogels. The liquid in the pores (excess water of the hydrolysis) of the wet-gel is first displaced by alcohol and then alcohol is displaced by liquid CO_2 at about 16-20^oC and 100 bar. After solvent exchange, the temperature of the system is increased to 40^oC and supercritical carbon dioxide is vented out of the system.[133]

In yet another method, the system is pressurized with carbon dioxide prior to drying. Through partial solvent exchange during heating, drying of the gel at temperatures much lower than the critical temperature of the solvent (alcohol) can be achieved. Also, gels can be dried at a wide range of temperature and pressure combinations where optimum tunable conditions (resulting in optimum pore and surface characteristics) can be determined for a variety of objectives and cases.[134]

REFERENCES

1 Hannay, and Hogarth, *Proc. Roy. Soc. A*, **29**, 324 (1879).
2 J. Timmermans, *J. Chim. Phys.*, **20**, 491 (1923).
3 G.M. Schneider, in Supercritical Fluids, **Fundamentals for Application**, E. Kiran, and J.M.H. Levent Sengers, Eds., *Kluver Academic Publishers*, Dordrecht, 1994, pp. 91-115.
4 G.M. Schneider, in **Water-A Comprehensive Treatise**, vol. 2, F. Frank Ed., *Plenum Press*, New York, 1973, Chp. 6.
5 E.U. Franck, in **Physical Chemistry: Advanced Treatise**, H. Eyring, D. Henderson, and W. Jost, Eds., Vol. 1, *Academic Press*, New York, 1971
6 M.A. McHugh, V.J. Krukonis, **Supercritical Fluid Extraction, Principles and Practice**, *Butterworth-Heinemann*, Boston, 1994.
7 C. J. Peters, in **Supercritical Fluids, Fundamentals for Application**, E. Kiran, and J. M.H. Levent Sengers, Eds., *Kluver Academic Publishers*, Dordrecht, 1994, pp. 117-146.
8 J. DeSwaan Arons, and T.W. deLoss, in **Models for Thermodynamic and Phase Equilibria Calculations**, S.I. Sandler, Ed., *Marcel Dekker*, New York, 1994, pp. 363-505.
9 P.H. Van Konynenburg, and R.L. Scott, *Philos. Trans. R. Soc.*, **298**, 495 (1980).
10 J.S. Rowlinson, F.L. Swinton, **Liquids and Liquid Mixtures**, *Butterworths*, London, 1982.
11 M.B. King, **Phase Equilibria in Mixtures**, *Pergamon Press*, Oxford, 1969.
12 J.C. Rainwater, in **Supercritical Fluid Technology**, T.J. Bruno, and J.F. Ely, Eds., *CRC Press*, London, 1991, pp. 57-162.
13 M.P. Ekart, J.F. Brenneke, and C.A. Eckert, in **Supercritical Fluid Technology**, T.J. Bruno, and J.F. Ely, Eds., *CRC Press*, London, 1991, pp. 163-192.

14 R. J. Sadus, **High Pressure Phase Behaviour of Multicomponent Fluid Mixtures**, *Elsevier*, Amsterdam, 1992.
15 W.B. Street, in **Chemical Engineering at Supercritical Fluid Conditions**, M.E. Paulatis, J.M.L. Penninger, R.D. Gray, and P. Davidson, Eds., *Ann Arbor Science*, Ann Arbor, MI, 1983.
16 E. Kiran, and W. Zhuang, in **Supercritical Fluids, Extraction and Pollution Prevention**, M.A. Abraham, and A.K. Sunol, Eds., *American Chemical Society*, Washington, DC, 1997, pp. 2-36.
17 Y. Tsekhankaya, M.B. Jomtev, and E.V. Mashkina, *Z. Fiz. Chim*., **38**, 2166 (1964).
18 E.H. Chimowitz and K.J. Pennisi, *AICHE J*., **32**, 1665 (1986).
19 R. Damnjanovic, N. Aslam, and A. Sunol PROCEEDINGS of the annual AIChE meeting, Nov 2005, Cincinnati, Ohio
20 S.G. Sunol, B.Mierau, I. Serifoglu, and A.K. Sunol, in **Supercritical Fluids, Extraction and Pollution Prevention**, M.A. Abraham, and A.K. Sunol Eds., *American Chemical Society*, Washington, DC, 1997, pp.188-206.
21 T.J. Bruno, in **Supercritical Fluid Technology**, T.J. Bruno, and J.F. Ely, Eds., *CRC Press*, London, 1991, pp. 293-324.
22 G. Brunner, **Gas Extraction**, *Springer*, New York, 1994.
23 J.W. Gibbs, *Trans. Conn. Acad. III*, **108** (1876), 343 (1878).
24 R.C. Reid, and B.L. Beegle, *AIChE J*., **23**, (1977).
25 M.L. Michelsen, and R.A. Heidemann, *AIChE J*., **27**, 521 (1981).
26 R.A. Heidemann, in **Supercritical Fluids, Fundamentals for Application**, E. Kiran, and J.M.H. Levent Sengers, Eds., *Kluver Academic Publishers*, Dordrecht, 1994, pp. 39-64.
27 K. Patel and A.K. Sunol, *Comput. Chem. Eng*., **33**, 1793 (2009).
28 J. Z. Huaa, J. F. Brennecke, and M. A. Stadther, Computers & Chemical Engineering S400 European Symposium on Computer Aided Process Engineering-6, 20, S395 1(996)
29 N. Aslam and A. K. Sunol, *Chem. Eng. Sci.*, **61**, 3419 (2006).
30 J.W. Tester, and M. Modell, **Thermodynamics and Its Applications**, *Prentice Hall PTR*, New Jersey, 1997.
31 A.Z. Panagiotopoulos, in **Supercritical Fluids, Fundamentals for Application**, E. Kiran, and J.M.H. Levent Sengers, Eds., *Kluver Academic Publishers*, Dordrecht, 1994, pp. 411-437.
32 K.S. Shing, in **Supercritical Fluid Technology**, T.J. Bruno, and J.F. Ely, Eds., *CRC Press*, London, 1991, pp. 227-244.
33 J.M.H. Sengers, in **Supercritical Fluids, Fundamentals for Application**, E. Kiran, and J.M.H. Levelt Sengers, Eds., *Kluver Academic Publishers*, Dordrecht, 1994, pp. 3-38.
34 J.V. Sengers, in **Supercritical Fluids, Fundamentals for Application**, E. Kiran, and J.M.H. Levelt Sengers, Eds., *Kluver Academic Publishers, Dordrecht*, 1994, pp. 231-272.
35 S.I. Sandler, H. Orbey, and B.-I. Lee, in **Models for Thermodynamic and Phase Equilibria Calculations,** S.I. Sandler, Ed., *Marcel Dekker*, New York, 1994, pp. 87-186.
36 D.Y. Peng, and D.B. Robinson, *Ind. Eng. Chem. Fundam.*, **15**, 59 (1976).
37 G.S. Soave, *Chem. Eng. Sci.*, **27**, 1197 (1972).
38 J.M. Prausnitz, R.N. Lichtenthaler, E.G. de Azevedo, 3rd ed., *Prentice Hall PTR*, New Jersey, 1999.
39 J.J. Martin, *Ind. Eng. Chem. Fundam*., **18**, 81 (1979).
40 A.Z. Panagiotopoulos and R.C. Reid, *Fluid Phase Equilibria*, **29**, 525 (1986).
41 D.S.H. Wong and S.L. Sandler, *AICHE J*., **38**, 671 (1992).
42 H. Orbey, and S.I. Sandler, **Modeling of Vapor-Liquid Equilibria**, *Cambridge University Press*, Cambridge, 1998.
43 I.C. Sanchez, and C. Panayiotou, in **Models for Thermodynamic and Phase Equilibria Calculations**, S.I. Sandler, Ed., *Marcel Dekker*, New York, 1994, pp. 187-285.
44 I.C. Sanchez, and R.H. Lacombe, *J. Phys. Chem*., **80**, 2352, 2568 (1976).
45 W.G. Chapman, G. Jackson, and K.E. Gubbins, *Molec. Phys.*, **65**, 1057 (1988).
46 N. Aslam and A.K. Sunol, *Ind. Eng. Chem. Res*., **45**, 3303 (2006).
47 V. Vesovic, and W.A. Wakeham, in **Supercritical Fluid Technology**, T.J. Bruno, and J.F. Ely, Eds., *CRC Press,* London, 1991, pp. 245-289.
48 W.D. Seider, J.D. Seader, and D.R. Lewin, **Process Design Principles**, *Wiley*, New York, 1999.
49 R.C. Reid, J.M. Prausnitz, and B Poiling, **The Properties of Gases and Liquids**, 4th ed., *McGraw Hill,* New York (1987).
50 H. Saad and E. Gulari, *Ber. Bunsenges. Phys. Chem*., **88**, 834 (1984).
51 G. Taylor, *Proc. Roy. Soc. A*, **219**, 186 (1953).
52 R. Aris, *Proc. Roy. Soc. A*, **235**, 67 (1956).

53 C.A.N. deCastro, in **Supercritical Fluid Technology**, T.J. Bruno, and J.F. Ely, Eds., *CRC Press*, London, 1991, pp. 335-363.
54 B. Unlusu, S. G. Sunol, and A. K. Sunol, *J. Non-Crystalline Solids,* **279**, 110 (2001).
55 R.T. Kurnik, and R.C. Reid, *J. Fluid Phase Equilib*., **8**, 93 (1982).
56 J.M. Dobbs, J.M. Wong, and K.P. Johnston, *Ind. Eng. Chem. Res*., **26**, 56 (1987)
57 A.K. Sunol, B. Hagh, and S. Chen, in **Supercritical Fluid Technology**, J.M.L. Penniger, M. Radosz, M.A. McHugh, and V.J. Krukonis, Eds., *Elsevier*, Amsterdam, 1985, pp. 451-464.
58 C.D. Hubbard and R. van Eldik, in **Chemistry Under Extreme or Non-Classical Conditions**, R. van Eldik, and C.D. Hubbard, Eds., *Wiley*, New York, 1997, pp. 53-102.
59 C.-S. Tan, and D.-C. Liou, *Ind. Eng. Chem. Res*., **29**, 1412 (1990).
60 C.-S. Tan, and D.-C. Liou, *Ind. Eng. Chem. Res*., **27**, 988 (1988).
61 U. Akman, A.K. Sunol, *AIChE J*., **37**, 215 (1991).
62 E.J. Beckman, J.L. Fulton, and R.D. Smith, in **Supercritical Fluid Technology,** T.J. Bruno, and J.F. Ely, Eds., *CRC Press*, London, 1991, pp. 405-449.
63 E. Lack, and H. Seidlitz, in **Extraction of Natural Products Using Near-Critical Solvents**, M.B. King, and T.R. Bott, Eds., *Blackie Academic & Professional,* Glasgow, 1993, pp. 101-139.
64 D.S. Gardner, in **Extraction of Natural Products Using Near-Critical Solvents**, M.B. King, and T.R. Bott, Eds., *Blackie Academic & Professional*, Glasgow, 1993, pp. 84-100.
65 N. Sanders, in **Extraction of Natural Products Using Near-Critical Solvents**, M.B. King, and T.R. Bott, Eds., *Blackie Academic & Professional*, Glasgow, 1993, pp. 34-49.
66 F Sahena, I.S.M. Zaidul, S. Jinap, A.A. Karim, K.A. Abbas, N.A.N. Norulaini, and A.K.M. Omar, *J. Food Eng.,* **95**, 240 (2009).
67 C. Crampon, O. Boutin, and E. Badens, *Ind. Eng. Chem. Res.*, **50**, 8941 (2011).
68 A. Capuzzo, M.E. Maffei, and A. Occhipinti, *Molecules*, **18**, 7194 (2013).
69 M.M.R. de Melo, A.J.D. Silvestre, C.M. Silva. *J. Supercrticical Fluids*, 115-176 (2014)
70 Barba *et al., Trends Food Sci.Technol*., 96-109 (2016)
71 J. McHardy and S. P. Sawan Eds. **Supercritical Fluid Cleaning**, *Noyes Pub*., New Jersey, 1998
72 J. Sunarso, and S. Ismadji, *J. Hazardous Mater.*, **161**, 1 (2009).
73 D.A. Moyler, in **Extraction of Natural Products Using Near-Critical Solvents**, M.B. King, and T.R. Bott, Eds., *Blackie Academic & Professional*, Glasgow, 1993, pp. 140-183.
74 U. Nguyen, D.A. Evans, and G. Frakman, in **Supercritical Fluid Processing of Food and Biomaterials,** H. Rizvi, Ed., *Blackie Academic & Professional,* London, 1994, pp. 103-113.
75 G.J. Gil-Chavez, J.A. Villa, J.F. Ayala-Zavala, J.B. Heredia, D. Sepulveda, E.M. Yahia, and G.A. Gonzales-Aguilar, *Comp. Rev. Food Sci. Food Safetty*, **12**, 5 (2013).
76 M. Herrero, J.A. Mendiola, A. Cifuentes, and E. Ibanez, *J. Chromat. A*, **1217**, 2495 (2010).
77 R.R. Maddox, J. Gibson, and D.F. Williams, *CEP*, June (1979).
78 A. Wilhelm, and K. Hedden, in **Supercritical Fluid Technology**, J.M.L. Penniger, M. Radosz, M.A. McHugh, and V.J. Krukonis, Eds., *Elsevier*, Amsterdam, 1985, pp. 357-375.
79 J.-H. Hsu, and C.-S. Tan, in **Supercritical Fluid Processing of Food and Biomaterials**, H. Rizvi, Ed. *Blackie Academic & Professional*, London, 1994, pp. 114-122.
80 M.B. King, and O. Catchpole, in **Extraction of Natural Products Using Near-Critical Solvents**, M.B. King, and T.R. Bott, Eds., *Blackie Academic & Professional*, Glasgow, 1993, pp. 184-231.
81 R. Eggers, in **Extraction of Natural Products Using Near-Critical Solvents**, M.B. King, and T.R. Bott, Eds., *Blackie Academic & Professional,* Glasgow, 1993, pp. 232-260.
82 G. Vetter, in **Extraction of Natural Products Using Near-Critical Solvents**, M.B. King, and T.R. Bott, Eds., *Blackie Academic & Professional*, Glasgow, 1993, pp. 261-298.
83 E. Stahl, K.W. Quirin, D. Gerard, **Dense Gases for Extraction and Refining**, *Springer-Verlag*, Berlin, 1988.
84 M.H.M. Caralp, A.A. Clifford, and S.E. Coleby, in **Extraction of Natural Products Using Near-Critical Solvents**, M.B. King, and T.R. Bott, Eds., *Blackie Academic & Professional,* Glasgow, 1993, pp. 50-83.
85 A. Akgerman, in **Supercritical Fluids, Extraction and Pollution Prevention**, M.A. Abraham, and A.K. Sunol Eds., *American Chemical Society*, Washington, DC, 1997, pp. 208-231.
86 B.Mierau, and A.K. Sunol, in **High Pressure Chemical Engineering**, Ph. R. von Ruhr, and Ch. Trepp Eds., *Elsevier*, 1996, Amsterdam, pp. 321-326.
87 B. Subramanian, and M.A. McHugh, *Ind. Eng. Chem. Res.*, **37**, 4203 (1998).
88 P.E. Savage, S. Gopalan, T.I. Mizan, C.J. Martino, and E.E. Brock, *AIChE J*., **41**, 1723 (1995).
89 S. Liu, and J. Xiao, J. of Molecular *Catalysis A: Chem.,* **270**, 1 (2007).
90 T. Ikaria, and Y. Kayaki, *Catalysis Surv. Japan*, **4**, 39 (2000).

91 A. Corma, and H. Garcia, *Chem. Rev.*, **103**, 4307 (2003).
92 R. Skouta, *Green Chem. Lett. Rev*., **2**, 121 (2009).
93 P.G. Jessop, J. Supercritical Fluids, **38**, 211 (2006).
94 M.J. Hernaiz, A.R. Alcantara, J.I. Garcia, and J.V. Sinisterra, *Chem. Eur. J*., **16**, 9422 (2010).
95 Z. Wimmer, and M. Zarevucka, *Int. J. Mol. Sci*., **11**, 233, (2010).
96 T. Ermenger, C. Guerrero-Sanchez, J Vitz, R. Hoogenboom, and U.S. Schubert, *Chem. Soc. Rev*., **39**, 3317 (2010).
97 A. Kruse, and H. Vogel, *Chem. Eng. Technol.*, **31**, 23, (2008).
98 A. Kruse, and H. Vogel, *Chem. Eng. Technol*., **31**, 1241, (2008).
99 A. Kruse, and H. Vogel, *Chem. Eng. Technol.*, **31**, 1391, (2008).
100 Qian *et al*., *Water Res.*, 118-131 (2016)
101 S. Deshpande, A. K. Sunol, G. Philippidis, WIRE's Energy and Environment, *Adv. Rev*., **6** (2017)
102 A.A. Clifford, in **Supercritical Fluids, Fundamentals for Application**, E. Kiran, and J.M.H. Levent Sengers, Eds., *Kluver Academic Publishers*, Dordrecht, 1994, pp. 449-479.
103 B.C. Wu, S.C. Paspek, M.T. Klein, and C. LaMarka, in **Supercritical Fluid Technology**, T.J. Bruno, and J.F. Ely, Eds., *CRC Press*, London, 1991, pp. 511-524.
104 G.P. Jessop, T. Ikariya, and R. Noyori, *Chem. Rev*., **99**, 474 (1999).
105 P.E. Savage, *Chem. Rev.*, **99**, 603 (1999).
106 M. Poliakoff, M.W. George, and S.M. Howdle, in **Chemistry Under Extreme or Non-Classical Conditions**, R. van Eldik, and C.D. Hubbard, Eds., *Wiley*, New York, 1997, pp. 189-218.
107 Q. Ji, E.M. Eyring, R. van Eldik, K.P. Johnston, S.R. Goates, M.L. Lee, J. Phys. Chem., **99**, 13461 (1995).
108 C.B. Roberts, J.F. Brennecke, and J.E. Chateauneuf, *AIChE J.*, **41**, 1306 (1995).
109 A. Baiker, *Chem. Rev*., **99**, 443 (1999).
110 Z.Y. Ding, M.A. Frisch, L. Li, and E.F. Gloyna, *Ind. Eng. Chem. Res.*, **35**, 3257 (1996).
111 M.D. Bermejo, and M.J. Cocero, *AIChE J*., **52**, 3933 (2006).
112 J.R. Kershaw, *J. Supercrit. Fluids,* **2**, 35 (1989).
113 A.K. Sunol, and G.H. Beyer, *Ind. Eng. Chem. Res*., **29**, 842 (1990).
114 A.K Sunol, I. Contreras, K. Cogswell, *J. Supercritical Fluids*, **25**, 151 (2015)
115 J.R. Vick Roy, and A.O. Converse, in **Supercritical Fluid Technology**, J.M.L. Penniger, M. Radosz, M.A. McHugh, and V.J. Krukonis, Eds., *Elsevier*, Amsterdam, 1985, pp. 397-414.
116 K.A. Sunol, **US Patent 5,041,192**.
117 Y. Matsumura, S. Hara, K. Kaminaka, Y. Yamashita, T. Yoshida, S. Inoue, Y. Kawai, T. Minowa, T. Noguchi, and Y. Shimizu, *J. Japan Petroleum Inst.*, **56**, 1, (2013).
118 A.A. Paterson, F. Vogel, R.P. Lachance, M. Froling, M.J. Antal, and J.W. Tester, *Energy Environ, Sci.*, **1**, 32 (2008).
119 K. Nakamura, in **Supercritical Fluid Processing of Food and Biomaterials**, S.S.H. Rizvi, Ed., *Blackie Academic & Professional,* London, 1994, pp. 54-61.
120 A.J. Mesiano, E.J. Beckman, and A.J. Russell, *Chem. Rev*., **99**, 623 (1999).
121 J.L. Kendall, D.A. Canelas, J.L. Young, and J.M. DeSimone, *Chem. Rev*., **99**, 543 (1999).
122 G. Sirinivasan, J.R. Elliot, I*nd. Eng. Chem. Res.*, **31**, 1414 (1992).
123 M. Champeau *et.al., J. Controlled Release,* 248-259 (2015).
124 P.G. Debedenetti, in Supercritical Fluids, **Fundamentals for Application**, E. Kiran, and J.M.H. Levent Sengers, Eds., *Kluver Academic Publishers*, Dordrecht, 1994, pp. 719-729.
125 A.K. Sunol, J. Kosky, M. Murphy, E. Hansen, J. Jones, B. Mierau, S. G. Sunol, in Proceedings of the 5th International Symposium on Supercritical Fluids, Tome 1, ISAFS, Nice, 1998.
126 A.K. Sunol, R. Carvallo, B. Smeltzer, *Clean Technol. Environ. Policy*, 1831-1836 (2015).
127 S. Aktas, H. Gevgilili, I. Kucuk, A. Sunol and D. M. Kalyon, *Polym. Eng. Sci.*, 2013.
128 Haitao Li, S. G. Sunol, A.K. Sunol, *Nanotechnology*, **23**, 40 (2012).
129 S.S. Kistler, *J. Phys. Chem.*, **36**, 52 (1932).
130 W.J. Schmitt, R.A. Grieger-Block, T.W. Chapman, in **Chemical Engineering at Supercritical Fluid Conditions**, M.E. Paulatis, J.M.L. Penninger, R.D. Gray, and P. Davidson, Eds., *Ann Arbor Science,* Ann Arbor, MI, 1983, p.445-460.
131 J.G. Van Lierop, A. Huitzing, W.C.P.M. Meerman, C.A.M. Mulder, *J. Non-Crystal. Solids*, **82**, 265, (1986).
132 R.J. Ayen, P.A. Iaobucci, *Rev. Chem. Eng.*, **5**, 157 (1988).
133 B. Rangarajan, C.R. Lira, *J. Supercritical Fluids*, **4**, 1 (1991).
134 S.G. Sunol, A.K. Sunol, O.Keskin, O. Guney, **Innovations in Supercritical Fluids Science and Technology**, K. W. Hutchenson, N. R. Foster Eds., *American Chemical Society*, Washington, DC, 1995, pp. 258-268.

20.2 IONIC LIQUIDS

David Rooney and Johan Jacquemin
School of Chemistry and Chemical Engineering, Queen's University Belfast, Belfast, Northern Ireland

20.2.1 INTRODUCTION

The first question one would ask is "**What is an ionic liquid?**" Ionic liquids can be described, in the crudest terms, as low temperature molten salts. The term "ionic liquid" could therefore be applied to all molten salt systems such as cryolite (Na_3AlF_6) used in aluminum production or even the molten table salt (NaCl). However the use of the word "molten" conjures up images of high temperature processes which are highly corrosive and difficult to design. In contrast to this, the ionic liquids discussed here are generally benign solvents which can be applied to a significant number of industrial processes leading to enhanced yields, greater recyclability and processes with an overall reduced environmental impact. Therefore an ionic liquid is normally described as a molten salt, which is fluid at room temperature, or close to room temperature and salts melting below 100°C are often considered in this category.[1]

An exponential increase and development of interest in these fluids, based on the number of publications and patents both by academia and industries,[1] has merited ionic liquids to be further investigated in chemical processes.[2,3] Interestingly specialized areas such as lubricants,[4] heat transfer fluids,[5] analytical applications,[6] metal separation,[7] nuclear application,[8] and energy storage[9] have been investigated by several research groups, for example. These materials are generally organic salts, which have a relatively low melting points when compared to inorganic salts. For example, many are fluid at temperatures below 25°C and these are often described as room temperature ionic liquids (RTILs). However, the term ionic liquid does not exclude those salts which have higher melting points and although this description is associated with salts which melt below 100°C, in reality there is no clear distinction between the term molten salt (often used for high temperature liquids), and the term ionic liquid. The expanding range of applications is not surprising given that approximately 10^{18} anion-cation combinations exist which could generate ionic liquids,[10] and thus these liquids could be classified as true designer materials, particularly since many of these designs include in-built functionality. Therefore given the potential range available it is possible for them to have properties suited to a particular application or, if desired, contradict some of the earlier perceived advantages of dealing with fluids consisting of only ionic species. For example their negligible vapor pressure has been well lauded, yet recently there have been reports of volatile ionic liquids,[11] and their distillation has been demonstrated.[12] Their biodegradability and toxicity has been questioned[13] yet nutritional or pharmacological ionic liquids are feasible.[14] Similarly while some ionic liquids could be used as flame-retardants[15] others are combustible and energetic ionic liquids are a reality.[16] This interest on ILs sparks from the liquid's

potential to be tuned for specific properties and functionalities depending on the approach to be used in solving a particular problem.[17]

In a number of indicated cases, these processes have been taken through the development process to a point of industrial commercialization. This is particularly the case for the first-generation of ionic liquid processes which were principally based on chloroaluminate(III) or halide anions.

The second-generation ionic liquid processes were based on other, less sensitive anions, and these continue to be investigated for industrial development in a variety of research laboratories around the world. Many of these processes utilize the ability of a range of ionic liquids to selectively immobilize transition metal catalysts for liquid-liquid two-phase catalysis while permitting easy, often trivial, extraction of products.[18-23]

> So why have these solvents not been used to rapidly replace the current volatile organics currently found in industry?

There are a number of answers to this, but the most significant reason is economics. By looking through any chemical catalogue, it is obvious that 1-methylimidizole (a precursor for the manufacture of ionic liquids) is considerably more expensive than standard solvents. By the time this compound is processed to the final ionic liquid product, its cost will have increased to many times that of normal solvents. This is not helped by the fact that at present there is a very limited market for these compounds, keeping retail prices high. It is envisaged that if ionic liquid technology continue to be widely accepted, then the cost of production will decrease rapidly. This has occurred since the original version of this chapter was published. Other quaternary ammonium salts and those that are based around pyridinium are of course cheaper alternatives (principally due to the scale of manufacture) especially Protic Ionic Liquids,[24] but economics is not the only problem.

As yet, there is still a significant deficit of deep critical analyses of their raw physical property data for engineers to use when designing new processes or retrofitting old plants. Interestingly, due to their very low volatility under ambient conditions, ionic liquids are often classified as novel and green materials,[12,25] even if this classification does not take into account other properties such as toxicity and chemical or thermal stability.[26] The knowledge, over a large temperature range, of the density of pure ILs and their fluid phase equilibria in mixtures with other molecular compounds reflects the purity and the chemical stability of studied samples and such information is crucial for novel materials like ionic liquids. It is very well documented by several groups[27-34] that the presence of impurities, such as water and/or halogenated compounds dramatically changes the physical properties of ionic liquids. In that sense, the identification of the impurities in the samples is of particular importance. Furthermore, it was reported in the literature that some second-generation ionic liquids, for example based on hexafluorophosphate, $[PF_6]^-$, and tetrafluoroborate, $[BF_4]^-$, are not water-stable since they hydrolyze easily in the presence of water. In this regard, more stable hydrophilic fluorine-based anions such as bis(trifluoromethylsulfonyl)imide ($[NTf_2]^-$) and the tris(perfluoroalkyl)-trifluorophosphate ($[FAP]^-$) were developed and have since become highly popular. The stability of these anions is well established and these salts have found many applications in the fields of catalysis;

however, one major drawback is their expense.[2] This has, in turn, led to the development of cheaper halide-free ionic liquids such as those based on the alkylsulfate, alkylphosphate and alklycarbonate anions. Of these the alkylsulfate ionic liquids, of which the ethyl analogue is industrially available, have received particular attention.[37] Despite the potential applications provided these ionic liquids are also known to be hydrolytically unstable. Wasserscheid *et al*. reported rapid hydrolysis of 1-ethyl-3-methylimidazolium ethylsulfate, [C_2-mIm][$EtSO_4$], by contaminating it artificially with a large excess of water at 353K.[38] Ficke *et al*. have also demonstrated that this IL decomposes to ethanol and 1-ethyl-3-methylimidazolium hydrogenosulfate, [C_2-mIm][HSO_4], over extended time periods.[39] Jacquemin *et al*. then demonstrated that the observed hydrolytic instability is thermodynamically driven and, therefore, competition between hydrolysis and transesterification is observed. The balance between the two reactions depends on the alkylsulfate chain length, affinity and mutual solubility of the component mixtures.[40] This information is of great importance in this field and must be taken into account in determining reference data.[41]

For the efficient design of any new industrial process incorporating ionic liquid technology, a complete understanding of the behavior of the solvent during operation is necessary. Physical properties such as viscosity, density, heat capacity, thermal conductivity and surface tension are all important during these early design stages. Others like electrochemical window and electrical conductivity, will be important for more specific applications. With the advent of computers, chemical engineers have been able to use powerful process simulation software packages to estimate how a particular process will behave under certain operating conditions. These software packages, like the manual calculations, which preceded them, predict the physical properties of organic solvents by using a number of empirical and semi-empirical equations that are available. To date, several research groups used/extended equations originally developed for molecular compounds. These include equations of state that require the prior knowledge of the critical temperature and pressure data, information which is now available for a large number of ionic liquids.[42-44] In addition, other techniques for predicting physical properties like surface tension,[45] involve using group contribution methods developed for neutral networks, which are now currently used for ionic species as well.[46-48] While there has been significant progress in recent years there are still advances which need to be made with regard to the predictive power of such models, especially those deriving from structure-property relationships needed in chemical engineering applications. It is also recognized that this requires a critical analysis of the physical property data which continue to become available in the literature.

20.2.2 FUNDAMENTAL PRINCIPLES OF THE FORMATION OF ROOM TEMPERATURE IONIC LIQUIDS

Since the last decade, a number of detailed reviews and articles have been published on the theory and development behind ionic liquid technology.[2,24,25,49-64] However in order to develop a greater understanding and appreciation of these solvents, we will summarize the main points here. Therefore the purpose of this section is to give an introduction to the nature and properties of room-temperature ionic liquids, with a particular emphasis being

placed upon their potential as solvents for industrially relevant catalytic reactions, and (more generally) for clean technology.

20.2.2.1 Development of ionic liquids

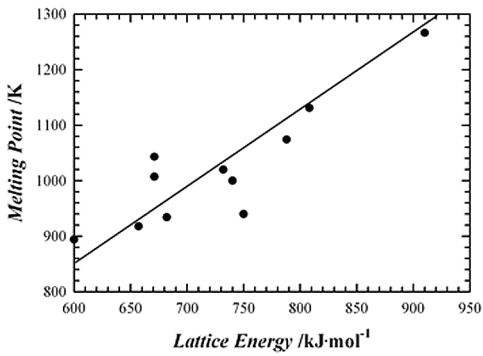


Figure 20.2.1. Showing the relationship between lattice energy[65] and melting point[66] for the Group 1 halide salts.

To begin with, the melting point of a salt is related to its lattice energy. In fact, if one was to plot the lattice energy of a series of salts, for instance the Group 1 halides, against the melting points in Kelvin, then one can see that there is reasonable linearity between the melting point and the lattice energy (see Figure 20.2.1).

Although not particularly accurate, this simple approach will give an estimated melting point of the Group 1 salts if the lattice energy is known. The deviations from this treatment are frequent and are usually due to other forms of bonding within the structure, as shall be explained later. The first theoretical treatment of lattice energy began with Born and Lande, and was then further developed by Kapustinskii into the what is known as the "*Kapustinskii equation*" (eqn. [20.2.1]):[67]

$$U = \frac{287.2 v Z^{+} Z^{-}}{r_0}\left(1 - \frac{0.345}{r_0}\right) \qquad [20.2.1]$$

where:

U	lattice energy;
v	number of ions per molecule;
r_0	sum of ionic radii;
Z^{+},Z^{-}	charge of the ionic species.

As shown in Table 20.2.1, by increasing the value of r_0, i.e., by using larger anionic and cationic components in the salt, it is possible then to lower this energy and therefore reduce the melting point.

Table 20.2.1. Melting points of various inorganic salts, melting points given in °C.[66]

Ion	Lithium	Sodium	Potassium	Rubidium	Caesium
Fluoride	842	988	846	775	682
Chloride	614	801	776	718	645
Bromide	550	747	734	693	636
Iodide	450	661	686	647	626

From this one can clearly see that as we increase both the size of the anion and the cation, the melting point decreases. From the Kapustinskii equation one must also note

that by increasing the ionic charge will tend to increase the lattice energy of the crystal. However the effect on melting point is complicated by the fact that according to Fajans' rules an increasing charge also results in increasing covalency particularly for small cations and large anions. The effect of size can even be observed in the melting points of the lithium halide series, where the small size of the lithium ion leads to a greater covalent character in the lithium halide bond, reducing the melting point when compared to the other Group 1 salts.

For a given cation, and singly charged cations and ions, equation [20.2.1] demonstrates that the lattice energy will become only be a function of r_0, and since r_0 is the sum of r^+ and r^-, then the lattice energy is only related to the anion size. The radius for simple anions can be found in a number of different sources.[66-68] However for more complex anions it becomes more difficult to assign unique values to the radii. Yatsimirskii[69] has shown that it is possible to determine the apparent values of the ionic radii of these ions indirectly from the lattice energy of the compounds containing them. These values are generally referred to as the thermochemical radii and a number are shown in Table 20.2.2. In most cases the fact that ions such as $[CNS]^-$ and $[CH_3COO]^-$, are markedly non-spherical makes these radii of limited use. However for the case of tetrahedral ions, the symmetry is sufficiently high enough for comparison purposes. If one were to plot the melting points a number of sodium salts against the opposing anions' thermochemical radius a clear relationship is observed (see Figure 20.2.2).

Table 20.2.2. Anionic and thermochemical radii.

Name	Anion	r_0/pm	Name	Anion	r_0/pm
Tetrachloroferrate[70]	$[FeCl_4]^-$	358	Chlorate[72]	$[ClO_3]^-$	201
Tetrachloroborate[70]	$[BCl_4]^-$	310	Thiocyanate[72]	$[CNS]^-$	195
Tetrachloroaluminate[70]	$[AlCl_4]^-$	295	Borate[72]	$[BiO_4]^-$	191
Tetrachlorogallate[70]	$[GaCl_4]^-$	289	Bromate[72]	$[BrO_3]^-$	191
Trifluoromethylsulfonate[71]	$[CF_3SO_3]^-$	267	Nitrate[72]	$[NO_3]^-$	188
Hexafluoroarsenate[71]	$[AsF_6]^-$	259	Cyanide[72]	$[CN]^-$	181
Hexafluorophosphate[71]	$[PF_6]^-$	253	Iodate[72]	$[IO_3]^-$	181
Periodate[72]	$[IO_4]^-$	249	Cyanate[72]	$[CNO]^-$	160
Perchlorate[72]	$[ClO_4]^-$	236	Formate[72]	$[HCO_2]^-$	160
Permanganate[72]	$[MnO_4]^-$	240	Acetate[72]	$[CH_3CO_2]^-$	156
Tetrafluoroborate[72]	$[BF_4]^-$	229	Nitrite[72]	$[NO_2]^-$	156
Trinitrophenoxide[72]	$[C_6H_2(NO_2)_3O]^-$	222	Amide[72]	$[NH_2]^-$	129

It should be noted that if one plotted the melting points and radii of the planar anions in Figure 20.2.2, they would not fall on the trend line. Since our desired goal is to produce a salt which melts at or around room temperature, we can extrapolate that we would require an anion with a radius of at least 400 pm. The number of such large anions is limited, and they also have a relatively high degree of covalence associated with the structure.

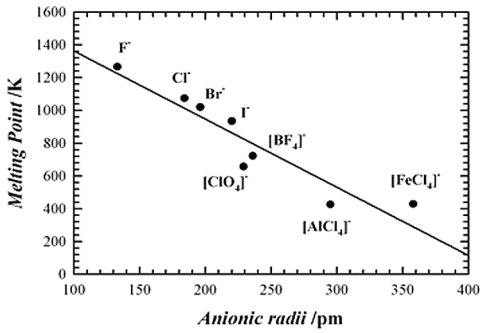


Figure 20.2.2. Showing the relationship between the size of similar anions containing halides and melting point of various sodium salts.[66,70-72]

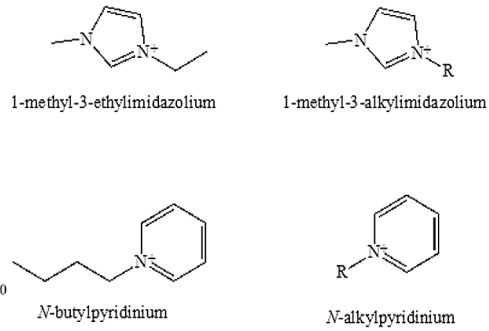


Figure 20.2.3. The aromatic heterocyclic N-butylpyridinium, 1-methyl ethylimidazolium cations, and general structural information for N-alkylpyridinium, $[NC_n\text{-}Py]^+$, and 1-methyl-3-alkylimidazolium, $[C_n\text{-}mIm]^+$ based ionic liquids.

However, as clear from above, it is also possible to reduce the lattice energy by increasing the size of the cation. By moving to organic salts the effect can be demonstrated more easily. For example the organic salt $[EtNH_3][NO_3]$ was shown in 1914 to have a melting point of 12°C and was hence the first room temperature ionic liquid.[73]

This concept can be taken further and applied to other organic systems, such as, the cations "butylpyridinium" and "1-methyl-3-ethylimidazolium" ($[NC_4\text{-}Py]^+$ and $[C_2\text{-}mIm]^+$), (see Figure 20.2.3). For the purpose of clarity we will simply refer to the length of the alkyl chain by the number of carbon atoms in that chain, hence ethyl is represented by C_2, butyl by C_4, etc.

In the case of the $[C_2\text{-}mim]^+$ cation, it can be observed that it has the lowest possible symmetry making it even more difficult for a crystal to form. Given this argument one would expect the melting point of salts based around this cation to be low. Indeed Wilkes *et al.*[74] have shown that the melting point for $[C_2\text{-}mIm]Cl$ is 84°C significantly lower than any of the Group 1 halides. The melting points of a number of $[C_2\text{-}mIm]^+$ salts have been reported over recent years, and some of these are summarized in Table 20.2.3.

Table 20.2.3. Some melting points for various $[C_2\text{-}mIm]^+$ – based ionic liquids.

Ionic Liquid	Melting Point, °C
$[C_2\text{-}mIm]Cl$[74]	84
$[C_2\text{-}mIm]Br$[75,76]	81
$[C_2\text{-}mIm]I$[75,76]	79-81
$[C_2\text{-}mIm][PF_6]$[77]	62
$[C_2\text{-}mIm][NO_2]$[78]	55
$[C_2\text{-}mIm][GaCl_4]$[79]	47
$[C_2\text{-}mIm][NO_3]$[78]	38

Table 20.2.3. Some melting points for various $[C_2\text{-mIm}]^+$ – based ionic liquids.

Ionic Liquid	Melting Point, °C
$[C_2\text{-mIm}][AlCl_4]$[74]	7
$[C_2\text{-mIm}][Ntf_2]$[77]	-15

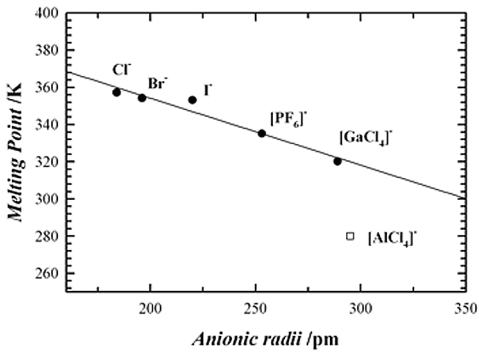
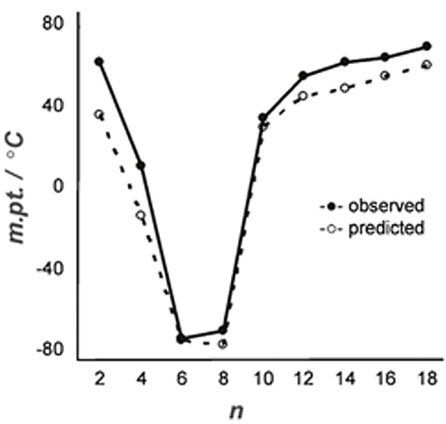


Figure 20.2.4. Relationship between the size of similar anions containing halides and the melting point of their $[C_2\text{-mIm}]$ salts.

In order to develop a greater understanding of these salts, the nature of the $[C_2\text{-mIm}]^+$ cation and how it interacts with various anions has been explored in both solution[80] and solid[81] phases and *via* theoretical studies.[82] It is now possible to produce a similar plot to Figure 20.2.2 showing the effect of anion on the melting point of the $[C_2\text{-mIm}]^+$ salts using the data in Table 20.2.3 as plotted in Figure 20.2.4.

The $[AlCl_4]^-$ anomaly can be partly explained by the fact that in the ionic liquid an equilibrium exists between the $[AlCl_4]^-$ anion and the larger $[Al_2Cl_7]^-$ anion. For a similar reason results from our own research have shown that the melting point for the $[FeCl_4]^-$ ionic liquid does appear to follow the given trend. In order to expand the number of potential ionic liquids the possibility also exists to increase the length of the alkyl group thereby further decreasing the lattice energy. For the $[C_n\text{-mIm}][PF_6]$ the result is a range of salts all of which have low melting points (some of which are below room temperature) as shown in Figure 20.2.5, though often at the cost of increased viscosity.[83]

One can observe that there is a maximum chain length allowed before other forms of bonding begin to dominate and the melting point increases. The melting points indicated below the 0°C line are in fact glass transition temperatures rather than true melting points.



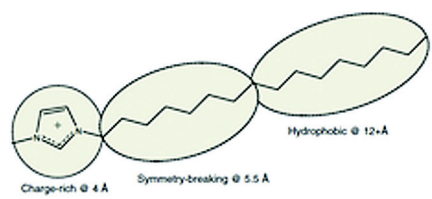


Figure 20.2.5a (left). Experimental and predicted phase diagram for the $[C_n\text{-mIm}][PF_6]$ ionic liquids. 20.2.5b (right). An optimized structure of a 1-methyl-3-octadecylimidazolium cation showing the structural regions that are important for determining the melting point.[83]

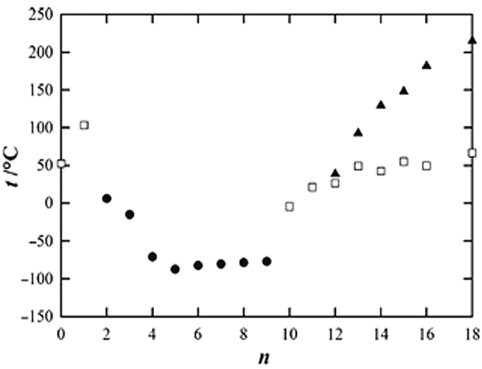


Figure 20.2.6. Phase diagram for the [C_n-mIm][BF_4] ionic liquids: *open* squares, melting point; *filled circles*, glass transition; *filled triangles*, clearing transition.[64]

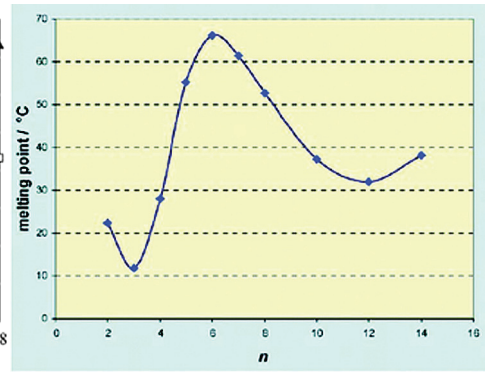


Figure 20.2.7. Phase diagram for the [$P_{666,n}$][PF_6] ionic liquids.[85]

As stated above, one point to note is that the viscosity of these room temperature liquids is very high and they would therefore have to be used at relatively high temperatures if required in a process. Interestingly, the solid-liquid phase diagram for these series was also supported by a computational study of anion and cation effects on the melting points of imidazolium salts, using a QSPR approach, for example.[83] Not only was the experimental melting point curve for the series [C_n-mIm][PF_6] remarkably well reproduced (see Figure 20.2.5a), but the predictions were also rationalized in terms of the cationic structure (see Figure 20.2.5b).

Figures 20.2.6 and 20.2.7 illustrate the significant variation in melting point which can be induced by simply changing the anion from [C_n-mIm][PF_6] to the [C_n-mIm][BF_4] ionic liquids, as well as by changing the cation from [C_n-mIm][PF_6] to the [$P_{666,n}$][PF_6].

From this figure it can be seen that those salts with short alkyl chains (n=2-10) are isotropic ionic liquids at room temperature and exhibit a wide liquid range, whereas the longer chain analogues are low melting mesomorphic crystalline solids which display an enantiotropic smectic A mesophase. The thermal range of the mesophase increases with increasing chain length and in the case of the longest chain salt prepared, [C_{18}-mIm][BF_4], the mesophase range is ca. 150°C.

According to the Figures 20.2.5, 20.2.6 and 20.2.7, the asymmetry of the cation is also an important factor in lowering the melting points: asymmetrical cations have a bigger effect than symmetrical cations. Moreover, conformational differences in the cations can frustrate crystallization, leading to glass formation and/or polymorphism.[86] Interestingly similar behavior was recently reported in the case of some protic ionic liquids indicating that the presence of large hydrogen bonds donor/acceptor sites seams to not affect this tendency.[87]

The liquidus range relates to the temperature range where the ionic liquid is in liquid form; for ionic liquids, in general this is the difference between the melting point and the decomposition temperature. However, it could also represent the temperature difference

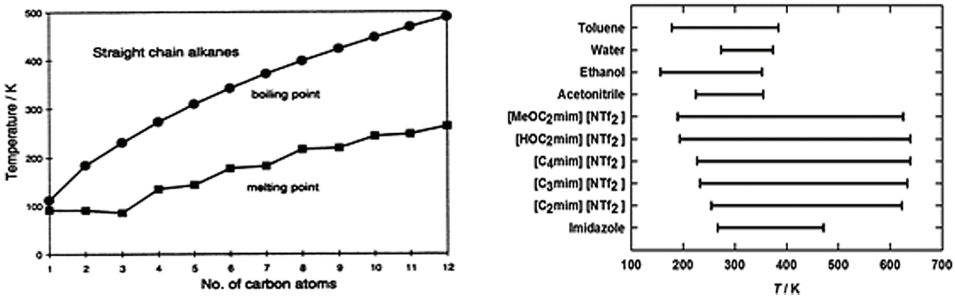


Figure 20.2.8a. (left) Melting and boiling points of straight-chain hydrocarbons.[66] 20.2.8b. (right) Liquid range temperatures of some ionic liquids[88] and usual organic solvents at atmospheric pressure.[66]

between glass transition point and boiling point, particularly for volatile compounds or in the case of protic ionic liquids. Accurate values for melting points for ionic liquids are scarce as, like in the case of inorganic salts, melting point and glass transition temperatures can be strongly affected by the presence of impurities.[30] In comparison with classical organic solvent like the alkanes (see Figure 20.2.8a) or other polar solvents (see Figure 20.2.8b), ionic liquids have a much larger liquidus range due to their very low melting point (in comparison with classical molten salts) and relatively high decomposition point, which is higher than normal boiling point of classical solvents.

Figure 20.2.8 shows the liquid range temperatures of some imidazolium-based ionic liquids and of usual solvents at atmospheric pressure. From this figure, it appears that the liquid range temperatures of selected ionic liquids are more important than those obtained with usual solvents at atmospheric pressure.

Clearly an increase of the alkyl chain length on the imidazolium cation decreases the melting point (mp), and thus increases, in this case, the liquid range temperature of the salts. Moreover, the addition of an oxygen atom on the cation alkyl chain increases also the liquid range temperature by decreasing the melting point (mp) of ionic liquids, showing in fact the importance of the moiety selection on the design of Task Specific Ionic Liquids.[87]

20.2.2.2 Binary ionic liquid systems

In Table 20.2.1 it was shown that the melting points of the Group 1 salts are significantly above room temperature, and far too high to form a generic medium for reactive chemistry. However by both increasing the size of the cation and the anion it has become possible to produce salts that are liquid at room temperature. It is well known that mixing together different salts deforms the crystal structure, leading to a lower lattice energy, and hence a lower melting point. At certain concentrations, referred to as eutectic points, the melting point has reached its minimum. This effect on melting point, obtained by combining the Group 1 chlorides into various mixtures can be seen in Table 20.2.4.

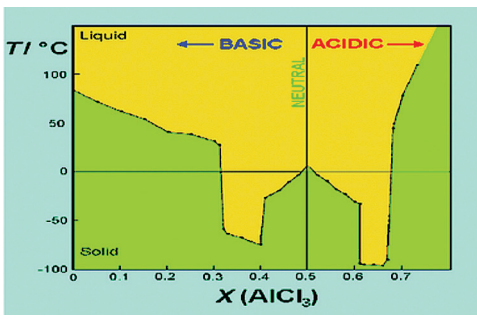
Table 20.2.4. Melting points of some Group 1 chlorides mixtures.[89]

System	Mole ratio	T_{fus}, °C
LiCl-LiF	70:30	496
LiCl-LiI	35:65	368
LiCl-NaCl	25:75	551
LiCl-CsCl	60:40	355
NaCl-KCl	50:50	658
CsCl-KCl	35:65	610

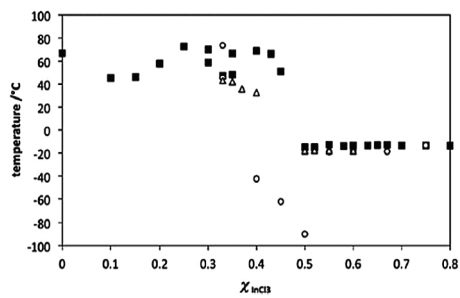
Table 20.2.5. Melting points of selected tetrachloroaluminate(III) salts.[89]

System	Mole ratio	T_{fus}, °C
LiCl-$AlCl_3$	35:65	80
LiCl-$AlCl_3$	50:50	132
NaCl-$AlCl_3$	39:61	108
NaCl-$AlCl_3$	50:50	151
RbCl-$AlCl_3$	30:70	148
RbCl-$AlCl_3$	50:50	336
KCl-$AlCl_3$	50:50	256

The melting points of the simple tetrachloroaluminate(III) salts of both the sodium and [C_2-mIm] cations have been shown to be significantly lower than their respective chloride salts, indeed [C_2-mIm][$AlCl_4$] was shown to be a liquid at room temperature.[61] Such salts are produced by combining equimolar quantities of either NaCl or [C_2-mIm]Cl



Figures 20.2.9. Phase diagram for the [C_2-mIm]Cl-$AlCl_3$ system.[74,85]



Figures 20.2.10. Phase diagram for the [C_2-mIm]Cl-$InCl_3$ system.[61]

with $AlCl_3$. However, as can be seen from Table 20.2.5, the 50:50 mole ratio does not usually correspond to the lowest melting point.

For the inorganic salts we now have melting points, which are in the maximum range of some of the high-boiling organic solvents (e.g., 1,4-dichlorobenzene, b.p. 174°C). Hence given that the 50:50 mole ratio does not correspond to the lowest melting point of the inorganic salts, one would expect the same to be true for the organic cations.

Figures 20.2.9 and 20.2.10 show the phase diagrams of $[C_2$-mIm]Cl when combined with varying quantities of $AlCl_3$[85] and $InCl_3$.[61]

Thus a large number of ambient temperature ionic liquids can be formed from a mixture of solid aluminium(III) chloride and solid 1-ethyl-3-methylimidazolium chloride. Mixing these two salts together results in an exothermic reaction and generation of a clear, colorless liquid, and an ambient temperature molten salt with low viscosity. We can see that depending on the proportions of the two components it is possible to obtain eutectics with melting points as low as -96°C.[74] These liquids are also thermally stable in excess of 200°C allowing for a tremendous liquidus range. When the molar proportions are equal, the system is a neutral stoichiometric salt 1-ethyl-3-methylimidazolium tetrachloroaluminate(III) chloride $[C_2$-mIm][$AlCl_4$] which melts at its congruent melting point of about 8°C. The lowest melting point is achieved when the molar ratio of the system is 1:2 $[C_2$-mIm]Cl:$AlCl_3$.[61]

Qualitatively these phase diagrams are similar to that reported by Hurley and Weir for the 1-ethylpyridinium bromide-$AlCl_3$ binaries in that they all show a characteristic "W" shape.[90] It has been shown that if the butyl and ethyl groups are exchanged for a generic linear alkyl function then a series of cations can be generated. These can then be balanced against any one of a number of opposing anions to produce a final salt. Given that the range of available anions and cations has expanded enormously in the past decade it is possible to produce a number of combinations. Indeed, it is our best estimate that, if binary and ternary mixtures are included (and there are very good practical and economic reasons for doing so), there are approximately one trillion (10^{18}) accessible room temperature ionic liquids.[10]

20.2.3 CATALYSIS IN IONIC LIQUIDS

The wide range of reactions that have been undertaken in low temperature ionic liquid solvents is quite remarkable.[85] It is limited simply by ones imagination. The specific and tunable solvent properties of ionic liquids are a key feature for their use as solvents and have been utilized, especially in combination with the catalytic properties of the chloroaluminate(III) ionic liquids, to develop a range of synthetically important catalytic reactions. Currently a number of these are being investigated as economically and environmentally viable alternatives to existing industrial processes. A number of reactions are summarized below; for a more detailed discussion in this area readers are recommended to the recent reviews.[2,49-64,85]

20.2.3.1 Reactions involving first-generation chloroaluminate(III) ionic liquids

The chloroaluminate ionic liquid mixtures are governed by the following primary equilibrium, equation:[61]

$$2[AlCl_4]^- \leftrightarrow [Al_2Cl_7]^- + Cl^-;\ k \approx 10^{-16} \qquad [20.2.2]$$

This is an acid base equilibrium under the Franklin definition. The $[Al_2Cl_7]^-$ species is the "acid" and the Cl^- is the base. Note that this is an aprotic equilibrium. Therefore if the mole ratio of $[C_2\text{-mIm}]Cl:AlCl_3$ is greater than, less than, or exactly equal to 50:50, the solvent behavior can be described as Franklin basic, Franklin acidic, or neutral (see Figure 20.2.9).

Considering that aluminum trichloride is a very important commercial catalyst such liquids containing aluminum trichloride and allowing for differing levels of acidity have been extensively studied as first generation ionic catalytic solvents in a wide variety of synthetic and catalytic processes. Ionic liquids could therefore be used as substitutes for conventional solid or suspended sources of aluminium(III) chloride. As liquid phase catalysts, they allow for tremendous control of reactor inventories and can be cleaned and recycled with ease. Therefore, ionic liquids, in ideal cases, have no waste associated with them, whereas the supported aluminium(III) chloride catalysts will require large (and annually rising) waste disposal costs.

An industrial example of the use of chloroaluminate ionic liquids in alkene catalysts was the development of the IFP Difasol process,[91] which can be used for alkene dimerization (typically propene and butanes). It was observed by Chauvin and coworkers[92-99] that chloroaluminate(III) ionic liquids would be good solvents for the nickel catalyst used in the reaction, and discovered that by using a ternary ionic liquid system ($[C_4\text{-mim}]Cl$-$AlCl_3$-$EtAlCl_2$) it was possible to form the active catalyst from a $NiCl_2L_2$ precursor and that, the ionic liquid solvent stabilized the active nickel species. Overall they found that the nickel catalyst remains selectively dissolved in the ionic liquid phase to the extent that over 250 kg of propene could be dimerized per 1 g of nickel catalyst. In addition the product was insoluble in the ionic liquid, which made product recovery facile.

Other studies have shown that a wide range of acidic chloroaluminate(III) and alkylchloroaluminate(III) ionic liquids can be used to catalyze the dimerization and oligomerization of olefins.[100,101] In the reaction, the olefinic feedstock may be mixed with, or simply bubbled through, the ionic liquid catalyst to produce oligomeric products. A significant outcome of this reaction is that the product has a low solubility in the ionic liquid and separates as a less dense organic phase, which is readily removed. In addition to the above reactions it was shown that isobutene can be polymerized in an acidic ionic liquid to poly(isobutene) with a higher molecular weight than is formed using other polymerization processes. Poly(isobutene), traditionally prepared by the Cosden process, is a valuable lubricant, and also a route to higher value-added materials. In general it was observed that the catalytic activity of the ionic liquids increases towards higher degrees of polymerization from short-chain oligomers as the alkyl chain length of the 1-alkyl-3-methylimidazolium or N-alkylpyridinium cation is increased.[102] The ionic liquid process has a number

of significant advantages over the industrial Cosden process. This system uses a supported or liquid phase aluminium(III) chloride catalyst.[102] Using the ionic liquid process, the polymer forms a separate layer, which is substantially free of catalyst and ionic liquid solvent. This effect greatly enhances the degree of control available to reduce undesirable secondary reactions (i.e., isomerization) without requiring alkali quenching of the reaction.

In addition Ziegler-Natta polymerization reactions have also shown some success when carried out in ionic liquids.[103] The most common production methods for this form of polymerization involve the use of triethylaluminium catalysts at ca. 100°C and 100 atmospheres pressure. Advances have been developed through the use of organometallic transition metal catalysts, typically nickel or titanium. Given the solvent characteristics of ionic liquids it should be possible to effectively immobilize such catalysts in an ionic liquid solvent. Indeed, Carlin and Wilkes[103] have reported the Ziegler-Natta polymerization of ethene in an ionic liquid solvent. In these reactions an acidic $[C_2\text{-mIm}]Cl\text{-}AlCl_3$ ionic liquid solvent was used to support dichlorobis(η^5-cyclopentadienyl)titanium(IV) with an alkylchloroaluminium(III) co-catalyst.

Electrophilic substitution[104] and other reactions of naphthalenes (alkylation, acylation, condensation and migration in acidic ionic liquids[105,106] have been reported. Anthracene undergoes photochemical [4+4] cycloaddition reactions[107,108] in acidic chloroaluminate(III) ionic liquids. One interesting study included a one-pot synthesis of anthraquinone from benzene giving a 94% yield. In general a much wider range of redox products are formed than occur in conventional solvents; the strong Brønsted acidity of the ionic liquid induces protonation of anthracene, by residual traces of HCl, to form an anthracenium species which couples readily *via* photochemically driven electron transfer mechanisms.

Both the Friedel-Crafts alkylations and acylations are of great importance to the fine chemical and pharmaceutical industries. Typically, these reactions are run in an inert solvent with suspended or dissolved aluminium(III) chloride as a catalyst, and may take six hours and go only to 80% completion giving a mixture of isomeric products. In addition, there are a number of problems, especially with misnamed "catalytic" Friedel-Crafts acylation reactions, which are actually stoichiometric, consuming 1 mole of $AlCl_3$ per mole of reactant. Annually, massive quantities of aluminium(III) chloride are consumed in these reactions causing a number environmental problems through waste disposal. Both alkylation and acylation reactions under Friedel-Crafts conditions have been demonstrated using chloroaluminate(III) ionic liquids as both solvent and catalysts.[105-116] Here it has been shown that reaction rates are much faster with total reagent conversion and often with surprising specificity to a single product.

Boon *et al*. have reported the alkylation of benzene with a wide number of alkyl halides in acidic chloroaluminate(III) ionic liquids[112] and general organic reactions in low melting chloroaluminate ionic liquids have also been described,[114,117] which include chlorinations and nitrations in acidic ionic liquids.[111,112,115]

One specific example is the alkylation of benzene with chloroethane, which gives a mixture of mono- to hexa-substituted products. The ionic liquid solvent/catalyst activates

the reaction and the alkylation can be performed even at temperatures as low as -20°C in the ionic liquid solvent. Again it was shown that the products have a low solubility in the ionic liquid leading to facile separation. Many acylation reactions have been demonstrated in acidic chloroaluminate(III) ionic liquids.[109,113] However as described above these processes are essentially non-catalytic in aluminium(III) chloride, which necessitates destroying the ionic liquid catalyst by quenching with water to extract the products. However, regioselectivity and reaction rates observed from acylation reactions in ionic liquids are equal to the best-published results. The Friedel-Crafts acylation of benzene has been shown to be promoted by acidic chloroaluminate(III) ionic liquids.[113] It was observed that the acylated products of these reactions have high selectivities to a single isomer for example toluene, chlorobenzene and anisole are acylated in the 4-position with 98% specificity.

Naphthalene is acylated in the 1-position which is the thermodynamically unfavored product. In addition to benzene and other simple aromatic rings, a range of organic and organometallic substrates (e.g., ferrocene) have been acylated in acidic chloroaluminate(III) ionic liquids.[118,119]

20.2.3.2 Reactions in neutral or second-generation ionic liquids

Acidic $[C_2\text{-mIm}]Cl\text{-}AlCl_3$ mixtures have been shown above to be very useful catalytic solvents for a number of industrially relevant reactions. However, reactions catalyzed by aluminum trichloride, whether used in an ionic liquid or as a solid phase reactions have one significant disadvantage, they are air and moisture sensitive. Using such liquids within an industrial process will therefore require that reactants are kept as dry as possible, adding to the overall process cost. We have seen how the activity and properties of the liquid can be readily controlled by both changing the anion or the cation present. By switching to neutral ionic liquids containing for example $[BF_4]^-$, $[PF_6]^-$ and $[SbF_6]^-$ anions, the reactive polymerization and oligomerization reactions of olefins catalyzed by acidic anions are not observed and more controlled, specific reactions can be catalyzed.

Since these ionic liquids cannot support the existence of reactive Lewis acid conjugate anions (such as $[Al_2Cl_7]^-$ i.e., there is no analogous mechanism to support $2[BF_4]^- \leftrightarrow [B_2F_7]^- + F^-$), they are much less reactive when used as solvents. Under these conditions, many conventional transition metal catalysts can be utilized. Again modification of the ionic liquid solvents allows the potential to immobilize catalysts, stabilizing the active species and to optimize reactant/product solubilities and to permit facile extraction of products. In general it has been found that charged, especially cationic transition metal complexes are most effectively “immobilized” in the ionic liquid solvents. In addition ionic liquids can immobilize less complex catalysts than two-phase aqueous-organic systems, where expensive, unstable, synthetically challenging ligands are often required.

Hydrogenation of olefins catalyzed by transition metal complexes dissolved in ionic liquid solvents have been reported using rhodium-,[120] and ruthenium- and cobalt-containing catalysts.[121] In these studies it was shown that hydrogenation rates where up to five times higher than the comparable reactions when carried out in propanone. The solubilities of the alkene reagents, TOFs, and product distributions where all strongly influenced by the nature of the anion in the ionic liquid solvent.

Chauvin *et al.* reported the asymmetric hydrogenation of acetamidocinnamic acid[122] to (S)-phenylalanine with a cationic chiral rhodium catalyst in [C_4-mIm][SbF_6] ionic liquid, more recently the 2-arylacrylic acid has been produced with a reasonable 64% yield[123] using a chiral ruthenium catalysts in [C_4-mIm][BF_4] ionic liquids. Palladium catalysts[124] immobilized in an ionic liquid-polymer gel membrane[125] containing either [C_2-mIm][CF_3SO_3] or [C_2-mIm][BF_4] have also been reported as catalysts for heterogeneous hydrogenation reactions.

Fuller *et al*. have also reported the hydroformylation[125] of pent-1-ene in [C_4-mIm][PF_6] using a rhodium catalysts showing both a high catalytic activity and product separation as a second organic phase. However it was observed that a small quantity of the neutral catalyst leached into the organic phase. Other commercially important reactions include the hydrodimerization of 1,3-butadiene to octa-2,7-dien-1-ol[126,127] carried out using palladium catalysts in [C_4-mIm][BF_4]. The catalyst precursor [$Pd(mim)_2Cl_2$] was prepared *in situ* from an imidazolium tetrachloropalladate(II) salt, [C_4-mIm]$_2$[$PdCl_4$], dissolved in the ionic liquid solvent. The reaction proceeds in a liquid-liquid two-phase system, where the products separate from the catalytic reaction mixture as a separate layer on cooling.

Ionic liquids have also been demonstrated as effective solvents for Diels-Alder reactions[128-130] where they have shown significant rate enhancements as well as high yields and selectivities when compared with the best results obtained in conventional solvents. To date, the biggest developments in Diels-Alder chemistry have come through reactions in Li[ClO_4]-Et_2O, where the high electrolyte concentrations are cited as beneficial through "salt-effects" and the high internal pressure of the solvent. However the use of such mixtures of perchlorate salts with organic molecules could cause a number of hazards when used on an industrial scale. Hence there is considerable potential for ionic liquids in this area.

The stability of the neutral ionic liquids allows them to be used in environments unsuitable to the tetrachloroaluminate(III) based ionic liquids. As such they offer considerable advantages allowing them to be used with "wet" process streams. The use of the fluorinated anions as shown in Figures 20.2.5 and 20.2.6, i.e., [PF_6] and [BF_4], introduces the concept of hydrophilic ionic liquids, which are partially immiscible with water. In fact all [PF_6] liquids are found to be immiscible with water and all [BF_4] liquids with chain lengths greater than C_4 will form two separate phases with water at sufficient concentrations. This property has prompted investigation into the application of these solvents as extraction solvents for a number of materials. Rogers *et al.*[131] have studied the partition of benzene with water and also the relationship between pH and extraction efficiency.[132] Figure 20.2.11 illustrates the qualitative partitioning of thymol blue in its three forms between aqueous (top) and [C_4-mIm][PF_6] (bottom) phases, as aqueous phase pH is changed from very acidic, to very basic. At low pH the thymol blue exists in its red form as a neutral zwitterion, which prefers the ionic liquid phase. As the pH is increased *via* the addition of NaOH, the yellow monoanion forms with some detectable increase in concentration in the aqueous phase. The blue dianion, above pH = 10, partitions quantitatively to

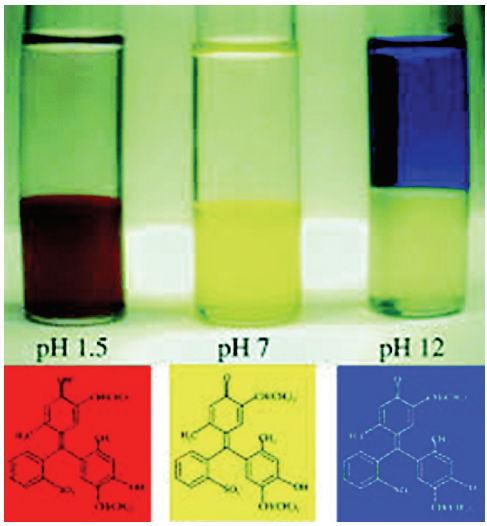


Figure 20.2.11. The phase preference of the three forms of thymol blue in [C_4-mIm][PF_6].[132]

the aqueous phase. The same result was also obtained by bubbling CO_2 and NH_3 through the ionic liquid phase.

Cull *et al.*[133] have also studied the use of ionic liquids in the extraction of erythromycin-A for the *Rhodococcus* R312 catalyzed biotransformation of 1,3-dicyanobenzene (1,3-DCB) in a liquid-liquid two-phase system. Here it was found that the ionic solvent was less harmful to the system than conventional molecular solvents with the specific activity of the biocatalyst in the water-[C_4-mIm][PF_6] system being almost an order of magnitude greater than in the water-toluene system. In addition, other reports have effectively shown the potential for combining ionic liquid and supercritical CO_2 systems for product extraction and separation[134] of naphthalene. Here it was found that the CO_2 was highly soluble in [C_4-mIm][PF_6] reaching a mole fraction of 0.6 at 8 MPa and after separation there was no detectable ionic liquid in the extract. Another example is a paper by Armstrong *et al.*,[135] where ionic liquids ([C_4-mIm][PF_6] and [C_4-mIm][BF_4]) where used as stationary phases for gas chromatography. From these studies it was concluded that the ionic liquids act as nonpolar stationary phases when separating nonpolar analytes, however they are highly interactive and retentive when used to separate molecules with somewhat acidic or basic functional groups.

20.2.4 ELECTROCHEMICAL APPLICATIONS

20.2.4.1 Energy storage

Since ionic liquids where first developed as an adjunct to the U.S. Naval program for use as battery electrolytes it seems only fair to begin this discussion by firstly looking at the electrochemical properties. One of the most important electrochemical properties of a solvent is its electrochemical window, the range of potentials over which a solvent system (including the solvent and any supporting electrolyte) is inert. The cathodic limit results from reduction of the solvent system; the anodic limit from its oxidation. Electrochemical windows are somewhat arbitrary as they are dependent upon the amount of background current which can be tolerated.

Figure 20.2.12 shows the electrochemical windows of a range of ionic liquids as well as more commonly used solvents such as water and acetonitrile. The electrochemical windows shown in Figure 20.2.12 were determined using cyclic voltametry at a glassy carbon disc electrode and are referenced against the Ag(I)/Ag couple (versus Ag(I)/Ag) and converted to the equivalent SCE potential. The reference electrode consisted of a silver wire immersed in a 0.1 M solution of $AgNO_3$ dissolved in [C_6-mIm][NO_3]. In chloroaluminate

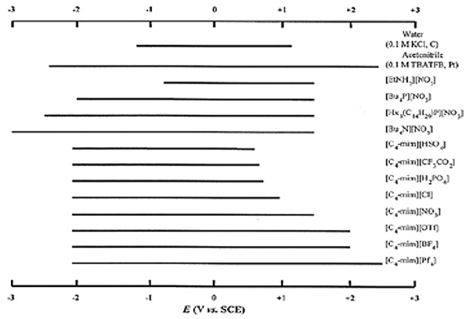


Figure 20.2.12. The electrochemical windows of a number of ionic liquids.[136]

ionic liquids, the most common reference electrode is an aluminum wire immersed in neat acidic ionic liquid (versus Al(III)/Al). It can be seen from Figure 20.2.12 that the [C_4-mIm] cation has a cathodic limit of approximately -2 V versus SCE and that this value is essentially the same for all of the $[C_n\text{-mIm}]^+$ cations. Given that the deposition potentials for many metals will fall positive of this potential, it becomes possible to use ionic liquids as electrolytes for metal plating and other similar processes.

The broad electrochemical windows (in some cases, over 4 V) indicate that a variety of organic and inorganic electrochemical oxidations and reduction should be possible in ionic liquids.

A wide variety of metals can be electrodeposited from room-temperature ionic liquids. The electrodeposition mechanisms of transition metals, lanthanides and Group 13 metals have been investigated[137-142] as have cobalt,[143-146] iron,[147] manganese,[148] tin,[149] gold,[150,151] silver,[152-155] palladium,[156,157] mercury,[158] cerium,[159] lead,[160] and the actinides.[161] In addition, ionic liquids have been used extensively to study the electrochemistry and spectrochemistry of metal-chloride complexes.[162-170]

Chloroaluminate ionic liquids have been used in the electrodeposition of aluminum and aluminum-transition metal alloys.[171] Transition metal-aluminum alloys are valued for their corrosion resistance and magnetic properties. A convenient method for creating thin alloy films is through the electrodeposition of two or more metals. The electrodeposition of aluminum and aluminum alloys from aqueous solutions is complicated by the fact that dihydrogen is evolved before aluminum is deposited. However, these materials can be electrodeposited from aprotic non-aqueous solvents or high temperature molten salts. The electrodeposition of aluminum alloys such as Cr-Al,[172] Mn-Al,[173,174] Ni-Al,[175] and Ti-Al[176] have been demonstrated from inorganic chloroaluminate molten salts, mainly Franklin acidic ($AlCl_3$-rich) $AlCl_3$-NaCl. One unfortunate drawback to the use of alkali-chloride based chloroaluminates such as $AlCl_3$-NaCl for the electroplating of these alloys is the substantial vapor pressure of Al_2Cl_6 associated with the acidic region of these melts.

This is of course not the case when working with room temperature ionic liquid systems. Electrochemical and spectroscopic studies of cobalt,[177] copper,[178] and nickel,[179] have been carried out in the $AlCl_3$-butylpyridinium chloride molten salt system. The direct current and pulsed current electrodeposition of Ni-Al alloys has also been shown in acidic $AlCl_3$-butylpyridinium chloride ionic liquids. This particular alloy has also been shown to be successful in $AlCl_3$-[C_2-mIm]Cl as have Co-Al and Cu-Al.[180] Electrochemical techniques can also be used to calculate the diffusion coefficients of metal ions. Table 20.2.6 shows the calculated diffusion coefficients and Stokes-Einstein products of cobalt(II),[143] copper(I),[181] nickel(II)[182] and zinc(II)[183] in the 40-60 mol% [C_2-mIm]Cl-$AlCl_3$ ionic liquid.

Table 20.2.6. Diffusion coefficients and Stokes-Einstein products of a number of species studied in the 40-60 mol% [C_2-mlm]Cl-$AlCl_3$ ionic liquids at 40°C.

	D_o 10^{-7} cm^2 s^{-1}	ηD_o T^{-1}, 10^{-10} g cm s^{-2} K^{-1}
Co(II)	6.6	2.6
Cu(I)	2	0.7
Ni(II)	10	3.5
Zn(II)	6.7	2.3

Electrochemical double layer capacitors (EDLCs), also known as supercapacitors, are today advancing as one of the most promising energy storage technology. In EDLCs, the charge is electrostatically stored at the electrode-electrolyte interface and, because of this storage mechanism; these devices can be charged and discharged within few seconds. Currently, the commercially available EDLCs contain activated carbon as active material and an electrolyte containing generally a quaternary ammonium salt, such as the tetraethylammonium tetrafluoroborate ($[Et_4N][BF_4]$), dissolved in the propylene carbonate (PC) or the acetonitrile (ACN).[184] To date, the most common commercial electrolytes used in supercapacitors are ACN-based electrolytes. These conventional EDLCs have operative voltages in the range from 2.3 to 2.7 V, display a high power (up to 10 $kW \cdot kg^{-1}$) and have an extremely high cycle life (>500,000).[185] These electrolytes, whilst having good conductivity and ion transport properties, also have high volatility, flammability and toxicity, which raise safety and environmental concerns.[15] Moreover, the use of acetonitrile generally limits their applications above 70°C due to the risk of cell rupture. Additionally, ACN has also a very low flash point ($\approx$ 6°C) and emits toxic combustion products.[186] Generally, the alternative electrolytes proposed so far can be divided into two main categories: ionic liquid and organic solvent based electrolytes. Several studies demonstrate that EDLCs containing an ionic liquid-based electrolyte have an operative voltage as high as 4 V, leading to higher energy storage in comparison with conventional EDLCs.[187-191] However, because of the relative high viscosity of these electrolytes, the maximum power of these ionic liquid-based EDLCs is often limited at room temperature. Particularly, their equivalent series resistance (ESR), which is considerably higher than those reported for EDLCs based on conventional electrolytes.[191] Furthermore, due to their unique and attractive properties – such as negligible vapor pressure, non-toxicity, large liquid range temperature, and good electrochemical stability – ionic liquids are very attractive for many electrochemical applications.[188-190] Based on which, ionic liquids have been used as electrolytes to build safe and stable supercapacitors and Li-ion batteries.[15,189] However, the main drawbacks of ionic liquids are their viscosity and cost, explaining in fact why their large-scale applications are still limited. In order to reduce the viscosity of ILs, which is typically many times higher than that of classical solvents,[192] binary mixtures containing an ionic liquid dissolved in a molecular solvent, usually the ACN or PC, have been optimized and used as electrolytes for EDLCs.[189] Generally, these mixtures used as electro-

lytes lead to an increase of the electrochemical performances of EDLCs. Thus, in the case of supercapacitors, the ESR value is reduced when the viscosity is decreased, thereby leading to an increase of the maximum power of the device ($P_{max} = U^2/4R_{ESR}$). In other words, the choice of the electrolyte is therefore very influential, and the prior knowledge of its physical properties, such as volumetric, thermal, transport and electrochemical properties, is essential to enhance the formulation of safer electrolytes for the realization of environmentally friendly EDLCs operating at high temperature.

20.2.4.1 Electrosynthesis

Electrosynthesis provides an attractive alternative to conventional methods used for performing synthetic chemistry. It can effect the clean, complete conversion of starting material to product without using hazardous or toxic experimental conditions. Ionic liquids possess many advantages over conventional solvents typically used in electrochemical experiments. Their polar nature allows them to dissolve large concentrations of a wide variety of organic and inorganic compounds. They possess no vapor pressure, are stable on heating and because they are completely ionized the need for a supporting electrolyte is eliminated. Such benefits are not associated with many of the non-aqueous systems employed in electrochemical applications.

Electrochemical studies in ionic liquids are common;[193-196] however the application of this technology to molecular synthesis remains largely unexplored. Some of the examples to date deal with electro-polymerizations. Osteryoung et al. prepared polyaniline on platinum and glassy carbon electrodes by anodic oxidation of the monomer in imidazolium based chloroaluminate ionic liquids.[197] Elsewhere the formation of polyfluorene was achieved by Janiszewska and Osteryoung.[198] Actual transformation of an organic moiety was achieved electrochemically in 1-methyl-3-butylimidazolium chloroaluminate systems. The reactions studied dealt with the reduction of aromatic ketones.[199] Reductions of perylene and phenazine have also been achieved electrochemically in basic mixtures of aluminum trichloride and 1-methyl-3-ethylimidazolium chloride.[200,201] The use of a neat ionic liquid 1-methyl-3-ethylimidazolium hydrogen dichloride [C_2-mIm][HCl_2] was also investigated with regard to the reduction of phenazine.[200] Most of the work in electrosynthesis has been carried out in air- and moisture-sensitive ionic liquids, those containing chloroaluminates and $[HCl_2]^-$; little investigation into the electrosynthetic possibilities presented by air and moisture stable ionic liquids has been attempted.[202]

20.2.5 PHYSICAL CHARACTERIZATION

20.2.5.1 Viscosity

Viscosity is probably the most important physical property for initially determining the "processability" of a solvent. It is necessary for all calculations involving fluid flow, (pumping, mixing, etc.) as well as in the estimation of heat transfer and diffusion coefficients. Information on the change in viscosity as a function of temperature, solvent or reagent addition is required for the efficient design of any handling equipment. Ideally one would like the viscosity of a fluid to be as low as possible allowing for the fluid to be pumped easily. In addition it is desired for the fluid to have only small changes in viscosity through the normal operating temperature range.

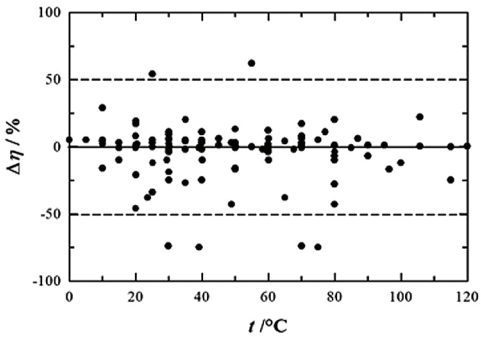


Figure 20.2.13. Example with the deviation of literature data for the [C_4-mIm][PF_6].

Over the last decade the published data on the viscosity of ionic liquids has increased. Most of this published literature on ionic liquids viscosity deals with low-pressure measurement generally limited at atmospheric pressure. Furthermore, the viscosity of any fluid is highly dependent on both the measuring technique used and the purity of the samples. Given this difficulty the reported values in the literature are often neither comparable or reproducible, as depicted in Figure 20.2.13.

However, it is known that the viscosities of ionic liquids vary widely depending on the type of cation and anion and are relatively high when compared to those of common organic solvents. Organic solvents typically have room temperature viscosities ranging from 0.2 to 100 cP whereas ionic liquids display, generally, a broad range of room temperature viscosities, from 10 to 40,000 cP.[85]

It can be seen in Figure 20.2.14 that the viscosity increases with alkyl chain length of imidazolium cation. For example, in the series of [C_n-mIm][PF_6] with n = 2,4-8, the viscosity at 298.15 K increases monotonously from 172.3 to 677.4 cP.

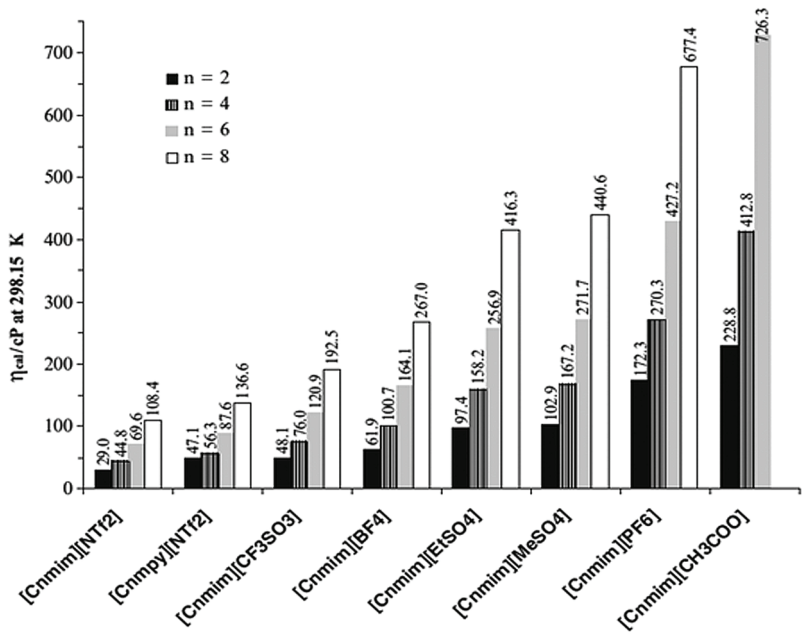


Figure 20.2.14. Viscosity at 298 K of some common ionic liquids as a function of chain length, n.[192]

Viscosities for the series of $[C_n\text{-mPy}][Ntf_2]$ ionic liquids are slightly higher than those of $[C_n\text{-mIm}][Ntf_2]$ ionic liquids. The increment with the alkyl chain length of imidazolium cation is more pronounced in case of ionic liquids containing the Cl^- anion, and seems to decrease with the symmetry of anion, showing the trend: $Cl^- > [CH_3CO_2]^- > [PF_6]^- > [BF_4]^- > [Ntf_2]^-$. In general ionic liquids having highly symmetric or almost spherical anions are more viscous and viscosity decreases with increasing anion asymmetry.[192]

Once again, the first studies of the viscosity where related to the development of ionic liquids as nonaqueous battery electrolytes as this property is often related to the iconicity of the solution. Classical Walden rule diagrams are used to determine the ionicity of ionic liquids and electrolytes.[203] From that the ionic mobilities were represented in a log scale through the equivalent conductivity, Λ (S cm^2 mol^{-1}) as function of fluidity (Poise^{-1}), $\varphi = 1/\eta$, of the medium, which is related to the ions mobility. In the case of the pure ionic liquids, the equivalent conductivity can be calculated using the molar volume of pure ionic liquid (i.e., $\Lambda = \sigma \cdot V_m$), while those for the solvent-based electrolytes needs to be determined using the salt concentration in the solution (i.e., $\Lambda = \sigma/C_{salt}$) as the function of temperature. To analyze together the equivalent conductivity and the fluidity as a function of temperature, a prior knowledge of the temperature dependence on the conductivity and on the viscosity over the same composition and temperature ranges is required. In the case of pure ionic liquids, these temperature dependences do not follow the Arrhenius law, equation [20.2.3] but are generally correctly fitted by using Vogel-Tamman-Fulcher, VTF, equation [20.2.4].[204]

$$\sigma = \sigma_0 \exp\left[\frac{-E_a^{\sigma}}{RT}\right], \quad \eta = \eta_0 \exp\left[\frac{E_a^{\eta}}{RT}\right] \qquad [20.2.3]$$

$$\sigma = \sigma_0 \exp\left[\frac{-B_{\sigma}}{T - T_0}\right], \quad \eta = \eta_0 \exp\left[\frac{B_{\eta}}{T - T_0}\right] \qquad [20.2.4]$$

where: η_0, σ_0, B_η, B_σ, ($B_i = E_a/R$), and T_0, are the fitting constants of the Arrhenius and VTF equations.

Additionally, ionic liquids are generally described in the literature as Newtonian fluids, in other words, their viscosities remain constant with increasing shear rates.[1,192] For example, Newtonian behaviors for alkylimidazolium (with the alkyl chain length between 1 and 8 carbon atoms) based ionic liquids with tetrafluoroborate, hexafluorophosphate, and bis(trifluoromethylsulfonyl)imide anions are reported in the literature. Nevertheless, this rheological behavior is strongly affected by the choice of ions constituting the ionic liquid. In fact, non-Newtonian behavior has been described for several ionic liquids.[204,205] For example, Seddon *et al.*[204] have shown that alkylimidazolium tetrafluoroborate family (number of carbon atoms typically 12) are thixotropic fluids whose viscosity decreases when increasing the shear rate. Kulkarni *et al.*[206] have reported that the flow behavior may change from Newtonian to non-Newtonian by increasing the alkyl chain length on the cation like alkyl-methylimidazolium-based ionic liquids. Non-Newtonian shear thinning behaviors have been then reported for different aprotic or protic ionic liquids.[207]

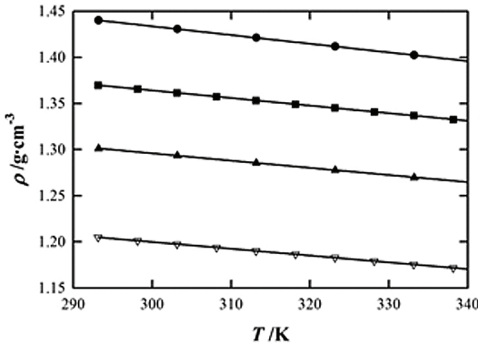


Figure 20.2.15. Effect of the anion on the densities of $[C_4mim]^+$ based ionic liquids: ●, $[NTf_2]^-$; ■, $[PF_6]^-$; ▲, $[OTf]^-$; ∇ , $[BF_4]^-$.[28,192]

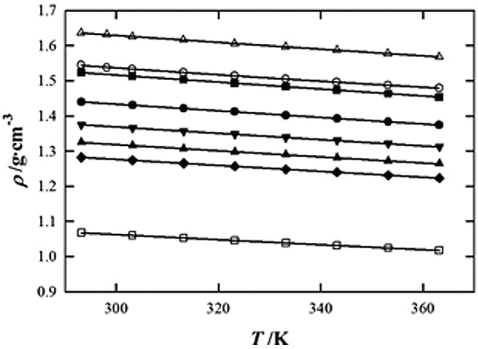


Figure 20.2.16. Effect of the cation on the densities of $[NTf_2]^-$ based ionic liquids: ■, $[C_2mim]^+$; ●, $[C_4mim]^+$; ▼, $[C_6mim]^+$; ▲, $[C_8mim]^+$; ▲, $[C_{10}mim]^+$; Δ, $[CNPy]^+$; O, $[CNmPyrro]^+$; □, $[P_{66614}]^+$.[28,192]

Clearly, many structural parameters affect the rheological properties of ionic liquids and a more exhaustive study is needed to rationalize all data available into the literature together. A deep and critical analysis of this property could then validate correlation models already available in the literature;[208-214] to further validate them or to develop a more realistic viscosity prediction model.

As it was mentioned above, care must be taken when comparing or using these data as different measuring techniques can yield different viscosity results and furthermore, have shown that the presence of traces of water or other impurities like halide and/or metal content can have a dramatic effect on viscosity.[204]

20.2.5.2 Density

Information on solvent density is also another important physical property. This is a particularly used in fluid flow calculations and for the design of liquid/liquid two phase mixer-settler units. Given that many of the ionic liquids have a “heavy” anion it would be expected that their density would be relatively high when compared to normal industrial solvents. A considerable amount of experimental data has been measured for the density as a function of the temperature for a range of ionic liquids. For pure materials, the values vary depending on the choice of anion and cation. Typically values range from (1.05-1.64) g cm^{-3} at 293K, decreasing with temperature to between (1.01-1.57) g cm^{-3} at 363K. Figures 20.2.15 and 20.2.16 show a range of measured densities of dried ionic liquids as a function of temperature at 0.1 MPa where it can be observed that the density is found to be a strong function of anion type and decreases with increasing alkyl chain length. In general the change of density with temperature is currently fitted to linear equations of the form:

$$\rho = aT + b \qquad [20.2.5]$$

where a and b are constants.

The most widely used method for ionic liquid density measurement is the vibrating-tube densitometer; a method which relies on a calibration as a function of temperature and pressure using appropriate reference fluid.[28] For many reported ionic liquids this is not routinely performed and corrections for the case of viscous fluids (i.e., >100 mPas) are often ignored.[28,192] Despite these factors the densities of ionic liquids measured with vibrating-tube densitometers have a standard uncertainty to within 0.1%. Alternative methods include the calculation of density through speed of sound measurements or piezometric methods.[28,192] Both approaches are relatively complex technically but present the advantage of providing extra thermodynamic property data.

Overall the density of ionic liquids is somewhat easier to predict as the function of temperature and pressure than the viscosity, which explains why many group contribution models are now already described into the literature within a good accuracy.[28,215-220] However, as with other physical properties impurities can have a significant effect. It was reported that the densities of the water-saturated IL samples were lower when compared with dried samples.[27] Similarly it has been reported that increasing halide (such as chloride and bromide) contamination also tends to decrease the density over a wide range of values.[31] In other words, the presence of any impurity in any ionic liquid can affect strongly their thermodynamic and physical properties as already mentioned above in the case of their transport properties.

20.2.6 SUMMARY

In summary ionic liquids have a proven ability to enhance current industrial chemistry. Within current industrial processes using conventional solvents, selectivities, TOF and reaction rates are not effectively controlled; however by using ionic liquid media for the catalysis, it is possible to have a profound influence on all these factors. Tailoring of the ionic liquid by a combination of subtle (i.e., changing cation substitution patterns) and gross (anion type) modifications can permit very precise tuning of reactions.

Ionic liquids have a proven ability to be used as effective solvents and catalysts for clean chemical reactions; as replacements for volatile organic and dipolar aprotic solvents (i.e. DMF, DMSO) and solid acid catalysts in reactions whether being used at the laboratory or industrial scale. Many of their physical properties are in the same region as organic solvents and as such could easily be incorporated into any future processes. Properties such as negligible vapor pressure and high density/variable interfacial tension offer considerable advantages in the design of unit operations such as evaporators, mixer-settlers and reactors. It is envisaged that as more information is gathered on their physical properties it will be possible to accurately design and optimize entire plants around these novel solvent systems. In a time where considerable emphasis is being placed on clean reactions and processes with minimal waste and efficient product extraction ionic liquids have emerged as a novel and exciting alternative to modern production methods. They are truly designer solvents.

REFERENCES

1 P. Wasserscheid, T. Welton, **Ionic Liquids in Synthesis** - Second Edition. *Wiley* (2008).
2 V.I. Pârvulescu, C. Hardacre, *Chem. Rev*., 107, (2007).
3 D.S. Silvester, R.G. Compton, *Z Phys. Chem*., 220, (2006).

4 J. Qu, J.J. Truhan, S. Dai, H. Luo, P.J. Blau, *Tribology Let*., 22, (2006).
5 J.D. Holbrey, *Chimica Oggi-Chemistry Today*, 25, (2007).
6 J.F. Liu, J.A. Jonsson, G.B. Jiang, *Trac-Trends in Analytical Chemistry*, 24, (2005).
7 K. Takao, T.J. Bell, Y. Ikeda, *Inorg. Chem.*, 52, (2013).
8 W.R. Pitner, A.E. Bradley, D.W. Rooney, D. Sanders, K.R. Seddon, R.C. Thied, J.E. Hatter, **NATO Science Series, Volume 92**, (2002).
9 M. Armand, F. Endres, D.R. MacFarlane, H. Ohno, B. Scrosati, *Nature mater*., 8, (2009).
10 A.R. Katritzky, A. Lomaka, R. Petrukhin, R. Jain, M. Karelson, R. Rodgers, *J. Chem. Inf. Comp. Sci.*, 42, (2002).
11 J.A. Widegren, Y.M. Wang, W.A. Henderson, J.W. Magee, *J. Phys. Chem. B*, 111, (2007).
12 M.J. Earle, J.M.S.S. Esperanca, M.A. Gilea, J.N. Canongia Lopes, L.P.N. Rebelo, J.W. Magee, K.R. Seddon, J.A. Widegren, *Nature*, 439, (2006).
13 A. Romero, A. Santos, J. Tojo, A. Rodríguez, *J. Hazardous Mater.*, 151, (2008).
14 W.L. Hough, M. Smiglak, H. Rodríguez, R.P. Swatloski, S.K. Spear, D.T. Daly, J. Pernak, J.E. Grisel, R.D. Carliss, M.D. Soutullo, J.H. Davis Jr., R.D. Rogers, *New J. Chem*., 31, (2007).
15 T. Abdallah, D. Lemordant, B. Claude-Montigny, *J. Power Sources*, 201, (2012).
16 H. Xue, B. Twamley, J.M. Shreeve, *J. Mat. Chem.*, 15, (2005).
17 R.D. Roger, K.R. Seddon, *Science*, 302, (2003).
18 A.Carmichael, M. Earle, J. Holbrey, P. McCormac, K. Seddon, *Org. lett.*, 1, (1999).
19 C. de Bellefon, E. Pollet, P. Grenouillet, *J. Mol. Cat. A-Chemical*, 145, (1999).
20 W. Chen, L. Xu, C. Chatterton, J. Xiao, *Chem. Commun.*, 13, (1999).
21 L. Simon, J. Dupont, R. de Souza, *Appl. Catalysis A-General*, 175, (1998).
22 S. Silva, P. Suarez, R. de Souza, J. Dupont, *Polym. Bull.*, 40, (1998).
23 Y. Chauvin, H. Olivier, C.N. Wyrvalski, L.C. Simon, R.F. de Souza, *J. Catalysis*, 165, (1997).
24 T.L. Greaves, C.J. Drummond, *Chem. Rev.*, 108, (2008).
25 J. Esperanca, J.N.C. Lopes, M. Tariq, L. Santos, J.W. Magee, L.P.N Rebelo, *J. Chem. Eng. Data*, 55, (2010).
26 E.M. Siedlecka, M. Czerwicka, S. Stolte, P. Stepnowski, *Curr. Org. Chem*., 15, (2011).
27 J. Jacquemin, P. Husson, A.A.H. Padua, V. Majer, *Green Chem*., 8, (2006).
28 J. Jacquemin, R. Ge, P. Nancarrow, D.W. Rooney, M.F. Costa Gomes, A.A.H. Padua, C. Hardacre, *J. Chem. Eng. Data*, 53, (2008).
29 P. Husson, L. Pison, J. Jacquemin, M.F.C. Gomes, *Fluid Phase Equilib*., 294, (2010).
30 K.R. Seddon, A. Stark, M.J. Torres, *Pure App. Chem*., 72, (2000).
31 J. Troncoso, C.A. Cerdeirina, Y.A. Sanmamed, L. Romani, L.P.N. Rebelo, *J. Chem. Eng. Data*, 51, (2006).
32 P.J. Carvalho, T. Regueira, L.M.N.B.F. Santos, J. Fernandez, J.A.P. Coutinho, *J. Chem. Eng. Data*, 55, (2010).
33 H.V. Spohr, G.N. Patey, *J. Chem. Phys*., 132, (2010).
34 B.F. Goodrich, J.C. de la Fuente, B.E. Gurkan, Z.K. Lopez, E.A. Price, Y. Huang, J.F. Brennecke, *J. Phys. Chem. B*, 115, (2011).
35 R.P. Swatloski, J.D. Holbrey, R.D. Rogers, *Green Chem*., 5, (2003).
36 M.G. Freire, Neves, C.M.S.S.; Marrucho, I.M.; Coutinho, J.A.P.; Fernandes, A.M. *J. Phys. Chem. A*, 114, (2010).
37 J. Esser, P. Wasserscheid, A. Jess, *Green Chem*., 6, (2004).
38 P. Wasserscheid, R. Van Hal, A. Bösmann, *Green Chem*., 4, (2002).
39 L.E. Ficke, H. Rodriguez, J.F. Brennecke, *J. Chem. Eng. Data*, 53, (2008).
40 J. Jacquemin, P. Goodrich, W. Jiang, D.W. Rooney, C. Hardacre, *J. Phys. Chem. B*, 117, (2013).
41 J. Jacquemin, P. Husson, *J. Chem. Eng. Data*, 57, (2012).
42 J.O. Valderrama, P.A. Robles, *Ind. Eng. Chem. Res*., 46, (2007).
43 J.O. Valderrama, W.W. Sanga, J.A. Lazzus, *Ind. Eng. Chem. Res*., 47, (2008).
44 J.O. Valderrama, R.E. Rojas, *Ind. Eng. Chem. Res*., 48, (2009).
45 O. Exner, *Nature*, 196, (1962).
46 M. Deetlefs, K.R. Seddon, M. Shara, *Phys. Chem. Chem. Phys*., 8, (2006).
47 R.L. Gardas, J.A.P. Coutinho, *Fluid Phase Equilib*., 265, (2008).
48 E. Ghasemian Lemraski, R. Zobeydi, *J. Mol. Liq.*, 193, (2014).
49 N.M. Correa, J.J. Silber, R.E. Riter, N.E. Levinger, *Chem. Rev*., 112, (2012).
50 M.G. Freire, A.F.M. Claudio, J.M.M. Araujo, J.A.P. Coutinho, I.M. Marrucho, J.N.C. Lopes, L.P.N. Rebelo, *Chem. Soc. Rev*., 41, (2012).
51 H. Niedermeyer, J.P. Hallett, I.J. Villar-Garcia, P.A. Hunt, T. Welton, *Chem. Soc. Rev*., 41, (2012).

52 S. Tang, G.A. Baker, H. Zhao, *Chem. Soc. Rev*., 41, (2012).
53 M. Tariq, M.G. Freire, B. Saramago, J.A.P. Coutinho, J.N.C. Lopes, L.P.N. Rebelo, *Chem. Soc. Rev.*, 41, (2012).
54 H. Wang, G. Gurau, R.D. Rogers, *Chem. Soc. Rev.*, 41, (2012).
55 Q. Zhang, K. De Oliveira Vigier, S. Royer, F. Jerome, *Chem. Soc. Rev*., 41, (2012).
56 T. Chivers, P.J.W. Elder, *Chem. Soc. Rev.*, 42, (2013).
57 M. Gericke, J. Trygg, P. Fardim, *Chem. Rev*., 113, (2013).
58 T.L. Greaves, C.J. Drummond, *Chem. Soc. Rev*., 42, (2013).
59 C. Maton, N. De Vos, C.V. Stevens, *Chem. Soc. Rev*., 42, (2013).
60 S.N. Riduan, Y. Zhang, *Chem. Soc. Rev*., 42, (2013).
61 J. Estager, J.D. Holbrey, M. Swadzba-Kwasny, *Chem. Soc. Rev.,* 43, (2014).
62 Z. Lei, C. Dai, B. Chen, *Chem. Rev.*, 114, (2014).
63 X. Meng, F.S. Xiao, *Chem. Rev*., 114, (2014).
64 E. Vazquez, F. Giacalone, M. Prato, *Chem. Soc. Rev*., 43, (2014).
65 C.L. Huheey, Inorganic chemistry, **Principles of structure and reactivity**, *Harper and Row*, (1972)
66 **CRC handbook**, 53rd ed, *CRC Press*, (1972).
67 A.F. Kapustinskii, *Z. Physik. Chem.* (Leipzig), **B22**, 257, (1933).
68 J. Emsley, The Elements, *Oxford*, (1989).
69 K.B. Yatsimirskii, Izvest, *Akad. Nauk SSSR*, Otdel, Khim. Nauk., 453, (1947).
70 R.D. Shannon, *Acta Crystallogr., Sect. A: Found. Crystallogr*., **32**, 751 (1976).
71 A. B. McEwen, H. L. Ngo, K. LeCompte, J. L. Goldman, *J. Elect. Chem. Soc.*, **146**, 5, (1999).
72 T.C. Waddington, *Adv. Inorg. Chem. Radiochem*., 1, (1959).
73 P. Walden, *Bull. Acad. Imper. Sci.* (St. Petersburg), 1800, (1914).
74 A. Fannin, D. Floreani, L. King, J. Landers, B. Piersma, D. Stech, R. Vaughn, J. Wilkes, J. Williams, *J. Phys. Chem*., 88, (1984).
75 A.Elaiwi, P. Hitchcock, K. Seddon, N. Srinivasan, Y. Tan, T. Welton, J. Zora, *J. Chem. Soc. Dalton Trans.*, 3467, (1995).
76 B. Chan, N. Chang, M. Grimmel, *Aust. J. Chem*., 30, (1977).
77 A. McEwen, H. Ngo, K. LeCompte, J. Goldman, *J. Electrochem. Soc.*, **146**, 5, (1999).
78 J. Wilkes, M. Zaworotko, *J. Chem. Soc., Chem. Com*., 965, (1992).
79 S. Wicelinski, R. Gale, *Themochem. Acta*, 126, (1988).
80 S. Tait, R. Osteryoung, *Inorg, Chem*., 23, (1984).
81 A. Abdul-Sala, A. greenway, P. Hitchcock, T. Mohammed, K. Seddon, J. Zora, *J. Chem. Soc., Chem. Commun*., 1753, (1986).
82 K. Dieter, C. Dymek, N. Heimer, J. Rovang, J. Wilkes, *J. Am. Chem. Soc*., **10**, 2711, (1988).
83 I. Lopez-Martin, E. Burello, P.N. Davey, K.R. Seddon, G. Rothenberg, *ChemPhysChem*, 8, (2008).
84 H. Chen, Y. He, J. Zhu, H. Alias, Y. Ding, P. Nancarrow, C. Hardacre, D. Rooney, C. Tan, *Int. J. Heat Fluid Flow*, 29, (2008).
85 N.V. Plechkova, K.R. Seddon, *Chem. Soc. Rev*., 37, (2008).
86 J.D. Holbrey, W.M. Reichert, M. Nieuwenhuyzen, S. Johnston, K.R. Seddon, R.D. Rogers, *Chem. Commun.*, (2003).
87 J. Jacquemin, J. Feder-Kubis, M. Zorebski, K. Grzybowska, M. Chorazewski, S. Hensel-Bielowka, E. Zorebski, M. Paluch, M. Dzida, *Phys. Chem. Chem. Phys*., 16 (2014).
88 A. Boisset, MPhil Thesis, unpublished results.
89 V. Posypaiko, E. Alekseeva, **Phase Equilibria in binary halides**, *IFI/Plenum*, (1987).
90 F. Hurley, T. Weir, *J. Electrochem. Soc*., **98**, 203, (1951).
91 D. Commereuc. Y. Chauvin, G. Leger, J. Gaillard, *Revue de L'Institut Francais du Petrole*, **37**, 639, (1982).
92 Y. Chauvin, D. Commereuc, A. Hirschauer, F. Hugues, L. Saussine, **French Patent, FR 2,611,700**.
93 Y. Chauvin, F. DiMarco, H. Olivier, B. Gilbert, Ninth International Symposium on Molten Salts, C.L. Hussey, D.S. Newman, G. Mamantov and Y. Ito (Eds.), The Electrochemical Society, Inc., San Francisco, California. USA, 617, (1994).
94 Y. Chauvin, S. Einloft, H. Olivier, *Ind. Eng. Chem. Res*., **34**, 1149, (1995).
95 Y. Chauvin, B. Gilbert, I. Guibard, *J. Chem. Soc., Chem. Commun*., 1715, (1990).
96 Y. Chauvin, B. Gilbert, I. Guibard, in Seventh International Symposium on Molten Salts, C.L. Hussey, S.N. Flengas, J.S. Wilkes and Y. Ito (Eds.), The Electrochemical Society, Montreal, Canada, 822, (1990).
97 Y. Chauvin, H. Olivier, C.N. Wyrvalski, L.C. Simon, R. De Souza, J. Dupont, *J. Catal.*, **165**, 275, (1997).
98 S. Einloft, F.K. Dietrich, R.F. de Souza, J. Dupont, *Polyhedron*, **15**, 3257, (1996).
99 H. Olivier, Y. Chauvin, A. Hirschauer, *Abst. Papers Am. Chem. Soc*., **203**, 75, (1992).

100 A.K. Abdul-Sada, P.W. Ambler, P.K.G. Hodgson, K.R. Seddon, N.J. Steward, **World Patent, WO 9521871**.
101 P.W. Ambler, P.K.G. Hodgson, N.J. Stewart, Butene Polymers, **European Patent Application, EP/0558187A0558181**, (1996).
102 K. Weissermel, H.J. Arpe, **Industrial Organic Chemistry**, *VCH*, Weinheim, 3rd edition, (1997).
103 R.T. Carlin, J.S. Wilkes, *J. Mol. Catal*., 63, 125, (1990).
104 L.M. Skrzynecki-Cooke, S.W. Lander, *Abst. Papers Am. Chem. Soc*., **193**, 72, (1987).
105 E. Ota, in Joint (Sixth) International Symposium on Molten Salts, G. Mamantov, M. Blander, C.L. Hussey, C. Mamantov, M.L. Saboungi and J.S. Wilkes (Eds.), The Electrochemical Society, Inc., 1002, (1987).
106 E. Ota, J. Electrochem. Soc., **134**, C512, (1987).
107 G. Hondrogiannis, C.W. Lee, R.M. Pagni, G. Mamantov, *J. Am. Chem. Soc.*, **115**, 9828, (1993).
108 R.M. Pagni, G. Mamantov, C.W. Lee, G. Hondrogannis, in Ninth International Symposium on Molten Salts, C.L. Hussey, D.S. Newman, G. Mamantov and Y. Ito (Eds.), The Electrochemical Society, Inc., San Francisco, California. USA, 638, (1994).
109 C.J. Adams, M.J. Earle, G. Roberts, K.R. Seddon, *Chem. Commun*., 207, (1998).
110 J.A. Boon, S.W. Lander, J.A. Levisky, J.L. Pflug, L.M. Skrynecki-Cooke, J.S. Wilkes, in Joint (Sixth) International Symposium on Molten Salts, G. Mamantov, M. Blander, C.L. Hussey, C. Mamantov, M.L. Saboungi and J.S. Wilkes (Eds.), The Electrochemical Society, Inc., 979, (1987).
111 J.A. Boon, S.W. Lander, J.A. Levisky, J.L. Pflug, L.M. Skrynecki-Cooke, J.S. Wilkes, *J. Electrochem. Soc.*, **134**, 510, (1987).
112 J.A. Boon, J.A. Levisky, J.L. Pflug, J.S. Wilkes, *J. Org. Chem*., **51**, 480, (1986).
113 M.B. Jones, D.E. Bartak, D.C. Stanley, *Abst. Papers Am. Chem. Soc*., **190**, 58, (1985).
114 J.A. Levisky, J.L. Pflug, J.S. Wilkes, in The Fourth International Symposium on Molten Salts, M. Blander, D.S. Newman, M.L. Saboungi, G. Mamantov and K. Johnson (Eds.), The Electrochemical Society, Inc., San Francisco, 174, (1984).
115 B.J. Piersma, M. Merchant, in Seventh International Symposium on Molten Salts, C.L. Hussey, S.N. Flengas, J.S. Wilkes and Y. Ito (Eds.), The Electrochemical Society, Montreal, Canada, 805, (1990).
116 J.S. Wilkes, in Molten salt chemistry: An introduction and selected applications, G. Mamantov and R. Marassi (Eds.), *D. Reichel Publishing Company*, Dordrecht, 405-416, (1987).
117 J.A. Levisky, J.L. Pflug, J.S. Wilkes, *J. Electrochem. Soc.*, **130**, C127, (1983).
118 P.J. Dyson, M.C. Grossel, N. Srinivasan, T. Vine, T. Welton, D.J. Williams, A.J.P. White, T Zigras, *J. Chem. Soc., Dalton Trans*., 3465, (1997).
119 J.K.D. Surette, L. Green, R.D. Singer, *Chem. Commun*., 2753, (1996).
120 P.A.Z. Suarez, J.E.L. Dullius, S. Einloft, R.F. De Souza, J. Dupont, *Polyhedron*, 15, 1217, (1996).
121 P.A.Z. Suarez, J.E.L. Dullius, S. Einloft, R.F. De Souza, J. Dupont, *Inorg. Chim. Acta*, 255, 207, (1997).
122 Y. Chauvin, L. Mussmann, H. Olivier, *Angew. Chem. Int. Ed. Engl*., 2698, (1995).
123 A.L. Monteiro, F.K. Zinn, R.F. De Souza, J. Dupont, *Tetrahedron Asymmetry*, **8**, 177, (1997).
124 R.T. Carlin, J. Fuller, *Chem. Commun*, 1345, (1997).
125 J. Fuller, A.C. Breda, R.T. Carlin, *J. Electrochem. Soc.*, 144, (1997).
126 J.E.L. Dullius, P.A.Z. Suarez, S. Einloft, R.F. de Souza, J. Dupont, J. Fischer, A. DeCian, *Organometallics*, **17**, 815, (1998).
127 S.M. Silva, P.A.Z. Suarez, R.F. De Souza, *Polym. Bull*., **40**, 401, (1998).
128 D.A. Jaeger, C.E. Tucker, *Tetrahedron Lett*., **30**, 1785, (1989).
129 M.J. Earle, P.B. McCormac, K.R. Seddon, *Green Chem*., 1, (1999).
130 T. Fischer, T. Sethi, T. Welton, J. Woolf, *Tetrahedron. Lett.*, **40**, 793, (1999).
131 J.G. Huddleston, H.D. Willauer, R.P. Swatloski, A.E. Visser, R.D. Rogers. *Chem Commun.*, 1765, (1998).
132 A.E. Visser, R.P. Swatloski, R.D. Rogers, *Green Chemistry*, **2**, 1, (2000).
133 S.G.Cull, J.D. Holbrey, V. Vargas-Mora, K.R. Seddon, G.J. Lye, *Biotechnol. Bioeng.*, 69, (2000).
134 L. A. Blanchard, D. Hancu, E. J. Beckman, J. F. Brennecke, *Nature*, 399, (1999).
135 D. Armstrong, L. He, Y, Liu, *Anal. Chem*., **71**, 17, (1999).
136 W.R. Pitner, Unpublished Results, *Queens University of Belfast*, 2000
137 Y. Liu, P.Y. Chen, I.W. Sun, C.L.Hussey, *J. Electrochem. Soc*., **144**, 7, 1997.
138 Y.F. Lin, I.W. Sun, *Electrochim. Acta*, **44**, 16, (1999).
139 Y.F. Lin, I.W. Sun, *J. Electrochem. Soc*., **146**, 3, (1999).
140 W. J. Gau, I.W. Sun, *J. Electrochem. Soc*., **143**, 1, (1996).
141 E.G.S. Jeng, I.W. Sun, *J. Electrochem. Soc*., **145**, 4, (1998).
142 W.J. Gau, I.W. Sun, *J. Electrochem. Soc*., **143**, 3, (1996).
143 J.A. Mitchell, W.R. Pitner, C.L. Hussey, G.R. Stafford, *J. Electrochem. Soc*., **143**, 11, (1996).

144 M.R. Ali, A. Nishikata, T. Tsuru, *Electrochim. Acta*, **42**, 12, (1997).
145 R.T. Carlin, P.C. Trulove, H.C. DeLong, *J. Electrochem. Soc*., **143**, 9, (1996).
146 R.T. Carlin, H.C. DeLong, J. Fuller, P.C. Trulove, *J. Electrochem. Soc*., **145**, 5, (1998).
147 S. Pye, J. Winnick, P.A. Kohl, *J. Electrochem. Soc*., **144**, 6, (1997).
148 H.C. Delong, J.A. Mitchell, P.C. Trulove, *High Temp. Mater. Proc*., **2**, 4, (1998).
149 G.P. Ling, N. Koura, *Denki Kagak*u, **65**, 2, (1997).
150 X.H. Xu, C.L. Hussey, *J. Electrochem. Soc*., **139**, 11, (1992).
151 M. Hasan, I.V. Kozhevnikov, M.R.H. Siddiqui, A. Steiner, N. Winterton, *Inorg. Chem.*, **38**, 25, (1999).
152 X.H. Xu, C.L. Hussey, *J. Electrochem. Soc.*, **139**, 5, (1992).
153 F. Endres, W. Freyland, B. Gilbert, *Ber. Der Bunsen-Gesellschaft-Phys. Chem. Chem. Phys*., **101**, 7, (1997).
154 C.A. Zell, F. Endres, W. Freyland, *Phys. Chem. Chem. Phys*., **1**, 4, (1999).
155 F. Endres, W. Freyland, *J. Phys. Chem. B*, **102**, 50, (1998).
156 I.W. Sun, C.L. Hussey, *J. Electroanal. Chem.*, **274**, 1-2, (1989).
157 H.C. Delong, J.S. Wilkes, R.T. Carlin, *J. Electrochem. Soc.*, **141**, 4, (1994).
158 X.H. Xu, C.L. Hussey, *J. Electrochem. Soc.*, **140**, 5, (1993).
159 F.M. Lin, C.L. Hussey, *J. Electrochem. Soc*., **140**, 11, (1993).
160 C.L. Hussey, X.H. Xu, *J. Electrochem. Soc*., **138**, 7, (1991).
161 D. Costa, W.H. Smith, *Abstr. Papers Amer. Chem. Soc*., **216**, 2, (1998).
162 S.K.D. Strubinger, I.W. Sun, W.E. Cleland, C.L. Hussey, *Inorg. Chem*., **29**, 5, (1990).
163 P.A. Barnard, C.L. Hussey, *J. Electrochem. Soc.*, **137**, 3, (1990).
164 S.K.D. Strubinger, I.W. Sun, W.E. Cleland, C.L. Hussey, *Inorg. Chem.*, **29**, 21, (1990).
165 D. Appleby, P.B. Hitchcock, K.R. Seddon, J.E. Turp, J.A. Zora, C.L. Hussey, J.R. Sanders, T.A. Ryan, *Dalton Trans.*, 6, (1990).
166 S.K.D Strubinger, C.L. Hussey, W.E. Cleland, *Inorg. Chem.,* **30**, 22, (1991).
167 C.L. Hussey, P.A. Barnard, I.W. Sun, D. Appleby, P.B. Hitchcock, K.R. Seddon, T. Welton, J.A. Zora, *J. Electrochem. Soc*., **138**, 9, (1991).
168 R. Quigley, P.A. Barnard, C.L. Hussey, K.R. Seddon, *Inorg. Chem*., **31**, 7, (1992).
169 C.L. Hussey, R. Quigley, K.R. Seddon, *Inorg. Chem*., **34**, 1, (1995).
170 R.I. Crisp, C.L. Hussey, K.R. Seddon, *Polyhedron*, **14**, 19, (1995).
171 Q. Liao, W.R. Pitner, G. Stewart, C.L. Hussey, G.R. Stafford, *J. Electrochem. Soc*., **144**, 3, (1997).
172 T.P. Moffat, *J. Electrochem. Soc*., 141, (1994).
173 G.R. Stafford, *ibid*., 136, (1989).
174 G.R. Stafford, B. Grushko, R.D. Mc Michale, *J. Alloys Compd*., 200, (1993).
175 T.P. Moffat, *J. Electrochem. Soc.*, 141, (1994).
176 G.R. Stafford, *ibid*., 945, (1994).
177 C.L. Hussey, T. M. Laher, *ibid*., 20, (1981).
178 C.L. Hussey, L.A. King, R.A. Carpio, *J. Electrochem. Soc*., 126, (1979).
179 R.J. Gale, B. Gilbert, R.A. Osteryoung, *Inorg. Chem*., 18, (1979).
180 W.R. Pitner, **PhD Thesis**, *University of Mississippi*, (1997).
181 B.J. Tierney, W.R. Pitner, C.L. Hussey, G.R. Stafford, *J. Electrochem. Soc*., 145, (1998).
182 W.R. Pitner, C.L. Hussey, G.R. Stafford, *J. Electrochem. Soc*., **143**, 1, (1996).
183 W.R. Pitner, C.L. Hussey, *J. Electrochem. Soc*., **144**, 9, (1997).
184 Z.-A. Zhang, Y.-Q. Lai, J. Li, Y.-X. Liu, *J. Cent. South Univ. Technol.*, 16, (2009).
185 B.E. Conway, **Electrochemical Supercapacitors: Scientific Fundamentals and Technological Applications**; *Kluwer Academic Plenum*: New York, (1999).
186 M. Hahn, R. Kötz, R. Gallay, A. Siggel, *Electrochim. Acta*, 52, (2006).
187 W. Lu, L. Qu, K. Henry, L. Dai, *J. Power Sources*, 189, (2009).
188 M. Galinski, A. Lewandowski, L. Stepniak, *Electrochim. Acta*, 51, (2006).
189 V. Ruiz, T. Huynh, S.R. Sivakkumar, A.G. Pandolfo, *RSC Adv.,* 2, (2012).
190 H. Kurig, A. Jänes, E. Lust, *J. Electrochem. Soc*., 157, (2010).
191 C. Arbizzani, M. Biso, D. Cericola, M. Lazzari, F. Soavi, M. Mastragostino, *J. Power Sources*, 185, (2008).
192 D. Rooney, J. Jacquemin, R. Gardas, *Top. Curr. Chem*., 290, (2009).
193 R.T. Carlin, P.C. Truelove, *Electrochim. Acta*, **37**, 14, (1992).
194 G.T. Cheek, R.A. Osteryoung, *J. Electrochem. Soc*., **129**, 11, (1982).
195 M. Lipsztajn, R.A. Osteryoung, *Inorg. Chem*., **24**, 5, (1985).
196 C.L. Hussey, L.A. King, The Second International Symposium on Molten Salts, Pittsburgh, USA, The Electrochemical Society, Inc., (1978).
197 J.S. Tang, R.A. Osteryoung, *Synthetic Metals*, **45**, 1, (1991).

198 L. Janiszewska, R.A. Osteryoung, *J. Electrochem. Soc.*, **135**, 1, (1988).
199 G.T. Cheek, R.B. Herzog, The Fourth International Symposium on Molten Salts, San Francisco, The Electrochemical Society, Inc., (1984).
200 J.E. Coffield, G. Mamantov, *J. Electrochem. Soc.*, **138**, 9, (1991).
201 J.E. Coffield, G. Mamantov, *J. Electrochem. Soc*., **139**, 2, (1992).
202 F. Fuller, R.T. Carlin, R.A. Osteryoung, *J. Electrochem. Soc.*, **144**, 11, (1997).
203 C.A. Angell, Y. Ansari, Z. Zhao, *Faraday Discuss.*, 154, (2012).
204 K.R. Seddon, A. Stark, M.J. Torres, Viscosity and density of 1-alkyl-3-methylimidazolium ionic liquids. In **Clean Solvents - Alternative Media for Chemical Reactions and Processing**, Abraham, M. A.; Moens, L., Eds. (2002).
205 J. Jacquemin, M. Anouti, D. Lemordant, *J. Chem. Eng. Data*, 56, (2011).
206 P.S. Kulkarni, L.C. Branco, J.G. Crespo, M.C. Nunes, A. Raymundo, C.A.M. Afonso, *Chem.-A Eur. J.*, 13, (2007).
207 G.L. Burrell, N.F. Dunlop, F. Separovic, *Soft Mater.*, 6, (2010).
208 H. Matsuda, H. Yamamoto, K. Kurihara, K. Tochigi, *Fluid Phase Equilib.,* 261, (2007).
209 M.H. Ghatee, M. Zare, A.R. Zolghadr, F. Moosavi, *Fluid Phase Equilib.*, 291, (2010).
210 R.L. Gardas, J.A.P. Coutinho, *Fluid Phase Equilib.*, 266, (2008).
211 R.L. Gardas, J.A.P. Coutinho, *AIChE J.*, 55, (2009).
212 C. Han, G. Yu, L. Wen, D. Zhao, C. Asumana, X. Chen, *Fluid Phase Equilib*., 300, (2011).
213 S.A. Mirkhani, F. Gharagheizi, *Ind. Eng. Chem. Res*., 51, (2012).
214 B.-K. Chen, M.-J. Liang, T.-Y. Wu, H.P. Wang, *Fluid Phase Equilib.*, 350, (2013).
215 C. Ye, J.M. Shreeve, *J. Phys. Chem. A*, 111, (2007).
216 R.L. Gardas, J.A.P. Coutinho, *Fluid Phase Equilib*., 263, (2008).
217 J.O. Valderrama, K. Zarricueta, *Fluid Phase Equilib*., **275**, 2, (2009).
218 Y. Qiao, Y. Ma, Y. Huo, P. Ma, S. Xia, *J. Chem. Thermodyn*., **42**, 7, (2010).
219 K. Paduszynski, U. Domanska, *Ind. Eng. Chem. Res.,* **51**, 1, (2012).
220 N.K. Patel, M.H. Joshipura, *Procedia Eng*., 51, (2013).

20.3 DEEP EUTECTIC SOLVENTS AND THEIR APPLICATIONS AS NEW GREEN AND BIORENEWABLE REACTION MEDIA

Joaquín García-Álvarez
Laboratorio de Compuestos Organometálicos y Catálisis (Unidad Asociada al CSIC), Departamento de Química Orgánica e Inorgánica, Instituto Universitario de Química Organometálica "Enrique Moles", Facultad de Química, Universidad de Oviedo, Julián Clavería 8, E-33006 Oviedo, Spain, e-mail: garciajoaquin@uniovi.es

20.3.1 INTRODUCTION

One of the largest areas of consumption of petroleum-based chemicals in a conventional chemical transformation are solvents used as reaction media (i.e., solvents account for 80-90% of mass utilization in a typical pharmaceutical/fine chemical operational process).[1] Thus, solvents are responsible for most of the waste generated in the chemical industries and laboratories. In this sense, and to face the diminution of oil supplies, there has been a global demand for the development of renewable solvents that are not based on crude petroleum. On the other hand, conventional volatile organic solvents (VOCs) commonly used as reaction media can cause well-established environmental problems due to their:

i) highly toxicity,
ii) non-biodegradability,
iii) accumulation in the atmosphere (low boiling points), and
iv) flammability.[2-4]

Despite these intrinsic drawbacks of VOCs, most of the chemical transformations are performed in solution to: i) achieve homogeneity of reagents and products; ii) efficiently control the heat flow, iii) ensure rapid and safe conversion, and iv) avoid undesired side products by dilution, thus enhancing the reaction rate. To overcome the aforementioned drawbacks of traditional VOCs and still benefit from the solvent effects,[5] remarkable research efforts have been focused on the replacement of traditional organic solvents by Green Solvents.[6] In theory, an ideal green solvent should be safe for both human beings and the environment, with its use and manufacture being also sustainable.[7] Therefore, to be qualified as a green medium, these solvents have to meet different criteria such as availability, non-toxicity, biodegradability, recyclability, non-flammability and low price. Up to now, these green solvents (the number of available green solvents is still limited) include:

i) supercritical fluids,
ii) ionic liquids (ILs),
iii) water, and
iv biomass-based solvents and
v) perflourinated solvents;

and occupy a strategic place within the framework of Green Chemistry.[8-11]

Ionic liquids (ILs), generally composed of an imidazolium or pyridonium cation in a stoichiometric combination with a weakly coordinating anion, have received great attention due to their:

i) non-flammability,
ii) thermal stability,
iii) low vapor pressure, and
iv) catalytic effect in many chemical transformations.[12-13]

However, their use as green solvents has to be re-evaluated as many reports pointed out to their high toxicity and poor biodegradability.[14]

Supercritical fluids, like $scCO_2$, can be considered as beneficial solvents as they are non-toxic, relatively inert and easily recyclable and removable. However, a wider utilization of these solvents is held back because:

i) they are poor solvents for many compounds, and
ii) require high-energetic and high-pressure reactors.[15-16]

Water can be considered an ideal solvent as it is cheap, non-toxic, non-flammable, sustainable and safe to the environment. However limitations arise when hydrolysis reactions can take place and extraction with organic solvents is required.[17-18]

Perfluorinated solvents. The strength of the C–F bond confers them both thermal and chemical stability (non-flammable, inert and non-toxic), which permits them to be used in a variety of temperatures and conditions. Nevertheless, their high prize and the fact that they persist in the environment are very important drawbacks.[19-20]

Biomass-based solvents (like, 2-methyl-THF, lactic acid, γ-valerolactone and glycerol) are emerging as very promising alternatives to traditional volatile organic solvents.[21] However, they present a very important drawback: the modulation potential of their physicochemical properties is reduced

With the ultimate goal of solving these environmental problems and to overcome the aforementioned limitations of traditional green reaction media, the development of a new generation of sustainable solvents is urgently needed. In this sense, recent pioneering work from several synthetic laboratories around the world has recognized the potential of Deep Eutectic Solvents (DESs) as superior green and biorenewable solvents. Therefore, it is not surprising that several reviews and accounts have been published in the field in the recent years.[22-29]

This chapter is intended to cover the progress made in the study of the physicochemical properties of DESs and their applications as environmentally-friendly reaction media in a variety of chemical applications (i.e., electrochemistry, biocatalysis, metal extraction, material chemistry, and metal-catalyzed organic reaction, among others). As this is a fast growing and widespread field, the author will try to give a general trend of this research area.

20.3.2 DEFINITION AND COMPOSITION OF DEEP EUTECTIC SOLVENTS

Deep Eutectic Solvents (DESs), also known in the literature as Deep Eutectic Ionic Liquids (DEILs), Low Melting Mixtures (LMMs), Low Transition Temperature Mixtures (LTTMs), or Natural Deep Eutectic Solvents (NADES), are defined as combinations of two or three components which are able to establish hydrogen bond interactions with each

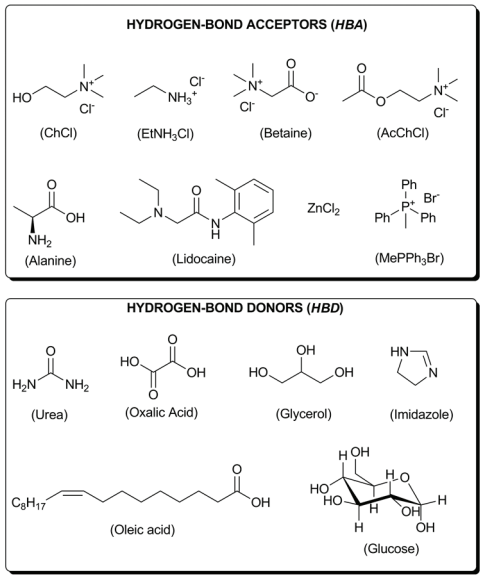


Figure 20.3.1. Structure of some hydrogen-bond acceptors (HBA) and hydrogen-bond donors (HBD) commonly used for DESs synthesis.

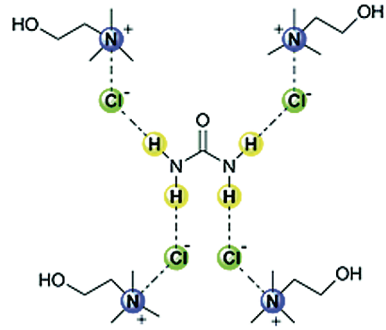


Figure 20.3.2. Interaction of urea (HBD) with choline chloride (HBA).

other to form an eutectic mixture, that is liquid melting at the desired temperature (most of them are liquid between room temperature and 70ºC) with a melting point lower than that of the each individual component. The concept "Deep Eutectic Solvent" was firstly coined by Abbott *et al.*[30] to describe the formation of a liquid eutectic mixture (melting point 12ºC) starting from two solid materials with high melting points: i) choline chloride (ChCl), (2-hydroxyethyl)trimethylammoniun chloride, melting point 133ºC, see Figure 20.3.1), and ii) urea (melting point 302ºC) in a ratio 1:2 (1ChCl/2Urea).[30,31] However, it is important to note that strictly speaking deep eutectic mixtures were used before to: i) lower the melting point of salts by forming metal-halide complexes,[32,33] and ii) reduce the lattice energy of halide salts by the addition of urea.[34] Taking into account the large pool of inexpensive, safe, renewable and biodegradable components which are capable of forming eutectic mixtures, the possibility of forming new green and biorenewable deep eutectic solvents is enormous (see Figure 20.3.1).

In the literature, all authors postulated the need of at least two components to synthesize the desired DES: i) a hydrogen-bond donor (HBD), and ii) a hydrogen-bond acceptor (HBA). However, different theories were developed for explaining the formation of these eutectic mixtures. Thus, some authors sustain the proposal of cluster formation, while others explicate the formation of these eutectic mixtures as a mechanical mixture of two components.[35,36] Abbott and co-workers postulated that the formation of DESs is due to the fact that the hydrogen-bond donor (e.g., urea) interacts with the anion of the hydrogen-bond acceptor (e.g., chloride anions form ChCl) and increases its effective size, which, in turn, reduce the anion interaction with the cation (e.g., ammonium cation from ChCl) and thus decrease the melting point of the mixture (Figure 20.3.2).[30] Recently, Edler and co-workers have employed neutron-diffraction techniques and atomistic modelling to study the liquid structure of the aforementioned eutectic mixture 1ChCl/2Urea.[37] These investi-

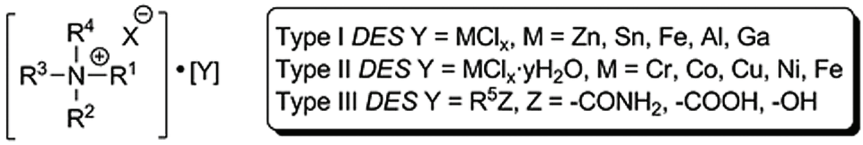


Figure 20.3.3. General formula of DESs containing quaternary ammonium salts.

gations showed the formation of a strong hydrogen-bond network in the liquid phase of the mixture 1ChCl/2Urea, with an important ordering interactions between the urea, the chloride anion and the choline cation (through its OH group); in an intricate sandwich-type structure that maximize the attractive interactions. Moreover, the authors also established that retention of this nanostructure is possible up to a 42% hydration of the 1ChCl/2Urea eutectic mixture. At higher percentages of water, the obtained mixture is better described as an aqueous solution of the isolated components of the eutectic mixture.[38]

In most of the cases, DESs are obtained by mixing a quaternary ammonium salt (HBA) with a hydrogen-bond donor (HBD) that has the ability to form a complex with the halide anion of the ammonium salt. These DESs can be defined by the general formula $[R^1R^2R^3R^4N^+X^-]\cdot[Y]$, firstly reported by Abbott and co-workers in 2007.[39] In theory, and using this general formula, three different families of DESs could be proposed (Type I-III, Figure 20.3.3). The same research group reported a fourth type of DESs which can be obtained by mixing different metal chlorides (e.g., $ZnCl_2$) with different hydrogen-bond donors (urea or glycerol).

One of the widespread ammonium salt (HBA) used for the synthesis of these DESs is the aforementioned choline chloride (ChCl). ChCl (so-called vitamin B_4,[40] an essential micro- and human nutrient) is produced on the scale of million metric tons per year (through a total atom economical process that employs $N(CH_3)_3$, HCl and ethylene oxide) as an additive for chicken feed and many other applications. This ammonium salt is not only cheap and easy to obtain (can be extracted from biomass) but also non-toxic and biodegradable.[41,42] In combination with different cheap and safe hydrogen-bond donors (HBD) ChCl is capable of forming: i) "drinkable" solvents (when ChCl is combined with the convenient anions such as saccharinate, lactate, and hexanoate),[43,44] and ii) the aforementioned natural deep eutectic solvents (NADESs), when urea, renewable carboxylic acids (e.g., oxalic, citric, succinic, or amino acids), renewable polyols (e.g., glycerol, carbohydrates) or even water are used as hydrogen-bond donors.[45,46] At this point, it is important to note that, although most DESs are made from ChCl as an ionic species, DESs cannot be considered as traditional ILs because: i) DESs are not entirely composed of ionic species, and ii) can also be obtained from non-ionic species. Also, and due to the nature of their components, DESs derived from ChCl gather many advantages as compared with traditional ILs: i) low price, ii) chemical inertness with water, iii) easy to prepare (since DESs are obtained by simply mixing two components, thus over-passing all problems of purification and waste disposal generally encountered with traditional ILs), and iv) most of them are biodegradable, biocompatible and non-toxic, reinforcing the greenness of these media.

20.3.3 PHYSICOCHEMICAL PROPERTIES OF DEEP EUTECTIC SOLVENTS

The study of the fundamental physicochemical properties of DESs is one of the major challenges in the development of new applications for this novel family of solvents, as their intrinsic properties will make them more or less suitable as reaction, separation or heat-transfer media. Similar to traditional ILs, DESs are chemically tailorable solvents since their properties can be fine-tuned by using different combinations of the hydrogen-bond donor (HBD) and the hydrogen-bond acceptor (HBA). Although physicochemical properties of the DESs are not yet predictable, they are directly related to the nature of the hydrogen bond interactions present in the mixture and the ratio of the components. In this sense, and as we will discusses in this section, the strength of the hydrogen bonds can be correlated with the melting point, stability and solvents properties (e.g., polarity, density, viscosity…) of DESs.[22-29] These solvent properties, in which both anions and cations as well as neutral molecules are present, differ considerably from those of traditional ionic liquids since, in addition to the electrostatic solvation, the substrates influencing chemical transformations can also establish a hydrogen-bond network with the solvent. In this section, the main physicochemical properties of DESs will be described and discussed.

20.3.3.1 Melting points of DESs

As previously mentioned in their definition, DESs are generally characterized by a melting point lower than that of the each individual component. For the majority of reported DESs, their melting points are below 150ºC. Although no correlation was found between the eutectic temperature and the enthalpy of formation of the starting materials, it was hypothesized that a relationship exists between the melting points and the lattice energy of the hydrogen-bond acceptor and the entropy changes when the eutectic liquid is formed.[47]

For the first-generation DESs ([R_4NX]/urea) in which the HBA is a quaternary ammonium salt, Abbott *et al*. reported that: i) the melting point of these eutectic mixtures decreased by decreasing the symmetry of the ammonium cations (compare entry 2 with entries 6-7 in Table 20.3.1), and ii) the melting points also decrease in the order $F^- > NO_3^- > Cl^- > BF_4^-$ (entries 2-5, Table 20.3.1).[28] More recently, Domínguez de María and co-workers demonstrated that not only the nature but also the molecular ratio of the hydrogen-bond donor (like carboxylic acids or saccharide-derived polyols) in their eutectic mixtures with ChCl, had a major effect on the melting temperature of the corresponding DESs, even though there was no fixed pattern.[48,49] The same random behavior was earlier reported by Kareem *et al*. in the study of the melting point of a variety of phosphonium-based DESs ([R_4PX]/HBD, Table 20.3.2), most of them having melting points below 100ºC.[50]

Table 20.3.1. Melting points (M_p) of DESs with general formula [$R^1R^2R^3R^4NX$]·Urea in a molecular ratio 1:2.

Entry	R^1	R^2	R^3	R^4	X^-	M_p (ºC)
1	Et	Et	Et	Et	Br^-	113
2	Me	Me	Me	CH_2CH_2OH	Cl^-	12
3	Me	Me	Me	CH_2CH_2OH	BF_4^-	67

Table 20.3.1. Melting points (M_p) of DESs with general formula $[R^1R^2R^3R^4NX]\cdot$Urea in a molecular ratio 1:2.

Entry	R^1	R^2	R^3	R^4	X^-	M_p (ºC)
4	Me	Me	Me	CH_2CH_2OH	NO_3^-	4
5	Me	Me	Me	CH_2CH_2OH	F^-	1
6	Me	Me	CH_2Ph	CH_2CH_2OH	Cl^-	-33
7	Me	Me	Et	CH_2CH_2OH	Cl^-	-38

Table 20.3.2. Melting points (M_p) of DESs with general formula $[R^1P(R^2)_3X]\cdot$[HBD].

Entry	$[R^1P(R^2)_3X]$	[HBD]	Ratio (HBA:HBD)	Mp (ºC)
1	$[MeP(Ph)_3Br]$	Gly[a]	1:1.75	–4.03
2	$[MeP(Ph)_3Br]$	EG[b]	1:4	–49.34
3	$[MeP(Ph)_3Br]$	CF_3CONH_2	1:8	–69.29
4	$[(PhCH_2)P(Ph)_3Cl]$	Gly[a]	1:5	50.36
5	$[(PhCH_2)P(Ph)_3Cl]$	EG[b]	1:3	47.91
6	$[(PhCH_2)P(Ph)_3Cl]$	CF_3CONH_2	3:1	99.72

[a]Gly is glycerol. [b]EG is ethylene glycol.

20.3.3.2 Density of DESs

The density of a solvent is one of the most important properties to bear in mind in the choice of the reaction media. In general, the density of ChCl-based DESs range from 1.12 to 2.4 $g\cdot cm^{-1}$ (similar to traditional ILs and higher than those of most organic solvents and water).[12] Table 20.3.3 lists the density data for common DESs. As previously observed for the melting point, the density of the eutectic mixtures is directly related to both the nature (entries 1-2, 6-8 in Table 20.3.3) and the ratio of the components (HBA and HBD, entries 10-12). For instance, in the ChCl/Gly eutectic mixture, the addition of ChCl to glycerol decreases the density of the corresponding DES, which can be explained in terms of free volume (see entries 3-5, Table 20.3.3).[51]

Table 20.3.3. Densities of various DESs at 25ºC.

Entry	HBA	HBD	Ratio (HBA/HBD)	Density ($g\cdot cm^{-1}$)
1	ChCl[a]	CF_3CONH_2	1:2	1.342
2	ChCl[a]	Urea	1:2	1.25
3	ChCl[a]	Gly[b]	1:1	1.16
4	ChCl[a]	Gly[b]	1:2	1.18

Table 20.3.3. Densities of various DESs at 25ºC.

Entry	HBA	HBD	Ratio (HBA/HBD)	Density ($g \cdot cm^{-1}$)
5	ChCl[a]	Gly[b]	1:3	1.20
6	ChCl[a]	EG[c]	1:2	1.12
7	ChCl[a]	MAc[d]	1:2	1.25
8	$EtNH_3Cl$	Acetamide	1:1.5	1.041
9	$EtNH_3Cl$	Urea	1:1.5	1.140
10	$Et_2(EtOH)NCl$[e]	Gly[b]	1:2	1.17
11	$Et_2(EtOH)NCl$[e]	Gly[b]	1:3	1.21
12	$Et_2(EtOH)NCl$[e]	Gly[b]	1:4	1.22
13	$Et_2(EtOH)NCl$[e]	EG[c]	1:2	1.10
14	$ZnCl_2$	Urea	1:3.5	1.63
15	$ZnCl_2$	Acetamide	1:4	1.36
16	$ZnCl_2$	EG[c]	1:4	1.45
17	$[MePPh_3]Br$	Gly[b]	1:2	1.31
18	$[MePPh_3]Br$	EG[c]	1:3	1.25

[a]ChCl is choline chloride. [b]Gly is glycerol. [c]EG is ethylene glycol. [d]MAc is malonic acid. [e]$Et_2(EtOH)NCl$ = N,N-diethyleneethanol ammonium chloride.

As expected, the density of the eutectic mixtures (e.g., ChCl/Gly, ChCl/Urea and their corresponding aqueous mixtures), decreases linearly with increasing temperature.[52] Finally, it is important to note that by using theoretical studies, Mjalli and co-workers, were able to predict the density of different DESs based on ammonium or phosphonium salts.[51,53-55]

20.3.3.3 Viscosity of DESs

Viscosity describes the resistance of a substance to flow and it is an important factor in the application of DESs as green reaction media, because their high viscosity (>100 cP at room temperature, except for ChCl/EG eutectic mixtures) is one of the most important issues that need to be addressed. These high values of viscosity can be attributed to the presence of an extensive hydrogen bond network established between the HBA and the HBD. As previously observed for the melting point and the density of DESs, the viscosity of the eutectic mixtures is mainly affected by: i) the chemical nature of the DESs components, ii) the molecular ratio of HBA and HBD, iii) the water content, and iv) the temperature. In this sense, entries 16-18 in Table 20.3.4 clearly demonstrate that the viscosity of $EtNH_3Cl$-based eutectic mixtures depends on the nature of the HBD [CF_3CONH_2 (64 cP at 40ºC); acetamide (256 cP at 40ºC) and urea (128 cP at 40ºC)]. Also, when the hydrogen-bond donor is EG (in a 1:3 ratio) the lowest viscosity was obtained (entry 4, 19 cP at 20ºC), while the highest viscosities are observed for polyols [glucose (entry 5, 34400 cP at 50ºC); xylitol (entry 12, 5230 cP at 30ºC); sorbitol (entry 13, 12730 cP at 30ºC)] or carboxylic acid (MAc, entry 14, 1124 cP, 25ºC) in their eutectic mixtures with ChCl.

The molecular ratio of the components (HBA:HBD) of the eutectic mixture has also a major impact in the viscosity of the obtained eutectic mixture. In this sense, for the eutectic mixture ChCl/Gly the increasing of the molecular ratio of ChCl produces a dramatic decrease of the viscosity. For example, at 20ºC, the viscosities of ChCl/Gly in a molar ratio of 1:4, 1:3 and 1:2 were 503, 450 and 376 cP (entries 7-9, Table 20.3.4). This experimental fact can be attributed to the partial rupture of the intermolecular hydrogen-bond network of glycerol. Thus, the HBA (i.e., ChCl which is present in large amounts in the DES) interferes with the intermolecular interactions of the HBD (Gly), generating more free volume and lowering the viscosity of the HBD. In this sense, Abbott *et al.* applied the hole theory to try to rationalize the unusual increase of viscosities in DESs. They proposed that the high values of viscosity of these eutectic mixtures (higher than most molecular solvents and molten salts),[22] can be correlated with the low free volume.[56] Finally, and as aforementioned for density, the viscosity of DESs decreases with the increase of temperature (entries 1-2, Table 20.3.4). The effect of the temperature on viscosity can be described by the following Arrhenius-type equation:

$$\ln\eta = \ln\eta_0 + \frac{E_\eta}{RT}$$

where:

- η viscosity of a chemical compound
- η_0 constant
- E_η the energy of activation of viscous flow
- R the gas constant
- T the temperature in Kelvin.

Table 20.3.4. Viscosities of various DESs at different temperatures (ºC).

Entry	HBA	HBD	Ratio (HBA/HBD)	Viscosity (cP)
1	ChCl[a]	Urea	1:2	750 (25ºC)
2	ChCl[a]	Urea	1:2	169 (40ºC)
3	ChCl[a]	EG[b]	1:2	36 (20ºC)
4	ChCl[a]	EG[b]	1:3	19 (20ºC)
5	ChCl[a]	Glu[c]	1:1	34400 (50ºC)
6	ChCl[a]	Gly[d]	1:2	376 (20ºC)
7	ChCl[a]	Gly[d]	1:2	259 (20ºC)
8	ChCl[a]	Gly[d]	1:3	450 (20ºC)
9	ChCl[a]	Gly[d]	1:4	503 (20ºC
10	ChCl[a]	CF_3CONH_2	1:2	77 (40ºC
11	ChCl[a]	Imidazole	3:7	15 (40ºC)
12	ChCl[a]	Xylitol	1:1	5230 (30ºC)
13	ChCl[a]	Sorbitol	1:1	12730 (30ºC)
14	ChCl[a]	MAc[e]	1:2	1124 (25ºC)

Table 20.3.4. Viscosities of various DESs at different temperatures (ºC).

Entry	HBA	HBD	Ratio (HBA/HBD)	Viscosity (cP)
15	$ZnCl_2$	Urea	1:3.5	11340 (25ºC)
16	$EtNH_3Cl$	CF_3CONH_2	1:1.5	64 (40ºC)
17	$EtNH_3Cl$	Acetamide	1:1.5	256 (40ºC)
18	$EtNH_3Cl$	Urea	1:1.5	128 (40ºC)

[a]ChCl is choline chloride. [b]EG is ethylene glycol. [c]Glu is glucose. [d]Gly is glycerol. [e]MAc is malonic acid.

20.3.3.4 Surface tension of DESs

The surface tension of a solvent could be defined as the contractive tendency of a liquid that allows it to resist an external force. In general, the surface tension of DESs (higher than those of organic solvents and comparable to those of ILs) follows the same trend of viscosity, since both properties depend on the strength of the intermolecular interaction between the HBA and the HBD.[22-29] In this sense, Abbott and co-workers reported the data for ChCl[47,57] and $ZnCl_2$-based[57] eutectic mixtures (see Table 20.3.5). These values are in good agreement with those reported for the surface tension of traditional ionic liquids (e.g., the surface tension of 1-butyl-3-methylimidazolium tetrafluoroborate [BMIM][BF_4] is 38.4 $mN \cdot m^{-1}$).[58]

Table 20.3.5. Surface tensions of various DESs.

Entry	HBA	HBD	Ratio (HBA/HBD)	Surface Tens. ($mN \cdot m^{-1}$)
1	ChCl[a]	MAc[b]	1:1	65.68
2	ChCl[a]	$PhCH_2CO_2H$	1:2	41.86
3	ChCl[a]	EG[c]	1:3	45.4
4	ChCl[a]	Gly[d]	1:3	50.8
5	$ZnCl_2$	Urea	1:3.5	72.0
6	$ZnCl_2$	Acetamide	1:4	53.0
7	$ZnCl_2$	EG[c]	1:4	56.9

[a]ChCl is choline chloride. [b]MAc is malonic acid. [c]EG is ethylene glycol. [d]Gly is glycerol.

Thus, and as previously described for viscosity, the surface tension of the DESs decreases as the ratio of the HBA increases, supporting again the fact that addition of the salt (i.e., ChCl or $ZnCl_2$) disrupts the extensive hydrogen bond network of the HBD (i.e., polyols, urea, carboxylic acids). Also, and as aforementioned for viscosity, the surface tension showed a linear correlation with temperature.[22-29] Shahbaz *et al*.[53] used the Othmer equation to predict the surface tension of different DESs with a mean percentage error of only 2.57%. The Othmer equation is as follows:

$$\sigma(T) = \sigma_{ref}\left[\frac{T_C - T}{T_C - T_{ref}}\right]^{11/9}$$

where:

σ_{ref}	reference surface tension
T_{ref}	reference temperature, respectively
T_C	critical temperature.

20.3.3.5 Polarity of DESs

Polarity is one of the most important properties of the solvent as it can significantly influence the course of the reaction.[59] Although different scales could be used to estimate the polarity of a solvent, the most commonly used is the electronic transition energy of a probe dye (e.g. Reichardt's Dye 30, $E_T(30)$).[60] In this method, the polarity is calculated from the wavelength (nm) of maximum absorbance of the standard solvatochromic dye 30 in solvents of different polarity at 25ºC, 1 bar of pressure and using the following equation:

$$E_T(30)\ (Kcal{\cdot}mol^{-1}) = hcv_{max}N_A = (2.8591{\times}10^{-3})U_{max}\ (cm^{-1}) = 28591/\lambda_{max}$$

where:

h	Planck's constant
c	the speed of light
v_{max}	the wavenumber of the maximum absorption
N_A	the Avogadro´s number.

Table 20.3.6 resumes the polarity data of various ChCl-based eutectic mixtures. The polarity values are in good agreement with those previously reported for traditional ionic liquids RNH_3X and R_2NH_2X. The data collected in Table 20.3.6 clearly reflect that an increase of the HBA (ChCl) produces a concomitant increase of the polarity (entries 2-5, Table 20.3.6).

Table 20.3.6. Solvent polarities $E_T(30)$ of various ChCl-based eutectic mixtures and molecular solvents.

Entry	HBA	HBD	Ratio (HBA/HBD)	$E^T(30)$ (Kcal·mol^{-1})
1	-	Gly[b]	–	57.17
2	ChCl[a]	Gly[b]	1:3	57.96
3	ChCl[a]	Gly[b]	1:2	58.28
4	ChCl[a]	Gly[b]	1:1.5	58.21
5	ChCl[a]	Gly[b]	1:1	8.49
6	–	EG[c]	–	56.1
7	–	Water	–	63.1
8	–	Ethanol	–	51.9

[a]ChCl is choline chloride. [b]Gly is glycerol. [c]EG is ethylene glycol.

As the dye $E_T(30)$ is quite sensitive to hydrogen bonding solvents, other dyes have been also used to study the polarity of DESs. In this sense, Nile red $E_T(NR)$ has also been used.[60] Table 20.3.7 reported the Nile red data $E_T(NR)$ for some sugar-based DESs (entries 1-7) and molecular solvents (entries 8-12) calculated following the equation:

$$E_T(NR)\ (Kcal{\cdot}mol^{-1}) = hcv_{max}N_A = 28591/\lambda_{max,NR}$$

Table 20.3.7. Solvent polarities [$E_T(NR)$ and $E_T(30)$] of some sugar-based DESs and molecular solvents.

Entry	Solvent	$E_T(NR)$ (Kcal·mol^{-1})	$E_T(30)$ (Kcal·mol^{-1})
1	Sorbitol/DMU[a]/NH_4Cl	50.16	68.1
2	Maltose/DMU[a]/NH_4Cl	50.60	67.1
3	Mannitol/DMU[a]/NH_4Cl	52.94	65.8
4	Lactose/DMU[a]/NH_4Cl	52.55	53.9
5	Fructose/Urea/NaCl	52.55	66.5
6	Glucose/Urea/NaCl	50.78	64.4
7	Mannose/DMU[a]	51.79	53.9
8	Water	48.21	63.1
9	EG[b]	50.60	56.1
10	2-propanol	52.94	48.5
11	DMSO[c]	52.07	45.0
12	DMF[d]	52.84	43.6

[a]DMU 1,3-dimethylurea. [b]EG ethylene glycol. [c]DMSO dimethylsulfoxide. [d]DMF N,N-dimethylformamide.

20.3.3.6 Ionic Conductivity of DESs

The ionic conductivity of a solvent is very important for its possible application in electrochemistry (in next sections, we will present the growing application of DESs for metal electrodeposition and as electrolytes for lithium-ion batteries). However, and due to their high viscosities, most of DESs display only modest ionic conductivities (see Table 20.3.8). In this sense, Abbott and co-workers were the first to report the conductivity of ChCl/Urea eutectic mixtures (entry 1, Table 20.3.8).[30] Latter, Kareem *et al.*[50] reported the effects of temperature in the conductivity of several phosphonium-based DESs. In general, the conductivity of these DESs increases with increasing the temperature, probably due to a decrease of the viscosity (only the conductivity of the eutectic mixtures $[(PhCH_2)PPh_3]Cl$/Gly and $[(PhCH_2)PPh_3]Cl$/EG decreased with temperature).

Table 20.3.8. Ionic conductivities of various DESs at different temperatures.

Entry	HBA	HBD	Ratio	Conductivity (mS·cm^{-1})
1	ChCl[a]	Urea	1:2	0.199 (40ºC)

Table 20.3.8. Ionic conductivities of various DESs at different temperatures.

Entry	HBA	HBD	Ratio	Conductivity ($mS \cdot cm^{-1}$)
2	ChCl[a]	EG[b]	1:2	7.61 (20ºC)
3	ChCl[a]	Gly[c]	1:2	1.05 (20ºC)
4	ChCl[a]	CF_3CONH_2	1:2	0.826 (40ºC)
5	ChCl[a]	Imidazole	3:7	12 (60ºC)
6	$ZnCl_2$	Urea	1:3.5	0.18 (42ºC)
7	Bu_4NBr	Imidazole	3:7	0.24 (60ºC)
8	$EtNH_3Cl$	CF_3CONH_2	1:1.5	0.39 (40ºC)
9	$EtNH_3Cl$	Acetamide	1:1.5	0.688 (40ºC)
10	$EtNH_3Cl$	Urea	1:1.5	0.348 (40ºC)

[a]ChCl is choline chloride. [b]EG is ethylene glycol. [c]Gly is glycerol.

As previously observed for the rest of physicochemical properties of DESs (melting point, density, viscosity, polarity…) the conductivity is strongly dependent on both the nature of the components (e.g., compare entries 1 and 2 in Table 20.3.8) and their molecular ratio. In this sense, the higher conductivities could be achieved by using small cations and anions (e.g., fluorinated) in the HBA, in agreement with the hole theory.[61] In 2011, the Abbott group reported that the conductivity of ChCl-based eutectic mixtures could be increased gradually with the addition of $ZnCl_2$.[62] Finally, the molecular ratio HBA:HBD also plays a pivotal role in the conductivity values of ChCl-based DESs. Consequently, an increase of the HBA percentage results in the concomitant increase of the conductivity. In this sense, when the molar fraction of ChCl is increased to 25 mol%, the conductivity of the ChCl/Gly eutectic mixture is enlarged to 0.85 $mS \cdot cm^{-1}$. At higher concentrations, this DESs is able to display similar conductivity (> 1 $mS \cdot cm^{-1}$) to traditional ILs.

20.3.3.7 Acid/Basic character of DESs

Due to the different acid-base properties of the wide variety of components which are able to form DESs (ionic salts, carboxylic alcohols, polyols, amides, aminoacids…) the acid or basic strength of the resulting eutectic mixtures could be fine-tuned. The Hammett function has been used to evaluate the acidity or alkalinity of different DESs by determining the ionization ratio of indicators in a system. When weak acids (HI) are chosen as indicators, the Hammett function (H_) follows the equation:

$$H_{\_} = pK(HI) + \log\left(\frac{[I^-]}{[HI]}\right)$$

where:

pK(HI) the ionization constant of the indicator in water

$[I^-]$ and [HI] the molar concentration of the anionic and the neutral forms of the indicator, respectively.

Firstly, and by using this equation, Han and co-workers reported the H_ of the eutectic mixture ChCl/Urea in a 1:2 ratio.[63] The reported H_ value (10.86) suggest that this DES is weak base (the highest the value of H_ the highest the alkalinity of the solvent). It is important to note the effect of the water content, as the H_ decreases to 10.65 (3 wt% of water), as part of the basic sites have been solvated by water. Lately, Kareem *et al.*[50] reported the pH values of different phosphonium-based DESs: i) [$MePPh_3$]Br/Gly (in a 1:1.75 ratio), which has a neutral pH, and ii) [$MePPh_3$]Br/CF_3CONH_2 (in a 1:8 ratio), which has a lower value (pH = 2.5 at 20ºC). Finally, for DESs based on mixtures of ChCl and sugar-derived polyols, the pH values are always neutral.[48]

20.3.3.8 Toxicity and biodegradability of DESs

As previously assessed in the introduction of this chapter, DESs are generally claimed to be biodegradable and environmentally friendly solvents. However, and like in the previously discussed properties of these eutectic mixtures, the toxicity and biodegradability of DESs will strongly depend on the nature of the components of the corresponding eutectic mixture.[22-29] In this sense, when toxic or non-biorenewable substances are used (e.g., phosphonium salts, imidazole…), non-biofriendly DESs are form. However, when safe, cheap, biodegradable and non-toxic components are used [e.g., ChCl, natural and renewable polyols (Gly, carbohydrates), carboxylic acids (oxalic, citric…), amino acids and urea], biorenewable and environmentally-friendly DESs can be easily obtained.

Only few studies reported the toxicity or biodegradability of DESs. In a preliminary report, Hayyan *et al.*[42] evaluate the toxicity of different ChCl-based eutectic mixtures (with Gly, EG, triethylene glycol and urea) using two gram-positive and two gram-negative bacteria as a model of prokaryotic organisms. In their study, Hayyan and co-workers pointed out that although no toxic effect was observed on any of the bacteria studied, the cytotoxicity of the tested DESs was much higher than that of their individual components. To the best of our knowledge, there are only two precedents in the literature that studies the biodegradability of different ChCl-based eutectic mixtures by means of closed bottle test.[64,65] However, the biodegradability of ChCl-containing ILs has been recently reported independently by the research groups of Dr. Pereira[41] and Dr. Ohno.[43] Thus, more studies on the toxicity and life-cycle of DESs are strongly needed, in order to claim their Green designation.

20.3.4 APPLICATIONS OF DES AS NEW GREEN AND BIORENEWABLE REACTION MEDIUM

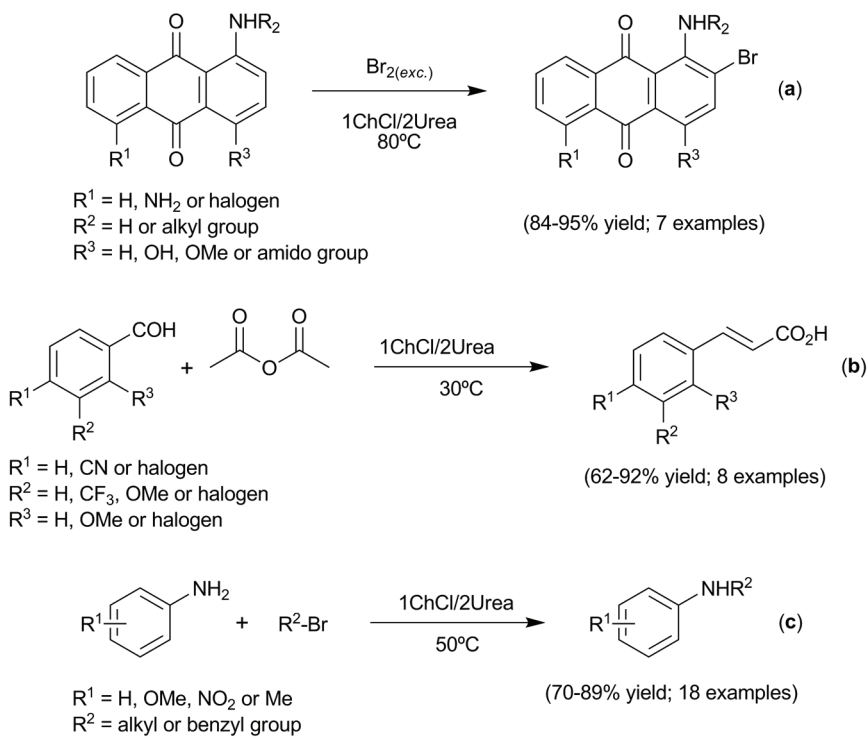
Due to the aforementioned advantages of DESs (i.e., low cost of components, easy to prepare, tunable physicochemical properties, negligible vapor pressure, biorenewability, biodegradability...), it is not surprising that these eutectic mixtures have found a wide variety of applications in different fields of modern chemistry.[22-29] This section provides an overview of the application of green and biorenewable DESs (most of them are ChCl-based eutectic mixtures) in the fields of: i) organic synthesis; ii) catalytic reactions; iii) dissolution of metal oxides, iv) electrodeposition of metals; and iv) material chemistry.

20.3.4.1 Organic synthesis in DESs

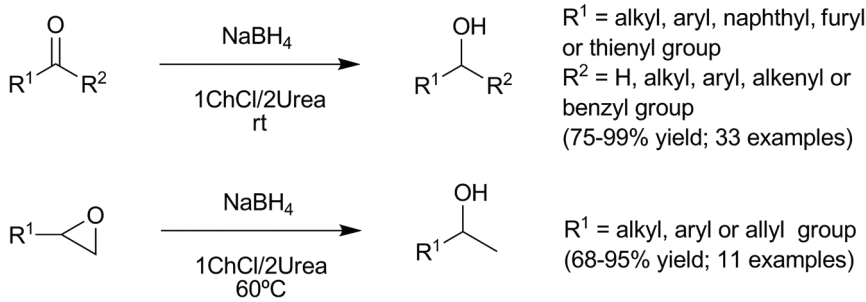
Deep eutectic solvents have been extensively used as an alternative green and biorenewable solvents to traditional VOCs in organic synthesis. Moreover, the addition of water to the reaction crude allows the easy separation (layer separation or precipitation) of the desired organic product. In most of these reactions, DESs were not only solvents for reactants, but also catalysts. In this sense, Shankarling and co-workers reported the reaction rate improvement of the electrophilic substitution of 1-aminoanthra-9,10-quinone derivatives in the eutectic mixture 1ChCl/2Urea as compared with conventional VOCs solvents such as methanol or chloroform (see reaction (a) in Scheme 20.3.1).[66] This rate enhancement could be related to the aforementioned basic nature of this eutectic mixture (Hammet function (H_) value 10.86). At the end of the reaction, the addition of water precipitates the dibrominated product (84-95% yield). The system was easily recycled (up to five consecutive times) by evaporation of water without appreciable lost in activity.

This eutectic mixture was lately used by the same research group for the synthesis of:

- cinnamic acids and its derivatives, *via* the Perkin reaction (see reaction (b) in Scheme 20.3.1).[67] Again and due to the basic properties of the eutectic mixture



Scheme 20.3.1. Synthetic organic reaction:. a. bromation, b. Perkin reaction, c N-alkylation of amines, performed in the basic eutectic mixture 1ChCl/2Urea described by Shankarling's research group.



Scheme 20.3.2. Reduction of carbonyl compounds and epoxides in the eutectic mixture 1ChCl/2Urea.

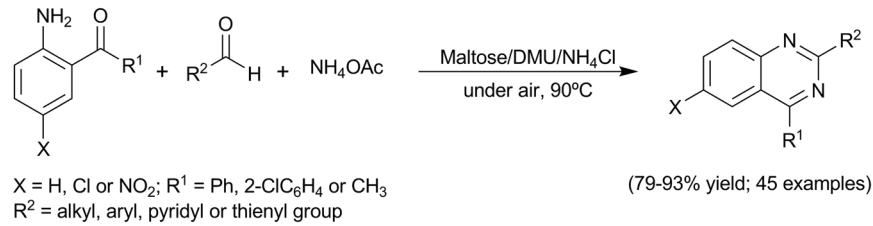
1ChCl/2Urea, the reaction proceeded efficiently under mild conditions and without the addition of any catalyst.[68]

- diphenylamine-based fluorescent styryl colorants, through the Knoevenagel condensation. The basic nature of the eutectic mixture 1ChCl/2Urea plays again a pivotal role in this condensation reaction; enabling the synthesis of a large variety of chromophores with high yields.[69] This method proceeds without formation of by-products and could be performed for five consecutive times without a significant decrease in the product yield.
- aromatic amines, by the mono-N-alkylation of primary amines (see reaction (c) in Scheme 20.3.1). It is important to note that, in this case, two different $ChCl^-$ based eutectic mixtures (1ChCl/2Urea and 1ChCl/2Gly) were used as both reaction media and catalyst. Best results were obtained with the most basic DESs (1ChCl/2Urea). Once more, the methodology was tolerant to a wide variety of amines and alkyl bromides and was successfully recycled up to five consecutive times by a liquid-liquid phase extraction.[70]

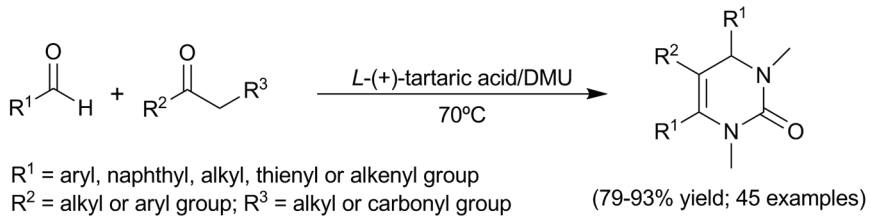
Azizi and co-workers reported the reduction of carbonyl compounds and epoxides with sodium borohydride, yielding the corresponding saturated alcohols with good to moderate yields with complete regio- and chemoselectivity (Scheme 20.3.2).[71]

Other eutectic mixtures apart from ChCl-based DESs have been used as reaction media in organic synthesis. In this sense, "sweet" deep eutectic solvents (also called low melting mixtures) based on carbohydrates (i.e., maltose) have been applied as green and biorenewable solvent in the high-yield synthesis of quinazoline derivatives *via* one-pot three-component coupling of 2-aminoaryl ketones, aldehydes and ammonium acetate (see Scheme 20.3.3).[72] However, the use of these carbohydrate-based DESs is limited because: i) they present relatively high melting points, and ii) their components are rather reactive.

Finally, the eutectic mixture L-(+)-tartaric acid/DMU was used as benign solvent, reactant (e.g. dimethylurea (DMU) in scheme 20.3.4) and catalyst for the synthesis of racemic dihydropyrimidones *via* Biginelli reaction.[73] Due to all these results DESs have begun to play a more important role in organic synthesis. In particular, an increasing number of publications have reported the use of eutectic mixtures as green reaction media in the synthesis of: i) dithiocarbamates in ChCl/Urea eutectic mixtures;[74,75] ii) β-hydroxy



Scheme 20.3.3. Synthesis of quinazoline derivatives on the DES maltose/DMU/NH_4Cl.



Scheme 20.3.4. Synthesis of 3,4-dihydropyrimidin-2-ones on the DES L-(+)-tartaric acid/DMU.

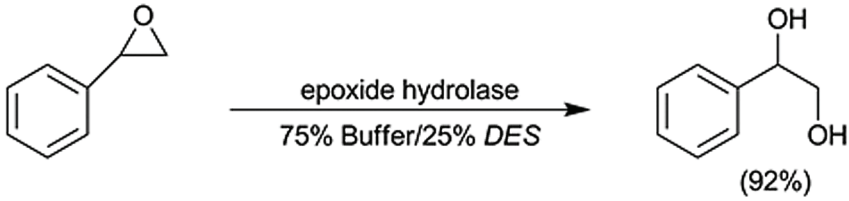
functionalized derivatives (including nitroaldols, β-hydroxy nitriles and β-hydroxy carboxylic acids) in a mixture of ChCl/Urea with methanol;[76] iii) aminooxazole derivatives *via* thermal and ultrasonic methods in ChCl/Urea;[77,78] iv) N-aryl-phthalimides starting from phthalic anhydride and primary aromatic amines in the eutectic mixture ChCl/MAc;[79] v) bis(indolyl)methanes through the electrophilic substitution of indoles with carbonyl compounds;[80] vi) coumarin styryl dyes based on 2-(1-(7-(diethylamino)-2-oxo-2H-chromen-3-yl)ethylidene)malononitrile;[81] vii) pyrimidinedione- and pyrimidinetriones-based compounds synthesized by conventional Knoevenagel condensation;[82] viii) 5-arylidene-2-imino-4-thiazolidinones *via* condensation of thioureas with chloroacetyl chloride and an aldehyde;[83] ix) pyrroles or furans using the Paal-Knorr reaction;[84] and x) Diels-Alder adducts in various carbohydrate-based eutectic mixtures.[85] As the reader may notice by reading this section of the chapter, this is a rapidly growing area with a large number of new publication reported each year. Thus, the interested reader is encouraged to consult recent outstanding reviews in this field.[29,86]

20.3.4.2 Catalytic reactions in DESs

This section of the chapter is intended to cover the progress made within three broad families of catalyzed organic reactions in DESs as green biorenewable media, which are bio-, metal- and organo-catalytic reactions, three fundamental processes in modern organic synthesis.

Biocatalytic Organic Reactions in DESs:

Most biocatalytic organic reactions are typically performed in water or traditional ILs, which share many characteristics with DESs. However the utilization of these eutectic mixtures as solvent in biotransformations has not been extensively studied till recent dates because strong hydrogen donors (such as urea) are known to denature proteins.[87,88] In this sense, Srienc, Kazlauskas and co-workers were the first to report the activity of var-

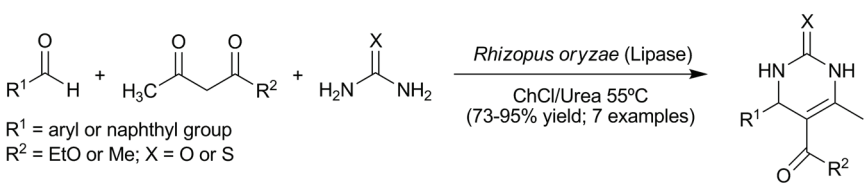


Scheme 20.3.5. Hydrolase-catalyzed biotransformation in deep eutectic mixtures.

ious hydrolases in ChCl/Urea mixtures showing good catalytic activity despite the presence of urea (which can denature enzymes) or alcohols (which can interfere with the hydrolase-catalyzed reactions).[89] In this sense, it is important to note that the conversion of 2-phenyloxirane (styrene oxide) to the corresponding diol catalyzed by epoxide hydrolase was 20-fold enhanced using ChCl/Urea as co-solvent (see Scheme 20.3.5). This positive effect of DESs as a cosolvent on a hydrolase-catalyzed reaction was later confirmed by Widersten *et al*. in the hydrolysis of 1S,2S-2-methylstyrene epoxide.[90] Among all DESs tested, the ChCl/Gly eutectic mixture was the most efficient medium as: i) the regioselectivity was improved (e.g., ring opening at the benzylic position became predominant), and ii) was capable of dissolving 1.5 times more epoxide than the phosphate buffer solution without affecting the optimal conversion rate.

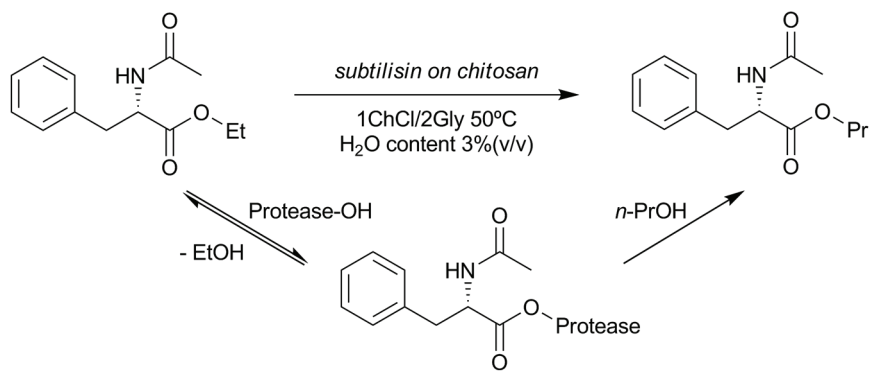
Deep eutectic solvents based on choline acetate (ChOAc), which have lower viscosities as compare to the ChCl/Urea eutectic mixture, have been also used as reaction media in several biocatalyzed transesterification reactions. In this sense, Zhao *et al.* reported the transesterification of ethyl sorbitate with 1-propanol by the lipase Novozym® 435 (*Candida Antarctica* lipase B immobilized on acrylic resins), achieving high initial rates (1 $\mu mol \cdot min^{-1} \cdot g^{-1}$) and selectivity (99%).[91] Furthermore, in a model biodiesel synthesis system, the authors examined the transeterification of the lipid Miglyol® oil 812 (a mixture of triglycerides of caprylic acid (C8) and capric acid (C10)) with methanol, catalyzed by Novozym® 435 in ChOAc/Gly (1:1.5 molar ratio). The biocatalytic reaction was very rapid in this eutectic mixture, with 97% conversion achieved after only 3 hours.

Subsequently, the lipase from *Rhizopus oryzae* was used as biocatalyst in the Biginelly reactions in the eutectic mixture ChCl/Urea yielding the corresponding dihydropyrimidines as a racemic mixture (see Scheme 20.3.6). The reaction was characterized by high efficiency and selectivity, short reaction time, and mild and environmentally friendly reaction conditions. It is important to note that the reuse of both the lipase and deep eutectic solvent was possible in four consecutive cycles.[92]



Scheme 20.3.6. Synthesis of dihydropyrimidinones on DESs catalyzed by lipase.

Apart from hydrolases and lipases, other enzymes have been successfully applied in biocatalytic organic reactions in DESs as solvents. In this sense, Zhao and co-workers reported the protease-catalyzed (subtilisin and α-chymotrypsin immobilized on chitosan) transesterification of N-acetyl-L-phenylalanine ethyl ester with 1-propanol in both ChOAc/Gly and ChCl/Gly eutectic mixtures.[93] These Gly-eutectic mixtures displayed better results than the corresponding urea mixtures. This experimental fact can be attributed to the greater instability of proteases (compared with lipases) which can suffer denaturalization processes with urea (Gly is less denaturant). Under the optimized reaction conditions depicted in Scheme 20.3.7, the activity of the protease reached high rate (2.9 $\mu mol \cdot min^{-1} \cdot g^{-1}$) and selectivity (98%) in the formation of the desired propyl ester. Interesting, the eutectic mixture ChCl/Gly provided much better results than conventional molecular organic solvents (i.e., tert-BuOH), indicating that this is the eutectic mixture of choice to achieve better results in biocatalytic reactions in DESs. Thus, it seems that the addition of Gly to ChCl prevents the denaturalization of the enzyme due to the strong interactions established between the HBA (ChCl) and the HBD (Gly) in the DES formed. This unexpected stability of enzymes in DESs was recently exploited by Gutiérrez *et al*.[94] to incorporate pure bacteria in ChCl/Gly mixtures by freeze-drying with the preservation of bacteria´s integrity and viability. In the same year, Hud and co-workers reported that four distinct nucleic acid structures of DNA can exist in DESs.[95] Finally, it should be noted that various cellulases have been recently applied as biocatalysts for the depolymerization of cellulose in the eutectic mixture ChCl/Urea, offering a new suitable tool for the conversion of biomass into platform reagents.[96]



Scheme 20.3.7. Protease-catalyzed transesterification of N-acetyl-L-phenylalanine ethyl ester in Gly-based DESs.

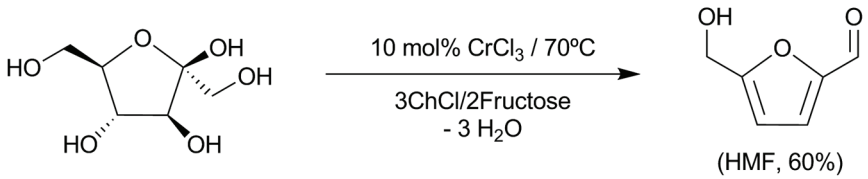
Since 2014, the use of enzymes as catalysts for organic synthesis in different eutectic mixtures has experimented an exponential grow. In this sense, DESs have been fruitfully employed as environmentally friendly reaction media in: i) benzaldehyde lyase (BAL) catalyzed carboligation of aldehydes (with C–C bond formation),[97] ii) whole-cell baker´s yeast enantioselective bioreduction of ethyl acetoacetate,[98] iii) alcohol dehydrogenase (ADH) catalyzed bioreduction of prochiral ketones,[99] iv) concomitant immobilize-CAL-B/prolinol catalyzed crossed aldol reaction with acetaldehyde,[100] v) bioreduction of 3-

chloropropiophenone with immobilized *Acetobacter sp.* CCTCC M209061 Cells,[101] vi) benzaldehyde lyase (BAL) biocatalyzed umpolung carboligation of furfural and hydroxymethylfurfural (HMF),[102] vii) diglycosidase-biocatalyzed deglycosylation of the rutinosylated flavonoid (hesperidin),[103] viii) enantioselective whole-cell baker's yeast bioreduction of arylpropanones,[104] ix) chemoenzymatic epoxidation of alkenes with *Candida antarctica* lipase B and hydrogen peroxide,[105] x) lipase-catalyzed enzymatic synthesis of α-monobenzoate glycerol (α-MBG) from glycerol and benzoic acid as substrates,106 and xi) R-regioselective bioreduction of aromatic ketones by *Lactobacillus reuteri* DSM 20016 whole cells.[107]

Metal-catalyzed organic reactions in DESs:

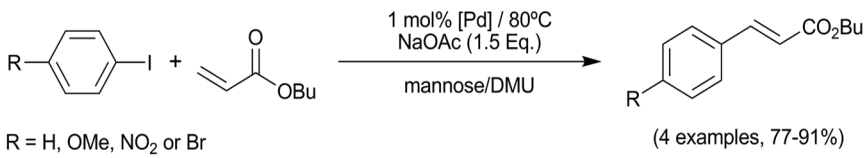
Metal-mediated organic reactions are one of the most frequently encountered methodologies in the synthetic chemist´s toolbox, providing powerful instruments to achieve elevated levels of chemo-, regio-, and stereoselectivity in the manufacture of highly functionalized organic products. Thus, it is not surprising that DESs have been already used as green and biorenewable media in metal-catalyzed organic reactions. In this sense, different metallic salts (i.e., $FeCl_3$, $ZnCl_2$, $CrCl_2$, $Sc(OTf)_3$, $AlCl_3$...) have been employed in the Lewis acid catalyzed dehydration of hexoses to 5-hydroxymethyl-furfural (HMF), using DESs as environmentally-friendly solvents.[108,109] These eutectic mixtures are the solvent of choice for the conversion of hexoses to HMF because: i) DESs can dissolve huge amounts of hexoses; ii) DESs can dilute the water released in the dehydration process, preventing the rehydration of HMF to the corresponding acids (levulinic and formic); iii) HMF can be easily separated from the reaction media by liquid-liquid extraction; and iv) DESs are not toxic compared with ILs, traditionally used as solvents in this dehydration process. Thus, Han and co-workers were the first to report the Lewis acid ($ZnCl_2$ or $CrCl_3$) catalyzed dehydration of fructose to HMF in various ChCl-based eutectic mixtures. However, this catalytic system displayed only moderate conversions and selectivities.[109] These unsuccessful results are in good agreement with those latter reported by König and coworkers, which also used different metal salts ($CrCl_2$, $CrCl_3$, $FeCl_3$ and $AlCl_3$) as catalysts in the dehydration of fructose in a eutectic mixture 1ChCl/2Urea. In this case, low yields (< 30%) of HMF were obtained due to the side reaction of urea and fructose.[91] To overcome this limitation, the same group reported the use of ChCl-based eutectic mixtures containing carbohydrates as HBD (see Scheme 20.3.8).[73] Apart from the monosaccharides D-fructose and D-glucose, the disaccharide sucrose and the polyfructan inulin were successfully converted into HMF. Finally, it should be noticed that Han and co-workers have demonstrated that conversion of hexoses to HMF without the help of metal catalyst can be achieved (76%, 80ºC, 1 h) by using DES containing carboxylic acid as both solvent and catalyst (i.e., ChCl/citric acid).[109] This idea was lately expanded by Jérôme *et al*. reporting the production of HMF from fructose and inulin by using a ternary eutectic mixture containing water, ChCl and betaine hydrochloride (BHC) as both solvent and catalyst for the dehydration process.[111] All these precedents seem to indicate that DESs will be the solvent

of choice in the future to succeed in the conversion of renewable raw materials (cellulose and lignin) to value-added chemicals (see section 20.3.4.5).[112]



Scheme 20.3.8. Metal catalyzed dehydration of fructose to HMF in DESs.

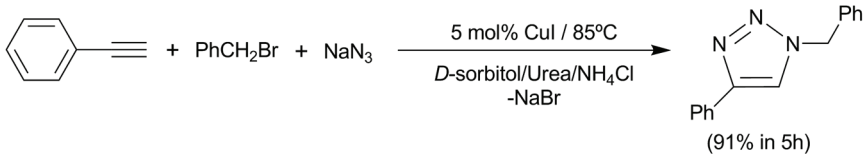
Metal-catalyzed, cross-coupling reactions between an organic electrophile, typically an organic halide, and an organic nucleophile have developed into a standard component of the synthetic chemistry toolbox for the formation of C–C and C-heteroatom bonds.[113] In this sense, DESs have been successfully applied as environmentally-friendly solvent with nearly every metal-catalyzed, cross-coupling reactions: i) Heck reactions, ii) Suzuki coupling, iii) Stille reactions, and iv) Sonogashira coupling. Thus, Heck reaction (Scheme 20.3.9) was performed in a carbohydrate-based DES (mannose/DMU), using the organometallic complex $[PdCl_2(PPh_3)_2]$ as catalyst precursor (10 mol%), at 80ºC and in the presence of an external base (NaOAc, 1.5 eq.). Under these optimized reaction conditions, the corresponding α,β-unsaturated aryl ester was obtained with moderate to good yields (77-91%). It is important to note that when the sugar-containing eutectic mixture (mannose/DMU) is changed to a L-carnitine/Urea mixture, reduced yields are observed.[114] Other cross-coupling reaction using different organometallic species like: i) organotin derivatives (Stille),[115] ii) organoboron compounds (Suzuki),[116] and iii) *in situ* generated acetylide anions (Sonogashira)[114] could be also performed in different sugar-based eutectic mixtures (mannose/DMU and maltose/DMU/NH_4Cl), allowing the synthesis of different substituted aryls in an environmentally-friendly reaction media.



Scheme 20.3.9. Pd-catalyzed Heck reaction using sugar-based DES as green solvent.

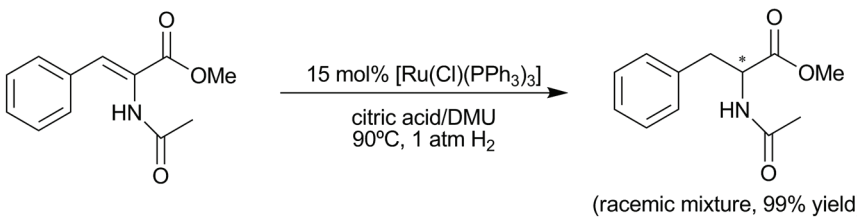
Since the independent discovery by Meldal, Sharpless, and co-workers of the regioselective copper(I) catalyzed 1,3-dipolar cycloaddition of organic azides and terminal alkynes (CuAAC) rendering 1,2,3-triazoles,[117,118] the applications of this catalytic process have grown tremendously. In this context, the eutectic mixture D-sorbitol/Urea/NH_4Cl has been used as environmentally friendly solvent in the three-component cycloaddition of terminal alkynes and *in situ* generated azides, yielding the corresponding triazoles in quantitative yields in the presence of 5 mol% of CuI (Scheme 20.3.10).[114] Although the reaction takes place in the absence of base, high temperatures (85ºC) were required to

achieve complete conversion (most of CuAAC reactions in VOCs, water or ILs proceed at room temperature). It should be noted that the reaction rate was slightly enhanced when the eutectic mixture L-carnitine/urea/NH_4Cl was used as a reaction medium. This experimental fact seems to indicate that L-carnitine is capable to form an organometallic complex with the copper salt, avoiding the intrinsic instability of Cu(I) species.



Scheme 20.3.10. Cu(I)-catalyzed 1,3-dipolar cycloaddition of phenylacetylene with *in situ* generated benzylazide in the eutectic mixture of D-sorbitol/Urea/NH_4Cl.

Metal-catalyzed hydrogenation reactions are among the most frequently encountered transformations in academic laboratories and industry, appearing as a core technology for the production of a large variety of commodity and fine chemicals, as well as pharmaceutical substances. Concerning the homogeneous version of these reactions using DESs as environmentally friendly solvents, König and co-workers reported the hydrogenation of methyl α-cinnamide in the presence of the Wilkinson catalyst [$RhCl(PPh_3)_3$]. Best results were obtained with the eutectic mixture citric acid/urea affording the hydrogenated product with quantitative yields at 90ºC and 1 atm of H_2 (see Scheme 20.3.11).[116] We must note that no enantiomeric excess was achieved by using chiral eutectic mixtures (i.e., sorbitol/DMU/NH_4Cl or mannitol/DMU/NH_4Cl). Finally, Vidal and co-workers reported recently the catalytic activity of several ruthenium complexes in the redox isomerization of allylic alcohols into saturated carbonyl compounds using the eutectic mixture ChCl/Gly as green and biorenewable reaction media.[119]



Scheme 20.3.11. Rh(I)-catalyzed hydrogenation of methyl α-cinnamide using the mixture of citric acid/DMU as a reaction medium.

Thanks to the aforementioned preliminary work in metal-catalyzed organic reactions in DESs, this field of research has experimented a dramatic growth during the last five years, and its research portfolio has been extended to: i) Rh-catalyzed hydroformylation of alkenes and Pd-catalyzed Tsuji-Trost reactions,[120,121] ii) $CuFeO_2$-catalyzed one-pot, three-component reaction of 2-aminopyridines, aldehydes, and alkynes,[122] iii) Au(I)-catalyzed cycloisomerization of alkynoic acids,[123] Z-enynols[124] and alkynyl amides,[125] iv) Fe(III)-

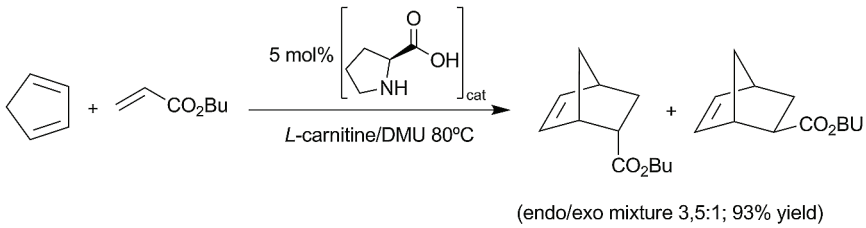
catalyzed oxidation of toluene with H_2O_2;[126] v) copper oxide catalyzed cross-dehydrogenative coupling for the synthesis of tetrahydroisoquinolines,[127] vi) the synthesis of thiophenes through Pd-catalyzed heterocyclodehydration and iodocyclization of 1-mercapto-3-yn-2- ols,[128] vii) revisited Pd-catalyzed C-C coupling reactions,[129-131] and viii) Pd-catalyzed aminocarbonylation of aryl iodides.[132] At this point, it is important to note that ChCl-based DESs have been described also as the solvent of choice for main-group mediated (RLi or RMgX) organic reactions. In this sense, it has been reported the possibility to trigger the chemoselective and ultrafast addition of organolithium (RLi) or organomagnesium (RMgX) reagents to ketones,[133-136] imines[137] or nitriles[138] at room temperature and in the absence of protecting atmosphere, thus building new bridges between main group chemistry and environmentally-friendly reaction conditions.[139] Bearing in mind that DESs have been previously used as eco-friendly solvent both in transition-metal-catalyzed reactions and main-group-mediated organic transformations, García-Álvarez and co-workers paved the pathway to follow in the combination of these two synthetic organic tools in DESs by describing the fruitful one-pot combination on the aforementioned Ru-catalyzed isomerization of allylic alcohols[119] with the concomitant addition of RLi/RMgX reagents to the transiently formed carbonyl intermediates,[140] producing the corresponding tertiary alcohols in good yields. To finish with this section, it is also important to highlight that this one-pot combination in DESs has been recently extended to tandem chemoenzymatic reactions, thus combining transition-metal-catalyzed organic reactions with enantioselective enzymatic processes for the synthesis of highly-added-value chiral alcohols starting from a racemic mixture of allylic alcohols.[141]

Organo-catalyzed organic reactions in DESs:

Over recent years, the golden age of organocatalysis (as coined by Dalko)[142] has influenced all the sections of synthetic chemistry. This influence is due to the fact that this mode of catalysis possessed the potential for saving in cost, time and energy, easier experimental procedures, and reduction of chemical wastes.

As some of the most powerful organocatalysts (i.e., amines, thioureas and proline-derivatives) are already present in some eutectic mixtures, the use of DESs as both benign solvent and catalyst in organic synthesis is well-known (see section 20.3.4.1 Organic synthesis in DESs). However there are some examples in the literature which described the use of an external organocatalyst in an organic synthetic reaction employing eutectic mixture as green and biorenewable solvent. In this sense, König *et al.* were the first to report the use of an external organocatalyst (L-proline) in a Diels-Alder reactions in DESs.[114] After four hours of heating (80ºC) in the eutectic mixture L-carnitine/Urea, the corresponding Diels-Alder adduct (see Scheme 20.3.12) was obtained with 93% yield. This result is comparable to the metal-catalyzed reaction ($Sc(OTf)_3$) performed in various sugar melts (i.e., Fructose/DMU). More recently, Coulembier and co-workers reported the organocatalyzed (DBU, 1,8-diazabicyclo[5,4,0]undecec-7-ene) copolymerization of lactide (LA) and 1,3-dioxan-2-one (TMC) which form an eutectic mixture at room temperature (1:1 ratio).[143] When the DBU (organocatalyst) and benzyl alcohol (initiator) are

added to the eutectic mixture LA/TMC at room temperature, the LA started to polymerize into poly(lactate) chains which crystallize from the eutectic mixture.



Scheme 20.3.12. Organo-catalyzed (L-proline) Diels-Alder reactions in sugar-based eutectic mixtures.

Since 2014, and after the aforementioned pioneering work in organocatalyzed organic reactions in DESs,[114,143] the following synthetic application have been added to this field of research: i) chincona-catalyzed Michael additions,[144] ii) L-isoleucine-catalyzed cross-aldol reaction between cyclohexanone and aromatic aldehydes,[145] iii) L-proline-catalyzed direct aldol reactions,[146,147] and iv) chiral 2-aminobenzimidazole-catalyzed Michael addition of 1,3-dicarbonyl compounds to β-nitroalkenes.[148]

20.3.4.3 Dissolution of metal oxides in DESs

It is well-known that DESs have the ability to dissolve a variety of metal oxides, because these eutectic mixtures are capable to donate or accept both electrons and protons. This special capacity of DESs opens a new gate to a greener separation and recycling of metals. First studies in the dissolution of amphoteric (ZnO, CuO) and basic (Fe_3O_4) metal oxides in various carboxylic acid-based DESs were reported by Abbott and co-workers in 2003.[47] The solubility value depends on both the nature of the oxide and the organic acid used. In this sense, Fe_3O_4 has the highest solubility (0.341 $mol \cdot L^{-1}$, 50ºC) in the eutectic mixture ChCl/Oxalic acid while CuO exhibits the highest solubility (0.473 $mol \cdot L^{-1}$, 50ºC) in the DES ChCl/Propionic acid. However, other oxides tested (i.e., aluminates and silicates) were insoluble in these acid-containing eutectic mixtures. The same research group studied the solubility of metal oxides in the basic eutectic mixture ChCl/Urea. In this case, the authors assessed that the dissolution of the metal oxides (M_xO_y) in this DES can be attributed to the formation of metallic complexes [MClO·urea] with the ligands present in the eutectic mixture (urea and the chloride anion). In the case of the ZnO, the presence of the corresponding metallic complex [ZnClO·urea] was proven by spectroscopic analysis (MS). This study was lately expanded to the analysis of the ability of ChCl/Thiourea eutectic mixtures to dissolve metal oxides.[143] As for its urea counterpart, this sulfur-containing eutectic mixture was capable of dissolve ZnO and CuO, although Al_2O_3 remained insoluble. This difference in solubility of metal oxides in DESs has been successfully applied to the separation and recovery of different metals. For example, the eutectic mixture ChCl/Urea was used for the separation of Zn and Pb from a waste material. Thus, while the DESs-soluble zinc and lead oxides are selectively extracted in solution, iron and aluminum oxides remain in the solid waste.[150] More recently, DESs have been employed for: i) separation of rare earth metals from used NdFeB magnets,[151] ii) dissolution of

pyrite and other Fe-S-As minerals,[152] and iii) dissolution of Mg, Zn, Co and Ni oxides to synthesize spinel-type ferrite nanoparticles MFe_2O_4.[153] Finally, and due to their ability to dissolve metal oxides, DESs have been also applied for surface cleaning and metallurgy.

20.3.4.4 Electrodeposition of metals in DESs

Analogous to traditional ILs, deep eutectic solvents have been successfully applied in electrochemistry as electrolytes for: i) electrodeposition of metals, ii) dyes-sensitized solar cells,[154,155] iii) electropolishing of metals,[156,157] and iv) lithium-ion batteries;[158-160] and v) metal separations.[161] In this section we will focus our attention on the electrodeposition of metals using different ChCl-based eutectic mixtures (ChCl/Urea and ChCl/EG).

In general, the electrodeposition of metals is a process which consists of the formation of solid metal material by electrochemical reaction in a liquid phase. The electrodeposition is usually performed in a three-electrode cell (composed of a reference electrode, a cathode and an anode). The cationic metal (M^{n+}), dissolved in the liquid electrolyte (DESs), is reduced and deposited as metal (M^0) in the cathode. Traditionally, ILs have been the solvent of choice for the electrodeposition of metals which exhibit a redox potential higher than that of water. Due to the aforementioned advantages of DESs as compared with traditional ILs, this field of research has been extensively investigated. However, the observed instability of the DESs during the electrodeposition process is a lasting challenge that needs to be solved.[162]

ChCl/Urea eutectic mixtures have been applied as green and biorenewable solvent in the electrodeposition of:

- Cobalt, Samarium and Co/Sm alloys. Gómez *et al*. examined the electrodeposition of cobalt and samarium independently on vitreous carbon. Concomitant deposition of cobalt and samarium can also be achieved in the eutectic mixture of ChCl/Urea, forming either film or nanowire, depending on the temperature.[163-165]
- Gallium and Cu/Ga alloys. The electrodeposition of gallium and copper-gallium alloys was checked to prepare semiconductors for use in thin solar cells. In this sense, Shivagan *et al.* reported the electrodeposition of (Cu-In-5Ga)-Se in the eutectic mixture ChCl/Urea.[166] Gallium can be also deposited over a Mo electrode in a reversible process, as recently reported by Dale and co-workers.[167]
- Nickel and Ni-Zn alloys. Ni(II) can be successfully deposited on both copper or platinum electrodes.[168-170] The addition of nicotinic acid or ethylenediamine to the eutectic mixture ChCl/Urea permits control of morphology, microstructure and redox behavior of the nickel deposited on the copper electrode. Ni-Zn alloys can be also deposited on copper electrodes using anhydrous nickel and zinc chlorides as starting materials.[171]
- Magnesium. As it is well-known, electrodeposition of magnesium from aqueous solution is difficult due to its reactivity with water. In this sense, Bakkar and Neubert have investigated the electrodeposition of Zn onto several Mg alloys in different eutectic mixtures (ChCl/EG, ChCl/Urea, ChCl/MAc and ChCl/Gly).[172] After comparing the efficiency of these DESs, ChCl/Urea was found to be the most suitable medium for the electrodeposition of Zn on Mg.[173]

- CdS, CdSe and ZnS alloys. Dale and co-workers have reported that by using a glassy carbon or fluorine doped with tin oxide as electrode, deposition of films of CdS, CdSe and ZnS can be achieved.[174]
- Selenium. Bougouma *et al*., recently reported the electrodeposition of Se over a polycrystalline gold electrode.[175]
- Electrodeposition of nano-Ni films on a Cu substrate from $NiCl_2$. The obtained Ni films can be controlled to form nanostructures depending on the nature of the DES (ChCl-based eutectic mixtures with urea or ethylene glycol as hydrogen bond donors were used).[176]

The electrodeposition of metals in the eutectic mixture ChCl/EG (which displays one of the lowest values of viscosity) has been mainly studied by Abbott´s research group. This research group has reported: i) the electrodeposition of Zn on a polished gold-coated quartz crystal by atomic force microscopy and quartz crystal microanalysis,[177] ii) the effect of additives (acetonitrile, ammonia, and ethylene diamine) in the electrodeposition of Zn,[178] and iii) the effect of the concentration of $ZnCl_2$ in the conductivity of the eutectic mixture.[62] More recently, the electrodeposition of the alloy Zn/Sn on carbon nanotubes was recently studied by Zheng and co-workers.[179]

- Copper can be also electrodeposited in a bright nano-structure using the eutectic mixture ChCl/EG as solvent, with copper concentration between 0.01 and 0.1 M. For lower Cu concentrations, formation of a black deposit was observed. Additionally, copper composite materials with Al_2O_3 or SiC can be also produced in this DES.[180,181]
- Silver was also successfully electrodeposited on either copper or platinum electrodes by Abbott and co-workers.[182,183] This methodology, which consists on the deposition of silver from a solution of AgCl in the eutectic mixture ChCl/EG, improved wear-resistant silver coatings. Later on, the deposition of silver on copper, reported by Tu *et al*.,[184] led to the formation of a self-assembled nanoporous network of Ag films.
- Nickel was electrodeposited on polished brass foil at different temperatures (Ni deposit roughness with temperature).[185] Also, Martis *et al*.[169] reported that compact nickel multiwalled carbon nanotube composites could be electrodeposited on a copper substrate using the eutectic mixture ChCl/EG as solvent. Later, electrodeposition of Ni-P alloys (with tunable phosphorous content) at room temperature was reported by You and co-workers.[186,187]
- Cr/Co alloys can be deposited on a cathode composed of brass and mild-steel plates in ChCl/EG mixtures. By using the direct current deposition method (DCD) an alloy composed of 80.04% of Co and 34.56% of Cr was obtained.[188]
- Organometallic complexes (i.e., ferrocene)[189] and organic polymers (i.e. polypyrrole films)[190] can also be electrodeposited from ChCl/EG eutectic mixtures.

Finally, other ChCl-containing eutectic mixtures like ChCl/Gly,[191,192] ChCl/CF_3CONH_2,[193] or ChCl/$CrCl_3$,[194] or $ZnCl_2$/Urea[195] have been used in the electrodeposition of different metals.

20.3.4.5 Material chemistry in DESs

Apart from their aforementioned use in electrodeposition, DESs have been successfully applied in the synthesis of different materials like: i) polymers, ii) metal phosphates, iii) metal-organic frameworks (MOFs), iv) nanoparticles, and v) carbon materials. In this section, we will give a general overview covering the use of green and biorenewable DESs in the synthesis of these materials.

Synthesis of polymeric materials in DESs

With the development of DESs, they have been applied on some polymerization reactions that are carried out at relatively high temperatures. In these synthetic processes, the eutectic mixtures can act as true solvent-template reactant systems, and thus the DES is at the same time the precursor, the template, and the reactant medium for fabrication of the desired polymeric material with a defined morphology or chemical composition.[196-198] Monte and co-workers have reported: i) the frontal polymerizations carried out in the eutectic mixtures ChCl/Acrylic acid and ChCl/Mac,[199,200] ii) the synthesis of poly(octanediol-co-citrate) elastomers using eutectic mixtures of 1,8-octanediol and lidocaine at temperatures below 100ºC (see Figure 20.3.4),[201] and iii) the synthesis of poly(acrylic acid)-carbon nanotube composites in the eutectic mixture ChCl/Acrylic acid.[202]

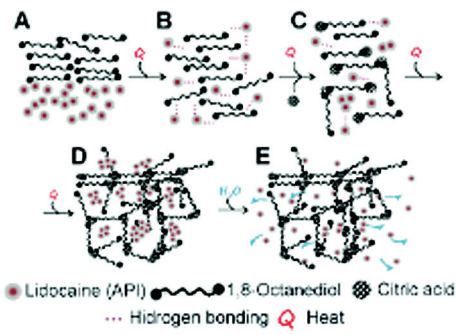


Figure 20.3.4. Schematic diagram representing the synthetic process-mixture of components in a heterogeneous solid phase (A), the lidocaine-based DES (B), the lidocaine-loaded prepolymer (C), and elastomer (D), and the lidocaine release based on polymer swelling and degradation (E).[201] [Adapted, by permission, from M. C. Serrano, M. C. Gutiérrez, R. Jiménez, M. L. Ferrer and F. Monte, *Chem. Commun.*, **48**, 579 (2012).]

Owing to these superior performances of DESs in polymer synthesis, in 2012, Fernandes reported the electrochemical synthesis of conducting polymers (polyaniline) in the eutectic mixture ChCl/EG.[203] Ramesh and co-workers have also described other conducing polymers composed of cornstarch or cellulose acetate, mixed with lithium bis(trifluoromethanesulfonyl)imide and the deep eutectic solvent ChCl/Urea.[204,205] Finally, Leroy *et al.* used the eutectic mixtures ChCl/Urea and ChCl/Gly as functional additives to develop an efficient polymer blend of thermoplastic starch.[206] After these pioneering works, the use of DESs as environmentally-friendly reaction media for different polymerization reactions has been extended to: i) preparation of crosslinked polymers (hydrogels and xerogels) starting from itaconic acid as a renewable monomer,[207] ii) fabrication of conductive paper based on *in-situ* polymerization of Polymerizable Deep Eutectic Solvents (PDESs) through a screen printing process,[208] iii) frontal polymerization of DESs based on acrylic or methacrylic acid as both the monomers and the hydrogen bond donors,[209] iv) $FeCl_3$-catalyzed oxidative polymerization of 3-octylthiophene for the synthesis of poly(3-octylthiophene),[210] and v) the enzyme-mediated free

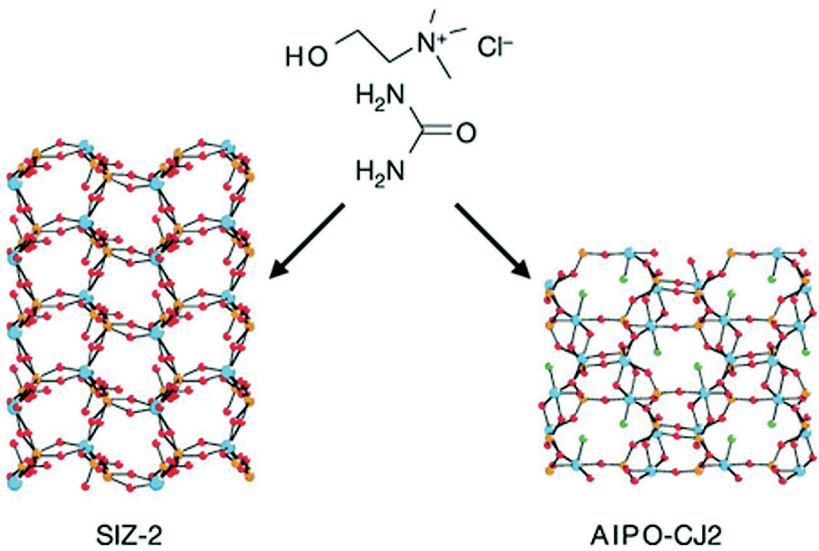


Figure 20.3.5 Synthesis of the zeotypes SIZ-2 and AlPO-CJ2 using a ChCl/Urea DES.[213] The structure directing agents have been omitted for clarity. [Adapted, by permission, from E. R. Cooper, C. D. Andrews, P. S. Wheatley, P. B. Webb, P. Wormald and R. E. Morris, *Nature*, **430**, 1012 (2004).]

radical polymerization of acrylamide in nearly non-aqueous ChCl/Urea or ChCl/Gly eutectic mixtures.[211]

Synthesis of metal phosphates in DESs

Recently, the ionothermal synthesis, (a new synthetic strategy for the preparation of inorganic materials) involving the use of traditional ILs or DESs as solvent, has been developed. In this synthesis, ILs or DESs can be used as both solvent and template (solvent-template reactant). One of the major advantages of this ionothermal synthesis when compared with traditional solvothermal synthesis is the fact that ionothermal synthesis can be conducted at low pressure (ambient pressure), due to the low volatility of the ionic solvents (ILs or DESs). In this context, deep eutectic solvents based in ChCl/Urea or ChCl/renewable carboxylic acids (which have notable advantages including biodegradability, low cost and low toxicity when compared with traditional ILs), have been used in ionothermal synthesis. In this section of the chapter some representative studies are summarized.[212] In 2004, the Morris group, first used the eutectic mixture ChCl/Urea as a solvent and template in the ionothermal synthesis of zeolite analogous and the eutectic mixture was successfully introduced in the framework shown in Figure 20.3.5.[213] This eutectic mixture (ChCl/Urea) was later used as reaction medium: i) for the synthesis and crystallization of a novel coordination polymer $[NH_4][Zn(O_3PCH_2CO_2)]$;[214] and ii) to address the ionothermal synthesis of aluminophosphates by ion-exchange.[215] Other ChCl-based eutectic mixtures have been used in the ionothermal synthesis. In this sense, the eutectic mixture ChCl/DMU was used to prepare borate-containing materials.[216] Also, several urea

derivatives [1,3-dimethyl urea, 2-imidazolindone (ethylene urea) and tetrahydro-2-pyrimidione] or carboxylic acids (succinic, glutaric and citric acid) mixed with ChCl have been used as eutectic mixtures in the synthesis of aluminophosphates[217] or cobalt-aluminophosphate[218] materials, respectively.

Three-dimensional[219] or layered zinc phosphates[220] can be selectively synthesized *via* ionothermal approaches using the eutectic mixtures ChCl/Imidazoline or ChCl/Oxalic acid as solvents. Dong and co-workers, demonstrated that by using eutectic mixtures of oxalic acid with different ammonium salts [(Pr_4N)Br or (Et_4N)Cl], both layered[221] or open-framework[222] zirconium phosphates can be selective prepared by ionothermal synthesis. Finally, tin(II) phosphates were prepared in the eutectic mixture ChCl/Pyrazol.[223] During the last years, and following the pathway opened by the aforementioned pioneering works, ionothermal synthesis in DESs has been applied for the synthesis of: i) new layered gallium phosphates in eutectic mixtures ChCl/2-imidazoline,[224] ii) four crystalline zinc diphosphonates starting from tetraethyl-p-xylene bis(phosphonate) and $Zn(OAc)_2$;[225] and iii) two oxalate-bridged Gd(III) coordination polymers.[226]

Synthesis of Metal-Organic Frameworks (MOFs) in DESs

During the last decade, the synthesis of metal-organic frameworks has emerged as one of the most important research topics in material chemistry due to their wide application in many fields such as hydrogen store, gas separation, catalysis, etc.[227,228] The ionothermal synthesis of MOFs in DESs has many advantages when compared with traditional ILs: i) DESs are green and low-priced reaction media (attractive route for large scale production of MOFs), and ii) the presence of neutral components in DESs (i.e., urea, Gly) can induce a structure-directing effect in the final material.[229] Thus, it is not surprising that great efforts were devoted to the synthesis of new porous MOFs in DESs. Bu and co-workers, described the synthesis of more than 40 structures by the assembly between: i) metal nitrate precursor (i.e. alkali, transition or lanthanide metal); ii) different ureas (i.e., ethylene urea hemihydrates, propyleneurea, tetramethylurea); iii) carboxylic acids (1,4-benzenedicarboxylic acid, 1,2,4-benzenetricarboxylic acid, naphthalene-1,4-dicarboxylic acid, thiophene-1,4-dicarboxylic acid, 1,3,5-benzene-tribenzoic acid); and iv) amide solvent (diethylformamide, dimethylforamide or 2-pyrrolidine).[230] Continuing with their pioneering work in ionosynthesis of metal phosphates in DESs, Morris *et al*., reported the production of vanadium (oxy)fluoride materials in both ChCl/DMU and ChCl/2-imidazoline eutectic mixtures.[231] Since 2014, DESs have been employed as ecofriendly solvent in the synthesis of: i) two new 2-dimensional Indium-based metal organic frameworks;[232] and ii) nano-/microscale UiO-66-NH_2 metal organic framework materials.[233]

Synthesis of nanomaterials in DESs

The unique characteristics (i.e., ultrathin thickness, high specific surface areas) and properties (i.e., magnetic, electrochemical, photonic and catalytic) of nanomaterials have attracted considerable attention.[234] Therefore, many researchers have applied DESs as green and biorenewable solvent in the synthesis of nanoparticles (NPs). Thus, in 2008, Sun and co-workers reported a novel route for the shape-controlled synthesis of gold NPs, at room temperature starting from $HAuCl_4 \cdot 4H_2O$.[235] In this case, the eutectic mixture ChCl/Urea was used in replacement of traditional surfactants. The obtained star-shaped

gold NPs exhibit high catalytic activity in H_2O_2 electrocatalytic reduction. More recently, Stassi and co-workers reported a modification of the experimental parameters for the above synthesis of gold-star NPs in eutectic mixtures.[236] Not only gold NPs but also gold nanowires can be selectively obtained in two different DESs (ChCl/Urea and ChCl/EG) by using $NaBH_4$ as reducing agent of the gold source ($HAuCl_4$). Chirea and co-workers described the synthesis of these gold nanowires, which were used as catalyst for the chemical reduction of p-nitroaniline with $NaBH_4$ in aqueous solution.[237] Also, nanoporous Ag films[238] and CuCl nanoparticles[239] were fabricated in the eutectic mixtures ChCl/EG and ChCl/Urea, respectively.

Taking into account the aforementioned capability of DESs to dissolve metal oxides, Wong and co-workers developed an environmentally benign "antisolvent approach" for the synthesis of various ZnO nanostructures, including twin-cones and nanorods with controllable dimensions.[240] In this "antisolvent" synthesis, ZnO powders were firstly dissolved in the eutectic mixture ChCl/Urea, followed by the precipitation of the ZnO nanostructures from the eutectic mixture upon addition of ethanol-water mixtures as "antisolvents". More recently, DESs have been used in the synthesis of: i) mesoporous silica (KIE-11) using the eutectic mixture ChCl/Urea as a templating agent,[241] ii) organosoluble silver nanoparticles, by using a wet chemical reduction route involving microwave (MW) heating with oleylamine acting both as a surfactant and reducing agent,[242] iii) gold nanoparticles for the development of a glucose biosensor,[243] iv) cellulose nanocrystals through a microwave-assisted DESs pretreatment followed by a high-intensity ultrasonication process,[244] v) high-index faceted gold nanocrystals,[245,246] vi) nickel/nickel nitride nanocomposites,[247] vii) cellulose nanofibrils in different urea-based-DESs,[248,249] viii) Bi_2S_3-sensitized BiOCl nanoparticles (at room temperature and in a one-pot procedure),[250] ix) magnetic nanocrystalline cellulose as supporter of papain,[251] and x) ultrathin and large gold nanosheets.[252]

Synthesis of carbon materials in DESs

In a similar way and as previously commented for metal phosphates, MOFs or nanomaterials, porous carbon materials can be obtained *via* ionothermal synthesis using DESs as green and biorenewable solvents. In this context, del Monte *et al*. reported the preparation of carbon and carbon-carbon nanotubes composites by resorcinol-formaldehyde polycondensation in the eutectic mixture ChCl/EG.[253] Following this seminal work, the same group reported the synthesis of hierarchical porous (bimodal, with micropores and mesoporous) carbon monoliths through formaldehyde condensation and subsequent carbonization in the eutectic mixtures ChCl/Resorcinol or ChCl/Urea/Resorcinol.[254] Other ternary resorcinol-based DESs (i.e., ChCl/3-hydroxipyridine/Resorcinol) have been used as both precursors and structure-directing agents in the synthesis of nitrogen-doped hierarchical carbon monoliths.[255] Finally, del Monte´s group reported the efficient synthesis of hierarchical porous multiwalled carbon nanotubes *via* furfuryl alcohol condensation using a ChCl/p-toluene sulfonic acid eutectic mixture;[256] and ii) macroporous poly(acrylic acid)-carbon nanotube composites.[202] Continuing with the aforementioned del Monte´s work, other international research groups have extended the use of DESs for the synthesis of: i) PdSn nanocatalysts supported on carbon nanotubes,[257] iii) high-index faceted platinum

concave nanocubes grown on multiwalled carbon nanotubes,[258] and iii) functionalized multiwalled carbon nanotubes *via* Diels-Alder reaction.[259]

20.3.4.6 Other applications of DESs

Similar to traditional ILs, deep eutectic solvents can dissolve a wide variety of molecules and materials of low solubility. Apart from the aforementioned capability of DESs to dissolve metal oxides, different eutectic mixtures have been used to dissolve several poorly soluble drugs like: i) benzoic acid, griseofulvin, danazol, and itraconazole,[260] ii) lidocaine hydrochloride,[261] and iii) commercially available crystalline salts of acidic or basic active pharmaceutical ingredients (APIs).[262] Also, and due to the presence of ionic species in DESs, these eutectic mixtures presented interesting solvent properties for high CO_2 dissolution. Han and co-workers reported that the solubility of CO_2 in the eutectic mixture ChCl/Urea increases by: i) increasing the CO_2 pressure, ii) decreasing the temperature, and iii) increasing the urea molar ratio in the eutectic mixture.[63] After this pioneering work, this field of research has suffer an exponential growth and since then DESs have been employed in: i) cycloaddition of CO_2 with epoxides[263-267] or aminobenzonitrile,[263] ii) efficient and reversible absorption of CO_2,[268] and iii) syngas production (by electrochemical CO_2 reduction).[269] Moreover, DESs have been also employed for the absorption of other gases, like ammonia[270] or sulfur dioxide.[271,272] In addition, different deep eutectic mixtures have been also used for the pretreatment and dissolution of naturally biopolymers like cellulose,[273-275] lignin,[276-281] xylan,[282] suberin,[283] or chitin.[284-286]

Owing to their high polarity, DESs have been also used for the separation of the residual glycerol from raw biodiesel. Abbott and co-workers reported the formation of eutectic mixtures by addition of quaternary ammonium salts (i.e., ChCl) to glycerol-containing raw biodiesel.[181] The *in situ* formed eutectic mixture (ChCl/Gly) is miscible with water and immiscible with the biodiesel. However, further studies on the nature of the eutectic mixture employed for the separation of glycerol were needed to achieve a significant decrease of glycerol in the raw biodiesel. Hayyan *et al.* demonstrated that the eutectic mixture ChCl/Gly can be used for the extraction of Gly from palm oil-derived biodiesel.[288] Later, the same research group reported that other ChCl-based eutectic mixtures (ChCl/EG and ChCl/CF_3CONH_2) can be also successfully employed for the purification of biodiesel.[289] Finally, DESs were also used in: i) the separation of aromatic hydrocarbons from naphthas,[290] ii) the extraction of benzene from benzene/hexane mixtures,[291] iii) separation of phenols from oils,[292,293] iv) adsorption of hyaluronic acid on a ChCl/Urea-modified cotton surface,[294] and v) removing the post-etch residues,[295] vi) the prevention of denaturalization of lysozyme,[296] vii) the dissolution of macrocyclic cyclodextrins and cucurbit[n]urils,[297] viii) controllable exfoliation of natural silk fibers into nanofibrils,[298] ix) extraction of artemisinin from *Artemisia annua* leaves,[299] x) extraction of DNA,[300] xi) effective denitrification and desulfurization of liquid fuel,[301] xii) extraction of collagen peptides,[302] xiii) extraction of proteins,[303] xiv) extraction of vitamin D from button mushroom (*Agaricus bisporus*),[304] xv) lipid extraction from microalga P. *Tricornutum*,[305] xvi) mechanochemical extraction of bioactive compounds from plants,[306] xvii) microextraction of polycyclic aromatic hydrocarbons from aqueous samples,[307] and xviii) polygodial extraction from pseudowintera colorata (Horopito) leaves.[308]

20.3.5 CONCLUSIONS AND FUTURE PERSPECTIVES OF DES AS NEW GREEN AND BIORENEWABLE SOLVENT

This chapter clearly exemplifies the maturity gained by Deep Eutectic Solvents as new green and biorenewable solvents in different applications of modern synthesis. As the reader have noticed, a huge number of synthetic reactions and chemical processes can be presently performed in eutectic mixtures as effectively as in classical organic media. More importantly, enhanced or completely new reactivities have been in some cases observed using DESs as a solvent. Despite all these promising applications, much effort is still needed in order to widen the utilization of DESs as green, low toxic and biocompatible reaction medium.

Certainly, the study of new synthesis and transformations in deep eutectic mixtures media will continue to be a fast-moving topic for the next several years, with the discovery of new applications being expected in the near future. In this sense, the easy fine-tuning of their physicochemical properties through the adequate selection of components [hydrogen-bond-donor (HBD) and hydrogen-bond-acceptor (HBA)], opens a new gate for the preparation of "a la carte" DESs.

20.3.6 ACKNOWLEDGMENTS

The author gratefully acknowledge the financial support from the Spanish MINECO (Projects CTQ2014-51912-REDC and CTQ2016-75986-P), the Gobierno del Principado de Asturias (Project GRUPIN14-006) and the Fundación BBVA (for the award of a "*Beca Leonardo a Investigadores y Creadores Culturales 2017*").[309]

REFERENCES

1 D. J. C. Constable, C. Jiménez-González and R. K. Henderson, *Org. Process Res. Dev*., **11**, 133 (2007).
2 J. H. Clark and S. J. Tavener, *Org. Process Res. Dev.*, **11**, 149 (2007).
3 P. G. Jessop, *Green Chem*., **13**, 1391 (2011).
4 An editorial in Organic Process Research and Development discourages chemists to use solvents that are either known to be toxic, dangerous for large scale preparations or expensive to dispose as waste. T. Laird, *Org. Process Res. Dev.*, **16**, 1 (2012)
5 C. Reichardt, **Solvents and Solvents Effects in Organic Chemistry**, *Wiley-VCH*, Weinheim, Germany, 3rd Edition, 2003.
6 P. T. Anastas, **Handbook of Green Chemistry**, Vol. 4, 5 and 6, **Green Solvents**: Volume 4: **Supercritical Solvents** (Eds. W. Leitner and P. G. Jessop); Volume 5: **Reactions in Water** (Eds. C.-J. Li); Volume 6: **Ionic Liquids** (Eds. P. Wasserschied and A. Stark); *Wiley-VCH,* Weinheim, 2010.
7 L. Moity, M. Durand, A. Benazzouz, C. Pierlot, V. Molinier and J.-M. Aubry, *Green Chem.*, **14**, 1132 (2012).
8 P. T. Anastas and J. C. Warner, **Green Chemistry Theory and Practice**, *Oxford University Press*, Oxford, 1998.
9 A. S. Matlack, **Introduction to Green Chemistry**, *Marcel Dekker*, New York, 2001.
10 M. Poliakoff, J. M. Fitzpatrick, T. R. Farren and P. T. Anastas, *Science*, **297**, 807 (2002).
11 M. Lancaster, **Green Chemistry: An Introductory Text**, *RSC Publishing*, Cambridge, 2002.
12 P. Wasserchеid and T. Welton, **Ionic Liquids in Synthesis**, *Wiley-VCH*, Weinheim, 2008.
13 J. P. Hallet and T. Welton, *Chem. Rev.*, **111**, 3508 (2011).
14 K. S. Egorova and V. P. Ananikov, *ChemSusChem*, **7**, 336 (2014).
15 P. G. Jessop, T. Ikariya and R. Noyori, *Chem. Rev*., **99**, 475 (1999).
16 C. A. M. Alfonso and J. G. Crespo, **Green Separation Processes**, *Wiley-VCH*, Weinheim-New York, 2005.
17 C.-J. Li and T.-H. Chan, **Comprehensive Organic Reactions in Aqueous Media** 2nd Edition, *Wiley*, New York, 2007.
18 P. H. Dixneuf and V. Cadierno, **Metal-Catalyzed Reactions in Water**, *Wiley-VCH*, Weinheim, Germany, 2013.

19 I. Ryu, H. Matsubara, C. Emnet, J. A. Gladysz, S. Takeuchi, Y. Nakamura and D. P. Curran, **Fluorous Solvents, in Green Reaction Media in Organic Synthesis**, *Blackwell*, Oxford, 2005.
20 M. Döbele, S. Vanderheiden, N. Jung and S. Bräse, *Angew. Chem. Int. Ed*., **49**, 5986 (2010).
21 F. Jérôme and R. Luque in **Bio-based solvents**, *Wiley*, Hoboken, USA, 2017.
22 A. P. Abbott, R. C. Harris, K. Ryder, C. D 'Agostino, L. Gladden and M. D. Mantle, *Green Chem*., **13**, 82 (2011).
23 C. Ru? and B. König, *Green Chem*., **14**, 2969 (2012).
24 D. Carriazo, M. C. Serrano, M. C. Gutiérrez, M. L. Ferrer and F. Monte, *Chem. Soc. Rev*., **41**, 4996 (2012).
25 Q. Zhang, K. De Oliveira Vigier, S. Royer and J. Jérôme, *Chem. Soc. Rev*., **41**, 7108 (2012).
26 M. Francisco, A. Van den Bruinhorst and M. C. Kroon, *Angew. Chem. Int. Ed.*, **52**, 3074 (2013).
27 E. L. Smith, A. P. Abbott and K. S. Ryder, *Chem. Rev.*, **114**, 11060, (2014).
28 J. García-Álvarez, *Eur. J. Inorg. Chem*., 5147 (2015).
29 D. A. Alonso, A. Baeza, R. Chinchilla, G. Guillena, I. M. Pastor and D. J. Ramón, *Eur. J. Org. Chem*., **612** (2016).
30 A. P. Abbott, G. Capper, D. L. Davies, R. K. Rasheed and V. Tambyrajah, *Chem. Commun*., 70 (2003).
31 A. P. Abbott, R. C. Harris, K. Ryder, C. D'Agostino, L. Gladden and M. D. Mantle, *Green Chem*., **13**, 82 (2011)
32 H. Laitinen, W. Ferguson and R. Osteryoung, *J. Electrochem. Soc*., **104**, 516 (1957).
33 F. Duke and M. Iverson, *J. Phys. Chem*., **62**, 417 (1958).
34 M. Gambino, P. Gaune, M. Nabavian, M. Gaune-Escard and J. Bros, *Thermochim. Acta*, **111**, 37 (1987).
35 R. Rastogi and P. S. Bassi, *J. Phys. Chem.*, **68**, 2398 (1964).
36 P. S. Savchenco, *Russ. J. Inorg. Chem*., **4**, 186 (1959).
37 O. S. Hammond, D. T. Brown and K. J. Edler, *Green Chem*., **18**, 2736 (2016).
38 O. S. Hammond, D. T. Brown and K. J. Edler, *Angew. Chem. Int. Ed*., **56**, 9782 (2017).
39 A. P. Abbott, J. C. Barron, K. S. Ryder and D. Wilson, *Chem. Eur. J*., **13**, 6495 (2007).
40 J. K. Blusztajn, *Science*, **281**, 794 (1998).
41 M. Petkovic, J. L. Ferguson, H. Q. N. Gunaratne, R. Ferreira, M. C. Leitão, K. R. Seddon, L. P. N. Rebelo and C. S. Pereira, *Green. Chem*., **12**, 643 (2010).
42 M. Hayyan, M. A. Hashim, A. Hayyan, M. A. Al-Saadi, I. M. Al Nashef, M. E. S. Mirghani and O. K. Saheed, *Chemosphere*, **90**, 2193 (2013).
43 Y. Fukaya, Y. Izuka, K. Sekikawa and H. Ohno, *Green Chem*., **9**, 1155, (2007).
44 Y. Xu, X. Lu, Q. Zhou, K. Dong, H. Yao and S. Zhang, *Chem. Eur. J*., **14**, 11174 (2008).
45 Y. H. Choi, J. van Spronsen, Y. Dai, M. Verberne, F. Hollmann, I. W. C. E. Arends, G. J. Witkamp and R. Verpoorte, *Plant. Physiol.*, **156**, 1701 (2011).
46 A. Paiva, R. Craveiro, I. Aroso, M. Martins, R. L. Reis and A. R. C. Duarte, *ACS Sustainable Chem. Eng*. **2**, 1063 (2014).
48 A. P. Abbott, D. Boothby, G. Capper, D. L. Davies and R. K. Rasheed, *J. Am. Chem. Soc*., **126**, 9142 (2004).
49 Z. Maugeri and P. Domínguez de María, *RSC Adv*., **2**, 421 (2012)
44 Carboxylic acids and sugar polyols have been described as the HBD that lead to the lowest melting point for a selected acceptor salt (HBA). See ref. 24.
50 M. A. Kareem, F. S. Mjalli, M. A. Hashim and I. M. AlNashef, *J. Chem. Eng. Data*, **55**, 4632 (2010).
51 K. Shahbaz, S. Baroutian, F. S. Mjalli and M. A. AlNashef, *Thermochim. Acta*, **527**, 59 (2012).
52 R. B. Leron, A. N. Soriano and M. Li, *J. Taiwan Int. Chem. Eng*., **43**, 551 (2012).
53 K. Shahbaz, F. S. Mjalli, M. A. Hashim and I. M. AlNashef, *Fluid Phase Equilib*., **319**, 48 (2012).
54 K. Shahbaz, F. S. Mjalli, M. A. Hashim and I. M. AlNashef, *Thermochim. Acta*, **515**, 67 (2011).
55 It has been demonstrated that, by using molecular dynamics (MD) simulations, the insertion of the urea in DESs could change the density distribution of cations and anions of the eutectic mixture and disrupt the structure of ChCl. H. Sun, Y. Li, X. Wu and G. Li, *J. Mol. Model.*, **19**, 2433 (2013).
56 A. P. Abbott, *ChemPhysChem*, **5**, 1242 (2004).
57 A. P. Abbott, R. C. Harris and K. S. Ryder, *J. Phys. Chem. B*, **111**, 4910 (2007).
58 G. Law and P. R. Watson, *Langmuir*, **17**, 6138 (2001).
59 C. Reichardt, **Solvent Effects on the Rates of Homogeneous Chemical Reactions**, *Wiley-VCH Verlag GmbH&Co KGaA*, Weinheim, Germany, 2004.
60 C. Reichardt, *Chem. Rev*., **94**, 2319 (1994).
61 A. P. Abbott, G. Capper and G. Gray, *ChemPhysChem*, **7**, 803 (2006).
62 A. P. Abbott, J. C. Barron, G. Frisch, S. Gurman, K. S. Ryder and A. F. Silva, *Phys. Chem. Chem. Phys*, **13**, 10224 (2011).

63 W. Li, Z. Zhang, B. Han, S. Hu, J. Song, Y. Xie and X. Zhou, *Green Chem*., **10**, 1142 (2008).
64 Q. Wen, J.-X. Chen, Y.-L. Tang, J. Wang and Z. Yang, *Chemosphere*, **132**, 63 (2015).
65 K. Radoševic, M. C. Bubalo, V. G. Srcek, D. Grgas, T. L. Dragicevic and I. R. Redovnikovic, *Ecotoxicol. Environ. Saf*., **112**, 46 (2015).
66 S. B. Phadtare and G. S. Shankarling, *Green Chem*., **12**, 458 (2010).
67 P. M. Pawar, K. J. Jarag and G. S. Shankarling, *Green Chem*., **13**, 2130 (2011).
68 As compare to the conventional route, the Perkin reaction in the eutectic mixture 1ChCl/2Urea proceed in a much lower temperature (30ºC vs. 140ºC).
69 Y. A. Sonawane, S. B. Phadtare, B. N. Borse, A. R. Jagtap and G. S. Shankarling, *Org. Lett.*, **12**, 1456 (2010).
70 B. S. Singh, H. R. Lobo and G. S. Shankarling, *Catal. Lett.*, **141**, 178 (2011).
71 N. Azizi, E. Batebi, S. Bagherpour and H. Ghafuri, *RSC Adv*., **2**, 2289 (2012).
72 Z.-H. Zhang, X.-N. Zhang, L.-P. Mo, Y.-X. Li and F.-P. Ma, *Green Chem*., **14**, 1502 (2012).
73 S. Gore, S. Baskaran and B. König, *Green Chem*., **13**, 1009 (2011).
74 N. Azizi and E. Gholibeglo, *RSC Adv*., **2**, 7413 (2012).
75 N. Azizi, M. Khajeh, M. Hasani and S. Dezfooli, *Tetrahedron Lett.*, **54**, 5407 (2013).
76 B. S. Singh, H. R. Lobo and G. S. Shankarling, *Catal. Commun*., **24**, 70 (2012).
77 B. S. Singh, H. R. Lobo, D. V. Pinjari, K. J. Jaraga, A. B. Pandit and G. S. Shankarling, *Ultrason. Sonochem*., **20**, 287 (2013).
78 B. S. Singh, H. R. Lobo, D. V. Pinjari, K. J. Jaraga, A. B. Pandit and G. S. Shankarling, *Ultrason. Sonochem*., **20**, 633 (2013).
79 H. R. Lobo, B. S. Singh and G. S. Shankarling, *Green Chem. Lett. Rev*., **5**, 487 (2012).
80 N. Azizi and Z. Manocheri, *Res. Chem. Intermed.*, **38**, 1495 (2012).
81 S. B. Phadtare, K. J. Jarag and G. S. Shankarling, *Dyes Pigm*., **97**, 105 (2013).
82 B. N. Borse, S. R. Shukla, Y. A. Sonawane and G. S. Shankerling, *Synth. Commun*., **43**, 865 (2013).
83 A. Mobinikhaledi and A. K. Amiri, *Res. Chem. Intermed*., **39**, 1491 (2013).
84 S. Handy and K. Lavender, *Tetrahedron Lett*., **54**, 4377 (2013).
85 G. Imperato, E. Eibler, J. Niedermaier and R. König, *Chem. Commun*., 1170 (2005).
86 P. Liu, J.-W. Hao, L.-P. Mo and Z.-H. Zhang, *RSC Adv*., **5**, 48675 (2015).
87 P. Domínguez de María and Z. Maugeri, *Curr. Opin. Chem. Biol*., **15**, 220 (2011).
88 J. T. Gorke, F. Srienc and R. J. Kazlauskas, *Biotechnol. Bioprocess Eng*., **15**, 40 (2010).
89 J. T. Gorke, F. Srienc and R. J. Kazlauskas, *Chem. Commun*., 1235 (2008).
90 D. Lindberg, M. de la Fuente Revenga and M. Widersten, *J. Biotechnol*., **147**, 169 (2010).
91 H. Zhao, G. A. Baker and S. Holmes, *Org. Biomol. Chem*., **9**, 1908 (2011).
92 B. N. Borse, V. S. Borude and S. R. Shukla, *Curr. Chem. Lett*., **1**, 59 (2012).
93 H. Zhao, G. A. Baker and S. Holmes, *J. Mol. Catal. B: Enzymatic*, **72**, 163 (2011)
94 M. C. Gutierrez, M. L. Ferrer, L. Yuste, F. Rojo and F. Monte, *Angew. Chem. Int. Ed*., **49**, 2159 (2010).
95 I. Mamajanov, A. E. Engelhardt, H. D. Bean and N. V. Hud, *Angew. Chem. Int. Ed.*, **49**, 6310 (2010).
96 C. Lehmann, F. Sibilla, Z. Maugeri, W. R. Streit, P. Domínguez de María, R. Martinez and U. Schwaneberg, *Green Chem*., **14**, 2719 (2012).
97 Z. Maugeri and P. Domínguez de María, *J. Mol. Catal. B*, **107**, 120 (2014).
98 Z. Maugeri and P. Domínguez de María, *ChemCatChem*, **6**, 1534 (2014).
99 C. R. Miller, I. Lavandera, V. Gotor-Fernández and P. Domínguez de María, *ChemCatChem*, **7**, 2654 (2015).
100 C. Müller, I. Meiners and P. Domínguez de María, *RSC Adv*., **4**, 46097 (2014).
101 P. Xu, Y. Xu, X.-F. Li, B.-Y. Zhao, M.-H. Zong and W.-Y. Lou, *ACS Sustainable Chem. Eng*., **3**, 718 (2015).
102 J. Donnelly, C. R. Müller, L. Wiermans, C. J. Chuckand and P. Domínguez de María, *Green Chem*., **17**, 2714 (2015).
103 G. Weiz, L. Braun, R. López, P. Domínguez de María and J. D. Breccia, *J. Mol. Catal. B: Enzym*., **130**, 70 (2016).
104 P. Vitale, V. Abbinante, M. Vicenzo, F. M. Perna, A. Salomone, C. Cardellichio and V. Capriati, *Adv. Synth. Catal*., **359**, 1049 (2017).
105 P. Zhou, X. Wang, B. Yang, F. Hollmann and Y. Wang, *RSC Adv*., **7**, 12518 (2017).
106 N. Guajardo, P. Domínguez de María, K. Ahumada, R. A. Schrebler, R. Ramírez-Tagle, F. Crespo and C. Carlesi, *ChemCatChem*, **9**, 1393 (2017).
107 P. Vitale, F. M. Perna, G. Agrimi, I. Pisano, F. Mirizzi, R. V. Capobianco and V. Capriati, *Catalysts*, **8**, 55 (2018).
108 HMF is a valuable molecule platform, especially for the fabrication of safer polymers and fuel additives.

See for example: R. Karinen, K. Vilonen and M. Niemelä, *ChemSusChem*, **4**, 1002 (2011).
109 S. Hu, Z. Zhang, Y. Zhou, B. Han, H. Fan, W. Li, J. Song and Y. Xie, *Green Chem*., **10**, 1280 (2008).
110 F. Illgen, D. Ott, D. Kralisch, C. Reil, A. Palmberger and B. König, *Green Chem*., **11**, 1948 (2009).
111 K. de Oliveira Vigier, V. A. Benguerba, J. Barrault and F. Jérôme, *Green Chem*., **14**, 285 (2012).
112 A. P. Abbott, A. D. Ballantyne, J. Palenzuela Conde, K. S. Ryder and W. R. Wise, *Green Chem*., **14**, 1302 (2012).
113 Y. Nishihara, **Applied Cross-Coupling Reactions**, *Springer*, Berlin, 2013.
114 F. Ilgen and B. König, *Green Chem.*, **11**, 848 (2009).
115 G. Imperato, R. Vasold and B. König, *Adv. Synth. Catal*., **348**, 2243 (2006).
116 G. Imperato, S. Höger, D. Leinor and B. König, *Green Chem.,* **8**, 1051 (2006).
117 V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, *Angew. Chem. Int. Ed*., **41**, 2596 (2002)
118 C. W. Tornøe, C. Christensen and M. Meldal, *J. Org. Chem*., **67**, 3057 (2002).
119 C. Vidal, F. J. Suárez, J. García-Álvarez, *Catal. Commun*., **44**, 76 (2014).
120 F. Jérôme, M. Ferreira, H. Bricout, S. Menuel, E. Monflier and S. Tilloy, *Green Chem*., **16**, 3876 (2014).
121 M. Ferreira, F. Jérôme, H. Bricout, S. Menuel, D. Landy, S. Fourmentin, S. Tilloy and E. Monflier, *Catal. Commun*., **63**, 62 (2015).
122 J. Lu, X.-T. Li, E.-Q. Ma, L.-P. Mo and Z.-H. Zhang, *ChemCatChem*, **6**, 2854 (2014).
123 M. J. Rodríguez-Álvarez, C. Vidal, J. Díez and J. García-Álvarez, *Chem. Commun.*, **50**, 12927 (2014).
124 C. Vidal, L. Merz and J. García-Álvarez, *Green Chem*., **17**, 3870 (2015).
125 M. J. Rodríguez-Álvarez, C. Vidal, S. Schumacher, J. Borge and J. García-Álvarez, *Chem. Eur. J.*, **23**, 3425 (2017).
126 N. Guajardo, C. Carlesi and A. Aracena, ChemCatChem, **7**, 2451 (2015).
127 X. Marset, J. M. Pérez and D. J. Ramón, *Green Chem*., **18**, 826 (2016).
128 R. Mancuso, A. Maner, L. Cicco, F. M. Perna, V. Capriati and B. Gabriele, *Tetrahedron*, **72**, 4239 (2016).
129 X. Marset, A. Khoshnood, L. Sotorríos, E. Gómez-Bengoa, D. A. Alonso and D. J. Ramón, *ChemCatChem*, **9**, 1269 (2017).
130 M. Iwanow, J. Finkelmeyer, A. Söldner, M. Kaiser, T. Gärtner, V. Sieber and B. König, *Chem. Eur. J*., **23**, 12467 (2017).
131 X. Marset, G. Guillena and D. J. Ramón, *Chem. Eur. J*., **23**, 10522 (2017).
132 F. Messa, S. Perrone, M. Capua, F. Tolomeo, L. Troisi, V. Capriati, A. Salomone, *Chem. Commun*., **54**, 8100 (2018).
133 C. Vidal, J. García-Álvarez, A. Hernán-Gómez, A. R. Kennedy and E. Hevia, *Angew. Chem. Int. Ed*., **53**, 5969 (2014).
134 V. Mallardo, R. Rizzi, F. C. Sassone, R. Mansueto, F. M. Perna, A. Salomone and V. Capriati, *Chem. Commun.*, **50**, 8655 (2014).
135 F. C. Sassone, F. M. Perna, A. Salomone, S. Florio and V. Capriati, *Chem. Commun*., **51**, 9459 (2015).
136 L. Cicco, S. Sblendorio, R. Mansueto, F. M. Perna, A. Salomone, S. Florio and V. Capriati, *Chem. Sci*., **7**, 1192 (2016).
137 C. Vidal, J. García-Álvarez, A. Hernán-Gómez, A. R. Kennedy and E. Hevia, *Angew. Chem. Int. Ed*., **55**, 16145 (2016).
138 M. J. Rodríguez-Álvarez, J. García-Álvarez,* M. Uzelac, M. Fairley, C. T. O'Hara, and E. Hevia, *Chem. Eur. J*., **24**, 1720 (2018).
139 J. García-Álvarez, E. Hevia, V. Capriati, *Chem Eur. J*., DOI: 10.1002/chem.201802873.
140 L. Cicco, M. J. Rodríguez-Álvarez, F. M. Perna, J. García-Álvarez and V. Capriati, *Green Chem*., **19**, 3069 (2017).
141 L. Cicco, N. Ríos-Lombardía, M. J. Rodríguez-Álvarez, F. Morís, F. M. Perna, V. Capriati, J. García-Álvarez and J. González-Sabín, *Green Chem*., **20**, 3468 (2018).
142 P. I. Dalko and L. Moisan, *Angew. Chem. Int. Ed.*, **43**, 5138 (2004).
143 O. Coulembier, V. Leumar, T. Josse, A. Minoia, J. Cornil and P. Dubois, *Chem. Sci.*, **3**, 723 (2012).
144 E. Masolo, S. Palmieri, M. Benaglia, V. Capriati and F. M. Perna, *Green Chem*., **18**, 792 (2016).
145 N. Fanjul-Mosteirín, C. Concello?n and V. del Amo, *Org. Lett.*, **18**, 4266 (2016).
146 R. Martínez, L. Berbegal, G. Guillena and D. J. Ramón, *Green Chem.*, **18**, 1724 (2016).
147 D. Brenna, E. Massolo, A. Puglisi, S. Rossi, G. Celentano, M. Benaglia and V. Capriati, *Beilstein J. Org. Chem*., **12**, 2620 (2016).
148 D. Ros Níguez, G. Guillena and D. A. Alonso, *ACS Sustainable Chem. Eng*., **5**, 10649 (2017).
149 A. P. Abbott, G. Capper and P. Shikrota, *Trans. Inst. Min. Metall., Sect. C*, **115**, 15 (2006).
150 For a systematic study of the solubility of transition metal oxides of the Period 4th of the periodic table see: A. P. Abbott, G. Capper, D. L. Davies, K. J. McKenzie and S. U. Obi, *J. Chem. Eng. Data*, **51**, 1280 (2006).

151 S. Riaño, M. Petranikova, B. Onghena, T. Vander Hoogerstraete, D. Banerjee, M. R. StJ. Foreman, C. Ekberg and K. Binnemans, *RSC Adv*., **7**, 32100 (2017).
152 A. P. Abbott, A. Z. M. Al-Bassam, A. Goddard, R. C. Harris, G. R. T. Jenkin, F. J. Nisbet and M. Wieland, *Green Chem*., **19**, 2225 (2017).
153 A. Söldner, J. Zach, M. Iwanow, T. Gärtner, M. Schlosser, A. Pfitzner and B. König, *Chem. Eur. J*., **22**, 13108 (2016).
154 H.-R. Jhong, D. Shan-Hill Wog, C.-C. Wan, Y.-Y. Wang and T.-C. Wei, *Electrochem. Commun*., **11**, 209 (2009).
155 C. L. Boldrini, N. Manfredi, F. M. Perna, V. Capriati and A. Abbotto, *Chem. Eur. J*., DOI: 10.1002/chem.201803668
156 A. P. Abbott, G. Capper, K. J. McKenzie and K. S. Ryder, *Electrochim. Acta*, **51**, 4420 (2006).
157 A. P. Abbott, G. Capper, K. J. McKenzie, A. Glidle and K. S. Ryder, *Phys. Chem. Chem. Phys*., **8**, 4214 (2006).
158 L. Millia, V. Dall'Asta, C. Ferrara, V. Berbenni, E. Quartarone, F. M. Perna, V. Capriati, P. Mustarelli, *Solid State Ionics*, **323**, 44 (2018).
159 B. Joos, T. Vranken, W. Marchal, M. Safari, M. K. Van Bael and A. T. Hardy, *Chem. Mater.*, **30**, 655 (2018).
160 A. Boisset, S. Menne, J. Jacquemin, A. Balducci and M. Anouti, *Phys. Chem. Chem. Phys*., **15**, 20054 (2013).
161 A. P. Abbott, G. Frisch, S. J. Gurma, A. R. Hilman, J. Hartley, F. Holyoak and K. S. Ryder, *Chem. Commun*., **47**, 10031 (2011).
162 For a general overview in electrodeposition and functional coating employing Deep Eutectic Solvents as electrolytes, see: R. Bernasconi, G. Panzeri, A. Accogli, F. Liberale, L. Niobili and L. Magagnin, **Electrodeposition from Deep Eutectic Solvents, in Progress and Developments in Ionic Liquids** (Ed. S. Handy); *IntechOpen Limited*, London, 2017.
163 E. Gómez, P. Cojocaru, L. Magagnin and E. Vallés, *J. Electroanal. Chem*., **658**, 18 (2011).
164 P. Guillamatt, M. Cortés, E. Vallés and E. Gómez, *Surf. Coat Tech*., **206**, 4439 (2012).
165 E. Gómez, E. Vallés, E. Cojocaru, P. Raygani and L. Magagnin, *ECS Trans*., **41**, 3 (2012).
166 D. D. Shivagan, P. J. Dale, A. P. Samantilleke and L. M. Peter, *Thin Solid Films*, **515**, 5899 (2007).
167 M. Steichen, M. Thomassey, S. Siebentritt and P. J. Dale, Phys. *Chem. Chem. Phys.*, **13**, 4292 (2011).
168 H. Yang, X. Guo, N. Birbilis, G. Wu and W. Ding, *Appl. Surf. Sci*., **257**, 9094 (2011).
169 P. Martis, V. S. Dilimon, J. Delhalle and Z. Mekhalif, *Electrochim. Acta*, **55**, 5407 (2010).
170 A. P. Abbott, K. El Ttaib, K. S. Ryder and E. L. Smith, *Trans. Inst. Met. Finish.*, **86**, 234 (2010).
171 H. Y. Yang, W. Guo, X. B. Chen, S. H. Wang, G. H. Wu, W. J. Ding and N. Birbilis, *Electrochim. Acta*, **63**, 131 (2012).
172 A. Bakkar and V. Neubert, *Electrochem. Commun*., **9**, 2428 (2007).
173 Deposition of Zn, Sn and Zn/Sn alloys from different DESs (ChCl/Urea and ChCl/EG) has been reported in: A. P. Abbott, G. Capper, K. J. McKenzie and K. S. Ryder, *J. Electroanal. Chem*., **599**, 288 (2007).
174 P. Dale, A. P. Samantilleke, D. D. Shivagan and L. M. Peter, *Thin Solid Films*, **515**, 5751 (2007).
175 M. Bougouma, A. V. Elewyck, M. Steichen, C. Buess-Herman and T. Doneux, *J. Solid State Electrochem*., **17**, 527 (2013).
176 S. Wang, X. Zou, Y. Lu, S. Rao, X. Xie, Z. Pang, X. Lu, Q. Xu and Z. Zhou, *Int. J. Hydrogen Energy*, **43**, 15673 (2018).
177 E. L. Smith, J. C. Barron, A. P. Abbott and K. S. Ryder, *Anal. Chem*., **81**, 8466 (2009).
178 A. P. Abbott, J. C. Barron, G. Frisch, K. S. Ryder and A. Fernando Silva, *Electrochim. Acta*, **56**, 5272 (2011).
179 A. Sun, H. Zhao and J. Zheng, *Talanta*, **88**, 259 (2012).
180 A. P. Abbott, K. El Ttaib, G. Frisch and K. J. McKenzie, *Phys. Chem. Chem. Phys.*, **11**, 4269 (2009).
181 D. Lloyd, T. Vanikka, L. Murtomäki, K. Kontturi and E. Ahlberg, *Electrochim. Acta*, **56**, 4942 (2011).
182 A. P. Abbott, S. Nandhra, S. Postlethwark, E. Smith and K. S. Ryder, *Phys. Chem. Chem. Phys*., **9**, 3735 (2007).
183 A. P. Abbott, K. Et Ttaib, G. Frisch, K. S. Ryder and D. Weston, *Phys. Chem. Chem. Phys*., **14**, 2443 (2012).
184 C. D. Gu, X. J. Xu and J. P. Tu, *J. Phys. Chem*., **114**, 13164 (2010).
185 C. Gu and J. Tu, *Langmuir*, **27**, 10132 (2011).
186 Y. You, C. Gu, X. Wang and J. Tu, *J. Electrochem. Soc.*, **159**, D642 (2012).
187 Y. You, C. Gu, X. Wang and J. Tu, *Int. J. Electrochem. Sci.*, **7**, 12440 (2012).
188 G. Saravanan and S. Mohan, *J. Alloys Compounds*, **522**, 162 (2012).

189 L. Bahadori, N. S. A. Manan, M. H. Chakrabarti, M. A. Hashim, F. S. Mjalli, I. M. AlNashef, M. A. Hussain and C. T. J. Low, *Phys. Chem. Chem. Phys*., **15**, 1707 (2013).
190 M. A. Skopek, M. A. Mohamoud, K. S. Ryder and A. R. Hillman, *Chem. Commun*., 935 (2009).
191 M. Figueiredo, C. Gomes, E. Costa, A. Martins, C. M. Pereira and F. Silva, *Electrochim. Acta*, **54**, 2630 (2009).
192 B. G. Pollet, J. Y. Hihn and T. J. Mason, *Electrochim. Acta*, **53**, 4248 (2008).
193 C. A. Nkuku and R. J. LeSuer, *J. Phys. Chem. B*, **111**, 13271 (2007).
194 A. P. Abbott, G. Capper, D. L. Davies and R. K. Rasheed, *Chem. Eur. J*., **10**, 3769 (2004).
195 K. Rong, L. Huang, H. Zhang, J. Zhai, Y. Fang and S. Dong, *Chem. Commun*., **54**, 8853 (2018).
196 For outstanding reviews in the synthesis of polymeric materials in DESs see references 24, 197 and 198.
197 F. del Monte, D. Carriazo, M. C. Serrano, M. C. Gutierrez and M. L. Ferrer, *ChemSusChem*, **7**, 999 (2014).
198 J. D. Mota-Morales, R. J. Sánchez-Leija, A. Carranza, J. A. Pojman, F. del Monte and G. Luna-Barcenas, *Prog. Polym. Sci.*, **78**, 139 (2018).
199 J. D. Mota-Morales, M. C. Gutiérrez, I. C. Sánchez, G. Luna-Bárcenas and F. Monte, *Chem. Commun*., **47**, 5328 (2011).
200 J. D. Mota-Morales, M. C. Gutiérrez, M. L. Ferrer, I. C. Sánchez, E. A. Elizade-Pena, J. A. Pojman, F. Monte and G. Luna-Bárcenas, *Int. J. Poym. Sci. A Polym. Chem*., **51**, 1767 (2013).
201 M. C. Serrano, M. C. Gutiérrez, R. Jiménez, M. L. Ferrer and F. Monte, *Chem. Commun*., **48**, 579 (2012).
202 J. D. Mota-Morales, M. C. Gutiérrez, M. L. Ferrer, R. Jiménez, P. Santiago, I. C. Sánchez, M. Terrones, F. Monte and G. Luna-Bárcenas, *J. Mat. Chem. A*, **1**, 3970 (2013).
203 P. M. V. Fernandes, J. M. Campiña, N. M. Pereira, C. M. Pereira and F. Silva, *J. Appl. Electrochem*., **42**, 997 (2012).
204 S. Ramesh, R. Shanti and E. Morris, *Carbohydr. Polym*., **87**, 701 (2012).
205 S. Ramesh, R. Shanti and E. Morris, *Carbohydr. Polym.*, **91**, 14 (2013).
206 E. Leroy, P. Decaen, P. Jacquet, G. Coativy, B. Pontoire, A. L. Reguerre and D. Lourdin, *Green Chem.*, **14**, 3063 (2012).
207 S. Bednarz, A. Wesolowska, M. Tr?tnowiecka and D. Bogdal, *J. Renew. Mat*., **4**, 18 (2016).
208 R.-ai Li, K. Zhang, G. Chen, B. Su, J. Tian, M. He and F. Lu, *Chem. Commun*., **54**, 2304 (2018).
209 K. F. Fazende, M. Phachansitthi, J. D. Mota-Morales, J. A. Pojman, *J. Polym. Sci. A: Polym. Chem*., **55**, 4046 (2017).
210 T.-J. Park and S. H. Lee, *Green Chem*., **19**, 910 (2017).
211 R. J. Sanchez-Leija, J. R. Torres-Lubian, A. Resendiz-Rubio, G. Luna-Barcenas and J. D. Mota-Morales, *RSC Adv*., **6**, 13072 (2016).
212 For an exceptional and complete review in the synthesis of inorganic materials in DESs see ref. 25.
213 E. R. Cooper, C. D. Andrews, P. S. Wheatley, P. B. Webb, P. Wormald and R. E. Morris, *Nature*, **430**, 1012 (2004).
214 J. Liao, P. Wu and Y. Bai, *Inorg. Chem. Commun*., **8**, 390 (2005).
215 M. M. Carvalho, L. A. M. Ruotolo and R. Fernández-Felisbino, *Microporous Mesoporous Mat.*, **165**, 163 (2013).
216 Z. Lin, D. S. Wragg, P. Lightfoot and R. E. Morris, *Dalton Trans*., **27**, 5287 (2009).
217 E. R. Parnham, E. A. Drylie, P. S. Wheatley, A. M. Z. Slawin and R. E. Morris, *Angew. Chem*., **118**, 5084 (2006).
218 E. A. Drylie, D. S. Wragg, E. R. Parnham, P. S. Wheatley, A. M. Z. Slawin, J. E. Warren and R. E. Morris, *Angew. Chem. Int. Ed*., **46**, 7839 (2007).
219 L. Liu, Y. Kong, H. Xu, J. P. Li, J. X. Dong and Z. Lin, *Microporous Mesoporous Mat*., **115**, 624 (2008).
220 P.-C. Jhang, N.-T. Chuang and S.-L. Wang, *Angew. Chem. Int. Ed.*, **49**, 4200 (2010).
221 L. Liu, Z.-F. Chen, H.-B. Wei, Y. Li, Y.-C. Fu, H. Xu, J.-P. Li, A. M. Z. Slawin and J. X. Dong, *Inorg. Chem*., **49**, 8270 (2010).
222 L. Liu, J. Yang, J. Li, J. X. Dong, D. Šišak, M. Luzzatto and L. B. McCusker, *Angew. Chem. Int. Ed*., **50**, 8139 (2011).
223 H.-L. Huang, Y.-C. Lai, Y.-W. Chiang and S.-L. Wang, *Inorg. Chem*., **51**, 1986 (2012).
224 F. Gao, L. Huang, Y. Ma, S. Jiao, Y. Jiang and Y. Bi, *J. Solid State Chem.*, **254**, 155 (2017).
225 L. Zhang, S. Li, L. Liu, J. Dong and Z. Lin, *CrystEngComm*, **19**, 2500 (2017).
226 Y. Meng, Y.-C. Chen, Z.-M. Zhang, Z.-J. Lin and M.-L. Tong, *Inorg. Chem*., **53**, 9052 (2014).
227 L. R. MacGillivray, **Metal-Organic Frameworks:Design and Application**; *Wiley-Interscience*: New York, 2010.
228 M. Schroder, **Functional Metal-Organic Frameworks: Gas Storage, Separation and Catalysis**; *Springer*: New York, 2010.

229 J. Zhang, T. Wu, S. Chen, P. Feng and X. Bu, *Angew. Chem. Int. Ed*., **48**, 3486 (2009).
230 J. Zhang, J. T. Bu, S. Chen, T. Wu, S. Zheng, Y. Chen, R. A. Nieto, P. Feng and X. Bu, *Angew. Chem. Int. Ed.*, **49**, 8876 (2010).
231 F. H. Aidoudi, P. J. Byrne, P. K. Allan, S. J. Teat, P. Lightfoot and R. E. Morris, *Dalton Trans.*, **40**, 4324 (2011).
232 Y.-H. Li, S.-L. Wang, Y.-C. Su, B.-T. Ko, C.-Y. Tsai and C.-H. Lin, *Dalton Trans*., **47**, 9474 (2018).
233 S.-L. Cao, D.-M. Yue, X.-H. Li, T. J. Smith, N. Li, M.-H. Zong, H. Wu, Y.-Z. Ma and W.-Y. Lou, *ACS Sustainable Chem. Eng*., **4**, 3586 (2016).
234 G. A. Ozin, A. C. Arsenault and L. Cademartiti, **Nanochemistry A Chemical Approach to Nanomaterials**. *The Royal Society of Chemistry*, 2nd Ed., 2009.
235 H.-G. Liao, Y.-X. Jiang, Z.-Y. Zhou, S.-P. Chen and S.-G. Sun, *Angew. Chem. Int. Ed*., **47**, 9100 (2008).
236 S. Stassi, V. Cauda, G. Canavese, D. Manfredi and C. F. Pirri, *Eur. J. Inorg. Chem.*, 2669 (2012).
237 M. Chirea, A. Freitas, B. S. Vasile, C. Ghitulica, C. M. Pereira and F. Silva, *Langmuir*, **27**, 3906 (2011).
238 C. Gu, X. Xu and J. Tu, *J. Phys. Chem. C,* **114**, 13614 (2010).
239 Y. Huang, F. Shen, J. La, G. Luo, J. Lai, C. Liu and G. Chu, *Part. Sci. Technol*., **31**, 18 (2013).
240 J.-Y. Dong, Y.-J. Hsu, D. S.-H. Wong and S.-Y. Lu, *J. Phys. Chem. C*, **114**, 8867 (2010).
241 D.-W. Lee, M.-H. Jin, J.-H. Park, Y.-J. Lee, Y.-C. Choi, J. Chan Park and D. H. Chun, *ACS Sustainable Chem. Eng.,* **6**, 12241 (2018).
242 L. Adhikari, N. E. Larm, N. Bhawawet and Gary A. Baker, *ACS Sustainable Chem. Eng.,* **6**, 5725 (2018).
243 S. Kumar-Krishnan, M. Guadalupe-Ferreira García, E. Prokhorov, M. Estevez-González, R. Pérez, R. Esparza and M. Meyyappanc, *J. Mater. Chem. B*, **5**, 7072 (2017).
244 Y. Liu, B. Guo, Q. Xia, J. Meng, W. Chen, S. Liu, Q. Wang, Y. Liu, J. Li, and H. Yu, *ACS Sustainable Chem. Eng*., **5**, 7623 (2017).
245 L. Wei, T. Sheng, J.-Y. Ye, B.-A. Lu, N. Tian, Z.-Y. Zhou, X.-S. Zhao and S.-G. Sun, *Langmuir*, **33**, 6991 (2017).
246 A. Li, Y. Chen, W. Duan, C. Wang and K. Zhuo, *RSC Adv*., **7**, 19694 (2017).
247 S. H. Gage, D. A. Ruddy, S. Pylypenko and R. M. Richards, *Catal. Today*, 306, **9** (2018).
248 P. Li, J. A. Sirvio?, A. Haapala and H. Liimatainen, *ACS Appl. Mater. Interfaces*, **9**, 2846 (2017).
249 T. Selkälä, J. A. Sirviö, G. S. Lorite and H. Liimatainen, *ChemSusChem*, **9**, 3074 (2016).
250 V. C. Ferreira, M. C. Neves, A. R. Hillman and O. C. Monteiro, *RSC Adv*., **6**, 77329 (2016).
251 S.-L. Cao, H. Xu, X.-H. Li, W.-Y. Lou and M.-H. Zong, *ACS Sustainable Chem. Eng*., **3**, 1589 (2015).
252 M. Tohidi, F. A. Mahyari and A. Safavi, *RSC Adv.*, **5**, 32744 (2015).
253 M. C. Gutiérrez, F. Rubio and F. Monte, *Chem. Mater*., **22**, 2711 (2010).
254 D. Carriazo, M. C. Gutiérrez, M. L. Ferrer and F. Monte, *Chem. Mater*., **22**, 6146 (2010).
255 M. C. Gutiérrez, D. Carriazo, C. O Ania, J. B. Parra, M. L. Ferrer and F. Monte, *Energy Environ. Sci*., **4**, 3535 (2011).
256 M. C. Gutiérrez, D. Carriazo, A. Tamayo, R. Jiménez, F. Pico, J. M. Rojo, M. L. Ferrer and F. Monte, *Chem. Eur. J*., **17**, 10533 (2011).
257 R.-X. Wang, Y.-J. Fan, Z.-R. Liang, J.-M. Zhang, Z.-Y. Zhou, S.-G. Sun, *RSC Adv*., **6**, 60400 (2016).
258 L. Wei, K. Liu, Y.-J. Mao, T. Sheng, Y.-S. Wei, J.-W. Li, X.-S. Zhao, F.-C. Zhu, B.-B. Xu and S.-G. Sun, *Phys. Chem. Chem. Phys.*, **19**, 31553 (2017).
259 C. M. Q. Le, X. T. Cao, T. T. K. Tu, T. K. Trang, W.-K. Lee and K. T. Lim, *Appl. Surf. Sci*., **450**, 122 (2018).
260 H. G. Morrison, C. C. Sun and S. Neervannan, *Int. J. Pharm*., **378**, 136 (2009).
261 R. J. Sanchez-Leija, J. A. Pojman, G. Luna-Barcenas and J. D. Mota-Morales, *J. Mater. Chem. B*, **2**, 7495 (2014).
262 H. Wang, G. Gurau, J. Shamshina, O. A. Cojocaru, J. Janikowski, D. R. MacFarlane, J. H. Jr Davis and R. D. Rogers, *Chem. Sci.*, **5**, 3449 (2014).
263 V. B. Saptal and B. M. Bhanage, *ChemSusChem*, **10**, 1145 (2017).
264 H. Lu, K. Wu, Y. Zhao, L. Hao, W Liao, C. Deng and W. Ren, *J. CO_2 Util*., **22**, 400 (2017).
265 Y.-H. Li, S.-L. Wang, Y.-C. Su, B.-T. Ko, C.-Y. Tsai and C.H. Lin, *Dalton Trans*., **47**, 9474 (2018).
266 K. Wu, T. Su, D. Hao, W. Liao, Y. Zhao, W. Ren, C. Deng, H. Lu, Hongying, *Chem. Commun*., **54**, 9579 (2018).
267 R. K. Tak, P. Patel, S. Subramanian, R. I. Kureshy and N.-u. H. Khan, *ACS Sustainable Chem. Eng*., **6**, 11200 (2018).
268 K. Zhang, Y. Hou, Y. Wang, K. Wang, S. Ren and W. Wu, *Energy Fuels*, **32**, 7727 (2018).
269 T. Pardal, S. Messias, M. Sousa, A. S. R. Machado, C. M. Rangel, D. Nunes, J. V. Pinto, R. Martins and M. Nunes da Ponte, *J. CO_2 Util.*, **18**, 62 (2017).

270 Y. Li, M. C. Ali, Q. Yang, Z. Zhang, Z. Bao, B. Su, H. Xing and Q. Ren, *ChemSusChem*, **10**, 3283 (2017).
271 T. Zhao, J. Liang, Y. Zhang, Y. Wu, and X. Hu, *Chem. Commun*., **54**, 8964 (2018).
272 D. Yang, Y. Han, H. Qi, Y. Wang and S. Dai, *ACS Sustainable Chem. Eng*., **5**, 6382 (2017).
273 Q. Zhang, M. Benoit, K. De Oliveira Vigier, J. Barrault and F. Jérôme, *Chem. Eur. J*., **18**, 1043 (2012).
274 S. Xia, G. A. Baker, H. Li, S. Ravula and H. Zhao, *RSC Adv*., **4**, 10586 (2014).
275 J. A. Sirviö and J. P. Heiskanen, *ChemSusChem*, **10**, 455 (2017).
276 H. Lian, S. Hong, A. Carranza, J. D. Mota-Morales and J. A. Pojman, *RSC Adv*., **5**, 28778 (2015).
277 C. Álvarez-Vasco, R. Ma, M. Quintero, M. Guo, S. Geleynse, K. K. Ramasamy, M. Wolcott and X. Zhang, *Green Chem*., **18**, 5133 (2016).
278 D. Di Marino, D. Stoeckmann, S. Kriescher, S. Stiefel and M. Wessling, *Green Chem*., **18**, 6021 (2016).
279 S. Hong, H. Lian, X. Sun, D. Pan, A. Carranza, J. A. Pojman and J. D. Mota-Morales, *RSC Adv.*, **6**, 89599 (2016).
280 For a recent review in the field of green processing of lignocellulosic biomass and its derivatives in DESs, see: X. Tang, M. Zuo, Z. Li, H. Liu, C. Xiong, X. Zeng, Y. Sun, L. Hu, S. Liu, T. Lei and L. Lin, *ChemSusChem*, **10**, 2696 (2017).
281 E. S. Morais, M. G. Freire, C. S. R. Freire, J. A. P. Coutinho, A. J. D. Silvestre, P. V. Mendonca and J. F. J. Coelho, *ChemSusChem*, **11**, 753 (2018)
282 Q.-P. Liu, X.-D. Hou, N. Li and M.-H. Zong, *Green Chem*., **14**, 304 (2012).
283 H. García, R. Ferreira, M. Petkovic, J. L. Ferguson, M. C. Leitão, H. Q. N. Gunaratne, K. R. Seddon, L. P. N. Rebeloa and C. S. Pereira, *Green Chem.*, **12**, 367 (2010).
284 M. Sharma, C. Mukesh, D. Mondal and K. Prasad, Kamalesh, *RSC Adv*., **3**, 18149 (2013).
285 D. G. Ramírez-Wong, M. Ramírez-Cardona, R. J. Sanchez-Leija, A. Rugerio, R. A. Mauricio-Sánchez, M. A. Hernandez-Landaverde, A. Carranza, J. A. Pojman, A. M. Garay-Tapia, E. Prokhorov, J. D. Mota-Morales and G. Lunas-Barcenas, *Green Chem*., **18**, 4303 (2016).
286 S. Hong, Y. Yuan, Q. Yang, P. Zhu and H. Lian, *Carbohy. Polym*., **201**, 211 (2018).
287 A. P. Abbott, P. M. Cullis, M. J. Gibson, R. C. Harris and E. Raven, *Green Chem*., **9**, 868 (2007).
288 M. Hayyan, F. S. Mjalli, M. A. Hashim and I. M. AlNashef, *Fuel Process Technol*., **91**, 116 (2010).
289 K. Shahbaz, F. S. Mjalli, M. A. Hashim and I. M. AlNashef, *Energy Fuels*, **81**, 216 (2011).
290 M. A. Kareem, F. S. Mjalli, M. A. Hashim, K. O. Mohamed, F. S. G. Bagh and I. M. Alnashef, *Fluid Phase Equilib*., **47**, 333 (2012).
291 M. A. Kareem, F. S. Mjalli, M. A. Hashim, I. M. Alnashef, *Fluid Phase Equilib*., **314**, 52 (2012).
292 K. Pang, Y. Hou, W. Wu, W. Guo, W. Peng and K. N. Marsh, *Green Chem*., **14**, 2398 (2012).
293 W. Gou, Y. Hou, W. Wu, S. Ren, S. Tian and K. N. Marsh, *Green Chem.*, **15**, 226 (2013).
294 D. Wibowo and C. Lee, *Biochem. Eng*., **53**, 44 (2010).
295 J. Taubert, M. Keswani and S. Raghavan, *Microelectron. Eng.*, **102**, 81 (2013).
296 I. Jha, A. Rani and P. Venkatesu, ACS Sustainable *Chem. Eng.*, **5**, 8344 (2017).
297 J. A. McCune, S. Kunz, M. Olesi?ska and O. A. Scherman, *Chem. Eur. J*., **23**, 8601 (2017).
298 X. Tan, W. Zhao and T. Mu, *Green Chem.*, **20**, 3625 (2018).
299 J. Cao, M. Yang, F. Cao, J. Wang and E. Su, *ACS Sustainable Chem. Eng*., **5**, 3270 (2017).
300 N. Li, Y. Wang, K. Xu, Q. Wen, X. Ding, H. Zhang and Q. Yang, *RSC Adv.*, **6**, 84406 (2016).
301 Z. Li, D. Liu, Z. Men, L. Song, Y. Lv, P. Wu, B. Lou, Y. Zhang, N. Shi and Q. Chen, *Green Chem*., **20**, 3112 (2018).
302 C. Bai, Q. Wei and X. Ren, *ACS Sustainable Chem. Eng.*, **5**, 7220 (2017).
303 J. Pang, X. Sha, Y. Chao, G. Chen, C. Han, W. Zhu, H. Li d and Q. Zhang, *RSC Adv*., **7**, 49361 (2017).
304 J. Patil, S. Ghodke, R. Jain and P. Dandekar, *ACS Sustainable Chem. Eng.*, **6**, 10578 (2018).
305 E. Tommasi, G. Cravotto, P. Galletti, G. Grillo, M. Mazzotti, G. Sacchetti, C. Samorì, S. Tabasso, M. Tacchini and E. Tagliavini, *ACS Sustainable Chem. Eng*., **5**, 8316 (2017).
306 M. Wang, J. Wang, Y. Zhou, M. Zhang, Q. Xia, W. Bi and D. Da Yong Chen, *ACS Sustainable Chem. Eng.,* **5**, 6297 (2017).
307 M. A. Farajzadeh, M. R. A. Mogaddam and B. Feriduni, *RSC Adv*., **6**, 47990 (2016).
308 J. Nadia, K. Shahbaz, M. Ismail and M. M. Farid, *ACS Sustainable Chem. Eng*., **6**, 862 (2018).

309 The *Fundación BBVA* accepts no responsibility for the opinions, statements and contents included in the project and/or the results thereof, which are entirely the responsibility of the authors.

20.4 NOVEL APPLICATIONS OF THE BIO-BASED SOLVENT ETHYL LACTATE IN CHEMICAL TECHNOLOGY

David Villanueva-Bermejo* and Tiziana Fornari **
***Department of Agricultural, Food and Nutritional Science, University of Alberta, T6G 2PS, Edmonton, Alberta, Canada**
****Instituto de Investigación en Ciencias de la Alimentación (CIAL), C/Nicolás Cabrera 9, Campus de la Universidad Autónoma de Madrid, CEI UAM+CSIC, 28049 Madrid, Spain**

20.4.1 THE GREEN SOLVENT ETHYL LACTATE

20.4.1.1 Introduction

Solvents are intensely applied in many operations in chemical industry and their manufacture, use and subsequent processing can involve a great environmental impact. Moreover, there is a growing interest to replace petroleum-derived feedstock due to several factors, such as the steady increase of oil price, the more severe environmental regulations and the increasing social awareness about ecological issues.[1] For this reason, there is a need for more environmentally acceptable processes. This trend towards what has become known as "Green Chemistry" seeks the implementation of profitable processes and, at the same time, assigns economic value to waste materials avoiding the use of toxic and/or hazardous substances in the production and application of chemical products. In this sense, solvents are one of the targets of Green Chemistry research, due to their comprehensive use and the large amount of waste that their use generates. Moreover, many of solvents commonly used at industry are toxic, flammable, and/or corrosive. Thus, there is a clear global trend to replace these conventional solvents by non-toxic and environmentally friendly solvents or "Green solvents", such as lower alcohols or esters.[2,3]

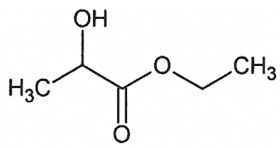


Figure 20.4.1. Molecular structure of ethyl lactate.

Green solvents are generally produced from the processing of agricultural crops. In this sense, lactate esters (primarily ethyl lactate) are candidates to replace many petroleum-derived and chlorinated solvents.[4] Ethyl lactate (ethyl 2-hydroxypropanoate; lactic acid ethyl ester; 2-hydroxypropanoic acid ethyl ester; actylol), is a hydroxyl ester with molecular formula $C_5H_{10}O_3$ (Figure 20.4.1) and can be either in levo (S) or dextro (R) form.

Ethyl lactate is an agrochemical "green solvent" derived from the processing of carbohydrate feedstocks, such as wastes from corn or sugar crops and it is found naturally in small quantities as a flavoring compound in a wide variety of fresh foods, such as meat, some fruits, soy products and fermented foods, such as wine and beer. This bio-derived solvent is a viable alternative to traditional liquid solvents since it is fully and rapidly biodegradable, non-corrosive, non-carcinogenic, non-teratogenic and non-ozone depleting.[5] It was affirmed as GRAS (Generally Recognized as Safe) and due to its low toxicity, it was approved by the U.S. Food and Drug Administration (FDA) as a pharmaceutical and food additive. Ethyl lactate has a high boiling point, low vapor pressure and low surface

tension. Furthermore, it is miscible with a great number of different polarity solvents in a wide range of operational conditions, so ethyl lactate is considered as a tunable solvent, which presents a high solvent power.[6,7]

Ethyl lactate can be produced by esterification of lactic acid with ethanol in biorefineries. In these plants, biomass is transformed into bio-based products, such as proteins, acids, alcohols, fibers or energy (biogas).[8] In the case of ethyl lactate, both ethanol and lactic acid can be obtained from a variety of biomass crops, such as sugar, starch, or cellulosic feedstock, particularly from wastes,[9] resulting in an economic revalorization of these by-products.

All these features have increased the attention to the use of ethyl lactate as a green solvent for many industrial applications, replacing traditional toxic halogenated and petroleum based solvents. The number of studies regarding processes with ethyl lactate has considerably increased in the last decade and new fields of application for this solvent are constantly arising.

20.4.1.2 Physicochemical and thermodynamic properties of ethyl lactate and mixtures containing ethyl lactate

Aparicio and Alcalde[10] carried out a theoretical study of S-ethyl lactate, the most stable enantiomer. The molecular structure of ethyl lactate is mainly defined by its capacity to develop intermolecular hydrogen bonds and, due to the relative position of the hydroxyl hydrogen with regard to the oxygen, its ability to form strong intramolecular hydrogen bonds between the hydroxyl hydrogen and carbonyl oxygen and/or alkoxy oxygen (intramolecular hydrogen bonds occur principally among hydroxyl and carbonyl groups rather than hydroxyl and alkoxy groups).

The effect of the surrounding medium on intramolecular hydrogen bonding has been studied. In this regard, the development of intramolecular hydrogen bonds is weakened when the relative permittivity of the surrounding medium increases.[11] Aparicio *et al.*[12] have reported an ethyl lactate relative permittivity value of 15.7 at 298.15 K, so it is a moderately polar solvent. Authors concluded that ethyl lactate develops preferably intermolecular hydrogen bonding with neighboring ethyl lactate molecules instead of intramolecular hydrogen bonding when ethyl lactate is mixed with a fluid having polarity comparable to that of ethyl lactate.

At both gas and liquid phase, the formation of multimers by ethyl lactate has been described.[10,13] These associations can be formed by 2, 3, and 4 molecules of ethyl lactate and they have different topologies and different hydrogen bond strengths. Several dimers with different morphologies have been analyzed for ethyl lactate. The most stable dimer consists of a symmetric dimer. In this case, the two ethyl lactate molecules are assembled by two reciprocal O–H···C=O interactions with the same length, leading to an eight membered ring structure.

With respect to the physical properties of ethyl lactate, liquid density, refraction index, and viscosity data have been measured and reported by several authors. Table 20.4.1 shows the experimental density values measured at atmospheric pressure and different temperatures. Table 20.4.2 presents the experimental refraction index of ethyl lactate as a function of the temperature.

Table 20.4.1. Experimental densities of ethyl lactate at different temperatures and atmospheric pressure.

Ref.	Density (g/cm^3) @ different temperatures (K)							
	278.15	**288.15**	**293.15**	**298.15**	**308.15**	**318.15**	**328.15**	**338.15**
9	1.050007	1.03927		1.02838	1.01742	1.00637	0.99523	0.98396
11				1.0289	1.0187	1.0075		
12				1.0272				
13			1.032939					
14				1.02802				

Table 20.4.2. Experimental refraction index (n_D) of ethyl lactate.

Ref.	n_D @ different temperatures (K)							
	278.15	**288.15**	**293.15**	**298.15**	**308.15**	**318.15**	**328.15**	**338.15**
9	1.41973	1.41515		1.41046	1.40604	1.40142	1.39654	1.39194
12			1.4124					
13			1.4129					
14				1.41050				

Furthermore, Aparicio and Alcalde[10] reported the density and dynamic viscosity of ethyl lactate for a wide range of pressures and temperatures. Density values are relatively large, pointing to an efficient packing of the ethyl lactate molecules. In addition to it, Chen and Chu[14] and Riddick *et al.*[15] reported the dynamic viscosity of ethyl lactate at atmospheric pressure (Table 20.4.3). Ethyl lactate does not have a viscosity so high as to hinder its application as a solvent in heat and mass transfer operations.

Table 20.4.3. Experimental dynamic viscosity (η) of ethyl lactate at atmospheric pressure.

Reference	η (mPas) @ different temperatures (K)		
	298.15	**308.15**	**318.15**
11	2.398	1.863	1.494
12	2.440		

With regards to other physicochemical properties, Riddick *et al.*[15], Peña-Tejedor *et al.*[16] and Resa *et al.*[17] measured the normal boiling point (ambient pressure) of ethyl lactate, determining values of 427.70, 427.65, and 424.98 K, respectively. Likewise, Snell

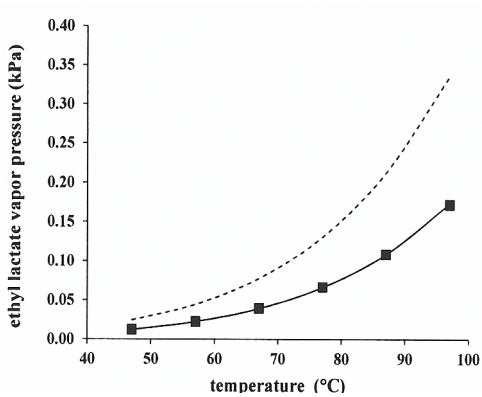


Figure 20.4.2. Experimental and calculated ethyl lactate vapor pressures: (■) experimental data;[19] (- - -) GC-EoS using Set 1 of functional groups; (—) GC-EoS using Set 2 of functional groups.

and Snell[18] determined a boiling point of 303.15 K at 5 mm Hg of pressure. Ínal[19] reported the experimental vapor pressure curve of ethyl lactate for pressures between 12-74 mm Hg and temperatures between 54-86°C (Figure 20.4.2). As can be observed, for ethyl lactate, the increase in pressure with temperature is very sharp. This result suggests a very high heat of vaporization value. Table 20.4.4 shows the Antoine constants in order to obtain the vapor pressures of the ethyl lactate at different temperatures, as reported by Riddick *et al.*[15]

Villanueva-Bermejo *et al.*[20] correlated the ethyl lactate vapor pressure with temperature using the Group Contribution Equation of State (GC-EoS) model. A complete explanation of the GC-EoS equation and fundamentals is given by Skjold-Jørgensen.[21] Summarizing, this thermodynamic model has two contributions to the residual Helmholtz energy of the system: a repulsive hard sphere Carnahan-Starling type term and an attractive term, which combines the group contribution approach with the local-composition mixing rules. The pure group energy parameters together with the group energy interaction parameters required for modeling the ethyl lactate vapor pressures are given in Appendix A.

Table 20.4.4. Ethyl lactate Antoine constants.[15]

	Antoine equation log[P(kPa)] = A – B/[T(°C) + C
A	7.8269
B	2489.7
C	273.15

Figure 20.4.2 shows the results of calculation of ethyl lactate vapor pressure carried out by Villanueva-Bermejo *et al.*[20] as a function of temperature in the range of T = (47-97)°C. According to the customary GC-EoS parameter table,[22] the chemical structure of ethyl lactate can be represented by means of two CH_3, one $COOCH_2$ and one OHCH groups (Set 1). Taking into account that ethyl lactate is the ester of lactic acid, the inclusion of an alcohol-ester functional group (CHOHCOO) seems to be more appropriate to define its chemical group composition (Set 2), as can be observed in Figure 20.4.2. The two different sets utilized by Villanueva-Bermejo *et al.*[20] to define the group composition of ethyl lactate are summarized in the Table 20.4.5.

Table 20.4.5. Different alternatives for the definition of the group composition of ethyl lactate molecule.

Chemical group	Set 1	Set 2
$-CH_3$	2	2
$-CH_2-$		1
$-C(O)OCH_2-$	1	
$-CH(OH)-$	1	
$-CH(OH)C(O)O-$		1

Using the GC-EoS model and Sets 1 and 2 of functional groups, the ethyl lactate vapor pressure was predicted and compared with the experimental data reported by Ínal.[19]

The absolute average deviations:

$$AAD = \frac{1}{N}\sum\left(\frac{P_{exp}^{vap} - P_{cal}^{vap}}{P_{exp}^{vap}}\right) \qquad [20.4.1]$$

obtained were: 96.7% and 0.39%, respectively, for Set 1 and Set 2. That is, the original ester group ($COOCH_2$) defined in the GC-EoS model cannot provide an accurate representation of ethyl lactate vapor pressure. On the contrary, using the ester-alcohol group (CHOHCOO) an excellent representation can be achieved (see Figure 20.4.2).

These results show the useful application of group contribution thermodynamic models to predict phase equilibria properties, and the necessity of a rational partition of a molecule into appropriate functional groups which takes into account the basis of its chemical bonding.

Other physical and thermodynamic properties of ethyl lactate, such as molar volume, critical temperature, critical pressure, critical volume, heat of vaporization, and liquid heat capacity, among others, can be found in the work reported by Pereira and coworkers.[9]

With the perspective of finding alternative benign media for different chemical applications, the physicochemical and thermodynamic behavior of liquid mixtures containing alkyl lactate family compounds has been studied, measured and reported in recent years. On the search of benign solvents to perform chemical reactions, as well as separation and extraction operations, gas-expanded liquid processes (GXLs) by using supercritical CO_2 present several advantages, such as tuning the polarity, transport and thermodynamic properties of a liquid solvent by the dissolution into it of a certain amount of gas, as well as allowing the combination of chemical reaction and product separation. In this context, Medina-Gonzalez *et al*.[23] reported swelling data, polarity/polarizability (π^*), hydrogen-bond donator ability (α), dielectric constants and solubility parameters of three alkyl lactates (methyl, ethyl and butyl lactate) expanded by CO_2, which were determined on the basis of experimental data and molecular modeling techniques. The authors demonstrated that CO_2 has a great effect on alkyl lactate networks since the physicochemical properties

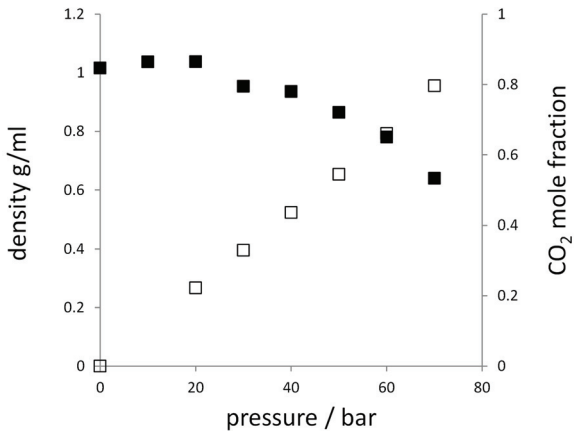


Figure 20.4.3. Variation of density and CO_2 mole fraction in the ethyl lactate + CO_2 liquid phase with pressure at 313 K.

can be significantly modulated by CO_2 dissolution, resulting from increasing the pressure. They concluded that the solubility parameter, π^* and α parameters decrease monotonically with increasing CO_2 pressure (see Table 20.4.6). Furthermore, the authors determined that density increased slightly at low concentrations of CO_2 but decreased at higher concentrations. Figure 20.4.3 shows the density and the CO_2 mole fraction in the ethyl lactate + CO_2 liquid phase as a function of pressure at 313 K. The density of ethyl lactate + CO_2 liquid mixtures is close to 0.6 g cm^{-3} at 70 bar. These observations are attributed to the higher free volume present in expanded solvents compared to non-expanded solvents. Finally, the authors found an increase of CO_2 solubility in the alkyl lactate phase with the hydrocarbon's chain length.

Table 20.4.6. Values obtained for the π^* and α parameters for the ethyl lactate + CO_2 system as a function of pressure. X_{CO2}: mole fraction of CO_2.[23]

P (bar)	X_{CO2}	π^*	α
0	0	0.8448	0.3513
20	0.2227	0.7646	0.3163
30	0.3297	0.7646	0.3163
38	0.4148	0.6728	0.6728
40	0.4361	0.6315	0.2583
42.5	0.4575	0.6625	0.6625
46.9	0.5115	0.6212	0.6212
49.5	0.5445	0.6108	0.6108
58.6	0.6483	0.4739	0.1896

Cunico and Turner[24] also reported density data of liquid solvents expanded by CO_2. The mixtures CO_2 + ethanol, CO_2 + ethyl lactate, CO_2 + glycerol + ethanol, and CO_2 + glycerol + ethyl lactate at 308 and 323 K, pressures between 5 and 30 MPa, and molar fraction of the organic solvent in the range (0.5-0.9) were measured. The solvents ethanol, ethyl lactate, and glycerol were chosen because they were green and applicable in food industry and presented different polarizabilities. They observed that while the density of CO_2 + ethanol increased with the increment of CO_2 dissolution, the opposite arose for the

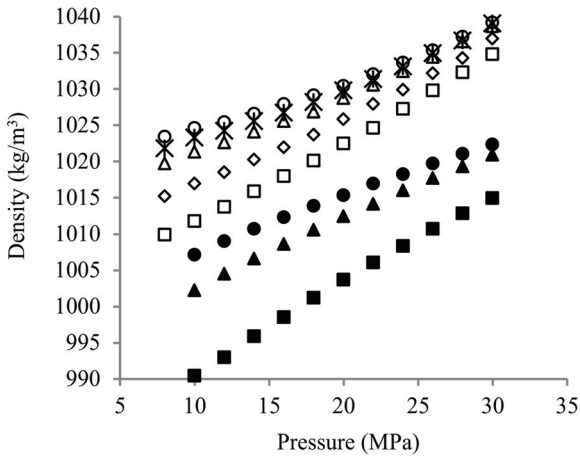


Figure 20.4.4. Density values for the system CO_2 + ethyl lactate at 308 K (empty symbols) and 323 K (filled symbols). Molar fraction of CO_2 in the mixture (x): x = 0.1 (circle); x = 0.2 (cross); x = 0.3 (triangle); x =0.4 (diamond); x = 0.5 (square).

mixtures of CO_2 + ethyl lactate (Figure 20.4.4). Nevertheless, when adding a small amount of glycerol to the binary mixtures, density increase was observed in both cases.

Insights into alkyl lactate + water mixed fluids were presented by García *et al.*[25] The authors studied the thermophysical properties of alkyl lactate + water binary mixtures at 298.15 K in the whole composition range. Table 20.4.7 presents the density, speed of sound and refractive index for the ethyl lactate + water mixture. In their analysis, they reported that the ethyl lactate + water mixture is highly non-ideal, with volume contraction upon mixing, and the largest deviations from ideality were around 0.75 water mole fraction.

Table 20.4.7. Density (ρ), speed of sound (u) and refractive index (η_D) at 298.15 K for the binary mixture ethyl lactate + water. x stands for water mole fraction.

x	ρ, gcm^{-3}	u, ms^{-1}	η_D
0.0500	1.02950	1294.20	–
0.1144	1.03124	1308.01	1.41074
0.2319	1.03197	1321.91	1.40963
0.3077	1.03389	1338.59	1.40878
0.4034	1.03536	1362.68	1.40696
0.4678	1.03643	1390.20	1.40536
0.5571	1.03791	1425.34	1.40179
0.7023	1.03828	1470.24	1.39689
0.8033	1.03681	1539.26	1.38817
0.8824	1.03204	1570.49	1.37470
0.9495	1.02031	1558.50	–

Density and speed of sound data were reported by Latha *et al.*[26] and Anila *et el.*[27] concerning binary liquid mixtures containing ethyl lactate. Latha *et al.*[26] referred to the pure solvent ethyl lactate and the binary mixtures of ethyl lactate with chosen organic carbonates (dimethyl carbonate, diethyl carbonate and propylene carbonate). Figures 20.4.5 and 20.4.6 show the data reported by Latha *et al.*[26] for the mixture ethyl lactate + dimethyl

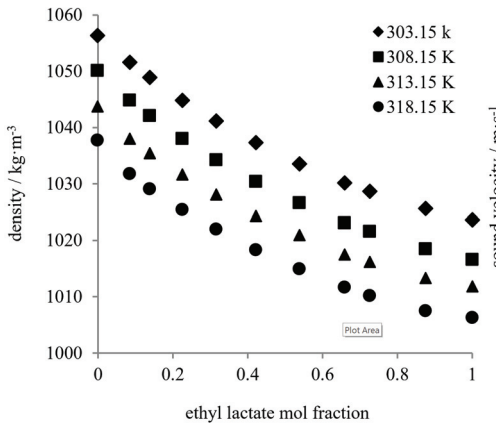


Figure 20.4.5. Densities of ethyl lactate + dimethyl carbonate liquid mixtures at atmospheric pressure and in the temperature range of 303.15-318.15 K.

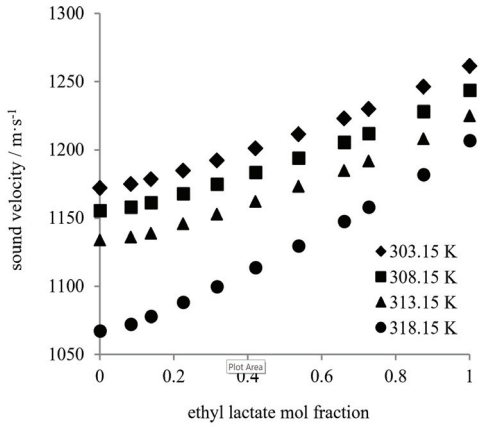


Figure 20.4.6. Sound velocities of ethyl lactate + dimethyl carbonate liquid mixtures at atmospheric pressure and in the temperature range of 303.15-318.15 K.

carbonate, as a function of ethyl lactate mole fraction. Similar behavior was observed for the densities of the mixture ethyl lactate + propylene carbonate (Figure 20.4.7) while sound velocity exhibited opposite behavior, as can be observed in Figure 20.4.8.

Likewise, Anila *et el*.[27] reported the densities and speeds of sound of the binary liquid mixtures of ethyl lactate with 2-methoxyethanol (2-ME), 2-ethoxyethanol (2-EE), and 2-butoxyethanol (2-BE). In both works, data were reported over the entire composition range at temperatures of 303.15-318.15 K. Furthermore, the experimental data was used to calculate thermodynamic parameters and the excess functions were fitted with the Redlich-Kister polynomial equation. Thermodynamic studies revealed strong intermolec-

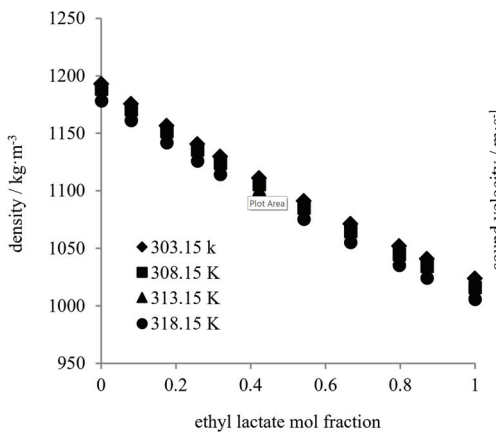


Figure 20.4.7. Densities of ethyl lactate + propylene carbonate liquid mixtures at atmospheric pressure and in the temperature range of 303.15-318.15 K.

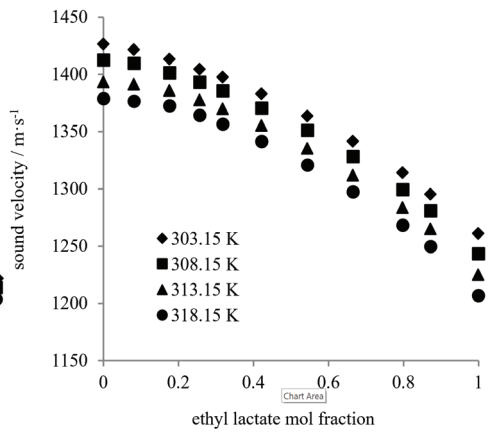


Figure 20.4.8. Sound velocities of ethyl lactate + propylene carbonate liquid mixtures at atmospheric pressure and in the temperature range 303.15-318.15 K.

ular interactions between ethyl lactate and 2-alkoxyethanol molecules, following the order EL + 2-BE > EL + 2-EE > EL + 2-ME.

Experimental measurements and modeling of volumetric properties, refractive index, and viscosity of binary systems of ethyl lactate with methyl ethyl ketone (MEK), n-methyl-2-pirrolidone (NMP) and toluene were reported by Bajic *et al*.[28] at atmospheric pressure in the temperature range of 288.15 to 323.15 K. Viscosity deviations were negative for the systems with MEK and toluene and positive for the system with NMP. The calculated excess molar volumes were negative for systems with MEK and NMP while in a solution with toluene positive excess molar volumes occurred.

20.4.1.3 Solubility and phase equilibria data of systems containing ethyl lactate

The physicochemical characteristics of ethyl lactate offer diverse solvent properties and the investigation related to the use of ethyl lactate as a green environmentally friendly solvent for the chemical industry has considerably increased. In order to attend the industrial goal, knowledge of the phase behavior of mixtures comprising ethyl lactate is necessary, as is paramount for the design of several technological processes.

20.4.1.3.1 Vapor-liquid equilibrium in ethyl lactate systems

Peña-Tejedor *et al.*[16] reported the vapor-liquid equilibria (VLE), density and excess volume data of the binary system ethanol + ethyl lactate at ambient pressure (101.3 kPa). Previously only a diagram with four experimental VLE data for the system ethanol + ethyl lactate had been reported by Benedict *et al*.[29], who investigated this system at atmospheric pressure just to check the azeotrope formation (fairly common in alcohol + ester mixtures). Both authors[16,29] confirmed the non-existence of azeotropes in the system ethanol + ethyl lactate (Figure 20.4.9). Later, Vu *et al*.[30] presented isothermal VLE data of mixtures ethanol + ethyl lactate (40.0, 60.1, and 80.2ºC) and water + ethyl lactate (40.0 and 60.0ºC). While the ethanol + ethyl lactate system showed a slightly non-ideal phase behavior, the water + ethyl lactate system revealed a minimum boiling azeotrope occurring at 5-7 mol% ethyl lactate (Figure 20.4.10). VLE data of the ethyl acetate + ethyl lactate and methyl acetate + ethyl lactate binary mixtures were reported by Resa *et al.*[17] As predictable, both systems presented nearly ideal behavior, with very small (close to zero) excess volumes.

VLE measurements of the quaternary system involved in the esterification of lactic acid with ethanol at 101.3 kPa was presented by Delgado *et al*.[31] The esterification reaction is equilibrium-limited and usually does not reach completion. Lactic acid esters are used as powerful high-boiling solvents, and they are produced by conventional esterification of lactic acid with the corresponding alcohol.

The effect of ethyl lactate as an entrainer for the separation of binary azeotropic systems was investigated by Matsuda *et al*.[32,33] The isobaric VLE of methyl acetate + ethyl lactate and methanol + ethyl lactate using an ebulliometric method were reported in 2016[32] and the data obtained (see Table 20.4.8) were represented by the Wilson and NRTL models. Furthermore, the VLE for the ternary system methyl acetate + methanol + ethyl lactate was also measured. The resulting data and calculated separation factors showed that ethyl lactate acted as an entrainer for extractive distillation of the binary azeotropic system methyl acetate + methanol.

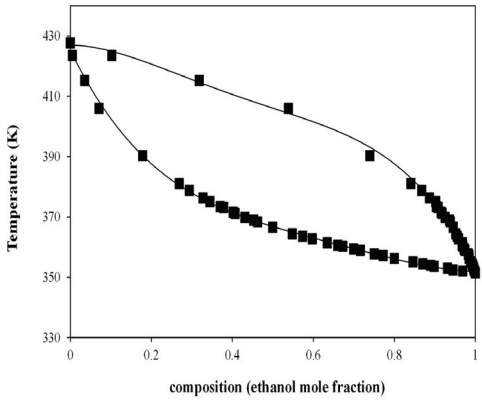


Figure 20.4.9. Vapor-liquid equilibria of the ethanol + ethyl lactate system at ambient pressure (101.3 kPa). [Adapted, by permission, from S. Peña-Tejedor, R. Murga, M.T. Sanz, and S. Beltrán, *Fluid Phase Equilib.*, **230**, 197 (2005)].

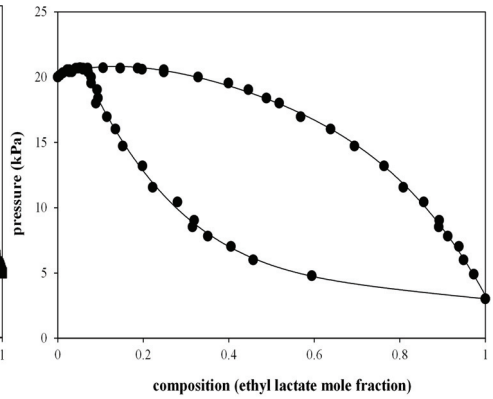


Figure 20.4.10. Vapor-liquid equilibria of the (water + ethyl lactate) system at 333K. [Adapted, by permission, from D.T. Vu, C.T. Lira, N.S. Asthana, A.K. Kolah, and D.J. Miller, *J. Chem. Eng.*, **51**, 1220 (2006)].

Table 20.4.8. Experimental boiling points, liquid phase mole fractions (x_1) and temperatures (T) for the binary systems methyl acetate (1) + ethyl lactate (2) and methanol (1) + ethyl lactate (2).

x_1	40.00 kPa	53.33 kPa	66.66 kPa	79.99 kPa	93.32 kPa	101.3 kPa
	T/K					
methyl acetate (1) + ethyl lactate (2)						
0.0000	396.91	405.49	412.44	418.34	423.47	426.10
0.1000	369.36	378.14	385.91	392.52	397.89	401.22
0.2000	353.28	362.97	370.83	376.97	382.75	386.00
0.2998	338.26	347.00	353.64	359.83	365.19	368.56
0.3999	331.08	340.09	347.02	352.17	357.48	360.37
0.5001	325.15	332.97	339.61	345.28	350.47	353.00
0.6000	318.77	326.57	333.17	338.72	343.93	346.56
0.7003	314.61	322.46	328.93	334.43	339.28	341.92
0.7998	311.23	318.69	325.09	330.67	335.30	337.88
0.9000	308.07	315.49	321.44	326.59	331.13	333.59
1.0000	305.65	312.68	318.45	323.36	327.68	330.04
methanol (1) + ethyl lactate (2)						
0.0000	396.91	405.49	412.44	418.34	423.47	426.10
0.1000	372.42	380.91	387.65	394.50	401.49	405.09

Table 20.4.8. Experimental boiling points, liquid phase mole fractions (x_1) and temperatures (T) for the binary systems methyl acetate (1) + ethyl lactate (2) and methanol (1) + ethyl lactate (2).

x_1	40.00 kPa	53.33 kPa	66.66 kPa	79.99 kPa	93.32 kPa	101.3 kPa
	T/K					
0.2000	355.98	364.10	370.86	374.40	379.00	382.88
0.2998	344.84	353.04	361.01	366.29	371.03	373.81
0.3999	336.70	344.04	349.97	355.27	359.94	362.22
0.5001	331.33	339.30	344.07	349.14	353.53	356.01
0.6000	327.05	333.90	339.52	344.31	348.49	350.82
0.7003	323.14	330.00	335.59	340.35	344.59	346.88
0.7998	320.18	327.13	332.67	337.56	341.76	344.04
0.9000	317.57	324.37	330.09	334.95	339.40	341.63
1.0000	315.49	321.98	327.23	331.66	335.51	337.60

Matsuda *et al*.[33] also tested ethyl lactate as an entrainer candidate for the separation of the binary methanol + dimethyl carbonate (DMC) azeotropic system by extractive distillation. Isobaric VLE for the binary system DMC + ethyl lactate were determined at pressures of (40.00 to 101.3) kPa (see Table 20.4.9). Furthermore, the experimental normal boiling temperature, density (at 298.15 K) and Antoine constants of ethyl lactate were reported and compared with values from the literature. The VLE data of the methanol + DMC + ethyl lactate ternary system were also reported, and the phase equilibria behavior was compared with the predictions using binary NRTL parameters and the NIST-modified UNIFAC model. Although the effect of ethyl lactate was inferior to that of some ionic liquids, the authors demonstrated that ethyl lactate could be a possible entrainer for the separation of the azeotropic system, in addition to be a greener low-price entrainer.

A thermodynamic study of the vapor-liquid equilibrium for the ternary system ethyl lactate + ethanol + water was performed by Puentes *et al*.[34] at 101.3 kPa and infinite dilution conditions regarding the content of ethyl lactate, for boiling temperatures ranging from 352.3 to 370.0K. The experimental measurements were carried out with a recirculation still and the equilibrium compositions of ethyl lactate were determined by gas chromatography. The equilibrium data was correlated using the NRTL and UNIQUAC models, with an average absolute relative deviation below 10%. Activity coefficients and Henry constants were derived from the equilibrium relations and volatilities were directly calculated from composition data. The authors demonstrated that the volatility of ethyl lactate decreased when the ethanol content in the liquid phase increased. Ethyl lactate is less volatile than ethanol and its relative volatility is reduced by a factor of four over the entire solvent composition range in the liquid phase. The ternary system exhibited positive deviation from ideality (activity coefficients > 1).

Table 20.4.9. Experimental boiling points, liquid mole fraction (x_1) and temperature (T) for the DMC (1) + ethyl lactate (2) binary system.

40.00 kPa		53.33 kPa		66.66 kPa	
x_1	T/K	x_1	T/K	x_1	T/K
0.0000	336.61	0.0000	344.29	0.0000	321.98
0.1001	326.03	0.1001	333.42	0.1001	339.62
0.2003	320.55	0.2003	327.92	0.2003	333.74
0.3001	318.06	0.3001	325.01	0.3001	330.72
0.4003	316.24	0.4003	323.28	0.4003	328.87
0.5001	315.46	0.5001	322.14	0.5001	327.57
0.5999	314.89	0.5999	321.56	0.5999	326.97
0.7002	314.57	0.7002	321.17	0.7002	326.41
0.7999	313.93	0.7999	320.64	0.7999	326.06
0.9000	314.53	0.9000	320.99	0.9000	326.24
1.0000	315.49	1.0000	321.98	1.0000	327.23
79.99 kPa		**93.33 kPa**		**101.3 kPa**	
x_1	T/K	x_1	T/K	x_1	T/K
0.0000	355.83	0.0000	360.49	0.0000	363.00
0.1001	344.81	0.1001	349.38	0.1001	351.94
0.2003	338.68	0.2003	343.07	0.2003	345.64
0.3001	335.49	0.3001	339.71	0.3001	342.01
0.4003	333.59	0.4003	337.79	0.4003	339.99
0.5001	332.32	0.5001	336.43	0.5001	338.71
0.5999	331.54	0.5999	335.53	0.5999	337.69
0.7002	330.92	0.7002	334.93	0.7002	337.14
0.7999	330.63	0.7999	334.62	0.7999	336.76
0.9000	330.67	0.9000	334.53	0.9000	336.63
1.0000	331.66	1.0000	335.51	1.0000	337.60

20.4.1.3.2 Phase behavior of ethyl lactate + CO_2 mixtures

Ethyl lactate is a novel ecofriendly solvent with potential applications in supercritical fluid technology, as a co-solvent of carbon dioxide, in high-pressure chemical reactions, supercritical extraction processes and anti-solvent precipitation processes. In view of this, knowledge of the phase behavior of the ethyl lactate + CO_2 binary system is essential for the modeling and design of such processes.

The first equilibrium data on the ethyl lactate + CO_2 system were reported by Chylinski and Gregorowicz[35] in 1998, and correspond to the solubility of ethyl lactate in the CO_2-rich phase at three different temperatures (311, 318 and 323 K) and pressures up to 8.1 MPa. Later, Villanueva-Bermejo *et al.*[20] measured the solubility of CO_2 in the ethyl lactate-rich phase at the same temperature and pressure range (see Table 20.4.10).

Table 20.4.10. Liquid phase composition of the binary system (ethyl lactate + CO_2) at T = (311, 318 and 323)K.[17]

T K	P MPa	CO_2 wt%	T K	P MPa	CO_2 wt%	T K	P MPa	CO_2 wt%
311	1.2	3.2	318	1.2	2.9	323	1.2	2.9
311	2.0	7.4	318	2.8	9.6	323	2.0	6.5
311	2.8	10.3	318	3.8	13.0	323	2.8	8.7
311	3.8	14.7	318	6.2	21.0	323	3.9	11.9
311	4.5	18.8	318	7.0	26.5	323	4.9	14.0
311	6.2	28.8	318	7.8	31.8	323	6.2	17.9
311	6.8	34.4	318	8.1	35.8	323	7.0	19.8
311	7.0	35.4				323	8.1	29.9
311	7.8	41.9						

Additionally, Cho *et al.*[36] also provided phase equilibrium data of the ethyl lactate + CO_2 mixture and more recently, Paninho *et al.*[37] presented the equilibrium compositions of both liquid and supercritical phases (see Figure 20.4.11) in a wide range of temperatures (313-329K) and pressures (0.4-17 MPa).

The data reported[35-37] show that ethyl lactate weight fractions in the liquid phase increase when temperature increases and pressure decreases. On the other hand, the weight fractions of ethyl lactate in the CO_2-rich phase increase with pressure, and the effect of temperature depends on the pressure applied. Nevertheless, some discrepancies could be observed between the data reported by Villanueva-Bermejo *et al.*[20] and the liquid phase compositions reported by the other authors[36,37] which could be due to the differences in the experimental methodology used or even in the purity of the ethyl lactate employed, specifically in the amount of water contained as a consequence of the hygroscopic nature of this solvent. Ethyl lactate is a very hygroscopic substance and the presence of water can greatly influence solubility and phase equilibria measurements (see for example Figure 20.4.14).

Paninho *et al.*[37] compared the solubility of CO_2 in ethyl lactate with the solubility of CO_2 in common solvents, such as ethanol and ethyl acetate. The relative affinity observed follows the order: ethyl acetate > ethyl lactate > ethanol. Besides the utilization of ethyl lactate as co-solvent of CO_2 for supercritical processing, as will be discussed in Section 20.4.5.3, the high solubility of CO_2 in ethyl lactate promotes different approaches in the perspective of expanded liquid solvents, i.e., an organic liquid in which CO_2 has been dis-

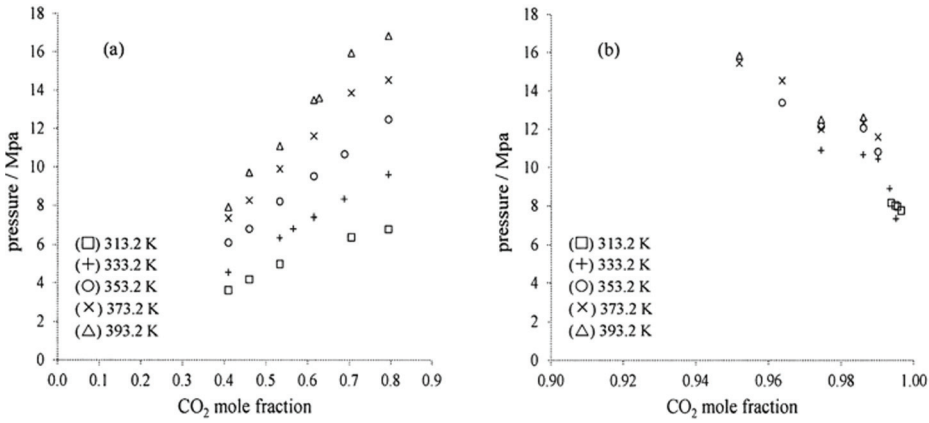


Figure 20.4.11. Vapor-liquid equilibria representation of the (ethyl lactate + CO_2) mixture. (a) liquid phase; (b) vapor phase. [Adapted, by permission, from A.B. Paninho, A.V.M. Nunes, A. Paiva, and V. Najdanovic-Visak, *Fluid Phase Equilib*., **360**, 129 (2013).]

solved. The exploitation of this new class of solvents is based on the possibility of modifying different liquid physical properties, such as viscosity, surface tension, diffusion rates, solubility of reagents, catalysts and substrates, density and polarities, by dissolving CO_2 at high pressure. In this context, ethyl lactate is a good candidate for supercritical processes, with the additional advantage of being itself a green solvent.

20.4.1.3.3 Liquid-liquid equilibrium data of systems comprising ethyl lactate

Liquid-liquid equilibrium (LLE) data for systems containing ethyl lactate has also been investigated and reported in the literature. Zakrzewska *et al*.[38] presented a comprehensive work in which the LLE of mixtures with ethyl lactate and various hydrocarbons (alkanes, alkenes, cyclohexane, alkyl cyclohexane and terpenes) were explored in the range of temperatures from 273.2 to 320.9K at atmospheric pressure. The respective temperature-composition phase diagrams were constructed and the influence of different variables (temperature, aliphatic chain length, and number of double bonds) on liquid phase behavior was discussed. The binary mixtures of ethyl lactate and low molecular weight alkenes (1-hexene, 1-heptene, 1-octene), cyclohexane and aromatic hydrocarbons (benzene, toluene) have shown complete miscibility in the studied temperature range. On the other hand, mixtures containing ethyl lactate and alkanes (hexane, heptane, octane, isooctane, nonane, decane or dodecane) exhibited partial liquid-liquid miscibility below certain temperature (the upper critical solution temperature, UCST), which increased approximately 7°C per carbon atom contained in the alkane chain. Moreover, the system ethyl lactate + 1-hexadecene also exhibited UCST behavior. According to the data compiled, the authors established that alkane branching provoked a decrease in UCST and higher mutual solubility. Comparing the ethyl lactate + alkane systems with the ethyl lactate + alkene systems, it was concluded that the presence of π-bonds considerably increased mutual solubility.

Other systems investigated included the ethyl lactate and poly(lactic acid) mixture[39] and ethyl lactate + lipid-type substances.[40,41] The lipophilic character of the ester part of

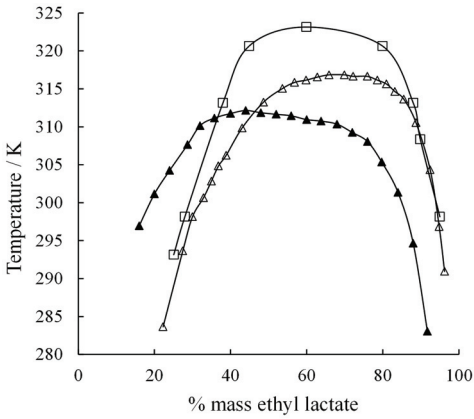


Figure 20.4.12. Transition temperature vs. composition (wt% ethyl lactate) for the binary mixtures (▲) (squalene + ethyl lactate) and (△) (olive oil + ethyl lactate), and the ternary mixture (□) squalene + olive oil (olive oil/squalene ratio = 70:30) and ethyl lactate, at atmospheric pressure.

the ethyl lactate molecule combined with the polarity of its hydroxyl group result in partial liquid-liquid miscibility of this solvent with oils and lipid derivatives, providing novel alternatives for the oil industry processing.

Hernandez *et al.*[40] determined the liquid-liquid phase boundary at ambient pressure of squalene + ethyl lactate; olive oil + ethyl lactate; and squalene + olive oil + ethyl lactate systems. Transition temperatures define the liquid-liquid region of a system and are usually determined by the cloud-point method, i.e. observing visually the onset of the phase transition. In general, mixtures of ethyl lactate with lipid-type substances exhibit partial liquid-liquid miscibility below certain temperature (the upper critical solution temperature, UCST) as is depicted in Figure 20.4.12 for the (squalene + ethyl lactate), (olive oil + ethyl lactate) and (squalene + olive oil + ethyl lactate) system.

UCSTs were 312.2 K and 316.9 K, for (squalene + ethyl lactate) and (olive oil + ethyl lactate) system, respectively. Figure 20.4.12 shows also the temperature-composition liquid-liquid phase diagrams of these two mixtures as a function of the ethyl lactate concentration in the corresponding binary mixture. The two transition curves intersect at 46 wt% of ethyl lactate. Since the main constituents of olive oil are triglycerides (96-98 wt%), mixtures with 0-46% of ethyl lactate will dissolve preferably triglycerides rather than squalene. For example, 30 wt% ethyl lactate will completely dissolve triglycerides at 298 K while higher temperatures are required to completely dissolve squalene. The opposite holds true for mixtures with concentrations of ethyl lactate higher than 46 wt% (right side of Figure 20.4.12). Thus, it can be presumed that, for example, 50 to 90 wt% of ethyl lactate added to a triglyceride + squalene mixture will dissolve squalene better than triglycerides at 313 K. This suggests that a selective liquid-liquid squalene extraction from squalene + triglyceride mixtures can be successfully realized using ethyl lactate as extraction solvent.

With respect to the transition temperatures of the squalene + olive oil + ethyl lactate mixture, Figure 20.4.12 depicts the data corresponding to the transition temperature of the (squalene + olive oil + ethyl lactate) mixture vs. ethyl lactate wt%. The mixture contained an olive oil/squalene ratio of 70:30 (this mixture is representative of oil deodorizer distillates). As can be observed in Figure 20.4.12, the UCST of the ternary system was higher (323.15 K) than the corresponding temperatures for squalene + ethyl lactate (312.15 K) and olive oil + ethyl lactate (317.15 K) mixtures, respectively.

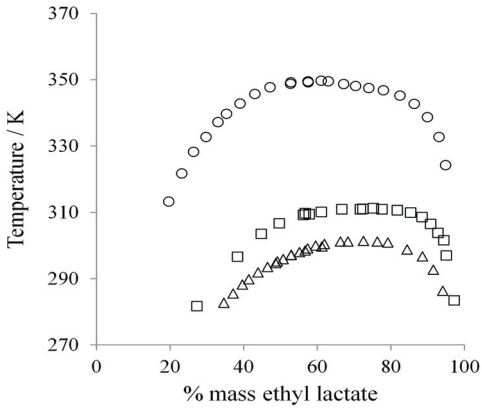


Figure 20.4.13. Temperature vs. ethyl lactate mass fraction phase diagrams at atmospheric pressure for the mixtures (□) (ethyl lactate + olive oil), (Δ) (ethyl lactate + olive oil with 11.60 wt% of oleic acid) and (O) (ethyl lactate containing 2.80 wt% of water + olive oil).

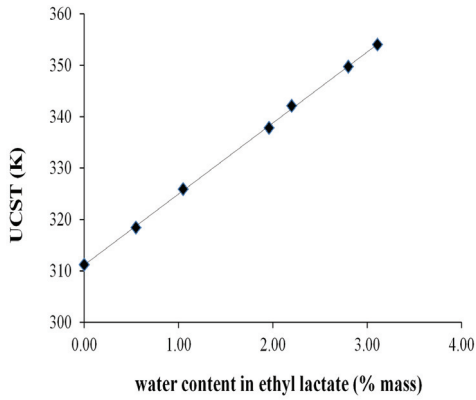


Figure 20.4.14. Effect of the presence of water in the ethyl lactate on the UCST of the mixture (ethyl lactate + olive oil): (◆) experimental data; (–) trend line.

Vicente *et al*.[41] determined the liquid-liquid transition temperatures at ambient pressure of the binary (ethyl lactate + olive oil) system, the pseudo-binaries (ethyl lactate + olive oil containing 11.60 wt% of oleic acid) and (ethyl lactate containing 2.80 wt% of water + olive oil), as well as the ternary (α-tocopherol + olive oil + ethyl lactate).

The three systems showed liquid-liquid partial miscibility when decreased the temperature at constant pressure, and thus presented upper critical solution temperature (UCST) behavior as depicted in Figure 20.4.13. As can be observed, the addition of oleic acid, which is a naturally occurring olive oil constituent, significantly improved the mutual solubility. The presence of 11.60 wt% of oleic acid in olive oil decreased by 11.2 K the UCST.

The observed critical temperature for the binary (ethyl lactate + olive oil) was 311.2 K which was lower by approximately 6 K than the values presented by Hernandez *et al*.[40] This difference is probably due to differences in the free fatty acid content of the olive oil employed in the present work (1.2 wt%) in comparison to the extra-virgin olive oil employed by Hernandez *et al.*,[40] which contained less than 0.8 wt% of free fatty acids.

On the other hand, water had a strong anti-solvent effect in this type of mixture. For example, the presence of 2.80 wt% of water in ethyl lactate increased the UCST by approximately 39 K, producing a higher immiscibility on the system. Figure 20.4.13 presents the UCST of the (olive oil + ethyl lactate) mixture as a function of the water content in ethyl lactate. The linear regression of data presented in Figure 20.4.14 reveals that the presence of 0.1 wt% water in ethyl lactate solvent leads to 1.4 K increase of UCST.

Mixtures of (α-tocopherol + olive oil) and (α-tocopherol + ethyl lactate) showed complete miscibility in the temperature range from 270 to 360 K as reported by Vicente *et*

al.,[41] while the ternary (α-tocopherol + olive oil + ethyl lactate) system presented liquid-liquid partial miscibility at that temperature range.

The cloud point data, which define the liquid-liquid phase boundary of the ternary (α-tocopherol + olive oil + ethyl lactate) mixture, are given in Table 20.4.11 at two different temperatures, 298.2 K and 288.2 K. Additionally, Table 20.4.12 presents the phase liquid-liquid composition data for both ethyl lactate-rich and olive oil-rich phases at equilibrium, as well as the respective overall compositions.

From Tables 20.4.11 and 20.4.12 it can be concluded that the mutual solubility of the ternary system decreases with temperature. This suggests that low temperatures are more suitable for extraction of α-tocopherol from olive oil using ethyl lactate as a solvent.

Table 20.4.11. Liquid-liquid transition temperature data for (α-tocopherol + olive oil + ethyl lactate) at 298.2K and at 288.2K.[41]

298.2 K			288.2 K		
composition, wt%					
α-tocopherol	olive oil	ethyl lactate	α-tocopherol	olive oil	ethyl lactate
8.2	44.5	47.3	7.3	57.6	35.2
11.1	35.7	53.2	11.8	46.6	41.6
8.0	13.9	78.1	13.7	27.9	58.4
5.0	10.1	84.9	7.2	6.9	85.9
4.3	54.1	41.7	13.4	40.9	45.8
10.9	26.6	62.5	13.7	21.6	64.7
10.2	20.1	69.7	11.7	13.5	74.8
			11.2	47.4	41.5
			13.3	37.2	49.6

Table 20.4.12. Tie-line data for (α-tocopherol + olive oil + ethyl lactate) system at 298.2 K and 288.2 K (atmospheric pressure). w_i: mass fraction; 1: α-tocopherol; 2: olive oil; 3: ethyl lactate.[41]

Olive oil-rich phase			Ethyl lactate-rich phase		
w_1	w_2	w_3	w_1	w_2	w_3
T=298.2 K					
0.0335	0.5549	0.4116	0.0295	0.0799	0.8906
0.0493	0.5388	0.4119	0.0519	0.1028	0.8453
0.077	0.4898	0.4332	0.0686	0.1428	0.7886
T=288.2 K					
0.0521	0.6075	0.3404	0.0675	0.074	0.8585
0.1011	0.4973	0.4016	0.1286	0.1427	0.7287

Taking into account the data provided in Table 20.4.12, the partition coefficient:

$$K_i = \frac{w_{i,\ \text{ethyl lactate-rich phase}}}{w_{i,\ \text{oil-rich phase}}} \qquad [20.4.2]$$

of α-tocopherol and olive oil can be calculated. The partition coefficient of α-tocopherol was very close to 1 at 298.2 K, while slightly higher values of 1.3 were obtained at 288.2 K. In the case of the partition coefficient for olive oil, no significant difference was observed when lowering the temperature. Thus, the separation factor between these two substances:

$$\alpha = \frac{K_{\alpha\text{-tocopherol}}}{K_{\text{olive oil}}} \qquad [20.4.3]$$

was higher at lower temperature. That is, low temperatures are more suitable for extraction of α-tocopherol from olive oil using ethyl lactate as a solvent.

Kamalanathan *et al.*[42] reported the cloud points (solubility curve) and tie-lines of three ternary ethyl lactate + water + inorganic salt systems at 298.2 K and 313.2 K and atmospheric pressure. For a certain composition range, these mixtures exhibit biphasic systems, with top and bottom phases rich in ethyl lactate and salt, respectively. The data are given in Tables 20.4.13 to 20.4.15 for three different salts (K_3PO_4, K_2HPO_4 and K_2CO_3).

Table 20.4.13. Cloud point data for the ternary systems containing ethyl lactate (EL), water and K_3PO_4 salt (mass fraction), at 298.2 K and 313.2 K (atmospheric pressure).

$w_{salt\ WEL}$			
T=298.2 K		**T=313.2 K**	
0.0050	0.8370	0.0050	0.9150
0.0080	0.7640	0.0080	0.8510
0.0140	0.6550	0.0120	0.8000
0.0240	0.5720	0.0160	0.7540
0.0410	0.4990	0.0220	0.7100
0.0580	0.4230	0.0320	0.6550
0.0740	0.3770	0.0440	0.5820
0.0890	0.3230	0.0550	0.5230
0.0980	0.3100	0.0880	0.4360
0.1140	0.2750	0.1050	0.3680
0.1240	0.2510	0.1330	0.3100
0.1350	0.2350	0.1670	0.2450
0.1440	0.2070	0.1890	0.1850
0.1580	0.1850	0.2210	0.1470

Table 20.4.13. Cloud point data for the ternary systems containing ethyl lactate (EL), water and K_3PO_4 salt (mass fraction), at 298.2 K and 313.2 K (atmospheric pressure).

$w_{salt\ WEL}$			
T=298.2 K		T=313.2 K	
0.1700	0.1620	0.2440	0.1110
0.1920	0.1150	0.2590	0.1020
0.1990	0.0950	0.2800	0.0820
0.2210	0.0580	0.2980	0.0800
0.2410	0.0410		
0.2500	0.0430		
0.2600	0.0410		
0.2890	0.0380		

The partial liquid-liquid miscibility of these systems was studied and exploited for the separation of aminoacids (L-phenylalanine, L-tryptophan and L-tyrosine) from their aqueous solutions. Kamalanathan *et al.*[42] measured the partition coefficients of these amino acids and their extraction efficiencies at two temperatures (298.2 K and 313.2 K). The highest partition coefficient values were observed for the system containing K_3PO_4, being the values 3.5, 3.7 and 11.9, respectively, for L-phenylalanine at 313.2 K, L-tyrosine at 298.2 K and L-tryptophan at 313.2 K. The results reported clearly showed that the biphasic systems based on ethyl lactate solvent are suitable for the efficient and sustainable recovery of amino acids from solutions with water.

Table 20.4.14. Cloud point data for the ternary systems containing ethyl lactate (EL), water and K_2HPO_4 (mass fraction), at 298.2 K and 313.2 K (atmospheric pressure).

$w_{salt\ WEL}$			
T=298.2 K		T=313.2 K	
0.0060	0.7930	0.0050	0.9210
0.0140	0.6440	0.0160	0.7500
0.0200	0.6120	0.0300	0.6830
0.0350	0.5000	0.0420	0.6470
0.0620	0.3920	0.0520	0.5510
0.0820	0.3430	0.0790	0.4210
0.1130	0.2570	0.1200	0.3250
0.1410	0.1720	0.1530	0.2810
0.1860	0.0980	0.1720	0.1930
0.2360	0.0500	0.2080	0.1310
0.2870	0.0350	0.2910	0.0720

Table 20.4.14. Cloud point data for the ternary systems containing ethyl lactate (EL), water and K_2HPO_4 (mass fraction), at 298.2 K and 313.2 K (atmospheric pressure).

$w_{salt\ WEL}$			
T=298.2 K		T=313.2 K	
0.3450	0.0200	0.3750	0.0550
0.3950	0.0140		

Table 20.4.15. Cloud point data for the ternary systems containing ethyl lactate (EL), water and K_2CO_3 salt at 298.2 K and 313.2 K at pressure of 0.1 MPa in mass fractions.

$w_{salt\ WEL}$			
T=298.2 K		T=313.2 K	
0.0030	0.7860	0.0120	0.8200
0.0060	0.7350	0.0220	0.7300
0.0150	0.6550	0.0580	0.6010
0.0430	0.5640	0.0980	0.4820
0.0600	0.5090	0.1190	0.4110
0.0920	0.4260	0.1480	0.3350
0.1170	0.3560	0.1920	0.2300
0.1450	0.2760	0.2110	0.1921
0.1600	0.2340	0.2350	0.1470
0.2020	0.1220	0.2710	0.0920
0.2290	0.0860	0.2870	0.0630
0.2920	0.0180	0.3090	0.0282
0.3340	0.0290	0.3500	0.0200

20.4.1.3.4 Solid-liquid equilibrium data of systems comprising ethyl lactate

With regards to solid-liquid systems, Manic *et al.*[43] carried out the solubility measurements of several naturally occurring bioactive compounds (Figure 20.4.15) in ethyl lactate at temperatures ranging from (293.2-343.2) K and ambient pressure. The compounds studied were two hydroxycinnamic acids: ferulic and caffeic acid (Table 20.4.16), a hydroxybenzoic acid: vanillic acid (Table 20.4.17), the alkaloid caffeine (Table 20.4.18) and the phenolic monoterpene thymol (Table 20.4.19). The authors reported the solubility values in dried (0.03 wt%) and non-treated (1.4 wt%) ethyl lactate in order to determine the effect that residual amounts of water could exert on the solubility of these compounds due to the hygroscopic character of this solvent.

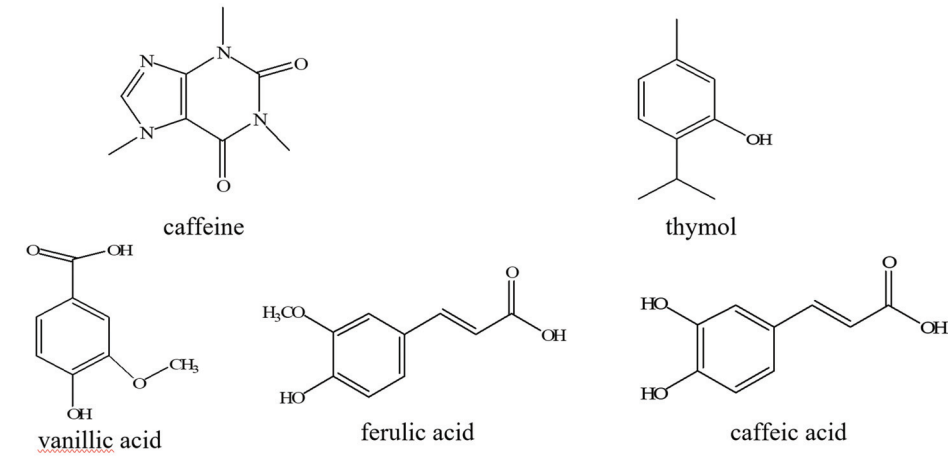


Figure 20.4.15. Chemical structures of solutes referred in Tables 20.4.16 to 20.4.20.

Table 20.4.16. Experimental solubility of ferulic and caffeic acid in ethyl lactate.[43]

1.40 wt% water in ethyl lactate		**< 0.03 wt% water in ethyl lactate**	
Ferulic acid			
T/K	**Solubility, wt%**	**T/K**	**Solubility, wt%**
298.2	12.55	296.2	4.47
313.2	14.56	303.1	5.61
328.2	16.33	312.7	6.85
343.2	17.99	323.0	8.36
		333.3	9.71
Caffeic acid			
T/K	**Solubility, wt%**	**T/K**	**Solubility, wt%**
298.2	1.95	296.2	1.35
313.2	2.50	303.1	1.56
328.2	3.06	312.7	1.80
343.2	3.47	323.0	2.15
		333.3	2.59

The chemical structures of ferulic acid and caffeic acids are quite similar (Figure 20.4.15) while their solubility in ethyl lactate are quite different (Table 20.4.16). For example, at 333.3 K the solubility of ferulic acid was 9.71 wt%, and that of caffeic acid

was 2.59 wt%. That is, the substitution of one hydroxyl group of caffeic acid by a methyl ether group enhanced significantly solubility. Furthermore, the solubilities observed for vanillic and ferulic acids at 333.3 K were 7.58 and 9.71 wt%, respectively, indicating that the presence of a longer acid alkyl chain in the phenolic acid only slightly increased the solubility.

Table 20.4.17. Experimental solubility of vanillic acid in ethyl lactate.[43]

1.40 wt% water in ethyl lactate		< 0.03 wt% water in ethyl lactate	
T/K	**Solubility, wt%**	**T/K**	**Solubility, wt%**
298.2	3.80	296.2	3.93
313.2	4.98	303.1	4.51
328.2	6.73	312.7	5.31
343.2	8.11	323.0	6.20
		333.3	7.58

The relative affinity of the studied solutes to ethyl lactate followed the order: thymol >> ferulic acid > vanillic acid > caffeine > caffeic acid. As expected, the solubility of all studied solutes in ethyl lactate was moderately enhanced by the temperature rise. Thymol is extremely soluble in ethyl lactate, reaching concentrations up to 91 wt% at 317.8 K, which could be explained by its relatively low melting point and enthalpy of fusion.

Table 20.4.18. Experimental solubility of caffeine in ethyl lactate.[43]

1.40 wt% water in ethyl lactate		< 0.03 wt% water in ethyl lactate	
T/K	**Solubility, wt%**	**T/K**	**Solubility, wt%**
298.2	3.12	296.2	2.35
313.2	4.92	303.1	3.21
328.2	6.69	312.7	4.09
343.2	8.09	323.0	5.14
		333.3	6.63

Table 20.4.19. Experimental solubility of thymol in ethyl lactate.[43]

1.40 wt% water in ethyl lactate		< 0.03 wt% water in ethyl lactate	
T/K	**Solubility, wt%**	**T/K**	**Solubility, wt%**
301.4	72.36	301.0	72.39
304.3	75.25	303.5	74.56
307.5	78.74	307.5	78.60

Table 20.4.19. Experimental solubility of thymol in ethyl lactate.[43]

1.40 wt% water in ethyl lactate		< 0.03 wt% water in ethyl lactate	
T/K	**Solubility, wt%**	**T/K**	**Solubility, wt%**
307.8	78.90	308.4	79.96
308.3	79.33	309.3	81.29
316.5	90.12	311.0	82.74
318.6	92.32	313.3	85.83
		317.8	90.95

The solubility data reviewed in Tables 20.4.16 to 20.4.19 reveal that the solubility of solutes was differently influenced by the presence of water in ethyl lactate. For example, the solubility of thymol was not changed by water, those of vanillic acid and caffeine were only slightly influenced, and a significant increase in the solubility of ferulic and caffeic acid was observed when the content of water in ethyl lactate was increased. Taking into account the low solubility of ferulic and caffeic acid in water, this solubility enhancement suggests a co-solvent effect which may have implications in potential extraction processes.

Table 20.4.20 shows a comparison between the solubility at ambient temperature (298 K) and pressure of several high valued bioactive substances in ethyl lactate and in water. As can be observed, caffeine has similar solubility in both solvents (around 2 wt%), while the solubility of phenolic acids and catechins are considerably higher in ethyl lactate than in water. As it will be discussed later, these physical characteristics can be exploited to study the development of novel extraction and separation processes for the food and phytochemical industry.

Table 20.4.20. Solubility (wt%) of several bioactive substances in ethyl lactate and water at ambient temperature and pressure (298 K and 101.3 kPa).

	Ethyl lactate	**Water**
Caffeic acid	1.4	0.1
Caffeine	2.3	2.2
Vanillic acid	3.9	0.2
Ferulic acid	4.5	0.6
(+)-Catechin	2.3	0.2
Chlorogenic acid	9.7	2.5

The experimental values obtained by Manic *et al.*[43] were further modeled. In the case of modeling the solubility of a pure solid solute in a liquid solvent (ethyl lactate), the equifugacity equilibrium condition for solvent (1) and the solid (2) is:

$$f_2^S = f_2^L \qquad [20.4.4]$$

where: f_2^S is the fugacity of the solute in the solid phase and f_2^L is the fugacity of the solute in the liquid ethyl lactate phase. The solute fugacity in the liquid phase can be referred to as the fugacity of the pure solute in liquid state f_2^0:

$$f_2^L = \gamma_2 x_2 f_2^0 \qquad [20.4.5]$$

where: γ_2 is the activity coefficient of the solute in the liquid phase, x_2 is its molar fraction (solubility) and f_2^0 is the liquid-phase standard state fugacity that typically is taken as the pure-liquid fugacity at the system temperature and at pure-liquid vapor pressure, with the corresponding corrections for pure-fluid vapor-phase non-ideality and for the effect of total pressure.

Replacing Eq. [20.4.5] in Eq. [20.4.4], the following relation for the solubility is obtained:

$$\ln x_2 = \ln((f_2^S/f_2^0) - \ln\gamma_2) \qquad [20.4.6]$$

When the mixture temperature is lower than the solute triple point temperature, f_2^0 stands for the pure solute in a hypothetical liquid state. Additionally, for most substances, there is a little difference between the triple point temperature and the normal melting temperature. Thus, the ratio f_2^S/f_2^0 can be calculated as follows:

$$\ln(f_2^S/f_2^0) = -\frac{\Delta H_{m_2}}{R T_{m_2}}\left(\frac{T_{m_2}}{T} - 1\right) + \frac{\Delta C_{p_2}}{R}\left[\left(\frac{T_{m_2}}{T} - 1\right) + \ln\left(\frac{T}{T_{m_2}}\right)\right] \qquad [20.4.7]$$

where: T_{m_2} and ΔH_{m_2} are, respectively, the solute normal melting temperature and the enthalpy of fusion, whereas ΔC_{p_2} is the difference between the heat capacity of the pure liquid and solid solute.

Eq. [20.4.6] and Eq. [20.4.7] were applied to calculate the solubility of phenolic acids (caffeic, vanillic and ferulic acids) in pure ethyl lactate. The solute activity coefficients were calculated using UNIFAC group contribution method.[44] The enthalpies of fusion, melting temperatures and differences in heat capacities of the solutes, along with the UNIFAC group interaction parameters were taken from the literature.[43] Appendix B includes pure solute physical properties together with UNIFAC model equations and group interactions parameters, which are required to carry out the solubility calculations.

Figure 20.4.16 shows a comparison between the experimental solubility given in Tables 20.4.16 and 20.4.17 (ethyl lactate with less than 0.03 wt% of water) and the solubility calculations performed with the UNIFAC model. The absolute average deviations (AAD) were calculated as follows:

$$AAD(\%) = \frac{1}{NP}\sum_i \frac{\left|w_i^{calc} - w_i^{exp}\right|}{w_i^{exp}} \times 100 \qquad [20.4.8]$$

where w_i^{calc} and w_i^{exp} is the calculated and experimental mole fraction solubility, respectively, and NP is the number of available solubility points. The AAD obtained were 11.4%

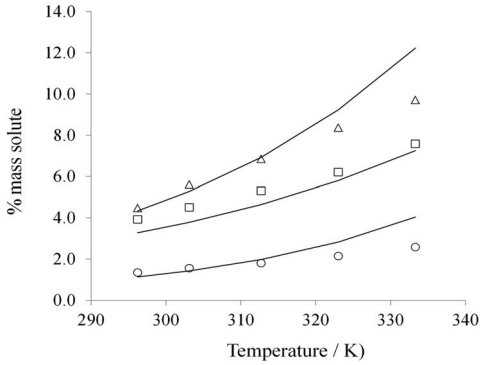


Figure 20.4.16. Solubilities of phenolic acids in ethyl lactate: (□) vanillic acid, (△) ferulic acid and (○) caffeic acid. Solid lines: thermodynamic modeling using UNIFAC.

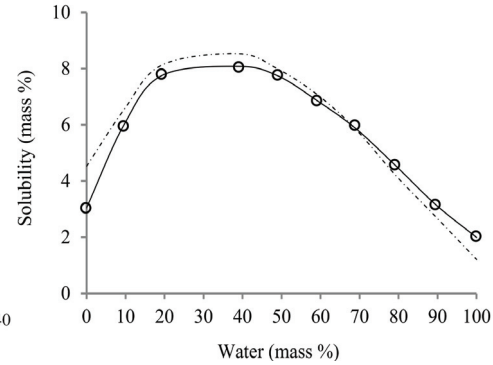


Figure 20.4.17. Solubility (mass %) of caffeine in ethyl lactate + water mixtures at atmospheric pressure and 25ºC: experimental values (○); UNIFAC (– –) and UNIQUAC (—).

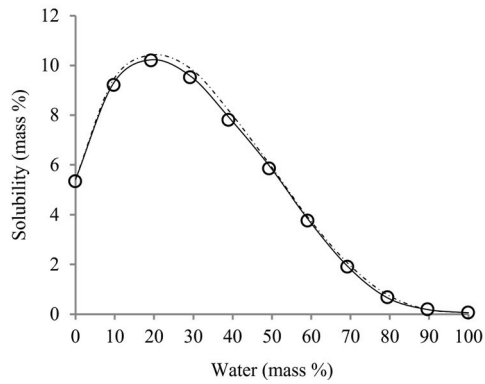


Figure 20.4.18. Solubility (mass %) of ferulic acid in ethyl lactate + water mixtures at atmospheric pressure and 25ºC: experimental values (○); UNIFAC (– –) and UNIQUAC (—).

for vanillic acid, 9.6% for ferulic acid and 24.7% for caffeic acid.

According to the deviations obtained, it can be concluded that a satisfactory prediction of the solubility of solid phenolic acid in ethyl lactate can be achieved using the equifugacity equilibrium condition and UNIFAC group contribution approach to calculate the activity coefficient of the phenolic acid in the liquid ethyl lactate-rich phase.

Based on the results reported by Manic *et al.*[43] and the possible co-solvent effect observed, Villanueva-Bermejo *et al.*[45,46] studied the solubility of caffeine[45] (Figure 20.4.17) and ferulic acid[46] (Figure 20.4.18) in a wide range of ethyl lactate + water solvent mixture compositions, at 25ºC and atmospheric pressure. The authors demonstrated that the solubility of both compounds in the mixtures was considerably higher than in the corresponding neat solvents. In the case of caffeine[45] (Figure 20.4.17), concentrations of water around 40-50% (mass%) in ethyl lactate led to a caffeine solubility close to 8% mass – values up to 3-fold higher than those in the pure solvents. In the case of ferulic acid,[46] the solubility attained a maximum of 10.2 mass% (mixture comprising 20% of water in ethyl lactate). This solubility was 2-fold higher than in pure ethyl lactate and almost 170-fold higher than its solubility in water (Figure 20.4.18).

Furthermore, Villanueva-Bermejo *et al.*[46] used UNIQUAC and modified UNIFAC (Dortmund) to represent the solubility of ferulic acid and caffeine in the ethyl lactate +

water mixed solvent. UNIQUAC model provided an excellent correlation capacity for both systems (the adjusted parameters are given in Table 20.4.21) with an overall AARD < 1.5%. On the other hand, UNIFAC model produced good results only for the ferulic acid solubility (AARD = 4.8%, see Figure 20.4.18) and just qualitative predictions for caffeine (AARD of 14.0%, see Figure 20.4.17), due to a lack of parameters in the UNIFAC matrix to represent the caffeine molecule (a combination of the existing functional groups that most closely resemble caffeine molecule were used).

Table 20.4.21. UNIQUAC parameters obtained in the modeling of the solubility of ferulic acid and caffeine in ethyl lactate + water mixtures.

Ferulic acid + ethyl lactate + water system			
	Ethyl lactate	**Water**	**Ferulic acid**
Ethyl lactate	–	3203.822	-291.214
Water	659.854	–	-314.750
Ferulic acid	411.230	-289.366	–
Caffeine + ethyl lactate + water system			
	Ethyl lactate	**Water**	**Ferulic acid**
Ethyl lactate	–	3509-218	-408.340
Water	702.340	–	-390.855
Ferulic acid	633.301	-335.929	–

20.4.2 INDUSTRIAL APPLICATIONS OF ETHYL LACTATE AND POTENTIAL USES

Ethyl lactate is a flavor compound found naturally in small quantities in a wide variety of foods such as meat, some fruits, soy products, as well as fermented foods such as wine or beer.

This organic ester has recently attracted a great attention due to its physical, chemical and environmentally benign properties. This is evidenced by the considerable number of applications reported in the last decade, in which ethyl lactate has been studied as a green and efficient alternative to traditionally employed solvents. On this basis, many processes have been studied and patented in order to reduce its production cost to a competitive level and to promote its use as a replacement of non-green solvents, whose average selling prices have increased drastically due to crude oil price rise.

Ethyl lactate was approved by the U.S. Food and Drug Administration (FDA) as a food additive. It is also used as an excipient in cosmetic industry, but its main application is as solvent. Ethyl lactate has many powerful features to be used as a solvent replacing traditional toxic halogenated and petroleum-derived solvents: low toxicity, non-flammability, good solvating ability, it is fully biodegradable, non-corrosive, non-carcinogenic, non-ozone depleting and was affirmed as GRAS (Generally Recognized as Safe).

Industrially, ethyl lactate, along with other lactate ester, is an attractive solvent for the coating industry (dissolution of coatings for wood, polystyrene, metals and magnetic tapes),[47] for the phytosanitary industry (dissolving active pesticide and herbicide com-

pounds) and an excellent cleaner solvent for the polyurethane industry (ethyl lactate can dissolve many polyurethane resins), for electronic and precision parts (where the solvent used for these cleaning applications cannot leave residues), and for a variety of metal surfaces. Moreover, ethyl lactate is able to successfully remove oils, paint, dried ink, adhesives and solid fuels.[6,48] This ability is owing to its high boiling point, low vapor pressure, low surface tension, and a high solvent power that allows covering a wide range of polarities.[6] These interesting properties cause ethyl lactate to be replacing solvents such as N-methyl pyrrolidone, butan-2-one (MEK), 4-methylpentan-2-one (MIBK), acetone, toluene, and xylene in numerous industrial processes.

Ethyl lactate has both pharmaceutical and cosmetic applications, since it can act as excipient improving the solubility of a great number of biologically active compounds (antihistamines, antivirals, antibiotics…) without undesirable side effects on health.[49] For instance, ethyl lactate can be used in embolic compositions as biocompatible embolic solvent to solubilize biopolymers responsible for embolization of the blood vessel for treating vascular lesions[50] or in veterinary anthelmintic and antifungal formulations.[51,52] Ethyl lactate can also act as topical penetration enhancing agent assisting the deep penetration delivery of cosmetic and pharmaceutical agents into dermal and subdermal layers of skin. Moreover this compound has a smooth emollient effect on skin. Thus ethyl lactate can be involved in creams, powders, masks, serums, pastes, sprays and other formulas, such as topical inflammation control massage lotions or solubilized vitamin C facial cleanser.[53] Ethyl lactate has also anti-acne properties. Combined with salicylic acid provides a new synergistic treatment for acne.[53,54] Furthermore, it has been observed that ethyl lactate might increase the protection time in insect repellent formulations against *Aedes aegypti* mosquitoes.[55]

Ethyl lactate is being studied as a solvent for soil washing treatments. For instance, the amendment with the highly biodegradable chelating agent ethylenediaminedisuccinic acid (EDDS) and ethyl lactate enhanced the removal of copper.[56] Ethyl lactate has demonstrated to be effective by itself or in combination with other agents (such as willow, ethanol, zero-valent magnesium, and Fenton´s reagent) for the remediation of polycyclic aromatic hydrocarbons and cadmium contaminated soils.[57-62]

Likewise, ethyl lactate has been studied as a candidate to be used for the dissolution/precipitation and processing of poly(lactic acid) (PLA), a biodegradable polymer produced from lactic acid which is used, among others, in packaging and in medical and pharmaceutical areas.[39,63]

This biorenewable solvent is also being explored as a green reaction medium for numerous and varied processes in chemical synthesis.[64,65] Due to the great importance that ethyl lactate is acquiring on this subject, which is reflected in the number of works reported in the last decade, the use of this bio-based solvents as a reaction medium for chemical synthesis is reviewed in Section 20.4.4.

Moreover, ethyl lactate is being studied as a substrate for the production of high value-added chemicals, such as 1,2-propanediol, a compound mainly used for the production of unsaturated polyester resins, and as excipient and additive in pharmaceuticals, cosmetics and foods.[66,67] Ethyl lactate has also been employed as a chiral template together

with L-arabinose for the synthesis of the bioactive compound (-)-synargentolide B and its analogous,[68] as well as for the production of optically pure propionate derivatives[69] and graphene sheets,[70] among others. Furthermore, ethyl lactate has been studied for the green synthesis of scaffolds, such as polylactic acid organogels[71] and polycaprolactone/graphene oxide microporous systems[72] with tailored properties aimed at biomedical applications for tissue engineering.

With regards to other applications, ethyl lactate has been explored as a greener alternative in analytical processes. In the analytical chemistry, the sample preparation stage and liquid chromatography require relative large amounts of high-purity organic solvents. One of the trends that is gaining more attention is the application of bio-based solvents, among them ethyl lactate, to replace the environmentally hazardous petroleum-derived solvents.[73,74]

Finally, it should be pointed out the research carried out in last years on ethyl lactate as an extraction solvent of food compounds. Several reported potential applications are related to the fractionation and extraction of edible oil compounds,[40,41,75,76] the extraction of carotenoids from different plants,[77,78] caffeine from green coffee beans and green tea leaves,[79,80] volatile oil compounds,[81,82] and phenolic compounds.[83] The use of ethyl lactate as a potential solvent for food industry is reviewed in more detail in Section 20.4.5.

20.4.3 PRODUCTION OF ETHYL LACTATE

An intense work is being carried out at present for the improvement and/or design of processes, more efficient and greener, to economically produce ethyl lactate. Ethyl lactate can be commercially produced by esterification of lactic acid with ethanol with water as by-product (Figure 20.4.19). Both building blocks, in turn, can be obtained in biorefineries from crops by-products and cellulose feedstock by fermentation. Lactic acid formed *via* fermentation needs an intensive purification since the fermented broth contains a considerable amount of impurities, such as residual sugars, bacterial cells, organic acids, and other organic compound, as well as materials added during the production process, such as calcium carbonate to neutralize the lactic acid.[84] These compounds interfere with the yield and purity of the final product. For that reason, different procedures (solvent extraction, electrodialysis, microfiltration, adsorption and electrodeionization, among others) have been introduced in order to purify the lactic acid from the fermentation broth.[85] On account of these limitations, other approaches and raw materials have been proposed in the last decade for the alternative production of alkyl lactates. In this sense, a number of works have described the synthesis of ethyl lactate through a different route from triose sugars, mainly dihydroxyacetone, which can be obtained from cellulose feedstock, and catalytically from glycerol, a by-product of oil transesterification in biodiesel production.[86] The process from trioses presents the advantage of not being equilibrium-limited and several heterogeneous catalysts, such as zeolites,[87,88] thin-modified materials,[89-92] and clays[93,94] have been recently investigated.

Ethyl lactate is also obtained from ammonium lactate instead of lactic acid (Figure 20.4.20). The fermentation process carried out in the presence of ammonia to produce ammonium lactate and the subsequent reaction of this ammonium lactate with ethanol gives ethyl lactate and ammonia as products.[95-97] By using ammonium lactate as a raw

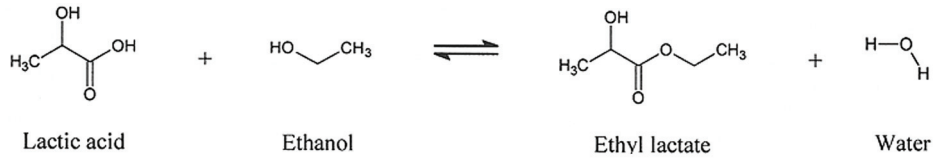


Figure 20.4.19. Esterification of lactic acid with ethanol.

material to produce ethyl lactate, some post-treatment steps can be avoided, such as the addition of calcium carbonate (used to neutralize the lactic acid during fermentation) and the subsequent acidification with sulfuric acid to convert the salt into lactic acid and insoluble calcium sulfate, preventing the gypsum-generating process. Furthermore, ammonium lactate is more soluble in water than calcium lactate.[98] Nevertheless, the esterification rate with ethanol is low and relatively large amounts of ammonium lactate are converted to lactamide, an undesired secondary product generated from the ammonia, especially when it is not removed rapidly from the fermentation broth.[99] On account of this, Kasinathan *et al.*[100] developed a process for the production of ethyl lactate, in which ammonium lactate was fragmented into ammonia and lactic acid at high temperature in an organic solvent. Ammonia was removed in order to prevent the lactamide production, lactic acid was dissolved in the organic solvent and finally it reacted with ethanol to produce ethyl lactate. Tributyl phosphate, triethyl phosphate, dimethyl sulfoxide and N-methyl pyrrolidine were assessed as solvents. Triethyl phosphate showed to be the most efficient solvent, which allowed achieving a higher ethyl lactate yield and lower by-products levels.

Another route to produce ethyl lactate involves the use of lactide, a cyclic dimer of lactic acid.[101,102] Lactide is the main building block for the production of the poly(lactic acid) biopolymer, which is replacing the traditional fossil-based polymers for packaging applications and it is being intensely studied for its application in other fields, as for exam-

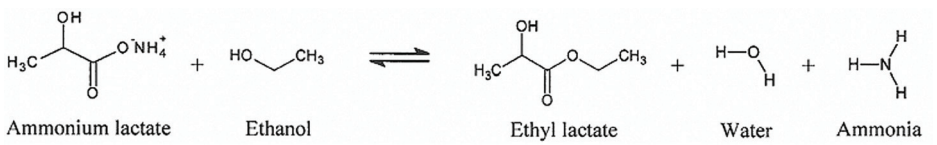


Figure 20.4.20. Esterification of ammonium lactate with ethanol.

ple, biomedicine. The polycondensation of lactic acid to obtain the biopolymer does not generate a high-quality product with a controlled molecular weight and low polydispersity. For this reason, manufacturers obtain this product *via* lactide, a cyclic intermediate which forms a higher molecular weight and monodisperse poly(lactic acid) through the ring-opening polymerization in a more controlled manner. The synthesis of lactide from lactic acid is currently performed by energy-intensive processes which involves a great part of the polylactide production costs.[103] Therefore, the use of lactide and polylactides as starting materials for the production of alkyl lactates is not economically viable at present.

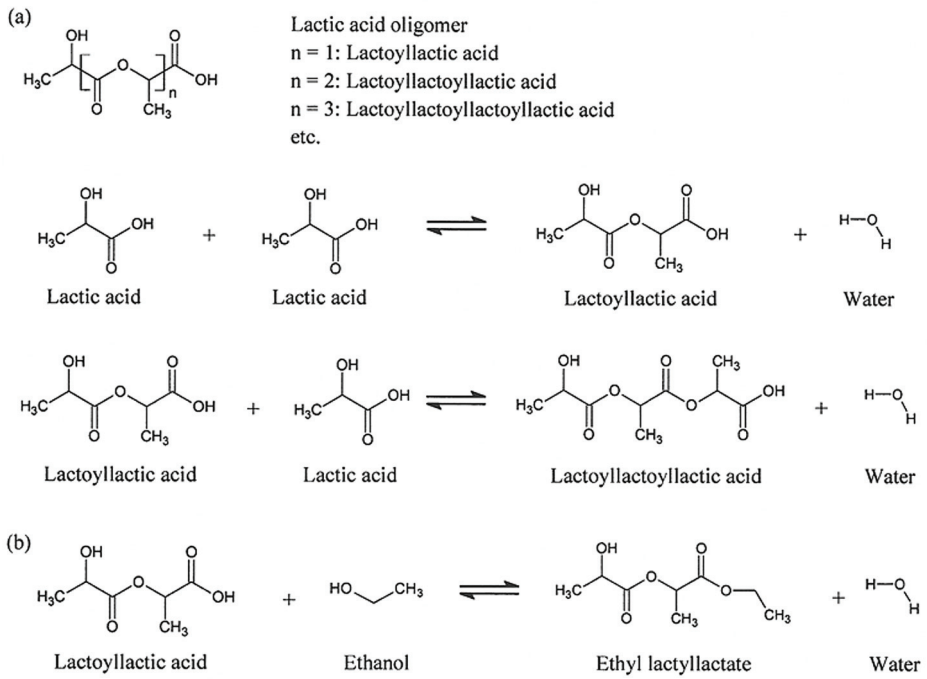


Figure 20.4.21. Lactic acid oligomerization (a), esterification of lactic acid oligomer (b) and hydrolysis equilibrium.

With regards to the esterification of lactic acid with ethanol, this process is important not only to produce ethyl lactate, but also as a step in the purification of lactic acid itself from the fermentation broth. Due to the selectivity and reactivity between carboxyl and hydroxyl groups, esterification can be applied as an effective downstream method to isolate lactic acid on account of the different boiling point of lactic acid esters. Lactic acid molecules are reacted with ethanol and other alcohols such as methanol and butanol to form alkyl lactates and, once they have been purified, lactate esters are hydrolyzed into lactic acid and a high-purity product can be obtained.[104-107]

Lactic acid has a carboxyl and hydroxyl functional group and because of its bifunctional nature, lactic acid can undergo intermolecular esterification to form linear dimers, trimers and higher lactic acid oligomers. At the same time, these polymers can be hydrolyzed into lactic acid monomers when water is present or can undergo esterification and transesterification (alcoholysis) with ethanol, leading to a mixture of acid and ester monomers and oligomers (Figure 20.4.21). The ethyl lactate yield and process layout are adversely affected as the self-esterification increases. It has been shown that dilute lactic acid solutions are almost exclusively formed by lactic acid monomers. At higher lactic acid concentrations, higher temperature and lower water and ethanol concentrations, oligomerization rises.[108-110] However, concentrated lactic acid solutions are required in

order to produce ethyl lactate economically. A certain amount of water might be beneficial to avoid oligomerization,[111] but an excess limits the esterification process and large quantities of alcohol and energy will be required.[112]

Esterification is a reversible self-catalyzed reaction, which is thermodynamically limited, thereby, lower conversions and low purity products are achieved. For this reason the use of catalysts is critical. Homogeneous mineral acids, such as sulfuric acid, phosphoric acid, or hydrogen chloride, have traditionally been used to promote efficiently the esterification of varied carboxylic acids, however, their use presents drawbacks, such as the production of corrosive liquid waste, corrosion of equipment, difficulties in recovering the catalyst, or a larger amount of side reactions. Unlike this, the use of greener heterogeneous acid catalysts, such as acid-treated clays, heteropolyacids, zeolites, ion exchange resins (the most commonly used solid catalysts for this purpose) like Amberlyst 15-wet and Nafion NR50, provide a longer lifetime and they are an alternative to the drawbacks described above.[9]

Several authors have reported kinetic studies on the esterification of lactic acid with ethanol, which have been carried out with different catalysts (mainly heterogeneous catalysts), at different temperatures, lactic acid-to-ethanol ratios and different concentrations of aqueous lactic acid.[104,110,113-117] In most studies, the presence of oligomers was not considered, even when high lactic acid concentrations were used.[9]

There is a considerable number of processes in which ethyl lactate is produced by esterification in batch reactors until a certain amount of water is formed, equilibrium is reached and then ethyl lactate is purified by distillation or other methods. These processes require excess of ethanol to overcome the equilibrium limitations and achieve higher conversions. In addition to this, the separation of the products from the equilibrium mixture is technically difficult, due to the mixture of compounds and unconverted reactants.[9] In order to improve the ethyl lactate production and reduce the investment and operating costs, an alternative to conventional method consists in combining a separation unit with the reaction stage. In these hybrid processes carried out in multifunctional reactors, at least one of the products is continuously removed from the reaction medium so equilibrium is shifted to products formation according to Le Châtelier's principle. In this regard, some reactive separation processes studied for the ethyl lactate production are presented below.

One of them employs membrane-based separation processes connected to the esterification reaction. In this respect, vapor permeation and pervaporation processes have been applied for the production of ethyl lactate in membrane reactors and different hydrophilic membranes, such as polymeric, ceramic, zeolites and organic-inorganic hybrid membranes have been tested. In one of the reported layouts, the membrane module for water removal is located outside the reactor unit and the retenate is recirculated to the reactor.[118,119] In another design, the membrane module is placed inside the reactor, but the membrane does not participate in the reaction directly and simply acts as a filter,[120,121] and in the third configuration, the membrane is impregnated with the catalyst (catalytic membrane reactor),[122] so it participates in the reaction catalysis and the intensive contact allows a high catalytic activity with negligible mass transport resistances.[123] Most recent works have been conducted by the application of catalytic membranes (see Table 20.4.22).

Zhang *et al*.[124] studied the effects of several operational parameters in a pervaporation-assisted esterification process catalyzed by Amberlyst 15. For the study, three different composite membranes were evaluated (glutaral crosslinked chitosan (GCCS)/carbomer (CP)/polyacrylonitrile (PAN); glutaral crosslinked gelatin (GCGE)/PAN; and glutaral crosslinked hyaluronic acid (GCHA)/hydrolysis modification (HM)-PAN). In general, the influence of the operational parameters on ethyl lactate yield for the three kinds of membrane systems showed the same trend. Medium-levels of catalyst and ethanol contents increased the ethyl lactate conversion. In the case of the catalyst, the increase in the loaded amount could accelerate the esterification rate and shorten the reaction time, but it could also affect the membrane separation performance. In this study, the increment from 3% to 4% (expressed as mass ratio of catalyst to lactic acid) only involved a slight increment in the conversion rate. An excess of ethanol promoted the esterification reaction. Moreover, in the system studied by authors, a higher molar ratio of ethanol to lactic acid implied a lower water concentration (the lactic acid purity employed in the feeding solution was 88 wt%) and the high removal of water led to a promotion of the reaction. Nevertheless, when the ethanol-to-lactic acid molar ratio was the largest (4:1), the low water content in the system reduced the dehydration performance of the membranes assayed. With regards to the temperature effect, the ethyl lactate conversion increased with the operating temperature due to the higher esterification rate and the improved dehydration performance of pervaporation membranes. At the optimal conditions (3 wt% catalyst, 3:1 ethanol-to-lactic acid molar ratio and 80ºC), the composite membrane GCHA/HM-PAN demonstrated to be the most effective.

Table 20.4.22. Catalytic membrane reactors applied for the production of ethyl lactate (EL) by esterification of lactic acid (LA) and ethanol (ETOH).

Catalyst	Membrane[a]	ETOH/LA molar ratio	Temp. ºC	Time h	EL[c] conversion	Ref.
Amberlyst 15	GCHA/HM-PAN	3:1	80	8	95[d]	124
Boric acid	CMC	3:1	75	7	83	125
Poly(styrenesulfonic acid)	CMC	1:1	75	7	80	126
p-Toluenesulfonic acid	Polypropylene	5500:1	65	–	30[e]	127
Amberlyst 36	CA	3:2[b]	60	–	75[f]	128
Rhizomucor miehei	Alginate	1:1	50	6	63	129
Thermomyces lanuginosus	Alginate	1:1	50	6	63	130

[a]GCHA/HM-PAN: glutaral crosslinked hyaluronic acid/ hydrolysis modification of polyacrylonitrile. CMC: carboxymethyl cellulose. CA: cellulose acetate. [b]Mass ratio. [c]Mass of LA converted/initial mass of LA. [d]Mass of EL obtained/maximal mass of EL achievable. [e]Concentration of LA in feed solution/concentration of EL in stripping solution. [f](initial concentration of LA – concentration of ETOH)/concentration of EL.

Nigiz and Hilmioglu[125] employed a boric coated crosslinked carboxymethyl cellulose composite catalytic membrane in a pervaporation-assisted membrane reactor to produce ethyl lactate. Authors concluded 1.5 wt% of carboxymethyl cellulose concentration

as the optimal to achieve the highest conversion. Higher concentrations reduced the chain mobility and the water transition. In the case of the catalyst concentration, with increasing loading, the conversion increased as well, but the membrane selectivity was lower. Temperature positively affected the reaction and the permeation rate, so 75ºC lead to the best results. The highest initial ethanol concentration enhanced the acid conversion. Moreover, the lactic acid employed for the experiments contained around 20% of water, so an excess of alcohol implied a lower water concentration and, therefore, the esterification run through the product side. Therefore, the highest lactic acid conversion (83%) was reached at 75ºC, 5% catalyst, 1.5% polymer and 3:1 (ethanol:lactic acid molar ratio).

In a further contribution, Nigiz and Hilmioglu[126] studied the esterification reaction by using a catalytic polymeric membrane composed of a blend of poly(styrenesulfonic acid)-carboxymethyl cellulose (PSSA/CMC). The influence of the PSSA/CMC mass ratio (0.5, 1 and 1.7%), temperature (55, 65 and 75ºC) and the initial feed ethanol-to-lactic acid mol ratio (1, 2 and 3) were evaluated. When the highest PSSA/CMC ratio and temperature (1.7 and 75ºC, respectively) were applied, the conversion of lactic acid increased up to 74%. Nevertheless a reduction in the water separation selectivity was produced, so the probabilities of a reactant loss increased. When the initial feed molar ratio increased, the conversion reached 93%. Nevertheless, the higher alcohol molar ratio in the reactor reduced the final purity of ethyl lactate. In this sense, when 1:1 ethanol-to-lactic acid molar ratio was formulated, 80% (v/v) purity ethyl lactate was obtained after 7 h reaction time. Teerachaiyapat and Ramakul[127] carried out the esterification of lactic acid and ethanol in a hollow fiber reactor by a liquid membrane mechanism and using p-toluene sulfonic acid as the catalyst. In the design performed (see Figure 20.4.22), the aqueous lactic acid in the feed solution was extracted-reacted with tri-n-octylamine to form complex species at the interface between the feed and liquid membrane. The formed species subsequently reacted with ethanol at the interface between the liquid membrane and the stripping phase to form ethyl lactate and revert to the original tri-n-octylamine, which diffused back to react with new lactic acid molecules in a new cycle. Authors evaluated as the main operational parameters on ethyl lactate yield, the concentration of tri-n-octylamine in the liquid membrane, the concentration of ethanol in the stripping solution and the temperature at different lactic acid concentrations. An increase in ethanol concentration and temperatures up to 65ºC led to higher ethyl lactate yields, while high tri-n-octylamine concentrations resulted in a lower conversion. At the optimal conditions, the yield of ethyl lactate was around 30% (expressed as the ratio

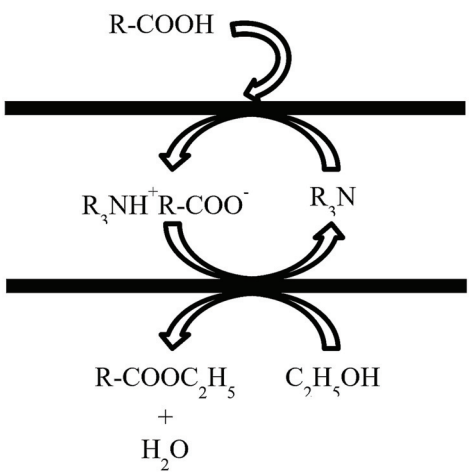


Figure 20.4.22. Scheme of the flow pattern in the hollow fiber reactor contained liquid membrane.

between the concentration of lactic acid in the feed solution and that for ethyl lactate in the stripping solution) when the concentration of lactic acid increased from 0.001 to 0.004 mol/L. However, when the concentration of lactic acid exceeded the aforementioned amount, the yield of ethyl lactate gradually decreased.

Okon *et al*.[128] studied the esterification process using different cation-exchange resin catalysts (Amberlyst 15, Amberlyst 16, Dowex 50W8x and Amberlyst 36) which impregnated a cellulose acetate pervaporation membrane, as well as a sweep gas at low pressure on the permeate side of the reactor to shift the chemical equilibrium to the product formation. Cellulose acetate membrane confirmed the selective removal of water from the esterification product. Amberlyst 36 and Amberlyst 16 were revealed as the most effective catalysts for the esterification process. In this case, an ethyl lactate yield of up to 75% was achieved by using a lactic acid-to-ethanol molar ratio of 2:3 wt% and 60ºC of temperature.

In other studies, lipase enzymes were used instead of heterogeneous catalysts for the esterification in biocatalytic membrane reactors (Table 20.4.22). In this case, the optimization of parameters, such as temperature and reactant concentrations are essential, not only to efficiently achieve a high yield in short times, but also to reach an optimal enzyme performance, avoiding its inactivation as a consequence of temperature and the high concentration of ethanol and lactic acid. Nigiz and Hilmioglu[129] studied the use of a *Rhizomucor miehei* lipase-coated alginate membrane for the esterification of ethyl lactate and ethanol in a pervaporation reactor. The increase in the amount of immobilized lipase led to higher lactic acid conversions. Nevertheless, a decreasing trend was observed with an enzyme loading of 1.25 g/110 cm^2 due to the agglomeration of the enzyme, which produced the block of enzyme active sites. In the case of temperature, a very sharp decline in conversion was observed at temperatures higher than 50ºC. On the other hand, membrane permeability, diffusion rates, the vapor pressure of components and flux increased with temperature. However, high temperatures decreased the selectivity of the membrane, so a better process performance was obtained at 50ºC. In the case of the alcohol-to-lactic acid molar ratio, good results were achieved when this value was 3:1. A significant decline was observed at 6:1 as a consequence of the inhibitory effect of substrate on the enzyme activity. In the case of the flux, the water caused a swelling of the membrane due to the hydrophilic nature of alginate polymer and the flux increased with increasing water content in the reaction medium. Therefore, the flux was favored by the high conversions. However, the excessive amount of swelling caused a non-selective permeation of compounds. Considering these facts, authors achieved an ethyl lactate yield of 63% after 6 h reaction time at the optimal conditions. In another contribution, authors explored *Thermomyces lanuginosus* as catalyst.[130] Authors assayed the same operational parameters as in the previous study for *Rhizomucor miehei*.[47] From both studies it can be concluded that both enzymes demonstrated the same efficiency for the production of ethyl lactate (see Table 20.4.22). Likewise, enzymes preserved their activity during the six experiments without a significant activity loss.

Another reactive separation process studied for the production of ethyl lactate is the reactive distillation (Figure 20.4.23). This concept is based on an integration of an esterification reactor and a reactive distillation column in the same unit. Gao *et al*.[131] studied the

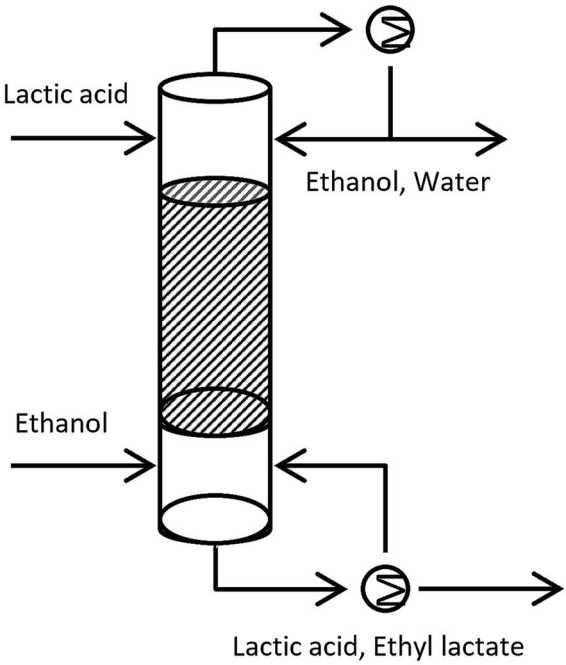


Figure 20.4.23. Basic schematic representation of a reactive distillation unit.

effect of several operation parameters on ethyl lactate yield: flow rate of feed lactic acid; ethanol-to-lactic acid ratio; and the effect of different feed points through the column. At studied conditions, only 52% of ethyl lactate yield was achieved. On the other hand, Asthana *et al.*,[112] using concentrated lactic acid solutions (88 wt%), achieved a lactic acid conversion of 93% and an ethyl lactate yield of 70%, with an ethyl lactate purity of 71% (mol%), avoiding the presence of water in the column bottom stream.

A novel reactive separation method consists of using a simulated moving bed reactor (SMBR), a type of continuous chromatographic reactor, which combines chemical reaction with continuous counter-current chromatography. Pereira *et al.*[132] reported an experimentally ethyl lactate productivity of 18.06 kg_{EL}/L_{resin}·day (mass of ethyl lactate produced per unit volume of catalyst employed and unit time) and an ethyl lactate purity of 95% at 50ºC. The catalyst used (Amberlyst 15 wet resin) acted also as water-absorbing resin. The maximum ethyl lactate productivity value achieved was 31.7 kg_{EL}/L_{resin}·day, 95% of purity and a lactic acid conversion of 100%, under optimal conditions. Nevertheless, a high consumption of ethanol was produced (7.6 L_{ETOH}/kg_{EL}).

In order to reduce the high ethanol consumption, Silva *et al.*[133] applied a theoretical approach to predict the production of ethyl lactate by a simulated moving bed membrane reactor (PermSMBR), in which hydrophilic membranes were integrated in the SMBR. In PermSMBR, each column contained the catalyst and a set of hydrophilic membranes to increase the water removal, leading to a better process performance. A theoretical model was developed to evaluate the PermSMBR process performance for different conditions. Authors concluded that ethanol consumption with SMBR and reactive distillation[112] was, respectively, 165% and 152% higher than that consumed with PermSMBR, for a similar ethyl lactate production.

Another reactive separation processes studied for ethyl lactate production is the catalytic extractive reaction (Figure 20.4.24). In this case, the esterification is performed in a biphasic liquid solvent system composed of a reactive polar liquid phase which contains

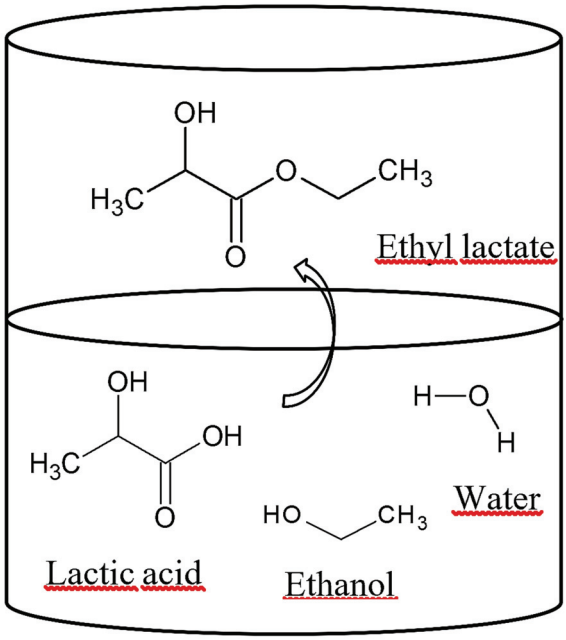


Figure 20.4.24. Scheme of the catalytic extractive reaction process.

the esterification constituents: lactic acid, ethanol and catalyst, and an extractive organic solvent, which is selective for the alkyl ester. Therefore, ethyl lactate should preferably be dissolved in the extractive organic phase shifting, in this way, the reaction equilibrium to the ester formation. The immiscible extractive solvent can be an aromatic or other solvent like toluene, benzene or diethyl ether, among others.[134] Nevertheless, it has also been used an immiscible solvent based on fatty acid methyl esters,[135,136] but in this case, the procedure represents a method to produce an organic biosolvent and not just ethyl lactate as solvent.

The production of ethyl lactate has also been studied through the enzymatic esterification of lactic acid with ethanol in ionic liquids (a non-conventional solvent), taking advantage of the enantioselectivity, regioselectivity, and chemoselectivity of enzymes such as lipase B from *Candida antárctica* (Novozyme 435), to produce enantiomerically pure ethyl lactate. Findrik *et al.*[137] employed an incubator working in batch mode and Cyphos 104 as ionic liquid. At 50°C, an ethanol to lactic acid ratio around 3:1, and 8% of water content in the lactic acid, authors obtained a lactic acid conversion of 60% after 5 h and almost 100% after 24 h. The temperature and water content were the most influential parameters of the variables studied.

Major *et al.*[111] evaluated the production of ethyl lactate by immobilized *Candida antarctica* lipase B (Novozyme 435) in two different types of media: organic solvents (hexane and toluene) and several ionic liquids. At the experimental conditions studied, the ionic liquids Cyphos 163, Cyphos 166, Cyphos 106, Cyphos 102, and Cyphos 110 showed self-catalytic activity unlike organic solvents. Cyphos 202 demonstrated to be the best medium for ethyl lactate production attending to the highest ethyl lactate yield (95%) obtained after 24 h of reaction. Moreover, this high yield was obtained with 20 times less enzyme than in toluene, and lactic acid could have been added more concentrated, reducing the amount of ionic liquid. The effect of the water content on ethyl lactate yield was also studied. Authors obtained a yield improvement when no water removal was done. In addition, a certain quantity may be necessary to avoid the formation of lactic acid poly-

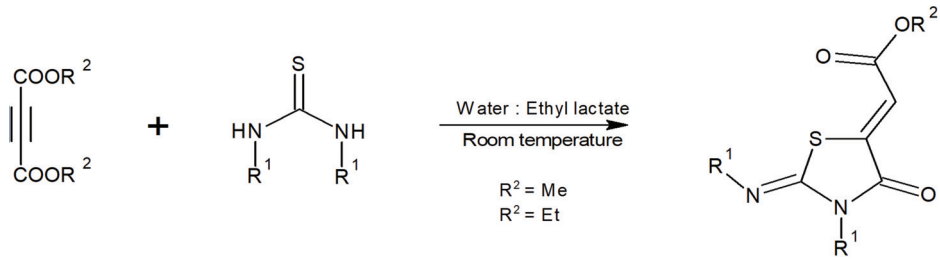
mers (and not only for the proper enzyme functioning) by shifting equilibrium towards dimerization, where water is formed again.

More recently, Koutinas *et al.*[138] explored different commercial and non-commercial enzymes and compared several organic media for the conversion of lactic acid and ethanol into ethyl lactate. Novozym 435 was selected as the catalyst to evaluate the performance of different lactic acid concentrations and organic solvents (ethyl acetate, 1,2-dichloroethane, chloroform, toluene, hexane, decane, lemon peel oil, and ethanol. The former acted both as reactant and solvent). Low yields were achieved by using the green solvents lemon peel oil and ethyl acetate. The production of ethyl lactate decreased when solvents with higher hydrophilicity (high logP values) were applied, probably due to a low solubility of the reactants. The increase in the lactic acid concentration led to lower yields, due to high acidity hindered the esterification activity of lipases and modified the solvent hydrophobicity character of the reaction medium. The highest yields were achieved in chloroform and hexane (88% and 75% yield, respectively). Afterwards, these two solvents were selected as the reaction medium to explore different commercial (Novozym 435, Lipozyme RM IM, Lipozyme TL IM) and non-commercial (heterologous enzymes from *Rhizopous oryzae* and *Candida rugose*) immobilized lipases. At the lowest lactic acid concentration (0.01 M), Novozym 435 was the most efficient lipase, especially in chloroform (88% ethyl lactate yield). In the case of non-commercial lipases, these enzymes did not carry out the esterification reaction under the conditions tested.

20.4.4 ETHYL LACTATE IN ORGANIC SYNTHESIS

With the exception of reactions carried out under solvent-free conditions,[139] the organic synthesis involves the use of solvents. In addition to act as a reaction medium, the solvents appear in the work up, purification, and final recrystallization steps, so the solvent selection is a critical step of the synthesis process and large amounts of waste may be generated.

Over the last decade, the interest in the agrochemical solvent ethyl lactate as a reaction medium for the organic synthesis, mainly of several biologically and drug-active molecules, has been rising with the aim of replacing the traditional toxic and non-environmental friendly organic solvents, such as chloroform, methylene chloride, and carbon tetrachloride, which have been commonly used in this area of chemistry. Besides the aforementioned green properties of ethyl lactate, such as being a biomass-based solvent, biodegradable, non-toxic and non-ozone depleting, it presents the advantage of being miscible with water and numerous organic solvents. This allows the polarity of ethyl lactate to be easily tuned, so that it makes this solvent especially useful for the chemical transformations. In this way, Bennett *et al.*[140] described the synthesis of different aryl almidines at ambient conditions using ethyl lactate. In order to evaluate the versatility of this solvent, authors used water as a co-solvent in different concentrations to optimize the solvent polarity, as well as 80% of d-limonene added to the ethyl lactate for the specific synthesis of the imine of p-anisidine and p-phenylbenzaldehyde. In all cases, the reactions were completed in short times and with yields higher than 90%. Subsequent to these findings, Choudhary and Peddinti[141] studied the production of thiazolidinone derivatives in water by tuning the polarity of the solvent with ethyl lactate. When the reaction was performed



R_1	Water : Ethyl lactate
Ph	40:60
C_6H_4-*m*-Me	50:50
C_6H_4-*p*-Me	50:50
C_6H_3-*m,m´*-dimethyl	50:50
C_6H_4-*p*-OMe	30:70
α-Naphthyl	40:60
Cyclohexyl	60:40
n-Propyl	60:40
Benzyl	20:80

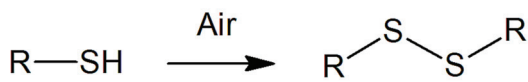
Figure 20.4.25. Synthesis of thiazolidinone derivatives in ethyl lactate:water mixtures.

using thiourea and dimethyl acetylenedicarboxylate (DMAD) in neat water, a high yield of product was obtained in few minutes without any further purification. Nevertheless, when N-substituted thiourea derivatives were assayed, the reaction took longer times for completion, low yields were achieved, and the product required purification steps. The addition of different concentrations of ethyl lactate to the water phase increased the solubility of reactants and led to obtaining a variety of thiazolidinone derivatives with yields higher than 93% and short reaction times (Figure 20.4.25). Likewise, Gao *et al.*[142] reported a strategy for the preparation of different bis(indolyl)methanes and 3,3-bis(indolyl)oxindoles *via* the condensation of indoles with aldehydes or isatins without catalyst by ultrasound-assisted organic synthesis. When benzaldehyde and indole were used as the model substrates, the reaction did not progressed or low yields were obtained by using water, ethyl lactate and other neat organic solvents (acetonitrile, PEG 400, ethyl acetate, methanol, chloroform, dioxane, dimethylformamide, and ethanol). However, yields higher than 90% were attained when an aqueous ethyl lactate mixture (3:2 v/v) was used. Subsequently, authors reacted a series of substituted aldehydes and isatins with indole under the same operational conditions to produce bis(indolyl)methanes and 3,3-bis(indolyl)oxindoles, respectively, and an array of these heterocyclic compounds were obtained with yields higher than 85%.

20.4.4.1 Ethyl lactate in coupling reactions

Ethyl lactate has been studied in coupling reactions for the transformation of different products, some of these being carried out without catalyst. Wan *et al*[143] was the first in developing a protocol to apply ethyl lactate as a reaction medium for Suzuki-Miyaura reactions. Various aryl bromides and iodides and arylboronic acids were assayed under ligand-free conditions and using a palladium catalyst in different ethyl lactate/water mixtures. The inclusion of aqueous ethyl lactate was tolerated by a broad range of substrates under mild reaction conditions, while the use of aqueous combinations with conventional organic solvents, such as DMF, DMSO, ethyl acetate, and dioxane, produced lower yields. Thus, ethyl lactate could act as a ligand in addition to improving the solubility of the organic reactants. Subsequently, Edwards *et al*.[144] carried out the Suzuki-Miyaura cross-coupling reaction in ethyl lactate using melamine as a ligand for a palladium acetate catalyst in open air conditions. Different aryl halides and aryl boronic acids were used and a wide tolerance was observed for the synthesis of ketones, amides, nitriles and thiophenes in high yields. Liu *et al*.[145] studied the ethyl lactate as a medium for the oxidative coupling reaction of thiols (Table 20.4.23) for the synthesis of aromatic disulfides under free-catalyst and additive conditions. The ability of ethyl lactate to dissolve oxygen from air promoted the thiol coupling reaction without the necessity of incorporating other external oxidants, since oxygen was the oxidant of the reaction, and the solubility of oxygen in the reaction medium may have played the main role in the transformation.

Table 20.4.23. Thiol-coupling reaction carried out in different organic solvents (1.0 mmol thiol, 1.5 mL solvent and stirred for 12 h).

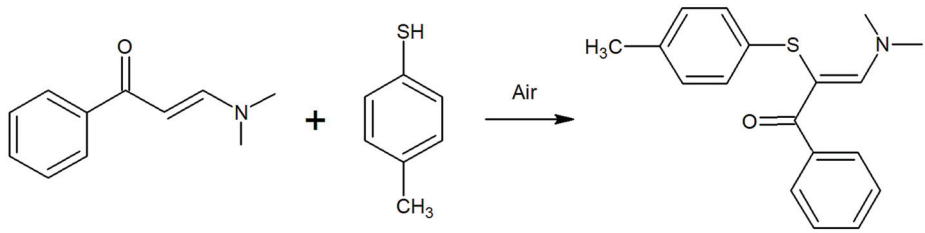


Solvent	Temperature (ºC)	Yield (%)
N,N-dimethylformamide	110	52
Toluene	110	15
Ethyl lactate	110	55
Ethyl lactate	90	68
Ethyl lactate	60	90
Ethyl lactate	40	19

Based on these findings, Wan *et al*.[146] investigated the ligand-free Glaser reaction of coupling terminal alkynes in ethyl lactate, using a copper catalyst in the presence of oxygen. The ethyl lactate-mediated protocol was applicable for several alkyl and aryl alkynes containing different groups, leading to the formation of homo- and cross-coupled 1,3-diynes. In this case, ethyl lactate acted not only as a medium in the reaction, but also as an external ligand of the cooper catalyst to promote the reactions. The oxygens from ester

and hydroxyl group in ethyl lactate act as chelating sites to form an active metal-ligand chelate complex with cooper that activates the catalyst to carry out the reaction. In another contribution, Wan *et al.*[147] envisaged the transition in metal-free catalytic synthesis of polyfunctionalized aminothioalkenes by sulfenylation of the alkene C–H bonds of different enaminones using KIO_3 as catalyst and ethyl lactate as the reaction medium in the presence of air. Based on the preliminary assays, the yields obtained with this organic solvent were higher than the achieved with conventional solvents, such as DMSO, dimethylformamide, and toluene (Table 20.4.24). Several aryl-, alkyl- and acyclic enaminones were conducted afterwards in ethyl lactate, which demonstrated a general tolerance in the synthesis of the corresponding aminothioalkenes.

Table 20.4.24. Synthesis of the aminothioalkene (3) from the enaminone (1) and thiophenol (2) in several organic solvents at different reaction conditions: reactive 1 (0.3 mmol) and 2 (0.36 mmol), catalyst (0.3 mmol), 12 h reaction time.

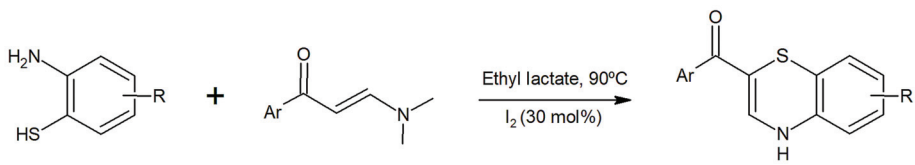


(1) (2) (3)

Solvent	Catalyst	Temperature, °C	Yield, %
DMSO	–	100	no product
DMSO	CuI	100	15
DMSO	KI	100	20
DMSO	$PhI(OAc)_2$	100	45
DMSO	KIO_3	100	60
DMSO	MnO_2	100	traces
N,N-dimethylformamide	KIO_3	100	70
Toluene	KIO_3	100	15
Acetonitrile	KIO_3	reflux	35
Ethanol	KIO_3	reflux	25
1,4-dioxane	KIO_3	100	18
Ethyl lactate	KIO_3	100	75
Ethyl lactate	KIO_3	100	80
Ethyl lactate	KIO_3	100	84
Ethyl lactate	KIO_3	100	80

Solvent	Catalyst	Temperature, °C	Yield, %
Ethyl lactate	KIO_3	100	78
Ethyl lactate	KIO_3	100	85
Ethyl lactate	KIO_3	100	80

Based on this, Zhong *et al.*[148] used 2-hydroxyphenyl-functionalized enaminones and thiophenol as the starting materials for the KIO_3-catalyzed synthesis of 3-thiolated chromones. Once again, ethyl lactate proved to be the most efficient reaction medium of those tested (DMF, toluene, ethanol, acetonitrile and water) to achieve the highest yields. By applying ethyl lactate as a solvent, a broad array of thiophenols and various enaminones were employed for the successfully synthesis of numerous 3-sulfenylated chromone products in high yields, even when heteroaryl thiols were used. Based on the promising results that ethyl lactate exhibited in mediating the enaminone C–H sulfenylation reaction[147] this green biobased solvent was applied for the synthesis of 1,4-benzothiazines by enaminone transamination and sulfenylation.[149] A series of metal-free tandem reactions between N,N-dimethyl enaminones and ortho-aminothiophenols provided the synthesis of several products *via* the generation of new C–S and C–N bonds by the cross-coupling of C(sp^2)–H and



Ar	R	Yield (%)
4-$CH_3C_6H_4$	H	84
C_6H_5	H	82
4-FC_6H_4	H	76
4-BrC_6H_4	H	75
2-$CH_3C_6H_4$	H	92
4-ClC_6H_4	H	70
4-$CH_3OC_6H_4$	H	85
4-$NO_2C_6H_4$	H	62
4-$CF_3C_6H_4$	H	66
3,4-$CH_2O_2C_6H_4$	H	81
3,4-$(CH_3)_2OC_6H_4$	H	80
3-$NO_2C_6H_4$	H	65
4-NCC_6H_4	H	74
napth-2-yl	H	84
napth-2-yl	5-CH_3	80
thiophen-2-yl	5-CH_3	66
4-$CH_3C_6H_4$	4-Cl	81

Figure 20.4.26. Synthesis of 1,4-benzothiazines in ethyl lactate.

C–N bond transamination using molecular iodine as catalyst. Polyfunctionalized enaminones containing groups such as alkyl, alkoxyl, halogen, trifluoromethyl, cyano in the aryl ring, as well as naphthyl and heteroaryl functionalized enaminones, exhibited fine tolerance to the synthesis (Figure 20.4.26).

In another work, Gao *et al.*[150] carried out the synthesis of several N,N-disubstituted β-enaminones and analogous nitro- and cyano-enamines *via* the transamination of N,N-dimethyl enaminones and secondary amines by employing ethyl lactate as medium without using a catalyst. Authors optimized the synthesis process and checked different media, including water, ethanol, dimethylformamide, acetonitrile, PEG-400, lactic acid, and ethyl lactate by reacting N,N-dimethyl enaminone and morpholine. The acidic condition of lactic acid avoided the formation of the reaction products. Compared to the other solvents, ethyl lactate provided the highest yield. Once the experimental conditions were optimized, the catalyst-free transamination of N,N-dimethyl enaminones and analogous enamines with different secondary amines was carried out, in general, with a good tolerance toward the synthesis of products. A possible role of ethyl lactate to carry out the transamination reaction could be through the hydrogen bond interactions of ethyl lactate with the dimethyl enaminone and the secondary amine, which could assist the substrates to keep close and facilitate the addition of the secondary amine to the enaminone C=C double bond.

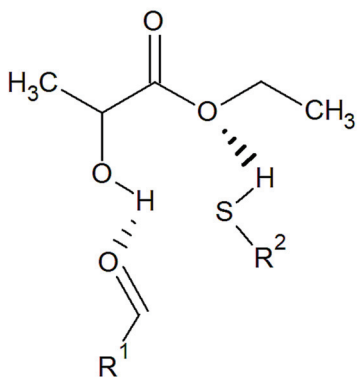


Figure 20.4.27. Proposed activation model of aldehydes and thiols by ethyl lactate.

In another contribution, Wan *et al.*[64] successfully employed ethyl lactate as a reaction medium for the thioacetalization of aldehydes with thiols and thiophenols at room temperature and without catalyst. The reaction of p-chlorobenzaldehyde with ethanethiol was conducted at different conditions, comparing ethyl lactate with other solvents (water, acetonitrile and p-xylene). According to the results, ethyl lactate was the best medium which allowed the formation of dithioacetal with higher yields and without using catalysts. After determining the optimal conditions, authors expanded the ethyl lactate-mediated synthetic protocol by subjecting different alkyl thiols, thiophenols and aldehydes to reaction. A number of functionalized dithioacetals were generally obtained with high diversity and relatively good yields (59-84%), especially by applying alkyl thiols as reactants. Here, ethyl lactate performed an important role other than providing the suitable environment for the reaction, as ethyl lactate also mediated the substrate activation. The hydroxyl group could activate the aldehyde *via* hydrogen bond and, simultaneously, the ethoxy group could do the same on the thiol substrate *via* interaction with the sulfhydryl group. An schematic representation of the proposed model is illustrated in Figure 20.4.27.

20.4.4.2 Ethyl lactate in multi-component and cycloaddition reactions

Paul and Das[151] performed the synthesis of coumarin fused indenodihydropyridine and dihydropyridine scaffolds. In preliminary experiments, several Lewis acid and organocatalysts were investigated using ethyl lactate as medium. In this case, ethyl lactate did not show a catalytic nature since the reaction proceeded slowly and low quantities of product were isolated in absence of catalyst. Organocatalysts demonstrated to be the most effective catalyst to carry out the reaction, especially lactic acid, which accelerated the reaction and provided a good yield. Subsequently, water and various green and non-green organic solvents (acetonitrile, dimethylformamide, acetonitrile, ethanol and ethylene glycol) were also screened. As can be observed in Table 20.4.25, ethyl lactate showed a higher efficiency (~85% yield), so the ethyl-L-lactate/lactic acid combination played a fundamental role for the synthesis. By means of this solvent/catalyst system, the reactions with unsubstituted benzaldehyde, electron-withdrawing and also with electron-donating para-substituted benzaldehydes ensued smoothly with moderate to good yields.

Table 20.4.25. Influence of the reaction medium over the synthesis of coumarin fused indenodihydropyridines. Reaction conditions: 4-nitrobenzaldehyde (1 mmol), 4-aminocumarin (1 mmol) and indane-1,3-dione (1 mmol) in the presence of lactic acid (2 mmol) at 100ºC and 2.0 equiv. catalyst.

Solvent	Yield, %
Ethyl lactate	85
Water	no product
Acetonitrile	no product
N,N-dimethylformamide	15
Ethanol	30
Ethylene glycol	40

Xu *et al*.[152] reported the ethyl lactate-mediated synthesis of dihydropyrimidinthiones (DHPMs) *via* three-component Biginelli reactions involving aldehydes, ethyl acetoacetate and thioureas. Several aldehydes and thiourea derivatives with and without N-alkyl substitution were employed to yield DHPMs with moderate to good yields. Kausar *et al*.[153] developed a catalyst-free green methodology for the synthesis of spirooxindole derivatives from the reaction between isatin, various amino compounds, and 1,3-dicarbonyl or 3-phenylisoxazolone by a three-component domino reaction in ethyl L-lactate medium. Isatin, 6-aminouracil, and 4-hydroxy-1-methylquinolinone were used as model substrates to check the effectiveness of ethyl lactate. For the purpose, the reaction was performed using pure ethyl L-lactate and then the polarity of the medium was modified by mixing this solvent with different proportions of water, ethanol and PEG-200. Pure ethyl L-lactate demonstrated to be the best solvent (90% yield after 60 min at room temperature) for the desired transformation. Moreover, it was more effective than highly polar mixed solvents, such as PEG-200/water and aqueous ethanol. By using ethyl lactate as a reaction medium,

authors could synthesize libraries of isoxazole-fused spirooxindole at mild conditions and achieving yields higher than 90% from a broad range of substrates.

Dandia *et al*.[154] used ethyl lactate to promote the synthesis of spirooxindole derivatives *via* 1,3 dipolar cycloaddition reaction of azomethine ylide, which was generated *in situ* by the decarboxylative condensation of substituted isatin and proline, with napthoquinone. Several solvents were explored by using isatin, proline, and naphthoquinone as model substrates to optimize the reaction. As can be observed from Table 20.4.26, neat ethyl lactate provided a yield considerably higher (82%) than the other organic solvents (in the case of biobased solvent ethanol, the reaction was not produced). After that, the polarity of ethyl lactate was tuned by adding different concentrations of water as a co-solvent (Table 20.4.26), being 80% ethyl lactate – the mixture that produced the most favorable polarity (93% yield). Different spiro[benzo[f]pyrrolo[2,1-a]isoindole-5,30-indoline]-20,6,11-trione derivatives were successfully synthesized at room temperature at high yields by means of this economical and green reaction medium.

Table 20.4.26. Influence of the reaction medium over the cycloaddition reaction of isatin (1.0 mmol), proline (1.0 mmol), and naphthoquinone (1.0 mmol) at room temperature.

Solvent	Yield, %
Toluene	22
Acetonitrile	16
Tetrahydrofuran	25
N,N-dimethylformamide	30
Methanol	no product
Ethanol	no product
100% Ethyl lactate	82
80% Ethyl lactate in water	93
60% Ethyl lactate in water	88
40% Ethyl lactate in water	80
20% Ethyl lactate in water	46

20.4.4.3 Ethyl lactate in light-induced synthesis

The use of visible light and unconventional solvents for the organic synthesis of compounds has received less attention for the moment. In the case of ethyl lactate, the first study of this category was performed by Ghosh *et al*.[155] using a modified multi-component Hantzsch synthesis under visible light irradiation in aqueous ethyl lactate at room temperature. By means of the protocol presented in this study, the synthesis of 1,4-dihydropyridines was carried out. Firstly, authors checked the effect of thermal energy and visible light (tungsten lamp) on the yield of a model reaction formed by 4-nitrobenzaldehyde, ethyl acetoacetate, ammonium formate, and ethyl lactate as the reaction medium. Once the visible light was determined as the most efficient source, some polar and nonpolar solvents were studied over the three-component reaction (Table 20.4.27). Ethyl lactate pre-

sented a higher yield than water and the other organic solvents studied. Based on this, the next step was to tune the polarity of ethyl lactate by adding different amounts of water in order to find the optimum solvent polarity. In this case, 50% ethyl lactate showed the best performance (Table 20.4.27). Different aldehydes could be applied together with ethyl acetoacetate and ammonium formate to produce symmetrical and unsymmetrical 1,4-dihydropyridines with high yields.

Table 20.4.27. Influence of the reaction medium over the synthesis of 1,4-dihydropyridines. Reaction conditions: 4-nitrobenzaldehyde (1.0 mmol), ethyl acetoacetate (2.0 mmol), and ammonium formate (1.5 mmol); 150 W tungsten lamp for 150 min at room temperature.

Solvent	Yield, %
Toluene	49
Acetonitrile	52
DMSO	67
Ethanol	70
Water	80
100% Ethyl lactate	75
85% Ethyl lactate in water	80
75% Ethyl lactate in water	86
50% Ethyl lactate in water	92
25% Ethyl lactate in water	82
10% Ethyl lactate in water	73
5% Ethyl lactate in water	66

The second and the last study so far was reported by Zhang *et al.*[156] who investigated the production of spirooxindole pyran derivatives *via* visible light promoted three component reactions of isatins, malononitrile and enolizable C–H activated compounds under various reaction conditions, at room temperature and in the absence of catalyst. A variety of green and conventional organic solvents were tested under visible light-emitting diode. The solvents, yields obtained and experimental conditions are presented in Table 20.4.28. As can be observed, the mixture ethyl lactate/water (3:2 v/v) was the best solvent system to reach yields higher than 90% under light irradiation. Once the optimal conditions were set, various isatins and 2-hydroxynaphthalene-1,4-dione; 4-hydroxycoumarine and dimedone as enolizable C–H activated compounds were evaluated in the three-component reaction. In general, the reactions proceed smoothly and provided the respective products with yields higher than 84%. In addition to it, the products could be isolated just washing with aqueous ethanol and after recrystallization from the solution.

Table 20.4.28. Influence of the reaction medium over the visible-light promoted synthesis of spirooxindole pyrans. Reaction conditions: isatin (1.0 mmol), malononitrile (1.0 mmol), 2-hydroxynaphthalene-1,4-dione (1.0 mmol) under light irradiation (18 W) at room temperature.

Light source	Solvent	Time, h	Yield, %
White	Dichloromethane	12	traces
White	Ethyl acetate	12	traces
White	Water	12	traces
White	Acetonitrile	12	16
White	Ethanol	12	20
White	Polyethylene glycol 400	12	69
White	N,N-dimethylformamide	12	71
White	Ethanol/Water (1:1)	12	16
White	Ethyl lactate	12	35
White	Ethyl lactate/Water (1:1)	6	63
White	Ethyl lactate/Water (2:1)	6	71
White	Ethyl lactate/Water (3:2)	6	95
Dark	Ethyl lactate/Water (3:2)	12	traces
Blue	Ethyl lactate/Water (3:2)	6	23
White (8 W)	Ethyl lactate/Water (3:2)	10	90
White (20 W)	Ethyl lactate/Water (3:2)	6	95
White	Ethyl lactate/Water (9:1)	6	42

20.4.4.4 Other organic chemistry reactions in ethyl lactate

Procopio *et al.*[157] used ethyl lactate as a eco-friendly system for the stereoselective synthesis of exclusively *trans*-4,5-diaminocyclopent-2-enones from different amines and furan-2-carboxyaldehyde at room temperature. Authors assayed morpholine as the reaction model and observed that using 1 mol% of erbium(III) trifluoromethanesulfonate ($Er(OTf)_3$) as catalyst in ethyl lactate, the same yield (>99%) as by employing acetonitrile was obtained just in 5 min. reaction. Moreover, by reducing 10 times the amount of catalyst (0.1 mol%) and using erbium(III) chloride hexahydrate instead of $Er(OTf)_3$, which is more expensive and toxic, quantitative yield was also obtained in only 30 min. Based on this finding, other secondary amines and anilines were reacted and it resulted in the formation of product derivatives in almost quantitative yields after 20-30 min reaction. Liu and Wen[158] carried out the synthesis of keto and aldoximes and, subsequently, the Beckmann rearrangement of the formed ketoxime in ethyl lactate. By this protocol, several ketones and aldehydes were tolerated. Ethyl lactate produced the activation of the hydroxyl amine molecule through the hydrogen bonding formed with the hydroxyl and carbonyl oxygen of

ethyl lactate molecules. This effect favors the condensation reaction without the use of any catalyst.

Shen *et al.*[159] developed a green approach to the synthesis of 4(3H)-quinazolinones from the cyclization of 2-aminobenzamides and 1,3-diketones *via* C–C bond cleavage in ethyl lactate and by using camphorsulfonic acid, a Bronsted acid, as a catalyst (Figure 20.4.28). Ethyl lactate showed a better performance than pure water, PEG-400, and PEG-200 as a reaction medium. The polarity of ethyl lactate allowed the suitable solubilization of organic reactants. The addition of water to ethyl lactate favored the inclusion of camphorsulfonic acid, which needs aqueous medium to efficiently act. A wide range of acyclic and cyclic 1,3-diketones showed enough tolerance to the protocol and a various 2-aryl-, 2-alkyl, and 2-(4-oxoalkyl)quinazolinones were obtained in high yield by using the mixture ethyl lactate-water (1:9).

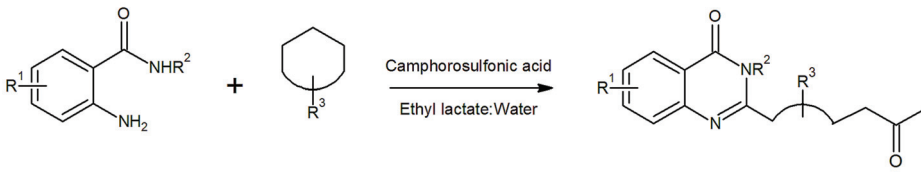


Figure 20.4.28. Synthesis of 4(3H)-quinazolinones in ethyl lactate.

Bhat *et al.*[65] carried out the synthesis of pyrazoline derivatives by a condensation reaction between chalcones and phenyl hydrazine using cerium chloride heptahydrate as a catalyst. To establish the optimal conditions, a series of experiments were carried out by varying the solvent, amount of catalyst and temperature. Table 20.4.29 shows the conditions assayed. Phenyl hydrazine was not soluble in water, so no product was obtained. In the case of ethanol, the reaction mixture was faintly turbid and the reaction failed. The best yield was obtained with 70% ethyl lactate (87%). At reflux temperature and using 20 mol% of catalyst, aqueous ethyl lactate was the most effective among the three green solvent evaluated. Despite no product was obtained with several chalcones, the substrates tolerated reasonable well the protocol and several 1,3,5-triaryl-2-pyrazoline derivatives were synthesized with a moderately high yield. Ethyl lactate may participate in the reaction increasing the nucleophilicity of the amino group by hydrogen bond formation in a similar manner as reported by Liu and Wen.[158] In order to evaluate the recyclability of the solvent and catalyst, authors analyzed the filtrate obtained after removal of the product. In this case, no product and reactant left in the medium and the filtrate was reused in three consecutive reactions. The yields achieved were very similar in each cycle without an appreciable loss of activity.

Table 20.4.29. Optimization of the reaction conditions for the synthesis of 1,3,5-triaryl-2-pyrazoline derivatives from chalcones (1.0 mmol) and phenyl hydrazine (2.0 mmol) using cerium chloride heptahydrate as a catalyst.

Solvent	Catalyst, mol%	Temperature	Time, h	Yield, %
Water	–	room	24	no product
Water	20	room	24	no product
Water	20	reflux	5	no product
Ethanol	15	reflux	5	no product
Ethanol	20	reflux	5	no product
70% Ethyl lactate in water	–	room	24	traces
70% Ethyl lactate in water	20	room	24	traces
70% Ethyl lactate in water	5	reflux	5	traces
70% Ethyl lactate in water	10	reflux	5	66
70% Ethyl lactate in water	15	reflux	5	69
70% Ethyl lactate in water	20	reflux	5	87
80% Ethyl lactate in water	20	reflux	5	72
100% Ethyl lactate	20	reflux	5	traces

20.4.5 ETHYL LACTATE IN FOOD APPLICATIONS

The application of ethyl lactate as a solvent in food technology is quite recent. The replacement of conventionally volatile organic solvents by green solvents is an important field of research in the food industry. In this case, the use of environmentally friendly solvents is essential, but also the employment of non-toxic solvents which could be used without any kind of legal restriction. Ethyl lactate fulfills these requirements and, besides, it is a tunable solvent which can cover a wide range of polarities, so it can be applied for the selective extraction of very different chemical structure compounds by itself or in combination with other organic solvents and water. For these reasons, it is not surprising the appearance and increase in the number of studies regarding the application of ethyl lactate for the extraction of bioactive food compounds in the last decade.

20.4.5.1 Extraction of oil related compounds

Ethyl lactate has been studied for the extraction and fractionation of different oil related compounds.

20.4.5.1.1 Recovery of squalene from olive oil deodorizer distillates

In Section 20.4.1.3.3 it was established that the mixtures of ethyl lactate with lipid type substances usually present partial liquid-liquid miscibility with upper critical solution temperature (UCST) point. This property could be exploited to study and develop new separation processes for the edible oil industry.

Squalene (2,6,10,15,19,23-hexamethyl tetracosahexane) is a very valued substance in both the cosmetic and pharmaceutical industries. The primary natural source of squalene is shark liver oil, but it can also be found as a minor constituent in olive oil. Thus, residues of the olive oil deodorization process are viable raw materials for the production of squalene from vegetal sources. Olive oil deodorizer distillates (OODD) may contain up to 30 wt% of squalene, together with free fatty acids (30-40%), fatty acid esters, (20-30%) and minor amounts of other compounds such as mono- and diglycerides, sterols, tocopherols, etc.

Esterification of OODD would occur in a mixture mainly comprised of triglycerides and squalene. Then the recovery of squalene from the triglyceride-rich mixture could be accomplished by different methods, including supercritical fluid extraction.

The possibility of a liquid-liquid extraction of squalene from squalene + triglyceride mixtures using ethyl lactate was first reported by Hernández *et al.*[40] Taking into account the liquid-liquid phase transition measured (Figure 20.4.29), these authors determined the liquid-liquid equilibrium compositions of two selected systems, namely, a mixture with 90 wt% ethyl lactate and another one with 80 wt% ethyl lactate, at two selected temperatures, 298.2 and 313.2 K. Both temperature-composition conditions were selected to promote the dissolution of squalene in the ethyl lactate-rich phase (see Figure 20.4.29).

The compositions of the equilibrium liquid phases obtained are given in Table 20.4.30 (L_1 and L_2) and reveal that in both cases a selective extraction of squalene could be attained. Particularly, at 298.2 K (ambient temperature) L_2 contains 42.0 wt% of squalene (solvent free basis). This means that a 1.4 fold increase of squalene was obtained.

Table 20.4.30. Compositions of equilibrium liquid phases (L_1 and L_2) of the system squalene + triglyceride (S+T) (30 wt% squalene) and ethyl lactate (EL).[40]

T/K	EL/S+T	L_1 (triglyceride-rich phase)			L_2 (ethyl lactate-rich phase)		
		wt%					
		S	T	EL	S	T	EL
298.2	9	12.5	59.5	28.0	2.1	2.9	95
313.2	4	12.8	49.2	38.0	4.1	7.9	88

Table 20.4.31 shows the partition coefficients k_i^{eq} (wt% in L_2/wt% in L_1) for the squalene (SQ) and triglycerides (TG) compounds, calculated on ethyl lactate free basis, together with the corresponding separation factors ($R = k_{SQ}/k_{TG}$). As can be observed from the values obtained, a high separation factor ($R > 3$) was obtained at 298.2 K. Then, a selective recovery of squalene from squalene + triglyceride mixtures using ethyl lactate is

feasible at ambient temperature (no heating requirements) and providing an ethyl lactate/ squalene-to-triglyceride ratio lower than 10 (low amount of solvent required).

Table 20.4.31. Partition coefficients k_{SQ}^{eq} and k_{TG}^{eq} (ethyl lactate-free basis) and separation factor $\alpha = k_{SQ}^{eq}/k_{TG}^{eq}$ of the squalene (SQ) + triglyceride (TG) (30 wt% squalene) and ethyl lactate (EL) mixture.

T/K	k_{SQ}^{eq}	k_{TG}^{eq}	$\alpha = k_{SQ}^{eq}/k_{TG}^{eq}$
298.15	2.419	0.702	3.447
313.15	1.615	0.840	1.922

20.4.5.1.2 Extraction of tocopherol from olive oil

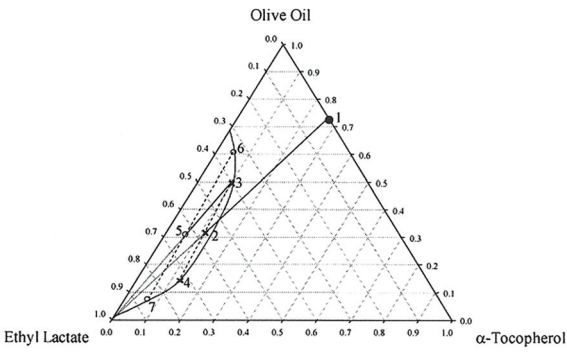


Figure 20.4.29. Liquid-liquid equilibria of a two-step extraction process to recover tocopherols from olive oil using ethyl lactate. [Adapted, by permission, from G. Vicente, A. Paiva, T. Fornari, and V. Najdanovic-Visak, *Chem. Eng. J.*, **172**, 879 (2011)].

As for the aforementioned fractionation of squalene from olive oil distillates (Section 20.4.5.1.1), this case study is based in the liquid-liquid equilibria (LLE) data presented in Section 20.4.3.3.

Tocopherols are substances with high biological activities, very well-known as vitamin E. Currently most of tocopherols are obtained by vacuum distillation of the residues produced in vegetable oil refining. This procedure requires several steps and involves abundant amounts of organic solvents. Thus, in the search for less costly and ambient-friendly alternatives, ethyl lactate appears as a very suitable solvent.

Tables 20.4.11 and 20.4.12 present the liquid-liquid equilibrium data for the ternary (ethyl lactate + olive oil + α-tocopherol) system at (288.2 and 298.2) K. Considering these data, Vicente *et al.*[41] suggested a liquid-liquid counter-current process to extract α-tocopherol from olive oil using the green solvent ethyl lactate. The tie-line data of Table 20.4.13 allows the calculation of extraction yield as presented in Figure 20.4.29 for the temperature of 288.2 K. A two-step extraction process is considered. If the (α-tocopherol + olive oil) raw material contains 27 wt% of α-tocopherol (point 1 in Figure 20.4.29) and is contacted with sufficient ethyl lactate, a biphasic mixture is formed (point 2) comprising an oil-rich phase (point 3) and ethyl lactate-rich phase (point 4, which is connected by the respective tie-line with point 3). If we further contact the oil rich phase with additional ethyl lactate, the resulting mixture (point 5) splits into two phases: oil-rich phase (point 6) and ethyl lactate-rich phase (point 7).

The tie-line data in Table 20.4.12 allows calculating the extraction yield of the proposed two-step counter-current extraction process according to:

$$Y = \frac{\text{mass of extracted } \alpha\text{-tocopherol}}{\text{mass of } \alpha\text{-tocopherol in raw material}} 100(\%) \qquad [20.4.9]$$

The extraction yield of the first-step is ca. 60% and that of second-step is 65%, while the extraction yield of the two-step process is 85%. Thus, both yield and separation factors obtained indicate good selectivity for the ethyl lactate used as a solvent to extract α-tocopherol from α-tocopherol + triglyceride mixtures. Hence, the results presented demonstrate the viability of liquid-liquid counter-current process to extract α-tocopherol from olive oil using green ethyl lactate extraction solvent.

20.4.5.1.3 Extraction of γ-linolenic acid from Arthrospira platensis

γ-Linolenic acid (GLnA) is a ω-6-polyunsaturated C18:3 fatty acid which is the first intermediate product in the conversion of linoleic acid into arachidonic acid.[160] The amount of GLnA in *Arthrospira platensis* (*Spirulina microalgae*) ranges from 18 to 21 wt% of total fatty acids. Golmakani *et al.*[75] evaluated the use of pressurized ethanol and ethyl acetate to obtain γ-linolenic acid-enriched fractions from this microalgae. Response surface methodology (RSM) concerning central composite design was employed for the statistical design of the extractions. The experimental temperature values ranged from 60 to 180ºC, pressures from 3.4 to 20.7 MPa and extraction times from 5 to 15 min (one extraction cycle). Different ethyl lactate/ethanol mixtures (from 0 to 100% ethyl lactate) were assayed.

The authors defined the extraction temperature as the most influential operational parameter. The increase in temperature had a positive effect on extraction yield and the opposite effect on GLnA concentration in the extract. On the contrary, pressure had a negligible effect on yield and it was not considered as a significant factor in any of the responses studied. The optimal extraction conditions were 180ºC, 20.7 MPa, 15 min and ethanol/ethyl lactate (50:50 v/v), achieving an overall yield of 21.5% and 63.9% of GLnA recovery. The relatively high yields obtained resulted in high recoveries of GLnA when used this extraction technique and the combination of both green solvents.

20.4.5.1.4 Extraction of thymol from Thymus genus

Villanueva-Bermejo *et al.*[81] reported a comparison between the performance of different green solvents to obtain thymol from thyme plants. The genus *Thymus* (*Lamiaceae* family) is an aromatic plant very rich in essential oil compounds, which are appreciated for food flavoring, in cosmetic, perfumery and in the pharmaceutical industry. Thymol (2-isopropyl-5-methylphenol) is the main monoterpene phenol in thyme essential oil. This compound has revealed several biological properties, such as antibacterial, antifungal, anti-inflammatory, antioxidant, and immunomodulatory.[161,162]

The authors carried out the pressurized liquid extraction (PLE) of three thyme varieties (*Thymus vulgaris, Thymus zygis,* and *Thymus citriodorus*) using ethanol, limonene and ethyl lactate. Moreover, the supercritical fluid extraction (SFE) of thymol was also tested by using the same green solvents as co-solvents. Additionally, the authors reported the solubility data of thymol in limonene and ethanol at ambient pressure and temperatures in the range of 30-43ºC and the results were compared with the solubility data in ethyl lactate previously reported.[43] In this respect, it was observed that thymol was very soluble in the three solvents, particularly in ethanol (concentrations around 90 wt% at the highest studied temperature), followed by ethyl lactate.

Despite the solubility of thymol in limonene was somewhat lower (~73 wt%), the highest concentration of thymol in the extracts was obtained from *T. vulgaris* with limonene, followed by ethyl lactate, at 60ºC (see Table 20.4.32). Therefore, although solubility of thymol in limonene was lower, the selectivity of limonene to extract thymol from thyme leaves was larger in comparison with the other two green solvents.

Table 20.4.32. Thymol concentration ($g \cdot g^{-1}$ extract x 100) obtained in the PLE of *Thymus vulgaris*.

	60ºC	130ºC	200ºC
Ethyl lactate	13.88 ± 0.10	11.78 ± 0.43	4.65 ± 0.02
Ethanol	6.59 ± 0.89	6.89 ± 0.78	4.88 ± 0.67
Limonene	18.15 ± 0.25	12.59 ± 0.49	10.06 ± 0.82

Regarding thymol yield (mg g^{-1} of plant), it was higher than the obtained by using traditional extraction methods, such as Soxhlet with hexane or steam distillation, and it was higher than the achieved by using subcritical water extraction (Table 20.4.33). Moreover, the yield was just slightly lower than those obtained by PLE extraction with non-green solvents like hexane, dichloromethane or ethyl acetate.[163,164]

Table 20.4.33. Thymol yield (mg g^{-1} plant) obtained by PLE[81,163,164] and by conventional methods.[112,113]

Pressurized liquid extraction (PLE)							Conventional methods	
Limonene	Ethyl lactate	Ethanol	Water	Hexane	Dichloro methane	Ethyl acetate	Soxlet hexane	Steam distillation
9.5	10.5	10.6	7.0	10.7	12.2	12.8	6.8	8.2

With respect to the SFE of *T. vulgaris*,[81] the extractions were carried out at 15 MPa, 40ºC (best operational condition assessed with pure CO_2) and using concentrations of 10% (mass%) of ethyl lactate, ethanol and limonene in the SC-CO_2. Taking into account the results obtained with pure CO_2 (10.27 mg thymol$\cdot g^{-1}$ plant at 15 MPa, 40ºC and 35 kg CO_2 kg^{-1} thyme ratio), no improvement on thymol recovery was observed when the co-solvents were used (recovery values in the range of 7-9 mg g^{-1}).

Authors concluded that any of the three green liquid solvents studied can efficiently extract thymol from thyme plants, with limonene being the solvent that produced the highest concentrations, due to its lipophilic character. Although the recovery of thymol by PLE was similar to that by SFE, considerably higher concentrations of thymol were obtained in SFE extracts (up to 31.0 wt%), supporting the selective extraction of volatile oil compounds from plants and herbs by using SC-CO_2.

20.4.5.2 Extraction of carotenoids from different plant matrices

Given that the use of ethyl lactate for the extraction of carotenoids was the first application reported about this solvent on food research, these oil compounds have been discussed

separately from Section 20.4.5.1. Carotenoids are tetraterpenoid organic pigments that are found in plants, algae, some bacteria, and fungi. Carotenoids can be divided into two classes of compounds: carotenes, which are hydrocarbon compounds without oxygen in their chemical structure and xanthophylls, which are the oxygenated compounds. Lycopene, α- and β-carotene, lutein, and zeaxanthin are carotenoids found in relatively larger amounts in fruits and vegetables.[165] The results obtained by using ethyl lactate invite to consider this green solvent as a potential substitute for toxic petroleum-derived solvents in the recovery of carotenoids from plant matrices.

20.4.5.2.1 Extraction of β-carotene, lutein and lycopene from carrots, white corn and tomatoes

Ishida and Chapman[54] studied the use of ethyl lactate to extract carotenoids from several vegetable sources. The authors determined the carotenoid yield (μg of carotenoid g^{-1} of material) at different conditions and the results were compared with extraction carried out with ethanol, methylene chloride/methanol/H_2O (MMH) (40/40/20) and ethyl acetate. With respect to the vegetable sources utilized, authors evaluated the extraction of β-carotene from carrots, lutein from white corn, *trans*-lycopene from red tomatoes and *tetra-cis*-lycopene from Tangerine tomatoes.

The addition of ethanol to ethyl lactate on carotenoid extraction was also studied using various ethanol + ethyl lactate mixtures (0, 40, 60, 80 and 100% of ethanol). Ethanol increased the carotenoid extraction yield. When 100% of ethanol was used, the largest amounts of lutein from white corn and β-carotene from carrots were obtained. In the case of *tetra-cis*-lycopene from Tangerine tomatoes, maximum yields were attained between 60 and 100% ethanol at 60ºC and 1 h of extraction time. Ethanol seemed to stabilize this isomer, partially avoiding the thermal degradation. In the case of *trans*-lycopene from red tomato, 100% ethyl lactate was the most efficient solvent at 30ºC. Isomerization of *trans*-lycopene into *cis*-lycopene at high temperatures was produced with both solvents, but in ethanol it was greater than in ethyl lactate. Thus, ethyl lactate and ethanol might have a protective effect on the integrity of *tetra-cis*-lycopene.

With regards to the use of neat solvents (60ºC for 2 h extraction time), ethanol was the most effective solvent for extracting lutein from white corn and β-carotene from carrots (8.38 and 1140.54 μg g^{-1} of dry weight, respectively), whereas the toxic MMA mixture was the most effective solvent for extracting *trans*-lycopene from red tomatoes and *cis*-lycopene from Tangerine tomatoes (558.48 and 1817.09 μg g^{-1}, respectively). Ethyl lactate extracted between 79-75% of the maximum *trans*-lycopene, β-carotene and lutein achieved, as well as the 65% of the maximum *cis*-lycopene obtained. Moreover, when red tomato was extracted at 45ºC for 1 h using ethyl lactate, the amount extracted (541 μg g^{-1} of dry weight) was almost equal to that obtained using MMH after 2 h at 60ºC. Therefore, ethyl lactate could be an efficient solvent for the extraction of carotenoids, particularly lycopene. This green solvent could replace toxic petroleum-derived solvents, such as methylene chloride, hexane and acetone which have been patented for extracting carotenoids from food.[167-169]

20.4.5.2.2 Extraction of lycopene from tomato waste

Strati and Oreopoulou[77] studied the capability of different organic solvents (hexane, acetone, ethanol, ethyl acetate and ethyl lactate) to extract carotenoids from tomato waste, composed of dry skin and seeds. In industry, tomato wastes generally account for 10 to 40% of the total tomato processed for tomato products.[170]

Different extraction parameters (type of solvent, extraction time, temperature, and number of successive extractions) were tested. Regarding the extraction temperature, the experiments were carried out at 25ºC. Carotenoid concentration (expressed as lycopene, since this carotenoid represents around 80-90% of total tomato carotenoids) increased with time and the equilibrium concentration was achieved at approximately 30 min of extraction time. At that point, the concentration was considerably low in ethanol (0.38 mg L^{-1}) and higher in ethyl lactate (12.52 mg L^{-1}) at equilibrium, while for the other solvents it was between 1.99-2.82 mg L^{-1}.

With respect to the effect of successive extractions steps, the carotenoid recovery was significantly affected by the number of extractions regardless of the solvent and temperature applied. The recovery of carotenoids using medium or nonpolar solvents (ethyl acetate and hexane) in the first cycle was higher than that obtained with more polar solvents (acetone, ethanol and ethyl lactate). In particular, 70.1-73.4% and 71.4-74.4% of total extracted carotenoids was recovered in the first cycle with hexane and ethyl acetate, respectively. In the case of ethyl lactate, the carotenoids recovered in the first cycle ranged between 57.5% and 67.0%. With regards to the effect of temperature and type of solvent on carotenoids extraction yield (mg carotenoid kg^{-1} dry tomato waste), the increase in extraction temperature generally increased the extraction yield. Nevertheless, there were no significant differences at 25 or 50ºC in the case of hexane and ethyl lactate.

In general, ethyl lactate presented remarkably higher yields at the different temperatures (202.73 mg kg^{-1} at 25ºC and 243.0 mg kg^{-1} at 70ºC), followed by acetone (13.7% at 25ºC and 21.4% at 50ºC of the maximum yield obtained with ethyl lactate). Ethanol showed the lowest yield (<10% of the maximum yield obtained with ethyl lactate at 70ºC). Therefore, 30 min extraction time at 70ºC, by applying several extraction steps with ethyl lactate proved to be a more advantageous method than employing ethyl acetate, which is the current green solvent employed to extract carotenoids for food applications.

20.4.5.2.3 Extraction of astaxanthin from Xanthophyllomyces dendrorhous

Astaxanthin is a keto-carotenoid pigment, belonging to xanthophylls group. This pigment confers the coloration to some birds, crustaceans and salmons and is used in food, cosmetics, and pharmaceutical application due to its antioxidant activity.[171] Wu *et al.*[172] developed an environmentally friendly extraction method to obtain astaxanthin from the red yeast *Xanthophyllomyces dendrorhous*.

First, the most efficient acid and organic solvent to, respectively, disrupt the yeast cell wall and extract astaxanthin were selected. Four acids were checked: hydrochloric, lactic, acetic, and citric acid, being lactic acid the most efficient. In the case of the extraction solvent, petroleum ether, acetone, ethanol, hexane, and ethyl lactate were assayed. Ethyl lactate was the most efficient, followed by ethanol, while petroleum ether and hexane showed the poorest performance. In the view of these results, ethyl lactate and

ethanol were used as extraction solvents and lactic acid was applied to disrupt the yeast cell.

Lyophilized yeast powder (0.2 g) was put in contact with 10 mL of 5 $mol \cdot L^{-1}$ lactic acid at controlled temperature. After cell disruption, the mixture was centrifuged and the liquid phase removed. Then the fraction of disrupted cells was extracted with 15 mL of organic solvent. Extraction time was the most important parameter for the extraction of astaxanthin. Authors concluded that the optimal conditions for the extraction of the carotenoid were 30 min of extraction time, 65ºC of disrupting temperature, 60 min of disrupting time, and ratio 1/1 of the ethyl lactate + ethanol solvent.

Different extraction methods with conventional solvents were additionally studied for the extraction of astaxanthin and compared with the new proposed method to corroborate its efficiency. In this sense, DMSO (for disrupting the cell wall) + acetone (extraction solvent) were compared with the use of lactic acid + ethyl lactate/ethanol solvent (1/1 v/v). The astaxanthin yields obtained were very similar (1484.85 $\mu g \cdot g^{-1}$ for DMSO and 1464.16 $g \cdot g^{-1}$ by using the ethanol/ethyl lactate mixture). Similar results were obtained using other conventional solvents, demonstrating that the method developed in this study could replace the traditional astaxanthin extraction with toxic and/or flammable solvents.

20.4.5.3 Decaffeination of green coffee beans and green tea leaves

In Section 20.4.5.1 and 20.4.5.2, the effectiveness of ethyl lactate for the extraction of lipophilic compounds has been discussed. Recently, ethyl lactate has also demonstrated to be a selective solvent for the extraction of caffeine from green coffee beans and green tea leaves. The good performance showed by ethyl lactate for the extraction of compounds having such a different polarity is, among other reasons, owing to the wide range of polarities covered by this green solvent, which is discussed throughout the present monograph.

Coffee and tea are two commodities which involve a great market worldwide. *Coffea arabica* and *Coffea robusta* are the two greatest economic and commercially important coffee varieties. Furthermore, Arabica coffee beans are preferred by consumers and are considered of superior quality. Caffeine content in Arabica green beans is around 1 wt%.[173] Green tea (*Camellia sinensis*) has been a much consumed drink in Asian countries over years, but nowadays is very popular all over the world. Green tea leaves contain around 20-40 mg g^{-1} of caffeine and 190-260 mg g^{-1} of catechins.[174,175] Catechins are recognized to be the most beneficial bioactive compounds of green tea due to their antioxidant, anticancer, anti-inflammatory, antibiotic and antiviral effects.[176,177]

Traditional decaffeination was attained using liquid solvents such as benzene, chloroform, trichloroethylene and dichloromethane. However, evidence suggested that chlorinated solvents are carcinogenic and thus, their use was firmly reduced. Extraction of caffeine with water requires a two-step process because water is not a selective solvent and many flavor and aroma substances are very soluble in water. Ethyl acetate is also employed for the decaffeination of food matrices and it is much more selective for caffeine and thus, extraction can be accomplished in a single-step contact process.[178] In the case of green tea, in addition to these commercial decaffeination methods, other solvents have been studied, such as acetone, ethanol and acetonitrile. Although good decaffeination

can be achieved, catechins are also considerably co-extracted and thus, the value of green tea as a functional healthy drink is reduced.

The solubility of caffeine in ethyl lactate is very similar to the values reported in water (see Tables 20.4.18 and 20.4.20). Thus, the agrochemical ethyl lactate could be a candidate to be employed as an environmentally friendly solvent to extract caffeine from natural matters, as proposed Villanueva-Bermejo *et al*.[79,45] In their works, pressurized liquid extractions (PLE) of green coffee beans[79] and green tea leaves[45] using ethyl lactate were investigated and compared with the use of other liquid solvents, namely ethyl acetate, ethanol, and water. The high temperatures applied in PLE (up to 200ºC) favored caffeine solubility. Furthermore, a compression effect was made on the vegetal particle, which also contributed to improve the extraction.

In the case of green coffee beans,[79] even though the highest concentrations of caffeine in the extracts were obtained with ethyl acetate, ethyl lactate provided the highest caffeine recovery (up to 60% of the caffeine contained in the beans was removed after 10 min of extraction time). Additionally, authors studied the co-extraction of other valuable compounds of coffee, namely phenolic compounds and oil. These substances have an important role during coffee roasting as precursors of key compounds of coffee flavor and aroma and thus, their removal from natural matter during extraction should be minimized. The selectivity of each solvent for these compounds was expressed as the distribution coefficient of caffeine and phenolic compounds, as well as caffeine and oil, according to:

$$S = k_1/k_2 \qquad [20.4.10]$$

where k_1 and k_2 represent, respectively, the distribution coefficient of caffeine and the other solute studied (phenolic compounds or oil in this specific case). The distribution coefficients were calculated considering the concentration (mass%) of each compound in the extract (y_i^{ext}) and in the vegetal material (x_i^{sol}) according to:

$$k_i = y_i^{ext}/x_i^{sol} \qquad [20.4.11]$$

Therefore, based on the Eq. 20.4.10, high caffeine-to-phenolic compounds and caffeine-to-oil selectivity ratios are desirable to preserve the organoleptic properties of beans. In the case of caffeine and phenolic compounds, the ratio was very similar for the three solvents (ethyl acetate, ethanol and ethyl lactate), with a selectivity value close to 5 at 200ºC. Nevertheless, the caffeine-to-lipid ratio with ethyl lactate was much higher (selectivity of 25.1) than the obtained with ethyl acetate (16.6), so ethyl lactate showed a good performance for the decaffeination of green coffee beans.

Manic *et al*.[43] reported a possible co-solvent effect on caffeine solubility when ethyl lactate contained small amounts of water (see Section 20.4.1.3.4), which was further corroborated by Villanueva-Bermejo *et al*.[45] An increase in the concentration of water (40-50 mass%) in ethyl lactate lead to a caffeine solubility up to 3-fold higher than that in the neat solvents (Figure 20.4.17). Based on these findings, the authors explored the use of compressed ethyl lactate, water and ethyl lactate + water mixtures for the decaffeination of green tea leaves.[45]

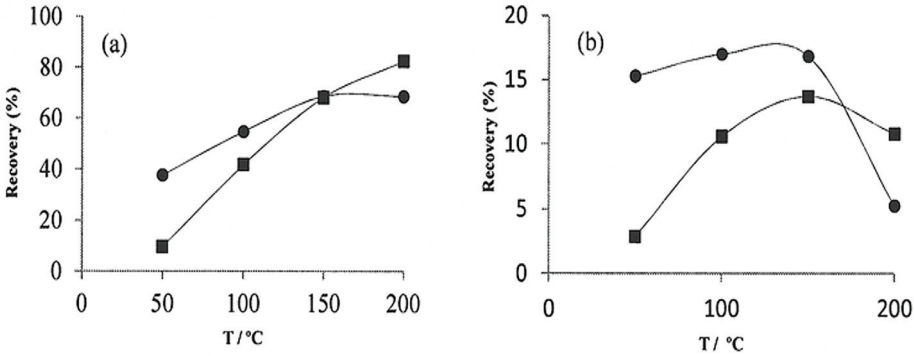


Figure 20.4.30. Recovery (mass extracted / mass in natural matter x 100) of (a) caffeine and (b) catechins in the PLE of green tea leaves using (●) water and (■) ethyl lactate.

In the same manner as the reported for green coffee beans,[79] the selectivity (Eq. 20.4.10) of ethyl lactate for the extraction of caffeine and catechins (a family of bioactive compounds with a great influence over the organoleptic and healthy properties of green tea) was evaluated. The addition of water to ethyl lactate favored the caffeine extraction yield. Nevertheless, the presence of water led to a higher undesirable co-extraction of catechins. In this sense, the highest selectivity values were obtained with pure ethyl lactate (selectivity of 5.5 at 150ºC).

The extraction of caffeine considerably increased at high temperatures. Almost the complete decaffeination of green tea leaves was achieved with ethyl lactate at 200ºC (92% of caffeine removed). However, the reduction in the recovery of catechins at that temperature denoted the possibility of thermal degradation of these compounds, which was more pronounced when water was used (Figure 20.4.30).

Another approach to decaffeinate foodstuffs, which has attained industrial application, is the supercritical fluid extraction (SFE) using carbon dioxide (SC-CO_2). Supercritical CO_2 is selective for the extraction of caffeine, there is no associated waste treatment of a toxic solvent and extraction times are moderate. SC-CO_2 coupled with ethanol or water as co-solvents have been investigated to extract caffeine from green coffee beans and green tea leaves.[174,179,180] In another contribution, Villanueva-Bermejo *et al.*[80] evaluated the effect of ethyl lactate, ethyl acetate and ethanol, added as a co-solvent of SC-CO_2 to extract caffeine from green tea leaves. Two extraction methods were tested: a static mode similar to the industrial process, in which green tea leaves were soaked with the co-solvent and loaded in the extraction vessel prior to the extraction with the SC-CO_2, and a dynamic mode, in which dry leaves were loaded into the extraction vessel and then SC-CO_2 and co-solvent were continuously pumped. The ethyl lactate extract contained the highest concentration of caffeine regardless of the extraction method employed (14.3% and 18.2% for the static and dynamic mode, respectively). These concentrations were between 1.4-1.8 and 1.8-3.3 higher than the obtained with ethanol and ethyl acetate, respectively. Likewise, the co-solvent ethyl lactate allowed achieving the highest caffeine yields (13.0 mg g^{-1} for the

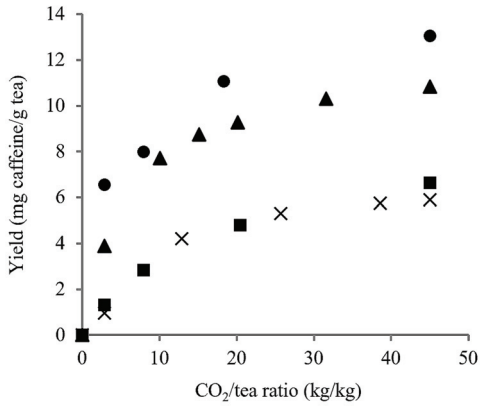


Figure 20.4.31. Overall extraction curves obtained by the static method at 30 MPa and 70ºC from green tea leaves: (●) CO_2 + ethyl lactate; (▲) CO_2 + ethanol; (■) CO_2 + ethyl acetate; (x) neat CO_2.

static, and 14.2 mg g^{-1} for the dynamic extraction). These results were 17-38% and 49-71% higher than the obtained, respectively, with ethanol and ethyl acetate.

The Figure 20.4.31 shows the overall extraction curves obtained in the static method. As can be observed, the greatest caffeine extraction rate at the early extraction stage was achieved with ethyl lactate. These results were correlated using the Sovová mass transfer model.[181] In this case, the mass transfer coefficient in the fluid phase obtained with ethyl lactate was 1.4 and 2.6 times higher than the achieved with ethanol and ethyl acetate, respectively. In addition to the aforementioned, the co-extraction of catechins was lower than 2% (mass%). Therefore, the SFE using ethyl lactate as co-solvent demonstrated to be a green, selective and efficient method for the removal of caffeine from green tea leaves.

Finally, Villanueva-Bermejo *et al.*[182] carried out the fractionation of a green tea extract in order to obtain a fraction rich in catechins and free of caffeine. Several methods and technologies, such as solvent partition, membrane technology and the use of adsorbents, have been studied for the separation of both groups of bioactive compounds (a more detailed description in relation to the methods applied to isolate catechins and caffeine from green tea extracts can be found in the work reported by Villanueva-Bermejo *et al.*[183]).

The authors reported a green method based on the use of SC-CO_2 as an anti-solvent (SAS) to precipitate catechins and phenolic compounds from a tea extract obtained by PLE with ethyl lactate and ethanol. In the case of ethyl lactate extracts, the SAS precipitation allowed obtaining a dry product practically free (less than 1%) of caffeine. Additionally, a catechins and phenolic compound enrichment was produced. In this sense, precipitates containing 23% and 58% (mass%) of catechins and total phenolic compounds, respectively, was obtained. These values represented an increase of up to 25% with respect to the concentration of phenolic compounds initially contained in the PLE extract. The total catechins/caffeine mass ratios obtained in precipitates by SAS from the ethyl lactate extract were up to 2.3 times higher than those produce from ethanolic extracts.

20.4.5.4 Extraction of phenolic compounds

Lores *et al.* [83] explored the extraction of phenolic compounds from *Cytisus scoparius* with ethyl lactate. A preliminary extraction with 50% water in ethyl lactate was carried out at 120ºC to compare the performance of this green solvent with that using 50% water in methanol. The total phenolic content (TPC), the radical scavenging activity and the profile of phenolic compounds obtained with both solvents were very similar. The TPC and anti-

oxidant activity of the aqueous ethyl lactate extract was 34.3 mg g^{-1} and 3.83 mM Trolox g^{-1}, respectively, while these values were 31.7 mg g^{-1} and 3.77 mM Trolox g^{-1} for the hydromethanolic mixture. Thus, ethyl lactate demonstrated a performance similar to methanol, an efficient solvent thoroughly studied for the extraction of phenolic compounds that presents the handicap of being toxic.

According to this finding, the authors employed the PLE for the extraction of different parts of the plant (flowers, branches and seed pods). The TPC and antioxidant activity of the extracts were considerably higher when an aqueous ethyl lactate mixture was used instead of 100% ethyl lactate, independently of the raw material used. In the case of the flowers, the TPC and antioxidant activity were, respectively, higher than 40 mg g^{-1} and close to 6 mM Trolox g^{-1} when 65% aqueous ethyl lactate was employed. The extraction performance of the PLE with ethyl lactate was considerably better than the obtained with the same solvent mixture at ambient temperature. Nevertheless, the phenolic profile obtained by the different extraction techniques was similar. The extracts obtained at ambient temperature showed certain antimicrobial activity against *S. aureus* and *Bacillus* spp.

20.4.6 FINAL REMARKS

Solvents are used in high quantities in chemical industry, so they considerably influence the environmental impact, safety and costs of a process. The increasing environmental regulations and social consciousness regarding ecological problems is promoting the development of the Green Chemistry, seeking for eco-friendly chemical processes and tending to replace conventional volatile organic solvents by green solvents.

Ethyl lactate is a solvent which has recently attracted a great attention in chemical industry due to its physical, chemical and environmentally benign properties. It should be pointed out the number of studies reported in the last decade relative to the knowledge of the physicochemical and thermodynamic properties of ethyl lactate and mixtures containing this solvent, as well as the phase behavior of systems comprising ethyl lactate, which are essential for the design and implementation of several technological processes.

Due to the importance that ethyl lactate is gaining, numerous processes, more efficient and greener, are continuously being reported and patented in order to reduce its production cost. Ethyl lactate is an agrochemical solvent which can be produced in biorefineries from the processing of carbohydrate feedstock, such as wastes from corn or sugar crops. In this regard, production methods aim at hybrid processes in which the separation and reaction stage are combined in multifunctional reactors to reduce the investment and operating costs. In the last years, the studies related to the application of membrane-based processes (vapor permeation and pervaporation processes) in catalytic membrane reactors have acquired a great relevance for the esterification of lactic acid and ethanol. Moreover, other approaches directed to solve the limitations of the fermentation process have been recently proposed for the alternative production of alkyl lactates, standing out the catalytic conversion from triose sugars and glycerol.

Ethyl lactate is fully biodegradable (it breaks down into carbon dioxide and water), non-corrosive, non-carcinogenic, non-teratogenic and non-ozone depleting and it has been affirmed as GRAS. This bio-based solvent has a high boiling point, low vapor pressure and low surface tension. It is remarkable that its molecular structure possesses a specific

topology, allowing the ability to form intra- and inter-molecular association *via* hydrogen bonds, either as proton donor or proton acceptor. As a consequence, ethyl lactate presents a high solvent power and it can cover a wide range of polarities. On account of these interesting properties, ethyl lactate has replaced several pollutant and toxic solvents traditionally used in some applications in phytosanitary, polyurethane, cosmetics, and coating industry. Furthermore, novel uses of this solvent are constantly arising in different fields, such as pharmacology, analytical chemistry, and environmental and materials science. It should be pointed out the interest that ethyl lactate has awaken in last years as a reaction medium in organic synthesis and as an extraction solvent for the food industry.

Besides as a reaction medium, solvents appear in the work up, purification, and final recrystallization steps in organic transformations. Thus, the solvent selection is a critical step due to it takes part in all operations of the synthesis process. Ethyl lactate has been successfully employed as an unconventional reaction medium for the production of a huge variety of chemical compounds resulting in high yields, as well as in a substantial number of chemical reactions, such as deacetylations, condensations, cycloadditions, multicomponent, and coupling reactions. For example, ethyl lactate has been successfully applied in Suzuki-Miyaura cross-coupling reactions, cross-coupling reactions of enaminones and thiophenols, the C=C bond cleavage of 1,3-diketones and enaminones, the thioacetalization of aldehydes, the reaction of furfural and amines, and the light-induced synthesis of dihydropyridines, among others.

The miscibility of ethyl lactate with water and many organic solvents allows the polarity of ethyl lactate to be easily tuned. Therefore, ethyl lactate is able to dissolve a great number of chemically different reagents and catalysts in a wide range of concentrations. Moreover, ethyl lactate allows carrying out a considerable number of reactions at room temperature and/or without catalysts, which implies a lowering of the production costs. Serve as an example the thioacetalization of aldehydes with thiols and thiophenols for the production of functionalized dithioacetals; and the condensation of indoles with aldehydes or isatins for the preparation of bis(indolyl)methanes and 3,3-bis(indolyl)oxindoles.

Ethyl lactate is a flavor compound found naturally in small quantities in a wide variety of foods such as meat, some fruits, soy products and fermented foods, such as wine or beer. Furthermore, it has been approved by the FDA as pharmaceutical and food additive. With respect to the food applications of ethyl lactate, its use as a solvent of food compounds is quite recent. The replacement of conventional volatile organic solvents by green solvents is an important field of research in food technology. In this case, the use of environmentally friendly solvents is essential, but also the employment of non-toxic solvents which could be used without any kind of legal restriction.

Ethyl lactate has been studied as an extraction solvent of different high-value bioactive substances, such as lipid related compounds, alkaloids, and phenolic compounds. Several potential applications are related to the recovery of thymol and volatile oil compounds from herbs, and the extraction of carotenoids from different plants, such us tomatoes, carrots, white corn and microalgae. On this point, ethyl lactate has demonstrated to be as efficient as toxic petroleum-derived solvents, such as methylene chloride, hexane

and acetone. Thus, ethyl lactate constitutes an efficient and green alternative for the extraction of carotenoids. Another important application of ethyl lactate is related with the edible oil industry, taking advantage of the partial liquid-liquid miscibility that the mixtures of ethyl lactate with squalene and tocopherol from olive deodorized distillates and olive oil present. This property could be exploited to develop new separation processes of these bioactive compounds in edible oil industrial applications.

Recently, ethyl lactate has been studied as a decaffeination solvent of green coffee beans and green tea leaves. In both cases, ethyl lactate has been more selective than ethanol, ethyl acetate and water (these two solvents are currently employed in decaffeination industry) for the extraction of caffeine. Compared to the other solvents, the co-extraction of other value compounds present in tea and coffee, such as oil and phenolic compounds, was minimized by using ethyl lactate.

Furthermore, ethyl lactate has emerged as a novel eco-friendly solvent for potential applications in supercritical fluid technology. As a co-solvent of carbon dioxide, ethyl lactate can be readily dissolved in CO_2 in the amounts usually employed in supercritical extraction processes (15-20 wt% or lower). Additionally, at the typical temperatures employed (35-70ºC), ethyl lactate + CO_2 systems present homogeneous (single) phase at relative low pressures. Ethyl lactate could be used as an efficient co-solvent for the supercritical fluid decaffeination of food matrices. In the case of green tea leaves, the use of ethyl lactate and carbon dioxide led to obtaining higher caffeine yields, lower catechins recoveries and larger caffeine mass transfer coefficients in comparison with ethanol and ethyl acetate.

Finally, since CO_2 exhibits high solubility in ethyl lactate (higher than in ethanol), it can be employed to promote different approaches in the perspective of expanded liquid solvents, such as high pressure chemical reactions and anti-solvent precipitation processes. By dissolving CO_2 in ethyl lactate at high pressure, the liquid solvent properties (viscosity, surface tension, diffusion rates, solubility of reagents, catalysts and substrates, density, and polarities) can be modified. In this respect, ethyl lactate is a good candidate to form gas expanded liquid solvents, with the additional advantage of being itself a green solvent. This strong anti-solvent effect produced when CO_2 dissolves into ethyl lactate has been explored for the fractionation of caffeine and phenolic compounds from green tea extracts. The obtaining of decaffeinated green tea powders containing high concentrations of phenolic compounds in short processing times represent a clear advantage in terms of efficiency and sustainability over the cutting-edge methods employed until present for that purpose, such as such liquid-liquid fractionation, membrane technology and the use of adsorbents.

ACKNOWLEDGMENTS

D. Villanueva Bermejo gratefully acknowledges the financial support provided by the Alfonso Martin Escudero Foundation (Spain).

APPENDIX A:

GC-EoS modeling of ethyl lactate vapor pressure

The Group Contribution Equation of State (GC-EoS) has two contributions to the residual Helmholtz energy of the system: a repulsive hard sphere Carnahan-Starling type term and an attractive term, which combines the group contribution approach with the local-composition mixing rules. A complete explanation of the model is given by Skjold-Jørgensen.[21]

The model parameters are the following: the critical hard sphere diameter (d_c) which is characteristic of each substance, five pure-group parameters (T*, q, g*, g' and g") and four binary interaction parameters (k_{ij}*, k_{ij}', α^{ij} and α_{ji}). The reference temperature (T*) and group surface area (q) are not adjustable parameters while the pure group parameters (g*, g' and g") are usually regressed using adequate vapor pressure data.

Figure A.1 shows the chemical structure of ethyl lactate. According to the current GC-EoS parameter table,[22] the group composition of ethyl lactate molecule can be described by means of two CH_3, one CH_2COO and one CHOH groups (Set 1). Nevertheless, considering that ethyl lactate is the ester of lactic acid, a more appropriate representation should include the definition of a new alcohol-ester functional group (CHOHCOO) (see Figure A1); thus the ethyl lactate molecule can be represented by two CH_3, one CH_2 groups, and the new CHOHCOO group (Set 2). The pure group and group interaction parameters were reviewed by Villanueva-Bermejo *et al.*[20] and are summarized in Tables A1 and A2 The critical temperature and pressure of ethyl lactate are T_c = 506.01K, p_c = 2.822 MPa, as reported by Villanueva-Bermejo *et al.*[20]

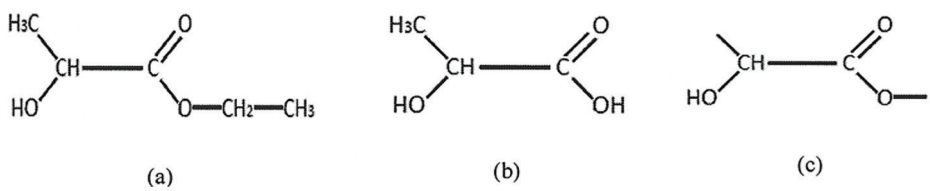


Figure A1. Chemical structure of (a) ethyl lactate, (b) lactic acid and (c) the alcohol-ester group.

Table A1. GC-EoS pure group parameters.

	Ref. temp.	Group surf. area	Pure group energy parameters		
	T*	q	g	g'	g"
CH_3	600	0.848	316910	–0.9274	0.0
CH_2	600	0.540	356080	–0.8755	0.0
$COOCH_2$	600	1.420	831400	–1.0930	0.0
OHCH	512.6	0.908	1207500	–0.6444	0.0
CHOHCOO	600	1.788	891900	–1.0993	0.0

Table A2. GC-EoS binary group interaction parameters.

i	j	Attractive energy parameters		Non-randomness parameters	
		k_{ij}	k'_{ij}	α_{ij}	α_{ji}
CHOHCOO	CH_3/CH_2	1.054	0.018	1.777	1.777
$COOCH_2$	CH_3	0.869	0.0	0.0	0.0
	CHOH	0.996	–0.163	0.654	–2.612
OHCH	CH_3	0.715	0.0	10.220	1.471

APPENDIX B:

Thermodynamic UNIFAC modeling of the solubility of phenolic acids in ethyl lactate

Model equations correspond to the modified UNIFAC (Dortmund) model.[184] The activity coefficient of solute (γ_i) is calculated considering a combinatorial (γ_i^C) and a residual (γ_i^R) contributions:

$$\ln\gamma_i = \ln\gamma_i^C + \ln\gamma_i^R$$

The combinatorial part is given by:

$$\ln\gamma_i^C = 1 - V'_i + \ln V'_i - 5q_i\left[1 - \frac{V_i}{F_i} + \ln\left(\frac{V_i}{F_i}\right)\right]$$

where:

$$V'_i = \frac{r_i^{3/4}}{\sum x_j r_j^{3/4}},\ V_1 = \frac{r_i}{\sum x_j r_j},\ r_i = \sum U_k^{(i)} R_k,\ F_i = \frac{q_i}{\sum x_j q_j},\ q_1 = \sum U_k^{(i)} Q_k$$

The residual part is calculated according to the following equation:

$$\ln\gamma_i^R = \sum U_k^{(i)}(\ln\Gamma_k - \Gamma_k^{(i)})$$

where:

$$\ln\Gamma_k = Q_k\left(1 - \ln(\sum Q_m\psi_{mk}) - \sum\frac{\theta_m\psi_{km}}{\sum\theta_m\psi_{nm}}\right)$$

$$\theta_m = \frac{Q_m X_m}{\sum Q_n X_n},\ X_m = \frac{\sum V_m^{(i)} x_j}{\sum\sum V_n^{(i)} x_j},\ \psi_{nm} = \exp\left(-\frac{a_{nm} + b_{nm}T + c_{nm}T^2}{T}\right)$$

The physical properties of pure phenolic acids were reported by Manic *et al.*[43] and are given in Table B1. The group compositions of phenolic acids and ethyl lactate are given in Table B1.

Table B1. Physical properties of phenolic acids.

Compound	T_m/K	ΔH_{fus}/kJmol^{-1}	ΔC_p/Jmol^{-1}K^{-1}
vanillic acid	480.7	29.1	64.4
ferulic acid	444.9	31.9	73.7
caffeic acid	464.1	39.85	162.7

Group interaction parameters were those reported Gmehling *et al.*,[184] except for the ACOH-COOH interaction, which were reviewed by Manic *et al.*[43] All group interaction parameters employed for solubility calculation are summarized in Table B2.

Table B2. Group composition of phenolic acids and ethyl lactate.

UNIFAC main group	Subgroup k	R_k group van der Waals volume	Q_k group van der Waals surface area	Compound group composition			
				caffeic acid	vanillic acid	ferulic acid	ethyl lactate
1. CH_2	CH_3	0.6325	1.0608				2
	CH_2	0.6325	0.7081				1
2. CH=CH	CH=CH	1.2832	1.2489	1		1	
3. ACH	AC	0.3763	0.2113	1	2	2	
	ACH	0.3763	0.4321	2	3	3	
4. $ACCH_2$	$ACCH_3$	0.9100	0.9490				
5. OH	OH(s)	1.0630	0.8663				1
8. ACOH	ACOH	1.0800	0.9750	2	1	1	
11. CCOO	CHCOO	1.2700	1.4228				1
13. CH_2O	OCH_3	1.1434	1.6022		1	1	
20. COOH	COOH	0.8000	0.9215	1	1		

Table B3. UNIFAC interaction parameters between main groups of Table B3.

n	m	a_{nm}	b_{nm}	c_{nm}	a_{mn}	b_{mn}	c_{mn}
1. CH_2	2. CH=CH	189.66	-0.2723	0.0	-95.418		0.0
	3. ACH	114.20	$0.933 \cdot 10^{-1}$	0.0	16.070	-0.2998	0.0
	4. $ACCH_2$	7.3390	-0.4538	0.0	47.200	0.3575	0.0
	5. OH	2777.0	-4.6740	$0.1551 \cdot 10^{-2}$	1606.0	-4.7460	$0.9181 \cdot 10^{-3}$
	8. ACOH	1381.0	-0.9977	0.0	1987.0	-4.6150	0.0
	11. CCOO	98.656	1.9294	$-0.3133 \cdot 10^{-2}$	632.22	-3.3912	$0.3928 \cdot 10^{-2}$
	13. CH_2O	233.10	-0.3155	0.0	-9.6540	$-0.3242 \cdot 10^{-1}$	0.0
	20. COOH	1182.2	-3.2647	$0.9198 \cdot 10^{-2}$	2017.7	-9.0933	$0.1024 \cdot 10^{-1}$
3. ACH	4. $ACCH_2$	139.20	-0.6500	0.0	-45.330	0.4223	0.0
	5. OH	3972.0	-13.160	$0.1208 \cdot 10^{-1}$	3049.0	-12.770	$0.1435 \cdot 10^{-1}$
	8. ACOH	1356.0	-2.1180	0.0	2340.0	-5.0430	0.0
	11. CCOO	1356.0	0.9149	0.0	622.73	-1.7605	0.0
	13. CH_2O	-87.080	-0.1859	0.0	179.00	$0.5615 \cdot 10^{-1}$	0.0
	20. COOH	69.561	1.8881	0.0	613.32	-1.5950	0.0
5. OH	8. ACOH	83.910	-1.2620	0.0	465.40	-1.8410	0.0
	11. CCOO	973.80	-5.6330	$0.7690 \cdot 10^{-2}$	310.40	1.5380	$-0.4885 \cdot 10^{-2}$
	13. CH_2O	1102.0	-7.1760	$0.9698 \cdot 10^{-2}$	1631.0	-7.3620	$0.1176 \cdot 10^{-1}$
	20. COOH	-1295.0	4.3634	0.0	1525.8	-4.9155	0.0
8. ACOH	11. CCOO	-212.90	0.0	0.0	-224.40	0.0	0.0
	13. CH_2O	-329.30	0.0	0.0	-80.580	0.0	0.0
	20. COOH	415.72	-1.97	0.0	120.50	-2.37	0.0
11. CCOO	13. CH_2O	195.30	-9.75	$0.4051 \cdot 10^{-1}$	824.20	-6.0090	$0.8271 \cdot 10^{-2}$
	20. COOH	62.031	1.0567	0.0	59.594	-0.7120	0.0
13. CH_2O	20 COOH	521.48	0.0	0.0	-310.82	0.0	0.0

REFERENCES

1 C.P. Ashcroft, P.J. Dunn, J.D. Hayler, and A.S. Wells, *Org. Process Res. Dev*., **19**, 740 (2015).
2 R.A. Sheldon, *Green Chem*., **7**, 267 (2005).
3 P. Anastas and N. Eghbali, *Chem. Soc. Rev*., **39**, 301 (2010).
4. E. Lynge, A. Anttila, and K. Hemminki, *Cancer Causes Control*, **8**, 406 (1997).
5 M. Tobiszewski, J. Namiesnik, and F. Pena-Pereira, *Green. Chem*., **19**, 1034 (2017).
6 R.K. Khandal, S. Kaushik, G. Seshadri, and D. Khandal, **Handbook of detergents Part F: Production**, *CRC Press*, Florida, 2009.
7 S. Abou-Shehada, J.H. Clark, G. Paggiola, and J. Sherwood, *Chem. Eng. Process*., **99**, 88 (2016).
8 S. Kromusa, B. Wachterc, W. Koschuha, M. Mandlc, C. Krotschecka, and M. Narodoslawsky, *Chem. Biochem. Eng. Q*., **18**, 7 (2004).
9 C.S.M. Pereira, V.M.T.M. Silva, and A.E. Rodrigues, *Green Chem*., **13**, 2658 (2011).
10 S. Aparicio, and R. Alcalde, *Green Chem*., 11, 65 (2009).
11 S. Aparicio, *J. Phys. Chem. A,* **111**, 4671 (2007).
12 S. Aparicio, S. Halajian, R. Alcalde, B. García, and J.M. Leal, *Chem. Phys. Lett*., 454, 49 (2008).
13 N. Borho, and M.A. Suhm, *Org. Biomol. Chem.*, **1**, 4351 (2003).

14 J-T. Chen, and H-P. Chu, *J. Chem. Eng*., **52**, 650 (2007).
15 J.A. Riddick, W.B. Bunger, and T.K. Sakano, **Organic solvents: physical properties and methods of purifications** 4th edition (vol. 2), *Wiley-Interscience,* New York, 1986.
16 S. Peña-Tejedor, R. Murga, M.T. Sanz, and S. Beltrán, *Fluid Phase Equilib*., **230**, 197 (2005).
17 J.M. Resa, J.M. Goenaga, and A.I. Sánchez-Ruiz, *J. Chem. Eng.*, **51**, 1294 (2006).
18 F.D. Snell, and C.T. Snell, **Dictionary of commercial chemicals** 3rd ed., *D. Van Nostrand Co*., New Jersey, 1962.
19 M. Inal, Ethyl lactate production by hybrid processes: determination of phase diagrams and evaluation of performance of organophilic pervaporation membranes, Master of Science Thesis, *Middle East Technical University*, Turkey, 2003.
20 D. Villanueva Bermejo, E. Ibáñez, R.P. Stateva, and T. Fornari, *J. Chem. Eng*., **58**, 301 (2013).
21 S. Skjold-Jørgensen, *Fluid Phase Equilib.*, **16**, 317 (1984).
22 T. Fornari, *Fluid Phase Equilib*., **262**, 187 (2007).
23 Y. Medina-Gonzalez, A. Jarray, S. Camy, J. Condoret, and V. Gerbaud, *Solution Chem*., **46**, 259 (2017).
24 LP. Cunico and C. Turner, *J. Chem. Eng. Data,* **62**, 3525 (2017).
25 G. García, M. Atilhan, and S. Aparicio, *J. Mol. Liq*., **199**, 215 (2014).
26 S.V. Latha, G.L. Flower, K.R. Reddy, C.V.N. Rao, and A. Ratnakar, *J. Mol. Liq*., **209**, 153 (2015).
27 P. Anila, K.R. Reddy, G.S. Rao, P.V.S. Sairam, D. Ramachandran, and C. Rambabuc, *Thermochim. Acta*, **620**, 1 (2015).
28 D.M. Bajic, E.M. Živkovic, J. Jovanovic, S.P. Šerbanovic, and M. Lj. Kijevcanin, *Fluid Phase Equilibr.*, **399**, 50 (2015).
29 D.J. Benedict, S.J. Parulekar, and S-P. Tsai, *Ind. Eng. Chem. Res*., **42**, 2282 (2003).
30 D.T. Vu, C.T. Lira, N.S. Asthana, A.K. Kolah, and D.J. Miller, *J. Chem. Eng*., **51**, 1220 (2006).
31 P. Delgado, M.T. Sanz, and S. Beltrán, *Fluid Phase Equilib.*, **255**, 17 (2007).
32 H. Matsuda, K. Inaba, H. Sumida, K. Kurihara, K. Tochigi, and K. Ochi. *Fluid Phase Equilibr*. **420**, 50 (2016).
33 H. Matsuda, K. Inaba, K. Nishihara, H. Sumida, K. Kurihara, K. Tochigi, and K. Ochi. *J. Chem. Eng. Data*, **62**, 2944 (2017).
34 C. Puentes, X. Joulia, P. Paricaud, P. Giampaoli, V. Athe?s, and M. Esteban-Decloux. *J. Chem. Eng. Data,* **63**, 365 (2018).
35 K. Chylinski, and J. Gregorowicz, *J. Chem. Thermodyn*., **30**, 1131 (1998).
36 D.W. Cho, M.S. Shin, J. Shin, W. Bae, and H. Kim, *J. Chem. Eng. Data*, **56**, 3561 (2011).
37 A.B. Paninho, A.V.M. Nunes, A. Paiva, and V. Najdanovic-Visak, *Fluid Phase Equilib.*, **360**, 129 (2013).
38 M.E. Zakrzewska, M.S. Manic, E.A. Macedo, and V. Najdanovic-Visak, *Fluid Phase Equilib*., **320**, 38 (2012).
39 R. Ferreira, N. Pedrosa, I.M. Marrucho, and L.P.N. Rebelo, *J. Chem. Eng*., **53**, 588 (2008).
40 E. J. Hernández, P. Luna, R.P. Stateva, V. Najdanovic-Visak, G. Reglero, and T. Fornari, *J. Chem. Eng.*, **56**, 2148 (2011).
41 G. Vicente, A. Paiva, T. Fornari, and V. Najdanovic-Visak, *Chem. Eng. J.*, **172**, 879 (2011).
42 I. Kamalanathan, L. Canal, J. Hegarty, and V. Najdanovic-Visak, *Fluid Phase Equilibr.*, **462**, 6 (2018).
43 M.S. Manic, D. Villanueva, T. Fornari, E.A. Macedo, and V. Najdanovic-Visak, *J. Chem. Thermodyn*., **48**, 93 (2012).
44 H. Ashihara, and A. Crozier, *TRENDS Plant. Sci.*, **6**, 407 (2001).
45 D. Villanueva-Bermejo, J.A. Mendiola, E. Ibañez, G. Reglero, and T. Fornari, *Food. Bioprod. Process.*, **96**, 106 (2015).
46 D. Villanueva-Bermejo, G. Reglero, R.P. Stateva, and T. Fornari, *Open Chem. Eng.. J.*, **10** (Suppl.-1, M7), 50 (2016).
47 S.M. Nikles, M. Piao, A.M. Lane, and D.E. Nikles, *Green Chem*., **3**, 109 (2001).
48 M. Henneberry, J.A. Snively, G.J. Vasek, and R. Datta. **US Patent 6,797,684**.
49 J. Muse and H.A. Colvin, **US Patent 0,287,179**.
50 R.J. Greff. **US Patent 6,051,607**.
51 C.M. Harvey. **US Patent 6,165,987**.
52 R. Sleven, E. Lanckacker, P. Delputte, L. Maes, and P. Cos, *Mycoses*, **59**, 327 (2016).
53 S.K. Gupta. **US Patent 0,110,415**.
54 Y-J. Wee, J-N. Kim, and H-W. Ryu, *Food Technol. Biotechnol.*, **44**, 163 (2006).
55 J. Drapeau, M. Verdier, D. Touraud, U. Kröckel, M. Geier, A. Rose, and W. Kunz, *Chem. Biodivers*., **6**, 934 (2009).
56 H. Guo, W. Wang, Y. Sun, H. Li, F. Ai, L. Xie, and X. Wang, *J. Hazard. Mater*., **174**, 59 (2010).

57 Y. Sun, L. Ji, W. Wang, X. Wang, and J. Wu, *J. Environ. Qual*., **38**, 1591 (2009).
58 M.R. Elie, R.E. Williamson, C.A. Clausen, and C.L. Yestrebsky, *Chemosphere*, **117**, 793 (2014).
59 S.P.J. Ahmadkalaei, S. Gan, and H.K. Ng, *Environ. Sci. Pollut. Res*., **23**, 22008 (2016).
60 C.L. Yap, S. Gan, and H.K. Ng, *Environ. Sci. Pollut. Res.*, **22**, 329 (2015).
61 S.P.J. Ahmadkalaei, S. Gan, H.K Ng, and S.A. Talib, *Environ. Sci. Pollut. Res*., **24**, 17779 (2017).
62 Y.Y. Sun, H.X. Xu, J.H. Li, X.Q. Shi, J.C. Wu, R. Ji, and H.Y. Guo, *Int. J. Phytoremediat.*, **18**, 150 (2016).
63 F. Gironi, S. Frattari, and V. Piemonte, *J. Polym. Environ*., **24**, 328 (2016).
64 J. Wan, Y. Jind, and Y. Liu, *Phosphorus Sulfur.*, **191**(10), 1302 (2016).
65 P. Bhat, G. Shridhar, S. Ladage, and L. Ravishankar, *J. Chem. Sci*., **129**(9), 1441 (2017).
66 P. Kasinathan, J-W. Yoon, D.W. Hwang, U-H. Lee, J-S. Hwang, Y.K. Hwang, and J-S. Chang, *Appl. Catal. A-Gen.*, **451**, 236 (2013).
67 S. Zhang, Z. Huo, D. Ren, J. Luo, J. Fu, L. Li, and F. Jin, *Chinese J. Chem. Eng*., **24**, 126 (2016).
68 Y. Gao, J. Liu, J. Qiao, Y. Liu, P. He, and Y. Du, *Tetrahedron Lett.*, **59**, 291 (2018).
69 D. Clemente-Tejeda, J.C. Ortiz Lara, S.Z. Zard, *Synthesis*, **48**, 3393 (2016).
70 M. Sharma, D. Mondal, N. Singh, and K. Prasad, Chem. Commun., **52**, 9074 (2016).
71 X. Punet, R. Levato, I. Bataille, D. Letourneur, E. Engel, and M.A. Mateos-Timoneda, *Polym*., **113**, 81 (2017).
72 S. Yildirim, T.T. Demirtas, C.A. Dinçer, N. Yildiz, and A. Karakeçili, *J. Supercrit. Fluids*, **133**, 156 (2018).
73 F. Micale, F. Albu, E. Iorgulescu, A. Medvedovici, and F. Tache, *J. Chromatogr. Sci*., **53**, 1701 (2015).
74 M. Tobiszewski and J. Namiesnik, *Curr. Opin. Green Sust. Chem*., **5**, 1 (2017).
75 M. Golmakani, J.A. Mendiola, K. Rezaei, and E. Ibáñez, *J. Supercrit. Fluids*, **62**, 109 (2012).
76 C. Abbas, A. M. Rammelsberg, and K. Beery. **US Patent 0,235,633**.
77 I.F. Strati and V. Oreopoulou, *Int. J. Food Sci.Technol*., **46**, 23 (2011).
78 Y.P.A. Silva, T.A.P.C. Ferreira, G.B. Celli, and M.S. Brooks, *Waste Biomass Valoriz*., **1**, (2018).
79 D. Villanueva-Bermejo, P. Luna, M.S. Manic, V. Najdanovic-Visak, G. Reglero, and T. Fornari, *Food Bioprod. Process*., **92**, 303 (2013).
80 D. Villanueva-Bermejo, E. Ibañez, G. Reglero, and T. Fornari, *J. Supercrit. Fluids*, **107**, 507 (2016).
81 D. Villanueva-Bermejo, I. Angelov, G. Vicente, R.P. Stateva, M. Rodríguez García-Risco, G. Reglero, E. Ibáñez, and T. Fornari, *J. Sci. Food Agric.*, **95**, 2901 (2015).
82 X.C. Tombokan, R.M. Aguda, D.A. Danehower, P.K. Kilpatrick, and R.G. Carbonell, *J. Supercrit. Fluids*, **45**, 146 (2008).
83 M. Lores, M. Pajaro, M. Alvarez-Casas, J. Dominguez, and C. García-Jares, *Talanta*, **140**, 134 (2015).
84 R. Datta, and M. Henry, *J. Chem. Technol. Biotechnol*., **81**, 1119 (2006).
85 H.G. Joglekar, I. Rahman, S. Babu, B.D. Kulkami, and A. Joshi, *Sep. Purif. Technol.*, **52**, 1 (2006).
86 A. Villa, S. Campisi, C. E. Chan-Thaw, D. Motta, D. Wang, and L. Prati, *Catal. Today*, **249**, 103 (2015).
87 P.Y. Dapsens, M.J. Menart, C. Mondelli, and J. Pérez-Ramírez, *Green Chem.*, **16**, 589 (2014).
88 P.Y. Dapsens, B.T. Kusema, C. Mondelli, and J. Pérez-Ramírez, J. Molec. *Catal. A: Chem.*, **388-389**, 141 (2014).
89 E. Pighin, V,K. Díez, and J.I. Di Cosimo, *Catal. Today*, **289**, 29 (2017).
90 N. Godard, A. Vivian, L. Fusaro, L. Cannavicci, C. Aprile, and D.P. Debecker, *ChemCatChem*., **9**, 2211 (2017).
91 N. Godard, X. Collard, A. Vivian, L.A. Bivona, S. Fiorilli, L. Fusaro, and C. Aprile, *Appl. Catal A-Gen*., **556**, 73 (2018).
92 E. Pighin, V,K. Díez, and J.I. Di Cosimo, *Appl. Catal. A-Gen*., **517**, 151 (2016).
93 J. Wang, Y. Masui, and M. Onaka, *Appl. Catal B-Environ.*, **107**, 135 (2011).
94 W. Oberhauser, C. Evangelisti, S. Caporali, V. Dal Santo, F. Bossola, and F. Vizza, *J. Catal*., **350**, 133.
95 E.M. Filachione, E.J. Costello, and C.H. Fisher, *J. Am. Chem. Soc*., **73**, 5265 (1951).
96 Y. Halpern. **US Patent 6,583,310**.
97 H. Kwak, D.W. Hwang, Y.K. Hwang, and J-S. Chang, *Sep. Purif. Technol.*, **93**, 25 (2012).
98 D. Bai, Z. Yan, Q. Wei, X. Zhao, X. Li, and S. Xu, *Biochem. Eng. J*., **19**, 47 (2004).
99 P. Kasinathan, H. Kwak, U. Lee, D.W. Hwang, Y.K. Hwang, and J-S. Chang, *Sep. Purif. Technol*., **76**, 1 (2010).
100 P. Kasinathan, D.W. Hwang, U. Lee, Y.K. Hwang, and J-S. Chang, *Chem. Eng. Sci.*, **66**, 4549 (2011).
101 D. Bykowski, A. Grala, and P. Sobota, *Tetrahedron Lett*., **55**, 5286 (2014).
102 R. Petrus, D. Bykowsky, and P. Sobota, *ACS Catal*., **6**, 5222 (2016).
103 P.V. Wouwe, M. Dusselier, E. Vanleeuw, and B. Sels, *ChemSusChem*, **9**, 907 (2016).
104 P. Delgado, M.T. Sanz, and S. Beltrán, *Chem. Eng. J.*, **126**, 111 (2007).
105 Q. Yixin, P. Shaojun, W. Shui, Z. Zhiqiang, and W. Jidong, *Chin. J. Chem. Eng*., **17**, 773 (2009).

106 J. Wang, G. Yao, and F. Jin. *Molec. Catal*., **435**, 82 (2017).
107 T.K. Mai, S. Rodtong, Y. Baimark, J. Rarey, and A. Boontawan, *J. Membr. Sci.*, **551**, 180 (2018).
108 D.T. Vu, A.K. Kolah, N.S. Asthana, L. Peereboom, C.T. Lira, and D. J. Miller, *Fluid Phase Equilib*., **236**, 125 (2005).
109 R. Montgomery, *J. Am. Chem. Soc*., **74**, 1466 (1952).
110 C.S.M. Pereira, S.P. Pinho, V.M.T.M. Silva, and A.E. Rodrigues, *Ind. Eng. Chem. Res.*, **47**, 1453 (2008).
111 B. Major, G. Németh, K. Bélafi-Bakó, and L. Gubicza, *Chem. Pap.*, **64**, 261 (2010).
112 N.S Asthana, A.K Kolah, D.T. Vu, C.T. Lira, and D.J. Miller, *Org. Process Res. Dev*., **9**, 599 (2005).
113 N.S. Asthana, A.K. Kolah, D.T. Vu, C.T. Lira, and D.J. Miller, *Ind. Eng. Chem. Res*., **45**, 5251 (2006).
114 K. Tanaka, R. Yoshikawa, C. Ying, H. Kita, and K. Okamoto, *Chem. Eng. Sci*., **57**, 1577 (2002).
115 Y. Zhang, L. Ma, and J. Yang, *React. Funct. Polym*., **61**, 101 (2004).
116 D.J. Benedict, S.J. Parulekar, and S-P. Tsai, *Ind. Eng. Chem. Res*., **42**, 2282 (2003).
117 R.A. Troupe, and E. Dimilla, *Ind. Eng. Chem*., **49**, 847 (1957).
118 D. J. Benedict, S.J. Parulekar, and S-P. Tsai, *J. Membr. Sci*., **281**, 435 (2006).
119 P. Delgado, M.T. Sanz, S. Beltrán, and L.A. Núñez, *Chem. Eng. J*., **165**, 693 (2010).
120 J.J. Jafar, P.M. Budd, and R. Hughes, *J. Membr. Sci*., **199**, 117 (2002).
121 P.M. Budd, N.M.P.S. Ricardo, J.J. Jafar, B. Stephenson, and R. Hughes, *Ind. Eng. Chem. Res.,* **43**, 1863 (2004).
122 C.S.M. Pereira, V.M.T.M. Silva, S.P. Pinho, and A.E. Rodrigues, *J. Membr. Sci*., **361**, 43 (2010).
123 T. Westermann, and T. Melin, *Chem. Eng. Process.-Process. Intensif*., **48**, 17 (2009).
124 M. Zhang, L. Chen, Z. Jiang, and J. Ma, *Ind. Eng. Chem. Res*., **54**, 6669 (2015).
125 F.U. Nigiz and N.D. Hilmioglu, *Reac. Kinet. Mech. Cat*., **118**, 557 (2016).
126 F.U. Nigiz and N.D. Hilmioglu, *Chem. Eng. Technol*., **41**(4), 836 (2018).
127 T. Teerachaiyapat and P. Ramakul, *Korean J. Chem. Eng*., **33**(1), 8 (2016).
128 E. Okon, H. Shehu, and E. Gobina, *Int. J. Hydrog. Energy*, **43**, 7703 (2018).
129 F.U. Nigiz and N.D. Hilmioglu, *Chem. Biochem. Eng. Q*., **30**(3), 381 (2016).
130 F.U. Nigiz and N.D. Hilmiouglui, *Res. Chem. Intermed*., **43**, 1149 (2017).
131 J. Gao, X.M. Zhao, L.Y. Zhou, and Z.H. Huang, *Chem. Eng. Res. Des*., **85**, 525 (2007).
132 C.S.M. Pereira, M. Zabka, V.M.T.M. Silva, and A.E. Rodrigues, *Chem. Eng. Sci*., **64**, 3301 (2009).
133 V.M.T.M. Silva, C.S.M. Pereira, and A.E. Rodrigues, *AIChE J.*, **57**, 1840 (2010).
134 M.A. Wicki, and K.E. Nielsen, **US Patent 0,143,599**.
135 T.H.T Vu, H.T. Au, T.H.T. Nguyen, T.T.T. Nguyen, M.H. Do, N.Q. Bui, and N. Essayem, *Catal. Lett.,* **143**, 950 (2013).
136 N. Essayem, T.T.H. Vu, T.T.H. Nguyen, T.T.T. Nguyen, and G. Sapaly. **WO Patent 2011/107712**.
137 Z. Findrik, G. Németh, L. Gubicza, K. Bélafi-Bakó, and D. Vasic-Racki, *Bioprocess Biosyst. Eng*., **35**, 625 (2012).
138 M. Koutinas, C. Yiangou, N.M. Osorio, K. Ioannou, A. Canet, F. Valero, and S. Ferreira-Dias, *Biores. Technol*., **247**, 496 (2018).
139 K. Tanaka, and F. Toda, *Chem. Rev.*, **100**, 1025 (2000).
140 J.S. Bennett, K.L. Charles, M.R. Miner, C.F. Heuberger, E.J. Spina, M.F. Bartels, and T. Foreman, *Green Chem.*, **11**, 166 (2009).
141 G. Choudhary, and R.K. Peddinti, *Tetrahedron Lett*., **55**, 5597 (2014).
142 G. Gao, Y. Han, and Z. Zhang, *ChemistrySelect*, **2**, 11561 (2017).
143 J. Wan, C. Wang, R. Zhou, and Y. Liu, *RSC Adv*., **2**, 8789 (2012).
144 G.A. Edwards, M.A. Trafford, A.E. Hamilton, A.M. Buxton, M.C. Bardeaux, and J.M. Chalker, *J. Org. Chem*., **79**, 2094 (2014).
145 Y. Liu, H. Wang, C. Wang, J. Wan, and C. Wen, *RSC Adv.*, **3**, 21369 (2013).
146 J. Wan, S. Cao, and Y. Jing, *Appl. Organomet. Chem*., **28**, 631 (2014).
147 J. Wan, S. Zhong, L. Xie, X. Cao, Y. Liu, and L. Wei, *Org. Lett.*, **18**, 584 (2016).
148 S. Zhong, Y. Liu, X. Cao, and J. Wan, *ChemCatChem*, **9**, 465 (2017).
149 J. Wang, S. Cao, C. Hu, and C. Wen, *Asian J. Org. Chem*., **7**, 328 (2018).
150 Y. Gao, Y. Liu, L. Wei, and J. Wan, *Res. Chem. Intermediat.*, **43**, 5547 (2017).
151 S. Paul, and A.R. Das, *Tetrahedron Lett*., **53**, 2206 (2012).
152 Z. Xu, Y. Jiang, S. Zou, and Y. Liu, *Phosphorus Sulfur*, **189**, 791 (2014).
153 N. Kausar, A. Al Masum, M.M. Islam, and A.R. Das, *Mol Divers*, **21**, 325 (2017).
154 A. Dandia, A.K. Jain, and A.K. Laxkar, *Tetrahedron Lett.*, **54**, 3929 (2013).
155 P.P. Ghosh, S. Paul, and A.R. Das, *Tetrahedron Lett.*, **54**, 138-142 (2013).
156 M. Zhang, Q. Fu, G. Gao, H. He, Y. Zhang, Y. Wu, and Z. Zhang, *Sustainable Chem. Eng*., **5**, 6175 (2017).

157 A. Procopio, P. Costanzo, M. Curini, M. Nardi, M. Oliverio, and G. Sindona, *Sustainable Chem. Eng.*, **1**, 541 (2013).
158 Y. Liu, and W. Wen, *Curr. Green Chem*., **2**, 399 (2015).
159 G. Shen, H. Zhou, P. Du, S. Liu, K. Zou, and Y. Uozumi, *RSC Adv.*, **5**, 85646 (2015).
160 M.G. Sajilata, R.S. Singhal, and M.Y. Kamat, *J. Food Eng*., **84**, 321 (2008).
161 K. Dimas, D. Kokkinopoulos, C. Demetzos, B. Vaos, M. Marselos, M. Malamas, and T. Tzavaras, *Leukemia Res*., **23**, 217 (1999).
162 J. Ivanovic, D. Misic, I. Zizovic, and M. Ristic, *Food Control*, **25**, 110 (2012).
163 A.L. Dawidowicz, E. Rado, D. Wianowska, M. Mardarowicz, and J. Gawdzik, *Talanta*, **76**, 878 (2008).
164 A.L. Dawidowicz, E. Rado, and D. Wianowska, *J. Sep. Sci*., **32**, 3034 (2009).
165 B.K. Ishida, and G.E. Bartley, **Encyclopedia of human nutrition** 2nd ed., *Elsevier*, Oxford, 2005.
166 B.K. Ishida, and M.H. Chapman, *J. Agric. Food Chem*., **57**, 1051 (2009).
167 M. Zelkha, M. Ben-Yehuda, D. Hartal, Y. Raveh, and N. Garti, **US Patent 5,837,311**.
168 M. Kawaragi, T. Kuraishi, H. Shirasawa, N. Takada, N. Takada, Y. Katsumi, and S. Kojima, **US Patent 5,871,574**.
169 K. Bortlik, L. Mortezavi, and F. Saucy, **WO Patent 01/38443**.
170 H. Al-Wandawi, M. Abdul-Rahman, and K. Al-Shaikhly, *J. Agric. Food Chem*., **33**, 804 (1985).
171 T. Nakano, M. Tosa, and M. Takeuchi, *J. Agric. Food Chem*., **43**, 1570 (1995).
172 W. Wu, M. Lu, and L. Yu, *Eur. Food. Res. Technol.*, **232**, 463 (2011).
173 H. Ashihara, and A. Crozier, *TRENDS Plant. Sci*., **6**, 407 (2001).
174 H.S. Park, H.J. Lee, M.H. Shin, K.W. Lee, H. Lee, Y.S. Kim, K.O. Kim, and K.H. Kim, *Food Chem*., **105**, 1011 (2007).
175 A. Perva-Uzunalic, M. Skerget, Z. Knez, B. Weinreich, F. Otto, and S. Gruner, *Food Chem.*, **96**, 597 (2006).
176 E. Tedeschi, H. Suzuki, and M. Menegazzi, *Ann. N.Y. Acad. Sci.,* **973**, 435 (2002).
177 R. Cooper, D.J. Morre, and D.M Morre, *J. Altern. Complement. Med*., **11**, 521 (2005).
178 Q.V. Vuong, and P.D. Roach, *Sep. Purif. Rev.,* **43**, 155 (2014).
179 K. Zosel, *Chemie*, **90**, 748 (1978).
180 W-J. Kim, J-D. Kim, J. Kim, S-G. Oh, Y-W. Lee, *J. Food Eng*., **89**, 303 (2008).
181 H. Sovová, *Chem. Eng. Sci*., **49**, 409 (1994).
182 D. Villanueva-Bermejo, E. Ibañez, G. Reglero, C. Turner, T. Fornari, and I. Rodriguez-Meizoso, *Sep. Purif. Tech*., **148**, 49 (2015).
183 D. Villanueva-Bermejo, G. Reglero, and T. Fornari, *Trends Food Sci. Tech*., **62**, 1 (2017).
184 J. Gmehling, J. Li, and M. Schiller, *Ind. Eng. Chem. Res*., **32**, 178 (1993).

21

Solvent Recycling, Removal, and Degradation

21.1 ABSORPTIVE SOLVENT RECOVERY

Klaus-Dirk Henning
CarboTech Aktivkohlen GmbH, Essen, Germany

21.1.1 INTRODUCTION

A variety of waste gas cleaning processes[1-4] is commercially available. They are used to remove organic vapors (solvents) from air emissions from various industries and product lines. The main applications of solvents in various industries are given in Table 21.1.1.

Table 21.1.1. Application of organic solvents. [After references 2-4].

Application	Solvents
Coating plants: adhesive tapes, magnetic tapes, adhesive films, photographic papers, adhesive labels	Naphtha, toluene, alcohols, esters, ketones (cyclohexanone, methyl ethyl ketone), dimethylformamide, tetrahydrofuran, chlorinated hydrocarbons, xylene, dioxane
Chemical, pharmaceutical, food industries	Alcohols, aliphatic, aromatic and halogenated hydrocarbons, esters, ketones, ethers, glycol ether, dichloromethane
Fiber production Acetate fibers Viscose fibers Polyacrylonitrile	 Acetone, ethanol, esters carbon disulfide dimethylformamide
Synthetic leather production	Acetone, alcohols, ethyl ether
Film manufacture	Alcohols, acetone, ether, dichloromethane
Painting shops: cellophane, plastic films, metal foils, vehicles, hard papers, cardboard, pencils	Amyl acetate, ethyl acetate, butyl acetate, dichloromethane, ketones (acetone, methyl ethyl ketone), butanol, ethanol, tetrahydrofuran, toluene, benzene, methyl acetate
Cosmetics industry	Alcohols, esters
Rotogravure printing shops	Toluene, xylene, heptane, hexane
Textile printing	Hydrocarbons
Drycleaning shops	Hydrocarbons, tetrachloroethane

Table 21.1.1. Application of organic solvents. [After references 2-4].

Application	Solvents
Sealing board manufacture	Hydrocarbons, toluene, trichloroethane
Powder and explosives production	Ether, alcohol, benzene
Degreasing and scouring applications Metal components Leather Wool	 Hydrocarbons, trichloroethylene, tetrachloroethylene, dichloromethane Tetrachloroethylene Tetrachloroethane
Loading and reloading facilities (tank venting gases)	Gasoline, benzene, toluene, xylene

The basic principles of some generally accepted gas cleaning processes for solvent removal are given in Table 21.1.2. For more than 70 years adsorption processes using activated carbon, in addition to absorption and condensation processes, were dominant in removal and recovery of solvents. The first solvent recovery plant for acetone was commissioned for economic reasons in 1917 by Bayer. In the decades that followed, solvent recovery plants were built and operated only if the value of the recovered solvents exceeded the operation costs and depreciation of the plant. Today such plants are used for adsorptive purification of exhaust air streams, even if the return is insufficient, to meet environmental and legal requirements.

Table 21.1.2. Cleaning processes for the removal and recovering of solvents.

	Basic principle	
Incineration	The solvents are completely destroyed by: thermal oxidation (>10 g/m^3) catalytic oxidation (3-10 g/m^3)	Only waste heat recovery possible
Condensation	High concentration of solvents (>50 g/m^3) are lowered by direct or indirect condensation with refrigerated condensers	- Effective in reducing heavy emissions, - good quality of the recovered solvents, - difficult to achieve low discharge levels
Absorption	Scrubbers using non-volatile organics as scrubbing medium for the solvent removal. Desorption of the spent scrubbing fluid	Advantageous if: - scrubbing fluid can be reused directly without desorption of the absorbed solvent - scrubbing with the subcooled solvent itself possible
Membrane permeation	Membrane permeation processes are suited for small volumes with high concentrations, e.g., to reduce hydrocarbon concentration from several hundred g/m^3 down to 5-10 g/m^3	To meet the environmental protection requirements a combination with other cleaning processes (e.g. activated carbon adsorber) is necessary
Biological treatment	Biological decomposition by means of bacteria and using bioscrubber or biofilter	Sensitive to temperature and solvent concentration

Table 21.1.2. Cleaning processes for the removal and recovering of solvents.

	Basic principle	
Adsorption	Adsorption of solvents by passing the waste air through an adsorber filled with activated carbon. Solvent recovery by steam or hot gas desorption	By steam desorption the resulting desorbate has to be separated in a water and an organic phase using a gravity separator (or a rectification step)

This contribution deals with adsorptive solvent removal,[2,12,13] recovery, and some other hybrid processes using activated carbon in combination with other purification steps. Due to more stringent environmental protection requirements, further increases in the number of adsorption plants for exhaust air purification may be expected.

21.1.2 BASIC PRINCIPLES

21.1.2.1 Fundamentals of adsorption

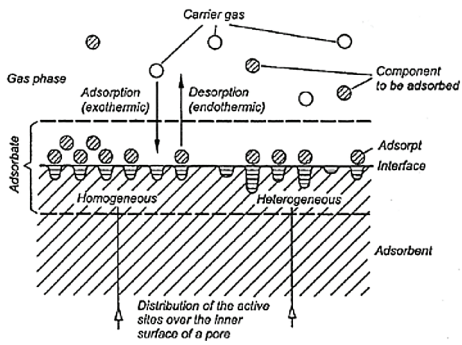


Figure 21.1.1. Adsorption terms [After reference 2].

To understand the adsorptive solvent recovery we have to consider some of the fundamentals of adsorption and desorption[1-9] (Figure 21.1.1). Adsorption is the term for the enrichment of gaseous or dissolved substances on the boundary surface of a solid (the adsorbent). The surfaces of adsorbents have what we call active sites where the binding forces between the individual atoms of the solid structure are not completely saturated by neighboring atoms. These active sites can bind foreign molecules which, when bound, are referred to as adsorpt. The overall interphase boundary is referred to as adsorbate. The term, desorption, designates the liberation of the adsorbed molecules, which is a reversal of the adsorption process. The desorption process generates desorbate which consists of the desorpt and the desorption medium.[2]

A distinction is made between two types of adsorption mechanisms: chemisorption and physisorption. Physisorption, is reversible and involves exclusively physical interaction forces (van der Waals forces) between the component to be adsorbed and the adsorbent. Chemisorption, is characterized by greater interaction energies which result in a chemical modification of the component adsorbed along with its reversible or irreversible adsorption.[2]

Apart from diffusion through the gas-side of boundary film, adsorption kinetics are predominantly determined by the diffusion rate through the pore structure. The diffusion coefficient is governed by both the ratio of pore diameter to the radius of the molecule being adsorbed and other characteristics of the component being adsorbed. The rate of adsorption is governed primarily by diffusional resistance. Pollutants must first diffuse from the bulk gas stream across the gas film to the exterior surface of the adsorbent (gas film resistance).

Due to the highly porous nature of the adsorbent, its interior contains by far the majority of the free surface area. For this reason, the molecule to be adsorbed must diffuse into the pore (pore diffusion). After their diffusion into the pores, the molecules must then physically adhere to the surface, thus losing the bulk of their kinetic energy.

Adsorption is an exothermic process. The adsorption enthalpy decreases as a load of adsorbed molecules increases. In activated carbon adsorption systems for solvent recovery, the liberated adsorption enthalpy normally amounts to 1.5 times the evaporation enthalpy at the standard working capacities which can result in a 20 K or more temperature increase. In the process, exothermic adsorption mechanisms may coincide with endothermic desorption mechanisms.[2]

21.1.2.2 Adsorption capacity

The adsorption capacity (adsorptive power, loading) of an adsorbent resulting from the size and the structure of its inner surface area for a defined component is normally represented by a function of the component concentration c in the carrier gas for the equilibrium conditions at a constant temperature. This is known as the adsorption isotherm $x=f(c)_T$. There are a variety of approaches proceeding from different model assumptions for the quantitative description of adsorption isotherms (Table 21.1.3) which are discussed in detail in the literature.[2,9,11]

Table 21.1.3. Overview of major isotherm equations [After reference 2].

Adsorption isotherm by	Isotherm equation	Notes
Freundlich	$x = k \times p_i^n$	low partial pressures of the component to be adsorbed
Langmuir	$x = \frac{x_{max} b p_i}{1 + b p_i}$	homogeneous adsorbent surface, monolayer adsorption
Brunauer, Emmet, Teller (BET)	$\frac{p_i}{V(p_s - p_i)} = \frac{1}{V_{MB} C} + \frac{C-1}{V_{MB} C} \frac{p_i}{p_s}$	homogeneous surface, multilayer adsorption, capillary condensation
Dubinin-Radushkevich	$\log V = \log V_s - 2.3 \left(\frac{RT}{\varepsilon_o \beta}\right) \left(\log \frac{p_s}{p_i}\right)^n$	potential theory; n = 1,2,3; e.g., n = 2 for the adsorption of organic solvent vapors on microporous activated carbon grades

where: K, n – specific constant of the component to be adsorbed; x – adsorbed mass, g/100 g; x_{max} – saturation value of the isotherm with monomolecular coverage, g/100 g; b – coefficient for component to be adsorbed, Pa; C – constant; T – temperature, K; p_i – partial pressure of component to be adsorbed, Pa; p_s – saturation vapor pressure of component to be adsorbed, Pa; V – adsorpt volume, ml; V_{MB} – adsorpt volume with monomolecular coverage, ml; V_s – adsorpt volume on saturation, ml; V_M - molar volume of component to be adsorbed, l/mol; R – gas constant, J(kg K); ε_o – characteristic adsorption energy, J/kg; β – affinity coefficient

The isotherm equation developed by Freundlich on the basis of empirical data can often be helpful. According to the Freundlich isotherm, the logarithm of the adsorbent loading increases linearly with the concentration of the component to be adsorbed in the carrier gas. This is also the result of the Langmuir isotherm which assumes that the bonding energy rises exponentially as loading decreases.

However, commercial adsorbents do not have a smooth surface but rather are highly porous solids with a very irregular and rugged inner surface. This fact is taken into account by the potential theory which forms the basis of the isotherm equation introduced by Dubinin.

At adsorption temperatures below the critical temperature of the component to be adsorbed, the adsorbent pores may fill up with liquid adsorpt. This phenomenon is known as capillary condensation and enhances the adsorption capacity of the adsorbent. Assuming cylindrical pores, capillary condensation can be quantitatively described with the aid of the Kelvin equation, the degree of pore filling being inversely proportional to the pore radius.

If several compounds are contained in a gas stream the substances compete for the adsorption area available. In that case, compounds with large interacting forces may displace less readily adsorbed compounds from the internal surface of the activated carbon.

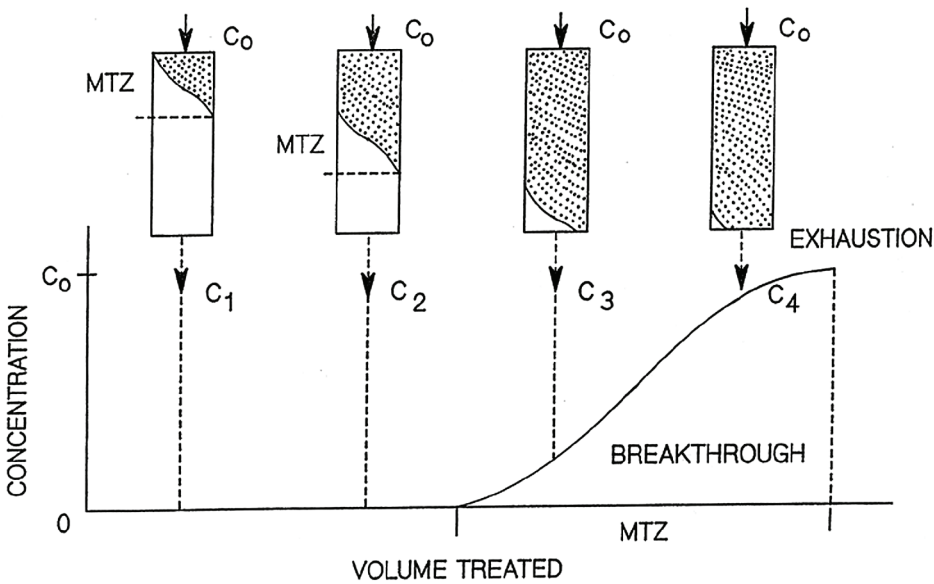


Figure 21.1.2. The idealized breakthrough curve of a fixed bed adsorber.

As previously stated, the theories of adsorption are complex, with many empirically determined constants. For this reason, pilot data should always be obtained on the specific pollutant adsorbent combination prior to full-scale engineering design.

21.1.2.3 Dynamic adsorption in adsorber beds

For commercial adsorption processes such as solvent recovery not only the equilibrium load, but also the rate at which it is achieved (adsorption kinetics) is of decisive importance.[9-15] The adsorption kinetics is determined by the rates of the following series of individual steps:

- transfer of molecules to the external surface of the adsorbent (border layer film diffusion)
- diffusion into the particle
- adsorption

The adsorbent is generally in a fixed adsorber bed and the contaminated air is passed through the adsorber bed (Figure 21.1.2). When the contaminated air first enters through the adsorber bed most of the adsorbate is initially adsorbed at the inlet of the bed and the air passes on with little further adsorption taking place. Later, when the inlet of the absorber becomes saturated, adsorption takes place deeper in the bed. After a short working time the activated carbon bed becomes divided into three zones:

- the inlet zone where the equilibrium load corresponds to the inlet concentration, c_o
- the adsorption or mass transfer zone, MTZ, where the adsorbate concentration in the air stream is reduced
- the outlet zone where the adsorbent remains incompletely loaded

In time the adsorption zone moves through the activated carbon bed.[18-21] When the MTZ reaches the adsorber outlet zone, breakthrough occurs. The adsorption process must be stopped if a predetermined solvent concentration in the exhaust gas is exceeded. At this point the activated carbon bed has to be regenerated. If, instead the flow of contaminated air is continued on, the exit concentration continues to rise until it becomes the same as the inlet concentration. It is extremely important that the adsorber bed should be at least as long as the mass transfer zone of the component to be adsorbed. The following are key factors in dynamic adsorption and help determine the length and shape of the MTZ:

- the type of adsorbent
- the particle size of the adsorbent (may depend on maximum allowable pressure drop)
- the depth of the adsorbent bed
- the gas velocity
- the temperature of the gas stream and the adsorbent
- the concentration of the contaminants to be removed
- the concentration of the contaminants not to be removed, including moisture
- the pressure of the system
- the removal efficiency required
- possible decomposition or polymerization of contaminants on the adsorbent

21.1.2.4 Regeneration of the loaded adsorbents

In the great majority of adsorptive waste gas cleaning processes, the adsorpt is desorbed after the breakthrough loading has been attained and the adsorbent reused for pollutant removal. Several aspects must be considered when establishing the conditions of regeneration for an adsorber system.[2-4,6,13-16] Very often, the main factor is an economic one, to establish that an in-place regeneration is or is not preferred to the replacement of the entire adsorbent charge. Aside from this factor, it is important to determine if the recovery of the contaminant is worthwhile, or if only regeneration of the adsorbent is required. The pro-

cess steps required for this purpose normally dictate the overall concept of the adsorption unit.

Regeneration, or desorption, is usually achieved by changing the conditions in the adsorber to bring about a lower equilibrium-loading capacity. This is done by either increasing the temperature or decreasing the partial pressure. For regeneration of spent activated carbon from waste air cleaning processes, the following regeneration methods are available (Table 21.1.4).

Table 21.1.4. Activated carbon regeneration processes [After references 2,16].

Regeneration method	Principle	Application examples	Special features
Pressure-swing process	Alternating between elevated pressure during adsorption and pressure reduction during desorption	Gas separation, e.g., N_2 from the air, CH_4 from biogas, CH_4 from hydrogen	Raw gas compression; lean gas stream in addition to the product gas stream
Temperature-swing process:			
Desorption	Steam desorption or inert gas desorption at temperatures of < 500°C	Solvent recovery, process waste gas cleanup	Reprocessing of desorbate
Reactivation	Partial gasification at 800 to 900°C with steam or other suitable oxidants	All organic compounds adsorbed in gas cleaning applications	Post-combustion, if required scrubbing of flue gas generated
Extraction with:			
Organic solvents	Extraction with carbon disulfide or other solvents	Sulfur extraction Sulfosorbon process	Desorbate treatment by distillation, steam desorption of solvent
Caustic soda solution	Percolation with caustic soda	Phenol-loads activated carbon	Phenol separation with subsequent purging
Supercritical gases	e.g., extraction with supercritical CO_2	Organic compounds	Separation of CO_2/ organic compounds

- Pressure-swing process
- Temperature-swing process
- Extraction process

In the solvent recovery plants, temperature-swing processes are most frequently used. The loaded adsorbent is directly heated by the stream of hot inert gas, which, at the same time, serves as a transport medium to discharge the desorbed vapor and reduce the partial pressure of the gas-phase desorpt. As complete desorption of the adsorpt cannot be accomplished in a reasonable time in commercial-scale systems, there is always heel remaining which reduces the adsorbent working capacity.

Oxidic adsorbents offer the advantage that their adsorptive power can be restored by controlled oxidation with air or oxygen at high temperatures.

21.1.3 COMMERCIALLY AVAILABLE ADSORBENTS

Adsorbers used for air pollution control and solvent recovery predominantly employ activated carbon. Molecular sieve zeolites are also used. Polymeric adsorbents can be used but are seldom seen.

21.1.3.1 Activated carbon

Activated carbon[1-8] is the trade name for a carbonaceous adsorbent which is defined as follows: Activated carbons[5] are non-hazardous, processed, carbonaceous products, having a porous structure and a large internal surface area. These materials can adsorb a wide variety of substances, i.e., they are able to attract molecules to their internal surface, and are therefore called adsorbents. The volume of pores of the activated carbons is generally greater than 0.2 ml g^{-1}. The internal surface area is generally greater than 400 m^2g^{-1}. The width of the pores ranges from 0.3 to several thousand nm.

All activated carbons are characterized by their ramified pore system within which various mesopores (r = 1-25 nm), micropores (r = 0.4-1.0 nm) and submicropores (r < 0.4 nm) each of which branch off from macropores (r > 25 nm).

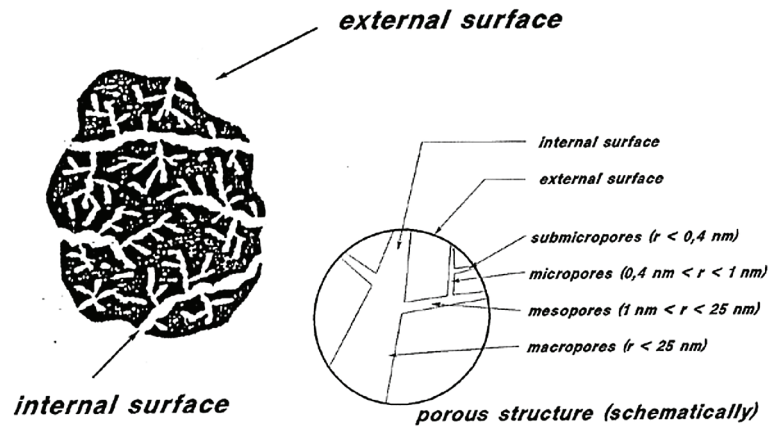


Figure 21.1.3. Schematic model of activated carbon. [Adapted, by permission, from K.-D. Henning, S. Schäfer, Impregnated activated carbon for environmental protection, *Gas Separation & Purification*, 1993, Vol. **7**, No. 4, p. 235.]

Figure 21.1.3 shows schematically the pore system important for adsorption and desorption.[17] The large specific surfaces are created predominantly by the micropores. Activated carbon is commercially available in shaped (cylindrical pellets), granular, or powdered form.

Due to its predominantly hydrophobic surface properties, activated carbon preferentially adsorbs organic substances and other non-polar compounds from gas and liquid phases. Activated alumina, silica gel, and molecular sieves will adsorb water preferentially from a gas-phase mixture of water vapor and an organic contaminant. In Europe, cylindrically-shaped activated carbon pellets with a diameter of 3 or 4 mm are used for solvent recovery because they assure a low-pressure drop across the adsorber system. Physical and chemical properties of three typical activated carbon types used in solvent recovery are given in Table 21.1.5.

Table 21.1.5 Activated carbon types for waste air cleaning *[After reference 2].*

Adsorbent	**Applications (typical examples)**	Compacted **density, kg/m^3**	Pore volume **for pore size d < 20 nm,** ml/g	Pore volume **for pore size d > 20 nm,** ml/g	Specific **surface area, m^2/g**	Specific **heat capacity,** J/kgK
Activated carbon, fine-pore	Intake air and exhaust air cleanup, odor control, adsorption of low-boiling hydrocarbons	400 - 500	0.5 - 0.7	0.3 - 0.5	1000-1200	850
Activated carbon, medium-pore	Solvent recovery, adsorption of medium-high boiling hydrocarbons	350 - 450	0.4 - 0.6	0.5 - 0.7	1200-1400	850
Activated carbon, wide-pore	Adsorption and recovery of high-boiling hydrocarbons	300 - 400	0.3 - 0.5	0.5 - 1.1	1000-1500	850

21.1.3.2 Molecular sieve zeolites

Molecular sieve zeolites[2,10,11] are hydrated, crystalline aluminosilicates which give off their crystal water without changing their crystal structure so that the original water sites are free for the adsorption of other compounds. Activation of zeolites is a dehydration process accomplished by the application of heat in a high vacuum. Some zeolite crystals show behavior opposite to that of activated carbon in that they selectively adsorb water in the presence of nonpolar solvents. Zeolites can be made to have specific pore sizes that impose limits on the size and orientation of molecules that can be adsorbed. Molecules above a specific size cannot enter the pores and therefore cannot be adsorbed (steric separation effect).

Substitution of the greater part of the Al_2O_3 by SiO_2 yields zeolites suitable for the selective adsorption of organic compounds from high-moisture waste gases.

21.1.3.3 Polymeric adsorbents

The spectrum of commercial adsorbents[2] for use in air pollution control also includes beaded, hydrophobic adsorber resins consisting of nonpolar, macroporous polymers produced for the specific application by polymerizing styrene in the presence of a crosslinking agent. Crosslinked styrene-divinylbenzene resins are available on the market under different trade names. Their structure-inherent fast kinetics offers the advantage of relatively low desorption temperatures. They are insoluble in water, acids, lye, and a large number of organic solvents.

21.1.4 ADSORPTIVE SOLVENT RECOVERY SYSTEMS

Stricter regulations regarding air pollution control, water pollution control, and waste management have forced companies to remove volatile organics from atmospheric emissions and workplace environments. But apart from compliance with these requirements, economic factors are decisive in solvent recovery. Reuse of solvent in production not only reduces operating cost drastically but may even allow profitable operation of a recovery system.

21.1.4.1 Basic arrangement of adsorptive solvent recovery with steam desorption

Adsorptive solvent recovery units have at least two, but usually, three or four parallel-connected fix-bed adsorbers which pass successively through the four stages of the operation cycle.[1-4,18-23]

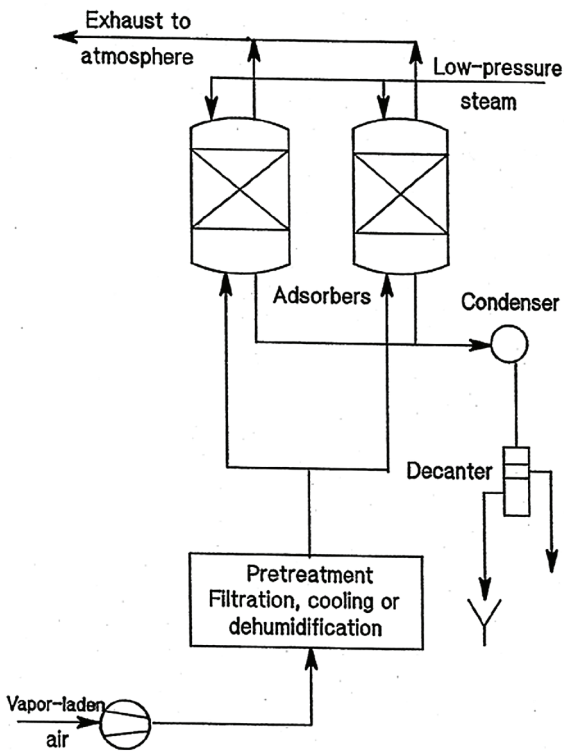


Figure 21.1.4. Flow sheet of a solvent recovery system with steam desorption.

- Adsorption
- Desorption
- Drying
- Cooling

Whilst adsorption takes place in one or more of them, desorption, drying, and cooling take place in the others. The most common adsorbent is activated carbon in the shape of 3 or 4 mm pellets or as granular type with a particle size of 2 to 5 mm (4 x 10 mesh). A schematic flow sheet of a two adsorber system for the removal of water-insoluble solvents is shown in Fig 21.1.4.

The adsorber feed is pretreated if necessary to remove solids (dust), liquids (droplets or aerosols) or high-boiling components as these can hamper performance. Frequently, the exhaust air requires cooling.

To prevent an excessive temperature increase across the bed due to the heat of adsorption, inlet solvent concentrations are usually limited to about 50 g/m^3. In most systems, the solvent-laden air stream is directed upwards through a fixed carbon bed. As soon as the maximum permissible breakthrough concentration is attained in the discharge clean air stream, the loaded adsorber is switched to regeneration. To reverse the adsorption of the solvent, the equilibrium must be reversed by increasing the temperature and decreasing the solvent concentration by purging.

For solvent desorption direct steaming of the activated carbon bed is the most widely used regeneration technique because it is cheap and simple. Steam (110-130°C) is very effective in raising the bed temperature quickly and is easily condensed to recover the solvent as a liquid. A certain flow is also required to reduce the partial pressure of the adsorbate and carry the solvent out of the activated carbon bed. A flow diagram for steam desorption for toluene recovery is given in Figure 21.1.5.

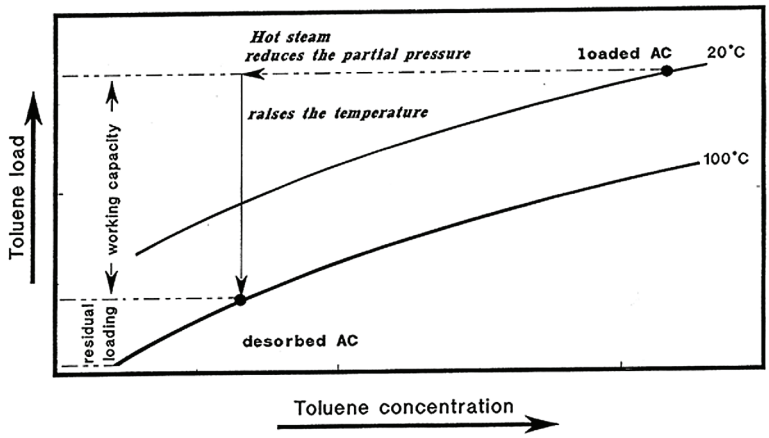


Figure 21.1.5. Principle of steam desorption.

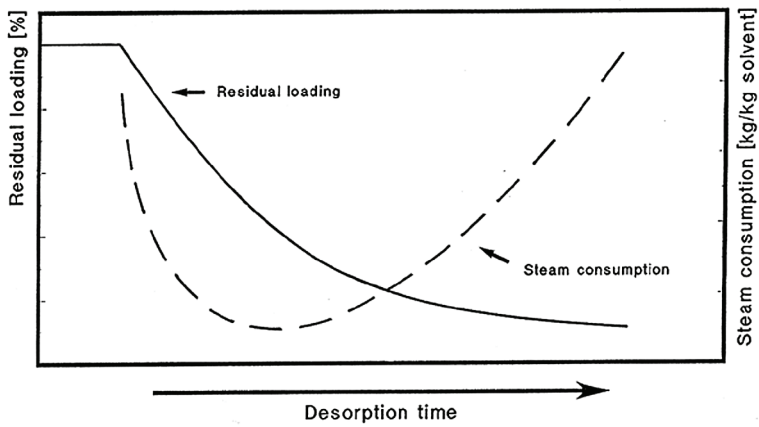


Figure 21.1.6. Desorption efficiency and steam consumption.

First, the temperature of the activated carbon is increased to approx. 100°C. This temperature increase reduces the equilibrium load of the activated carbon. Further reduction of the residual load is obtained by the flushing effect of the steam and the declining toluene partial pressure. The load difference between spent and regenerated activated carbon – the "working capacity" – is then available for the next adsorption cycle.

The counter-current pattern of adsorption and desorption favors high removal efficiencies. Desorption of the adsorbed solvents starts after the delay required to heat the activated carbon bed. The specific steam consumption increases as the residual load of the activated carbon decreases (Figure 21.1.6). For cost reasons, desorption is not run to completion. The desorption time is optimized to obtain the acceptable residual load with a minimum specific steam consumption. The amount of steam required depends on the

interaction forces between the solvent and the activated carbon. The mixture of steam and solvent vapor from the adsorber is condensed in a condenser. If the solvent is immiscible with water the condensate is led to a gravity separator (making use of the density differential) where it is separated into an aqueous and solvent fraction.

If the solvents are partly or completely miscible with water, additional special processes are necessary for solvent separation and treatment (Figure 21.1.7). For partly miscible solvents the desorpt steam/solvent mixture is separated by enrichment condensation, rectification or by a membrane processes. The separation of completely water-soluble solvents requires a rectification column.[2]

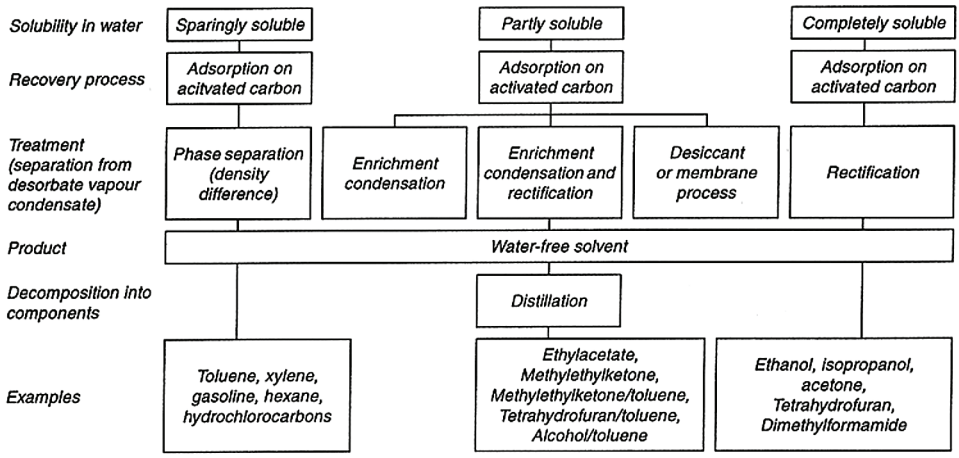


Figure 21.1.7. Options for solvent recovery by steam desorption [After references 2, 3,12].

After steam regeneration, the hot and wet carbon bed will not remove organics from air effectively, because high temperature and humidity do not favor complete adsorption. The activated carbon is therefore dried by a hot air stream. Before starting the next adsorption cycle the activated carbon bed is cooled to ambient temperature with air. Typical operating data for solvent recovery plants and design ranges are given in Table 21.1.6.

Table 21.1.6. Typical operating data for solvent recovery plants.

Operating data	Range of design
Air velocity (m/s): 0.2-0.4	Solvent concentration (g/m^3): 1-20
Air temperature (°C): 20-40	Solvent adsorbed by activated
Bed height (m): 0.8-2	carbon per cycle (% weight): 10-20
Steam velocity (m/s): 0.1-0.2	Steam/solvent ratio: 2-5:1
Time cycle for each adsorber	Energy (kWh/t solvent): 50-600
Adsorption (h): 2-6	Cooling water (m^3/t solvent): 30-100
Steaming (h): 0.5-1	Activated carbon (kg/t solvent): 0.5-1
Drying (hot air, h): 0.2-0.5	
Cooling (cold air, h): 0.2-0.5	

21.1.4.2 Designing solvent recovery systems

21.1.4.2.1 Design basis[1-3,18-23]

Designing an activated carbon system should be based on pilot data for the particular system and information obtained from the activated carbon producer. The basic engineering and the erection of the system should be done by an experienced engineering company. Solvent recovery systems would also necessitate the specification of condenser duties, distillation tower sizes, holding tanks and piping and valves. Designing of a solvent recovery system requires the following information (Table 21.1.7).

Table 21.1.7. The design basis for adsorption systems by the example of solvent recovery [After references 1-3].

Site-specific conditions	Emission sources: Production process(es), continuous/shift operation Suction system: Fully enclosed system, negative pressure control Available drawings: Building plan, machine arrangement, available space, neighborhood Operating permit as per BimSchG (German Federal Immission Control Act)
Exhaust air data (max., min., normal	Volumetric flow rate (m^3h) Relative humidity (%) Solvent concentration by components (g/m^3) The concentration of other pollutants and condition (fibers, dust) Temperature (°C) Pressure (mbar)
Characterization of solvents	Molecular weight, density Critical temperature Water solubility Stability (chemical, thermal) Safety instructions as per German Hazardous Substances Regulations (description of hazards, safety instructions, safety data sheets) Physiological effects: irritating, allergenic, toxic, cancerogenic Boiling point, boiling range Explosion limits Corrosiveness Maximum exposure limits (MEL)
Utilities (type and availability)	Electric power Steam Cooling water Cooling brine Compressed air, instrument air Inert gas
Waste streams (avoidance, recycling, disposal)	Solvent Steam condensate Adsorbent Filter dust
Guaranteed performance data at rated load	Emission levels: pollutants, sound pressure level (dB(A)) Utility consumption, materials- Availability

After this information has been obtained, the cycle time of the system must be determined. The overall size of the unit is determined primarily by economic considerations, balancing low operating costs against the capital costs (smaller system → shorter cycle time; bigger adsorber → long cycle time). The limiting factor for the adsorber diameter is normally the maximum allowable flow velocity under continuous operating conditions. The latter is related to the free vessel cross-section and, taking into account fluctuations in the gas throughput, selected such (0.1 to 0.5 m/s) that it is sufficiently below the disengagement point, i.e., the point at which the adsorbent particles in the upper bed area are set into motion. Once the adsorber diameter has been selected, the adsorber height can be determined from the required adsorbent volume plus the support tray and the free flow cross-sections to be provided above and below the adsorbent bed. The required adsorbent volume is dictated by the pollutant concentration to be removed per hour and the achievable adsorbent working capacity.

From the view point of adsorption theory, it is important that the bed be deeper than the length of the transfer zone which is unsaturated. Any multiplication of the minimum bed depth gives more than proportional increase in capacity. In general, it is advantageous to size the adsorbent bed to the maximum length allowed by pressure drop considerations. Usually, fixed-bed adsorber has a bed thickness of 0.8-2 m.

21.1.4.2.2 Adsorber types

Adsorbers for solvent recovery[1-3] units (Figure 21.1.8) are built in several configurations:

- the vertical cylindrical fixed-bed adsorber
- the horizontal cylindrical fixed-bed adsorber
- vertical annular bed adsorber
- moving-bed adsorber
- rotor adsorber (axial or radial)

For the cleanup of high volume waste gas streams, multi-adsorber systems are preferred. Vertical adsorbers are most common. Horizontal adsorbers, which require less overhead space, are used mainly for large units. The activated carbon is supported on a cast-iron grid which is sometimes covered by a mesh. Beneath the bed, a 100 mm layer of 5-50mm size gravel (or Al_2O_3 pellets) is placed which acts as a heat accumulator and it stores part of the desorption energy input for the subsequent drying step. The depth of the carbon bed, chosen in accordance with the process conditions, is from 0.8 to 2 m. Adsorbers with an annular bed of activated carbon are less common. The carbon in the adsorber is contained between vertical, cylindrical screens. The solvent laden air passes from the outer annulus through the outer screen, the carbon bed and the inner screen then exhausts to atmosphere through the inner annulus. The steam for regeneration of the carbon flows in the opposite direction to the airstream. Figure 21.1.8 illustrates the operating principle of a counter-current flow vertical moving bed adsorber. The waste gas is routed in counter-current to the moving adsorbent and such adsorption systems have a large number of single moving beds. The discharge system ensures a uniform discharge (mass flow) of the loaded adsorbent. In this moving bed system adsorption and desorption are performed in a separate column or column sections. The process relies on an abrasion resistant adsorbent with good flow properties (beaded carbon or adsorber resins). After the adsorption stage

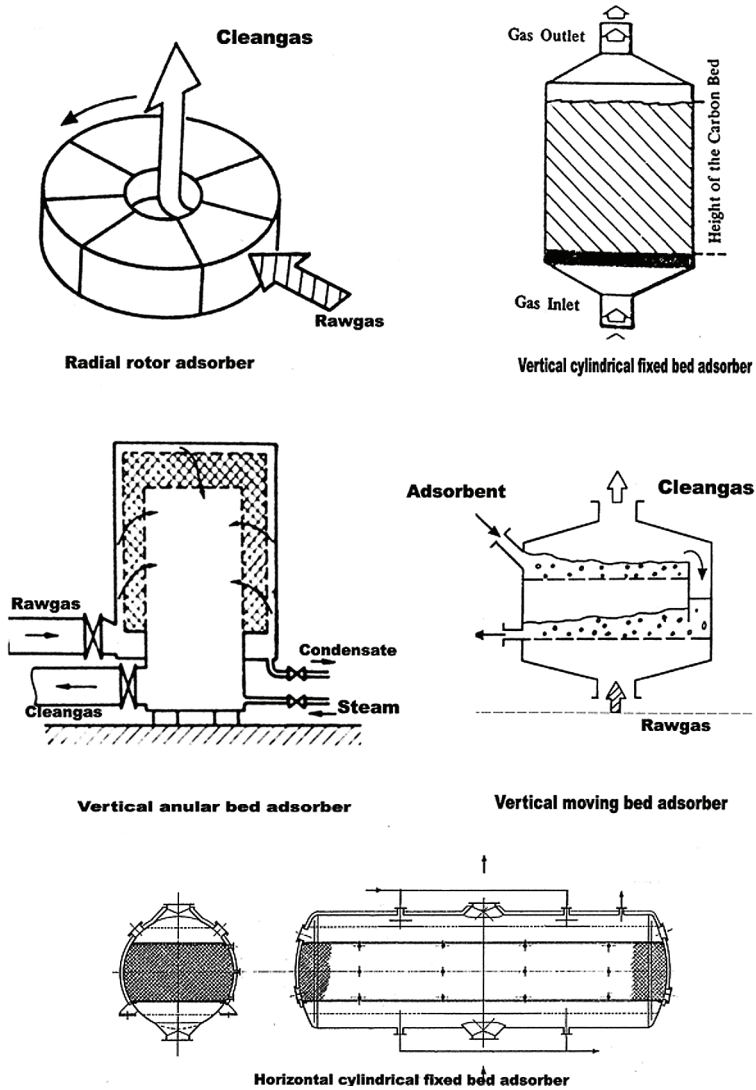


Figure 21.1.8. Adsorber construction forms.

of a multi-stage fluidized-bed system, the loaded adsorbent is regenerated by means of steam or hot inert gas in a moving-bed regenerator and pneumatically conveyed back to the adsorption section.[2] When using polymeric adsorbents in a comparable system, desorption can be carried out with heated air because the structure-inherent faster kinetics of these adsorbents require desorption temperatures of only 80 to 100°C.

Rotor adsorbers allow simultaneous adsorption and desorption in different zones of the same vessel without the need for adsorbent transport and the associated mechanical stresses. Rotor adsorbers can be arranged vertically or horizontally and can be designed for axial or radial gas flow so that they offer great flexibility in the design of the adsorption system.

The choice of the rotor design[2,27,33] depends on the type of adsorbent employed. Rotor adsorbers accommodating pellets or granular carbon beds come as wheel type baskets divided into segments to separate the adsorption zone from the regeneration zone. Alternatively, they may be equipped with a structured carrier (e.g., ceramics, cellulose) coated with or incorporating different adsorbents such as

- activated carbon fibers
- beaded activated carbon
- activated carbon particles
- particles of hydrophobic zeolite

The faster changeover from adsorption to desorption compared with fixed-bed adsorbers normally translates into a smaller bed volume and hence, a reduced pressure loss. Hot air desorption is also the preferred method for rotor adsorbers. Hot air rates are about one-tenth of the exhaust air rate. The desorbed solvents can either be condensed by chilling or disposed of by high-temperature or catalytic combustion.

In some cases, removal of the concentrated solvents from the desorption air in a conventional adsorption system and subsequent recovery for reuse may be a viable option. The structural design of the adsorber is normally governed by the operating conditions during the desorption cycle when elevated temperatures may cause pressure loads on the materials. Some solvents when adsorbed on activated carbon, or in the presence of steam, oxidize or hydrolyze to a small extent and produce small amounts of corrosive materials. As a general rule, hydrocarbons and alcohols are unaffected and carbon steel can be used. In the case of ketones and esters, stainless steel or other corrosion resistant materials are required for the solvent-wetted parts of the adsorbers, pipework, and condensers, etc. For carbon tetrachloride and 1,1,1-trichloroethane and other chlorinated solvents, titanium has a high degree of resistance to the traces of acidity formed during recovery.

21.1.4.2.3 Regeneration

The key to the effectiveness of solvent recovery is the residual adsorption capacity (working capacity) after in-place regeneration. The basic principles of regeneration are given in Sections 21.1.2.4 and 21.1.4.1. After the adsorption step has concentrated the solvent, the design of the regeneration system[1-3,13-16] depends on the application and the downstream use of the desorbed solvents whether it be collection and reuse or destruction. Table 21.1.8 may give some indications for choosing a suitable regeneration step.

Table 21.1.8. The basic principle of regeneration.

Regeneration step	Basic principle	Typical applications
Off-site reactivation	Transportation of the spent carbon to a reactivation plant. Partial gasification at 800-900°C with steam in a reactivation reactor. Reuse of the regenerated activated carbon	Low inlet concentration odor control application solvents with boiling points above 200°C polymerization of solvents
Steam desorption	Increasing the bed temperature by direct steaming and desorption of solvent. The steam is condensed and solvent recovered.	Most widely used regeneration technique for solvent recovery plants. Concentration range from 1-50 g/m^3
Hot air desorption	Rotor adsorber are often desorbed by hot air	Concentration by adsorption and incineration of the high calorific value desorbate
Hot inert gas desorption	Desorption by means of a hot inert gas recirculation. Solvent recovery can be achieved with refrigerated condenser	Recovery of partly or completely water soluble solvents. Recovery of reactive solvents (ketones) or solvents which react with hot steam (chlorinated hydrocarbons)
Pressure swing adsorption/ vacuum regeneration	Atmospheric pressure adsorption and heatless vacuum regeneration. The revaporized and desorbed vapor is transported from the adsorption bed *via* a vacuum pump	Low-boiling and medium-boiling hydrocarbon vapor mixes from highly concentrated tank venting or displacement gases in large tank farms. Recovery of monomers in the polymer industry
Reduced pressure and low-temperature steam desorption	Increasing the bed temperature by direct steaming and desorption of solvent. The steam is condensed and solvent recovered.	Recovery of reactive solvents of the ketone-type. Minimizing of side-reactions like oxidizing, decomposing or polymerizing.

21.1.4.2.4 Safety requirements

Adsorption systems including all the auxiliary and ancillary equipment needed for their operation are subject to the applicable safety legislation and the safety requirements of the trade associations and have to be operated in accordance with the respective regulations.[2,19]

Moreover, the manufacturer's instructions have to be observed to minimize safety risks. Activated carbon or its impurities catalyze the decomposition of some organics, such as ketones, aldehydes, and esters. These exothermic decomposition reactions[25,26] can generate localized hot spots and/or bed fires within an adsorber if the heat is allowed to build up. These hazards will crop up if the flow is low and the inlet concentrations are high, or if an adsorber is left dormant without being completely regenerated. To reduce the hazard of bed fires, the following procedures are usually recommended:

- Adsorption of readily oxidizing solvents (e.g., cyclohexanone) require increased safety precautions. Instrumentation, including alarms, should be installed to monitor the temperature change across the adsorber bed and the outlet CO/CO_2 concentrations. The instrumentation should signal the first signs of decomposition so that any acceleration leading to a bed fire can be forestalled. Design parameters should be set so as to avoid high inlet concentrations and low flow. A

minimum gas velocity of approximately 0.2 m/s should be maintained in the fixed-bed adsorber at all times to ensure proper heat dissipation.
- A virgin bed should be steamed before the first adsorption cycle. Residual condensate will remove heat.
- Loaded activated carbon beds require constant observation because of the risk of hot spot formation. The bed should never be left dormant unless it has been thoroughly regenerated.
- After each desorption cycle, the activated carbon should be properly cooled before starting a new adsorption cycle.
- Accumulation of carbon fines should be avoided due to the risk of local bed plugging which may lead to heat build-up even with weak exothermic reactions.
- CO and temperature monitors with alarm function should be provided at the clean gas outlet.
- The design should also minimize the possibility of explosion hazard
- Measurement of the internal adsorber pressure during the desorption cycle is useful for monitoring the valve positions.
- Measurement of the pressure loss across the adsorber provides information on particle abrasion and blockages in the support tray.
- Adsorption systems must be electrically grounded.

21.1.4.3 Special process conditions

21.1.4.3.1 Selection of the adsorbent

The adsorption of solvents on activated carbon[1-4] is controlled by the properties of both the carbon and the solvent and the contacting conditions. Generally, the following factors, which characterize the solvent-containing waste air stream, are to be considered when selecting the most well-suited activated carbon quality for waste air cleaning:

for solvent/waste air:
- solvent type (aliphatic/aromatic/polar solvents)
- concentration, the partial pressure
- molecular weight
- density
- boiling point, boiling range
- critical temperature
- desorbability
- explosion limits
- thermal and chemical stability
- water solubility
- adsorption temperature
- adsorption pressure
- solvent mixture composition
- solvent concentration by components
- humidity
- impurities (e.g., dust) in the gas stream

for the activated carbon type:
General properties:
- apparent density
- particle size distribution
- hardness
- surface area
- activity for CCl_4/benzene
- the pore volume distribution curve

For the selected solvent recovery task:
- the form of the adsorption isotherm
- the working capacity
- and the steam consumption

The surface area and the pore size distribution are factors of primary importance in the adsorption process. In general, the greater the surface area, the higher the adsorption capacity will be. However, that surface area within the activated carbon must be accessible. At low concentration (small molecules), the surface area in the smallest pores, into which the solvent can enter, is the most efficient surface. With higher concentrations (larger molecules) the larger pores become more efficient. At higher concentrations, capillary condensation will take place within the pores and the total micropore volume will become the limiting factor. These molecules are retained at the surface in the liquid state, because of intermolecular or van der Waals forces. Figure 21.1.9 shows the relationship between maximum effective pore size and concentration for the adsorption of toluene according to the Kelvin theory.

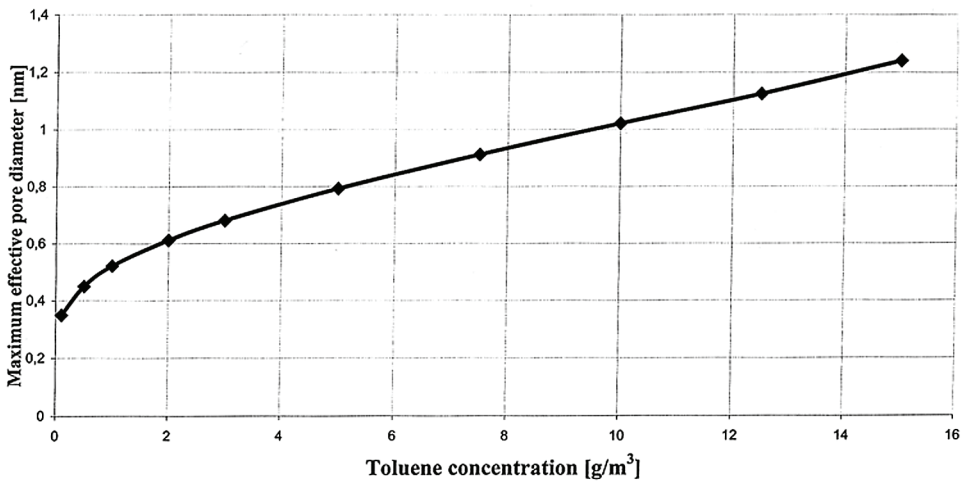


Figure 21.1.9. The relationship between maximum effective pore diameter and toluene concentration.

It is evident that the most valuable information concerning the adsorption capacity of a given activated carbon is its adsorption isotherm for the solvent being adsorbed and its

pore volume distribution curve. Figure 21.1.10 presents idealized toluene adsorption isotherms for three carbon types:

- large pores predominant
- medium pores predominant
- small pores predominant

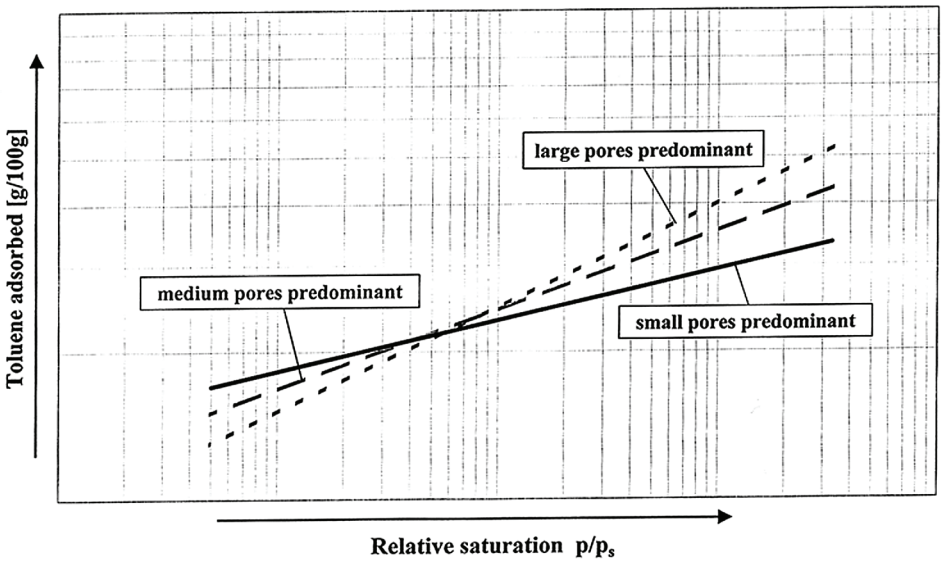


Figure 21.1.10. Idealized toluene adsorption isotherms.

The adsorption lines intersect at different concentrations, depending on the pore size distribution of the carbon. The following applies to all types of activated carbon: As the toluene concentration in the exhaust air increases, the activated carbon load increases.

From the viewpoint of adsorption technology, high toluene concentration in the exhaust air is more economic than a low concentration. But to ensure safe operation, the toluene concentration should not exceed 40% of the lower explosive limit. There is, however, an optimum activated carbon type for each toluene concentration (Figure 21.1.10).

The pore structure of the activated carbon must be matched to the solvent and the solvent concentration for each waste air cleaning problem. Figure 21.1.11 shows Freundlich adsorption isotherms of five typical solvents as a function of the solvent concentrations in the gas stream. It is clear that different solvents are adsorbed at different rates according to the intensity of the interacting forces between solvent and activated carbon.

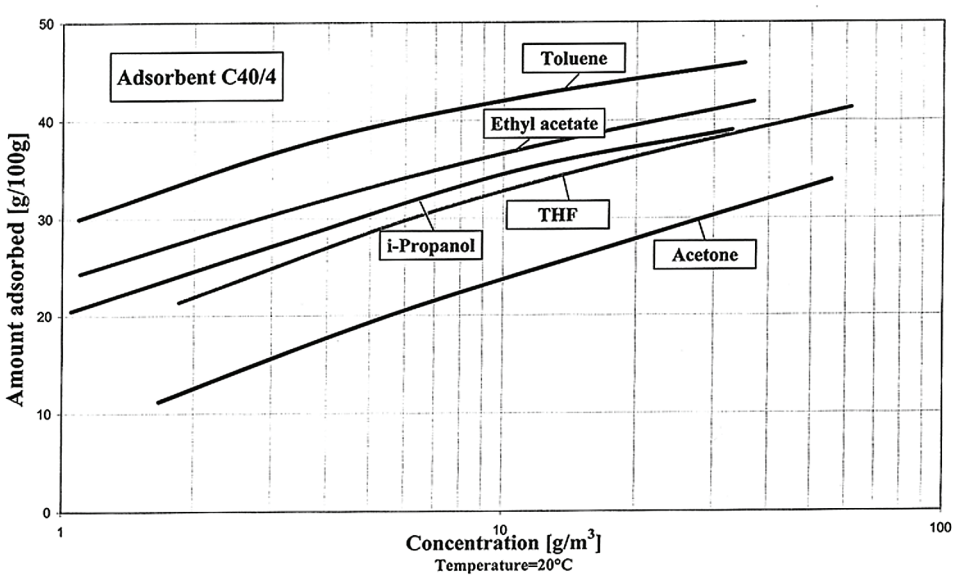


Figure 21.1.11. Adsorption isotherm of five typical solvents (After reference 13).

Physical-chemical properties of three typical activated carbons used in solvent recovery appear in Table 21.1.9.

Table 21.1.9. Activated carbon pellets for solvent recovery [After reference 13].

AC-Type	C 38/4	C 40/4	D 43/4
Appearance	cylindrically shaped		
Bulk density (shaken), kg/m^3	380±20	400±20	430±20
Moisture content, wt%	<5.0	<5.0	<5.0
Ash content, wt%	<6.0	<6.0	<5.0
Particle diameter, mm	4	4	4
Surface area (BET), m^2/g	>1250	>1250	>1100
Carbon tetrachloride activity, wt%	80±3	75±3	67±3

Producers[13] of activated carbon are in the best position to provide technical advice on

- selecting the right activated carbon type
- contributing to the technical and economic success of a solvent recovery plant

21.1.4.3.2 Air velocity and pressure drop

In solvent recovery systems, air velocity rates through the bed should be between 0.2 to 0.4 m/s. The length of the MTZ is directly proportional to the air velocity. Lower veloci-

ties (<0.2 m/s) would lead to better utilization of the adsorption capacity of the carbon, but there is a danger that the heat of adsorption is not to be carried away, which would cause overheating and possibly ignition of the carbon bed.

The power to operate the blowers to move waste air through the system constitutes one of the major operating expenses of the system. Pressure drop (resistance to flow) across the system is a function of

- air velocity
- bed depth
- activated carbon particle size

Small particle size activated carbon will produce a high-pressure drop through the activated-carbon bed. Figure 21.1.12 compares the pressure drop of cylindrically-shaped activated carbon pellets with activated-carbon granulates. The activated carbon particle diameter must not be excessively large because the long diffusion distances would delay adsorption and desorption. Commercially, cylindrical pellets with a particle diameter of 3 to 4 mm have been most efficient.

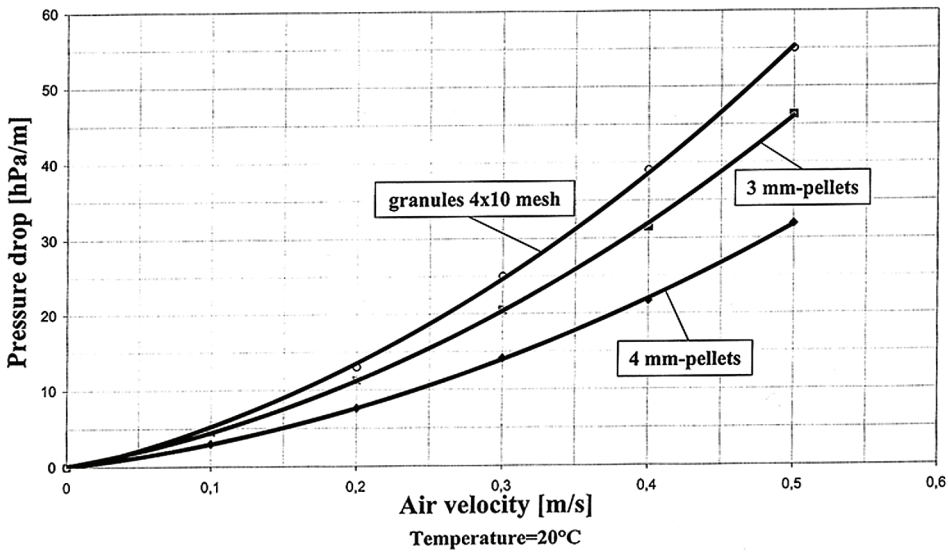


Figure 21.1.12. Pressure drop for various activated carbon types.

21.1.4.3.3 Effects of solvent-concentration, adsorption temperature and pressure

For safety reasons, the concentration of combustible solvent vapors should be less than 50% of the lower explosive limit. The adsorption capacity of adsorbents increases as the concentration of the solvents increases. But the length of the MTZ is proportional to the solvent concentration. Because of the adsorption heat, as the adsorption front moves through the bed also a temperature front follows in the same direction. To deal with the adsorption heat the inlet solvent concentration is usually limited to about 50 g/m^3.

The adsorption capacity of the adsorbent increases with pressure because the partial pressure of the solvent increases. An increase in adsorber temperature causes a reduction in adsorption capacity. Because the equilibrium capacity is lower at higher temperatures, the dynamic capacity (working capacity) of the activated carbon adsorber will also be lower. To enhance adsorption, the inlet temperature of the adsorber should be in the range of 20-40°C. In Figure 21.1.13 the adsorption isotherms of tetrahydrofuran on activated carbon D43/3 for several temperatures are shown.[13]

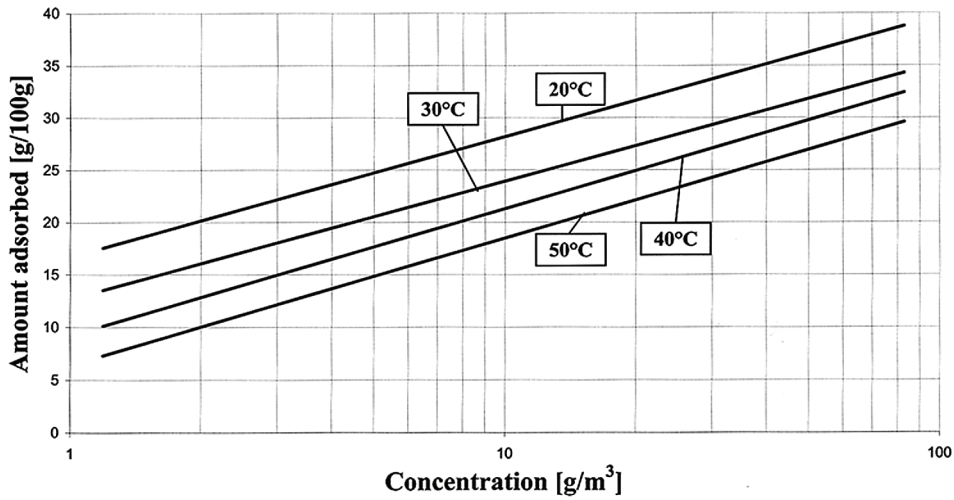


Figure 21.1.13. Adsorption isotherm of tetrahydrofuran for several temperatures.

21.1.4.3.4 Influence of humidity

Activated carbon is basically hydrophobic; it adsorbs preferably organic solvents. The water adsorption isotherm (Figure 21.1.14) reflects its hydrophobic character. Below a relative gas humidity of about 40% co-adsorption of water can be neglected in most applications. However, higher humidity of the waste gases may affect the adsorption capacity of the activated carbon. Figure 21.1.15 demonstrates, using toluene as an example of how the relative humidity of the exhaust air influences the activated carbon loads.

Experimental work[24] has shown that

- relative humidity rates below 30% will neither reduce the adsorption capacity nor the adsorption time,
- relative humidity rates above 70% substantially reduce the adsorption capacity,
- the humidity of the gas will affect the adsorption capacity much more with low toluene concentrations than with high concentrations,
- with toluene concentrations between 10 and 20 g/m^3 the negative influence of the humidity is small.

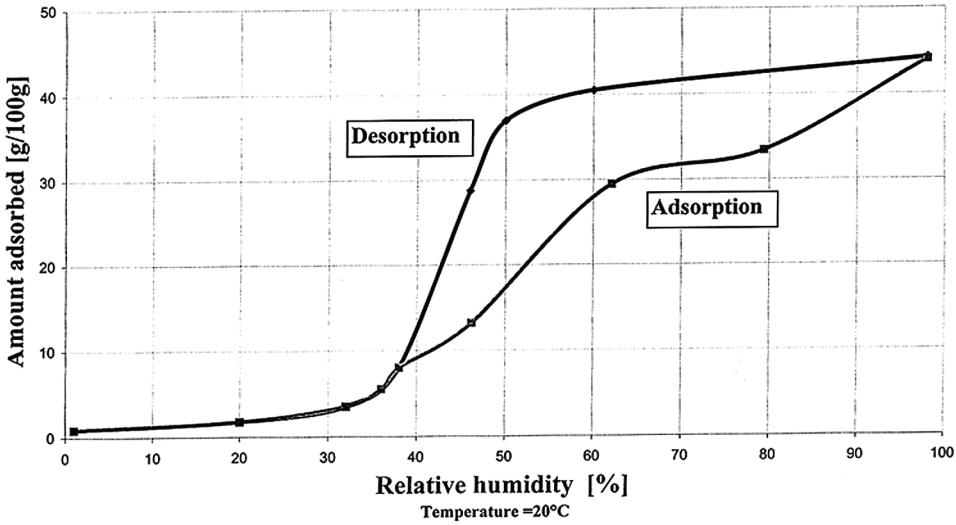


Figure 21.1.14. Water isotherm on activated carbon D43/4.

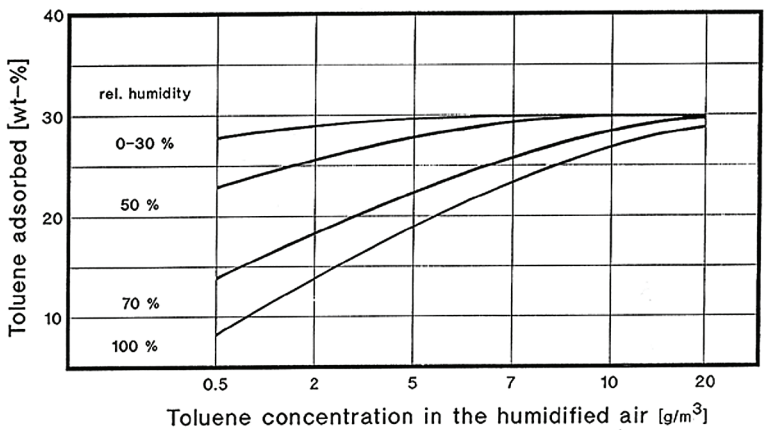


Figure 21.1.15. Dynamic toluene adsorption from humidified air [after reference 24].

The water content of the activated carbon after desorption may constitute another problem. The purification efficiency of each activated carbon is the better the less water is present after desorption. Unfortunately, the desorbed activated carbon in the vicinity of the adsorber walls usually contains high proportions of water (approx. 10 to 20%). With such a high water content, it is difficult to remove all the water even when drying with hot-air over longer periods. The wet and poorly-regenerated activated carbons in these zones fre-

quently lead to higher solvent concentrations in the purified air, and this is even at the beginning of the adsorption cycle. Some proposals for improvement include:

- good insulation of the adsorber walls,
- sufficient drying after each regeneration cycle,
- cycle the desorption steam and the drying air counter-current to the direction of the adsorptive stream.

21.1.4.3.5 Interaction between solvents and activated carbon

The majority of solvents are effectively recovered by adsorption on activated carbon and, when this is the case, the operation of the plant is straightforward. But some solvents may decompose, react or polymerize when in contact with activated carbon during the adsorption step and the subsequent steam desorption.[19,25,26]

Chlorinated hydrocarbon solvents can undergo hydrolysis to varying degrees on carbon surfaces, resulting in the formation of hydrogen chloride. Each activated carbon particle which is in contact with a metal screen or other constructional component may then act as a potential galvanic cell in the presence of moisture and chloride ions.

Carbon disulfide can be catalytically oxidized to sulfur which remains on the internal surface of the activated carbon.

Esters such as ethyl acetate are particularly corrosive because their hydrolysis results in the formation of acetic acid (or other acids).

Aldehydes and phenol or styrene will undergo some degree of polymerization when in contact with hot activated carbon.

During the adsorptive removal of ketones such as methyl ethyl ketone or cyclohexanone a reduced adsorption capacity has been measured. Corrosion problems were also apparent and in some cases, even spontaneous ignition of the activated carbon occurred.

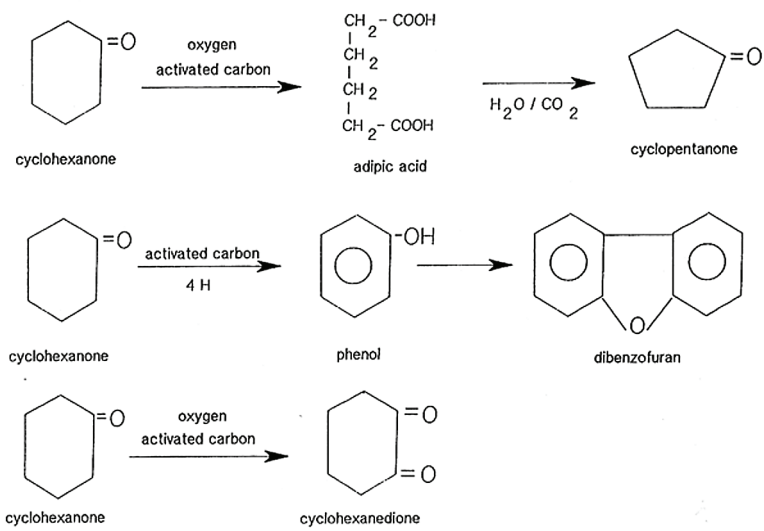


Figure 21.1.16. Surface reaction of cyclohexanone on activated carbon [After reference 25].

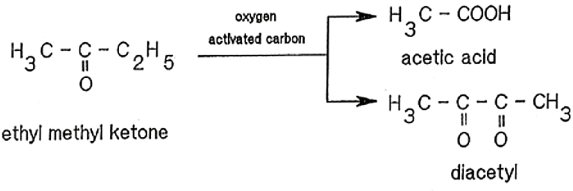


Figure 21.1.17. Surface reaction of methyl ethyl ketone on activated carbon [After reference 25].

Activated carbon acts, in the presence of oxygen, as a catalyst during adsorption and even more frequently during desorption because of higher temperature.[25,26] Figure 21.1.16 shows that the catalytic reactions occurring with cyclohexanone are predominantly of the oxidation type. Adipic acid is first formed from cyclohexanone. Adipic acid has a high boiling point (213°C at a 13 mbar vacuum). Further products identified were: cyclopentanone as a degradation product from adipic acid, phenol, toluene, dibenzofuran, aliphatic hydrocarbons and carbon dioxide. The high-boiling adipic acid cannot be desorbed from the activated carbon in a usual steam desorption. Consequently, the life of the activated carbon becomes further reduced after each adsorption/desorption cycle.

During adsorption of methyl ethyl ketone in the presence of oxygen, some catalytic surface reactions occur (Figure 21.1.17). The reaction products are acetic acid, diacetyl, and presumably also diacetyl peroxide. Diacetyl has an intensive green coloration and a distinctive odor. Important for the heat balance of the adsorber is that all of the reactions are strongly exothermic.

Unlike the side products of cyclohexanone, acetic acid the reaction product of the MEK (corrosive!) is removed from the activated carbon during steam desorption. Adsorption performance is thus maintained even after a number of cycles.

Operators of ketones recovery plants should adhere to certain rules and also take some precautions.[25]

- Adsorption temperature should not be higher than 30°C (the surface reaction rates increase exponentially with temperature).
- The above requirement of low-adsorption temperatures includes:
  a adequate cooling after the desorption step;
  b flow velocity of at least 0.2 m/s in order to remove the heat of adsorption.

Since ketones will, even in an adsorbed state, oxidize on the activated carbon due to the presence of oxygen, these further precautions should be taken:

- keep the adsorption/desorption cycles as short as possible,
- desorb the loaded activated carbon immediately at the lowest possible temperatures,
- desorb, cool and blanket the equipment with inert gas before an extended shutdown.

21.1.4.3.6 Activated carbon service life

Activated carbon in solvent recovery service will have a useful service life of 1 to 10 years, depending on the attrition rate and reduction in adsorption capacity.

Attrition rates are usually less than 1-3% per year. The actual rate will depend on carbon hardness. Particle abrasion and the resulting bed compaction leads to an increased

pressure loss after several years of service. After 3-5 years of service screening to its original size is necessary.

Adsorption capacity can be reduced by traces of certain high-boiling materials (resins, volatile organosilicon compounds) in the waste air which are not removed during the desorption cycle. Some solvents may decompose, react or polymerize when in contact with activated carbon and steam (Section 21.1.4.3.5).

This gradual loading will decrease the carbon's activity. While carbon can remain in service in a reduced capacity state, it represents a non-optimal operation of the system that results in

- reduced amount of solvent removed per cycle
- increased steam consumption
- higher emissions
- shorter adsorption cycles

Eventually, recovering capacity will diminish; it is more economical to replace carbon than continue its use in a deteriorated state. In replacing spent activated carbon there are two options:

- replacing with virgin carbon and disposal of the spent carbon.
- off-site reactivation of the spent carbon to about 95% of its virgin activity for about one-half of the cost of a new carbon

Some activated carbon producers offer a complete service including carbon testing, off-site reactivation, transportation, adsorber-filling and carbon make-up.[13]

21.1.5 EXAMPLES FROM DIFFERENT INDUSTRIES

Some examples of solvent recovery systems in different industries show that reliable and trouble-free systems are available.

21.1.5.1 Rotogravure printing shops

Process principle

Adsorptive solvent recovery with steam desorption and condensation units with gravity separator and a stripper have become a standard practice in modern production plants. The solvents-laden air (toluene, xylene) is collected from emission points, e.g., rotogravure printing machines, drying ducts by means of a blower and passed through the recovery plant.

Design example[30]

In 1995, one of Europe's most modern printing shops in Dresden was equipped with an adsorptive solvent recovery system (Supersorbon® process (Figure 21.1.18.)).

Design data

(First stage of completion)	
Exhaust air flow rate	240,000 m^3/h
(expandable to	400,000 m^3/h)
Solvent capacity	2,400 kg/h (toluene)
Exhaust air temperature	40°C
Toluene concentration in clean air (half-hour mean)	max. 50 mg/m^3

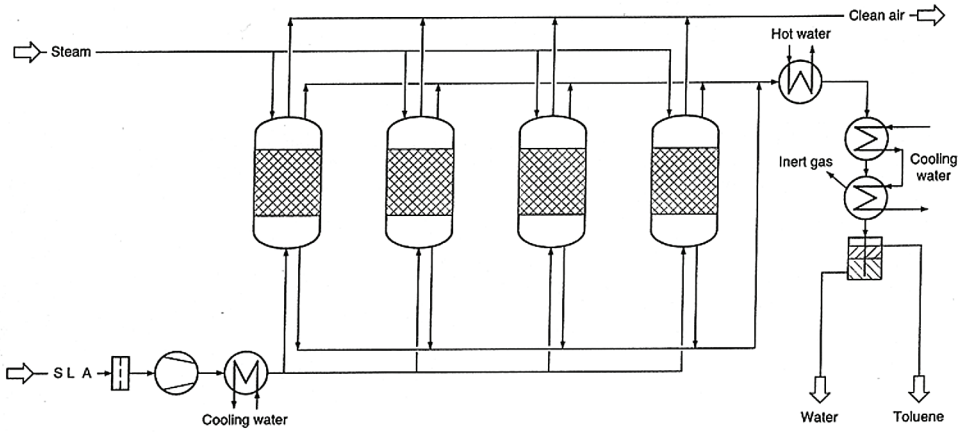


Figure 21.1.18. Supersorbon® process for toluene recovery [After reference 30].

Solvent-laden air is exhausted at the three rotogravure printing presses by several fans operating in parallel and is routed in an upward flow through four adsorbers packed with Supersorbon® activated carbon. The solvent contained in the air is adsorbed on the activated carbon bed. Adsorption continues until breakthrough when the full retentive capacity of the adsorbent for solvent vapors is used up.

The purity of the clean exhaust air complies with the regulation for emission level of less than 50 mg/m^3. Regeneration of the adsorbent takes place by desorbing the solvent with a countercurrent flow of steam. The mixture of water and toluene vapors is condensed and the toluene, being almost insoluble in water, is separated by reason of its different density in a gravity separator. The recovered toluene can be reused in the printing presses without further treatment. Very small amounts of toluene dissolved in the wastewater are removed by stripping with air and returned to the adsorption system inlet together with the stripping air flow. The purified condensate from the steam is employed as make-up water in the cooling towers.

Operating experience

The adsorption system is distinguished by an extremely economical operation with a good ratio of energy consumption to toluene recovery. Solvent recovery rate is about 99.5%.

21.1.5.2 Packaging printing industry

In the packaging printing industry solvents like ethyl acetate, ethanol, ketones, tetrahydrofuran (THF), hexane and toluene are used in printing. The solvent laden air generally contains between 2 and 15 g/m^3 of solvent and, depending on the season, 5-18 g/m^3 of water.

Adsorptive recovery with steam desorption was widely used for many years but its disadvantage is that the solvents are recovered in various mixtures containing large amounts of water. The recovery of solvents is complicated because most solvents produce azeotropes with water which are not easily separated and, consequently, the wastewater fails to meet the more stringent environmental regulations. In the last 10 years, the adsor-

bent regeneration with hot inert gas has become the more favored process in the packaging printing industry.

21.1.5.2.1 Fixed bed adsorption with circulating hot gas desorption[31,32]

Activated carbon preferentially adsorbs non-polar organic solvents, while adsorbing relatively little water. Thus activated carbon allows the passage of 95-98% of the water while retaining the solvents from the gas stream. During the adsorption step solvent laden air or gas is delivered to the bed through the appropriate valves. As adsorption starts on a fresh bed, the effluent gas contains traces of solvent. Through time, the solvent level increases and when it reaches a predetermined value, the adsorption is stopped by closing the feed gas valves. The adsorption step usually lasts for 4-16 hours. An example of a solvent recovery plant with 5 activated carbon beds and hot gas desorption is shown in Figure 21.1.19.

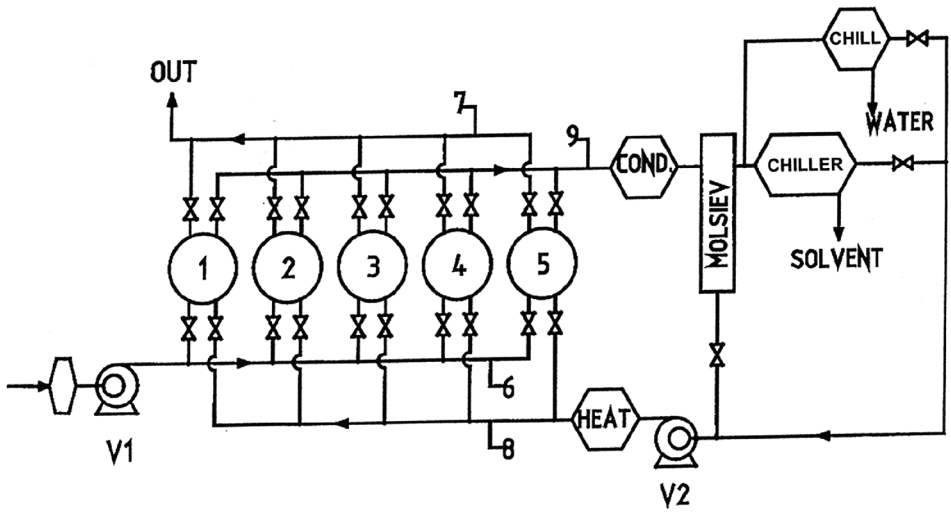


Figure 21.1.19. Fixed bed adsorption with circulating hot gas desorption [After references 31,32].

If necessary, feed air is cooled to 35°C and sent by the blower V-1 to the main heater 6 from which it enters 4 beds simultaneously, while one bed is being regenerated. The cleaned air is collected in header 7 and vented.

After the adsorption step, the air is displaced from the bed by an inert gas such as nitrogen. A circulating inert gas at 120-240°C serves for heating and stripping the solvent from the carbon. The solvent is recovered by cooling and chilling the circulating gas. The optimum chilling temperature depends on the boiling point of the solvent. Generally, chilling temperatures are between +10 and −30°C.

During the heating step, the temperature of the effluent gas gradually increases until a predetermined value (for example, 150°C) is reached, after which the heater is bypassed and the bed is cooled down by cold gas. Typical solvent recovery plants will have from 2

to 8 beds. All beds go through the same adsorption, inertization, heating and cooling steps but each at a different time.

Referring to the flow sheet in Figure 21.1.19, the regeneration gas is circulated by blower V-2 to the gas heater, the header 8 to the bed being regenerated. The effluent gas is passed to the header 9, cooler, molecular sieves (or water condenser), to the chiller for solvent condensation and back to the blower V-2. At the end of the adsorption step, the bed contains 10-30% solvent and 1-2% water.

There are various ways to remove the water separately and to recover a solvent containing between 0.1 and 1.5% water (Table 21.1.10).

Table 21.1.10. Process conditions and water content in the solvent [After references 32,33].

	Water in the raw solvent	Investment cost, %	Heat needed, kWh/kg S	Power, kWh/kg S
Basic process with molsieve beds	0.1	100	2.2	1.0
Chiller instead of molsieve	1.5	91	1.5	1.0
Chiller and 1 carbon bed	0.4-1.0	93	1.1	1.0
Chiller, and 1 carbon bed molsieve	0.1	96	1.1	1.0

Using molecular sieves

Beds of molecular sieves are used to recover a solvent with 0.1%. This process requires around 2-2.5 kWh heat/kg of recovered solvent. Regeneration loop pressure drops are high, because of the additional molsieve beds and valves.

Separate condensation of water

Initially, when regenerative heating of the bed starts, a very little solvent is desorbed, but much of the water (about 87%) is desorbed. The circulating gas is first passed through a cooler and then a separate chiller for the condensation or freezing of the water. Subsequently, the gas is passed to the chiller where the water is condensed or frozen. From 1 to 1.8% water is recovered. This process is simpler than the molecular sieves process.

Two separate chillers

Two separate chillers are used in another adsorption process which offers further substantial improvements. A third activated carbon bed is added so that while two of the beds are being regenerated one of these is being cooled and transferring its heat to the other bed which is being heated. This not only gives excellent heat recovery but also provides a means of reducing the water content of the recovered solvent. The cooled bed absorbs the water vapor from the gas stream coming from the chiller. This dry gas stream is transported to the bed which is being heated and the desorbed solvent from the heated bed remains dry. The solvents recovered at this stage contain only 0.4 to 0.5% water. Solvent which is removed from the bed being cooled is readsorbed on the bed being heated.

The process, which is patented, brings important benefits of regeneration gas flow rates. Such low flow rates mean that the process requires less heat, less refrigeration, and a

lower cost regeneration loop. The overall efficiency is high because the low residual solvent loading of the regenerated beds leads to increased solvent recovery.

Two separate chillers plus molecular sieve bed

A two chiller system with a molecular sieve bed has to be regenerated only about once per week since most of the water is removed in the chiller and readsorbed on the cooled carbon bed. This process offers a high solvent recovery rate giving a solvent with only 0.1% water at greatly reduced heat consumption, lower investment, and higher solvent recovery rate.

Key plants with all the above-mentioned processes are offered by special engineering companies.[31,32] The investment cost for a typical recovery plant with hot gas regeneration can be estimated by the following equation:

$$\text{COST (in 1000 Euro)} = 200 + 0.4 \times A^{0.7} + 15 \times S^{0.7}$$

where:

A feed air rate in Nm^3/h
S solvent flow rate in kg/h

21.1.5.2.2 Solvent recovery with adsorption wheels

Adsorption wheels[33] are used for the continuous purification of large volumes of exhaust air containing relatively low solvent concentrations.

The adsorption wheel consists of a number of identical chambers arranged axially around a vertical axis. All chambers contain adsorbent. The wheel rotates and each chamber passes in sequence over an exhaust air duct and solvent molecules are adsorbed. As wheel continues to rotate, the chamber in which adsorption had occurred now moves into a desorption position in which hot air is passed through the chamber and over the adsorbent. This removes the adsorbed solvent. The hot air flow in the desorption sector is at relatively low flow rate compared to that of the contaminated gas stream. The number of chambers in the desorption zone is much greater than the number in the absorption zone so the desorption stream is many times more concentrated in the solvent than was the exhaust stream. At this higher concentration, the desorption stream can now be economically treated in one of the ways:

- The adsorption stream is purified by means of recuperative or regenerative oxidation. This approach is advantageous in painting applications with solvent mixtures that cannot be reused in production.
- For solvent recovery by condensation, the desorption stream is cooled down in a cooling aggregate and the liquid solvent is recovered for reuse. Water contents below 1% can be achieved without further purification.

Example:

A manufacturer who specializes in flexible packaging, i.e., for confectionary, always adds the same solvent mixture (ethanol, ethyl acetate, ethoxypropanol) to his printing ink.

Adsorptive solvent removal of the solvent mixture by use of an adsorption wheel (Figure 21.1.20) and solvent recovery *via* condensation has been technically and economically proven. 10,000 to 65,000 Nm^3/h of exhaust air from printing machines and washing plants at a temperature maximum of 45°C and a maximum solvent loading of 4.6 g/m^3 is

to be cleaned. Depending on the air volume two adsorption wheels with a capacity of 26,000 Nm^3/h and 39,000 Nm^3/h and separate desorption circuits are used either alternatively or together. The total desorption air of max. 11,000 Nm^3/h is being concentrated to max. 27 g/m^3, which corresponds to 50% of the lower explosion limit. The condensation unit for the solvent recovery process is gradually adjusted to small, medium or large exhaust air volumes. The recovered solvents are stored and returned to the production process.

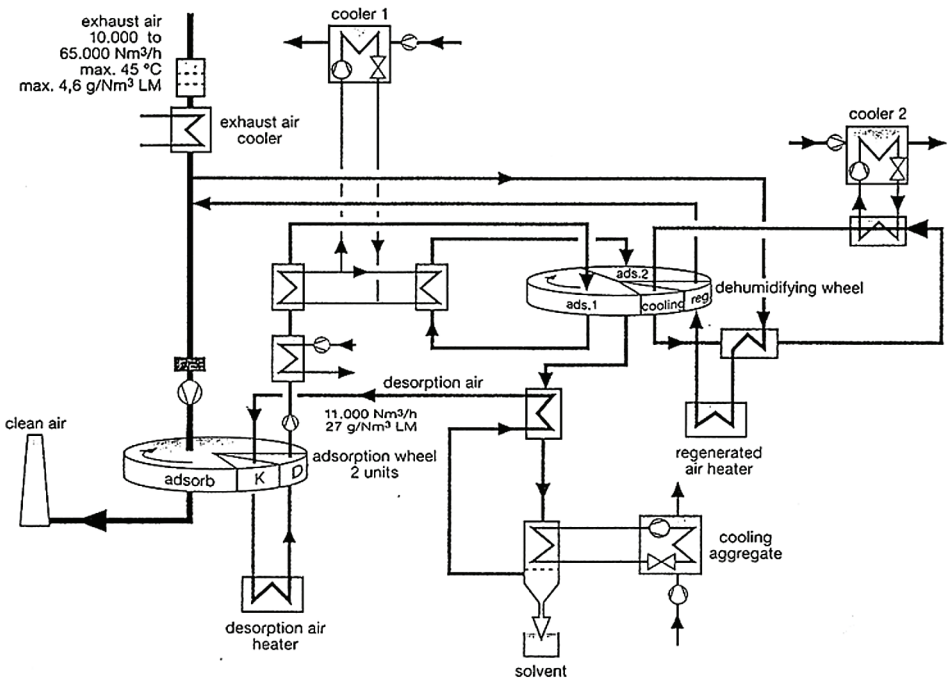


Figure 21.1.20. Adsorption wheel for solvent recovery in packaging printing [After reference 33].

21.1.5.3 Viscose industry

In plants which produce viscose fiber (stable fiber), viscose filament yarn (rayon) and viscose film (cellophane), large volumes of exhaust air contaminated with carbon disulfide (CS_2) and hydrogen sulfide (H_2S) have to be cleaned. Typical waste gas volumes and concentration of CS_2 and H_2S are given in Table 21.1.11.

Table 21.1.11. Waste gas in the viscose industry [After reference 35].

Product	Spec. waste gas volume, m^3	Concentration (mg/m^3)	
		H_2S	CS_2
Rayon	400,000-700,000	60-130	300-800

Table 21.1.11. Waste gas in the viscose industry [After reference 35].

Product	Spec. waste gas volume, m^3	Concentration (mg/m^3)	
		H_2S	CS_2
Staple fibre	50,000-90,000	700-1800	2300-4000
Viscose fibre	100,000-150,000	280-400	1000-3000

Different cleaning/recovery processes are available for the removal of each of the two sulfur-containing compounds:[2,17,34,35]

Hydrogen sulfide

Absorption of H_2S in a NaOH-scrubber

Catalytic oxidation of H_2S to elemental sulfur on iodine impregnated activated carbon (Sulfosorbon-process)

$$2H_2S + O_2 \rightarrow 2S + 2H_2O$$

The sulfur is adsorbed at the internal surface of the carbon-catalyst.

Carbon disulfide

Adsorptive removal on activated carbon and recovery by steam desorption. For simultaneous H_2S and CS_2 removal, the Sulfosorbon-process uses adsorbers packed with two different activated carbon types

- Iodine impregnated wide-pore activated carbon for H_2S oxidation in the bottom part (gas inlet) of the adsorber
- Medium-pore activated carbon for the adsorption of CS_2 in the upper layer of the fixed bed.

As soon as the CS_2 concentration in the treated air approaches the emission limit, the exhaust air stream is directed to a regenerated adsorber. After an inert gas purge, the carbon disulfide is desorbed with steam at 110 to 130°C. The resulting CS_2/steam mixture is routed through a condenser and cooler, before entering a gravity separator where phase separation occurs.

At the usual CS_2 and H_2S concentrations in viscose production exhaust air, the CS_2 adsorption/desorption cycles can be run for a prolonged periods before the first layer loaded with elemental sulfur has to be regenerated.

The regeneration process of the sulfur loaded activated carbon involves the following steps:

- washing out of sulfuric acid with water
- extraction of elemental sulfur with carbon disulfide
- desorption of carbon disulfide with steam
- air drying and cooling of activated carbon

The elemental sulfur present in the carbon disulfide in dissolved form can be separated by distillation and recovered as high-purity sulfur.

Design example[34]

In the production of viscose filament yarn, a Supersorbon®-system combined with a NaOH-scrubber system (Figure 21.1.21) has been in use since 1997. A very high standard

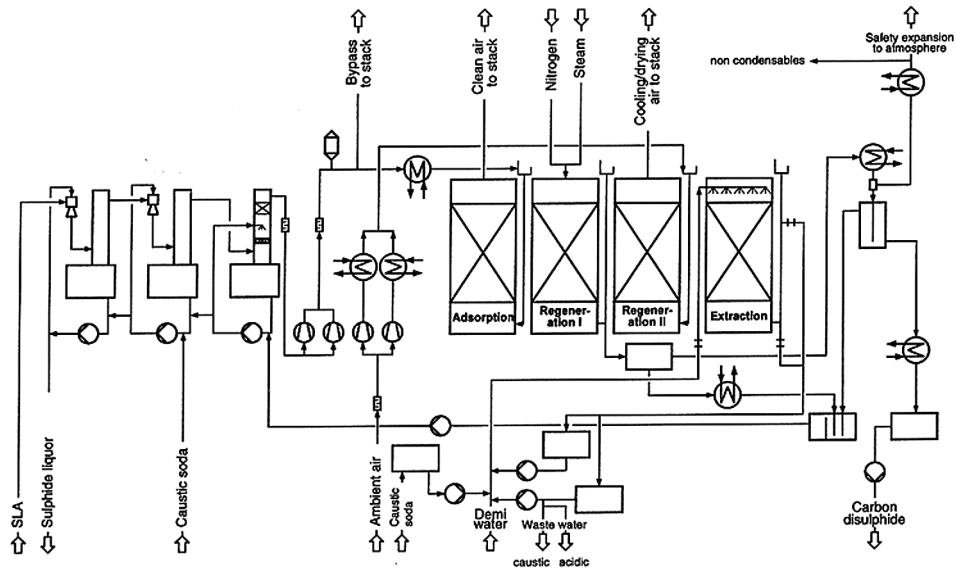


Figure 21.1.21. H_2S and CS_2 removal in the filament yarn production [After reference 34].

of safety engineering is implemented in the treatment system owing to the flammability of the CS_2 and the toxic nature of the constituents to be removed from the exhaust air.

System concept

First treatment stage:

Absorption of H_2S in two NaOH jet scrubbers and one water-operated centrifugal scrubber.

Second treatment stage:

Fixed-bed adsorption for purification of exhaust air and CS_2 recovery.

Treated air stream

Exhaust air from viscose filament yarn plant.

Design data:

Exhaust air flow rate	12,000 Nm^3/h
Solvent capacity	27 kg CS_2/h and 7.5 kg H_2S/h
Exhaust air temperature	15-30°C
Clean air solvent concentration	
CS_2: max.	100 mg/Nm^3 (24-hour mean)
H_2S: max.	5 mg/Nm^3 (24-hour mean)

H_2S-removal

The exhaust air, saturated with water vapor, is first treated in an absorption unit for removal of H_2S by routing it through two successive jet scrubbers working with a dilute caustic soda solution. Downstream of these, a centrifugal scrubber is installed as an

entrainment separator. The sulfide-containing solution rejected from the scrubbers is used to precipitate zinc in the wastewater treatment system of the production plant. By-products adsorbed on the activated carbon, such as sulfuric acid and elemental sulfur, are removed periodically by water and alkaline extraction.

CS_2-removal and recovery

The pre-cleaned airstream containing carbon disulfide vapors passes through two or three parallel adsorbers, in which the CS_2 is absorbed on a bed of Supersorbon® activated carbon. As soon as the adsorbent is saturated it is regenerated by desorbing the solvent with a countercurrent flow of steam. The resulting mixture of water and CS_2 vapors is condensed and separated by gravity settlers. The recovered CS_2 is returned to the viscose production without further treatment. The condensed steam is stripped of residual CS_2 in the centrifugal scrubber and used as dilution water for operation of the jet scrubbers.

Operating experience

The specified purity of the treated exhaust air is reliably achieved with the Supersorbon® process[34] with respect to both CS_2 and H_2S. The CS_2 recovery rate is about 95%. The purity of the recovered solvent meets viscose production specifications. A widely varying CS_2 concentration in the exhaust air has not adversely affected operation of the adsorption system.

21.1.5.4 Refrigerator recycling

Condensation process

Condensation processes are especially suitable for the cleaning of low flow highly concentrated streams of exhaust gas.[36] The entire waste gas stream is cooled below the dew point of the vapors contained therein so that these can condense on the surface of the heat exchanger (partial condensation). Theoretically, the achievable recovery rates depend only on the initial concentration, the purification temperature and the vapor pressure of the condensable at that temperature. In practice, however, flow velocities, temperature profiles, the geometry of the equipment, etc. play decisive roles, as effects such as mist formation (aerosols), uneven flow in the condensers and uncontrolled ice formation interfere with the process of condensation and prevent an equilibrium concentration from being reached at the low temperatures.

The Rekusolv process[37] uses liquid nitrogen to liquefy or freeze vapors contained in the exhaust gas stream. In order to reduce the residual concentrations in the exhaust to the legally required limits, it is often necessary to resort to temperatures below −100°C. The Rekusolv process is quite commonly used in the chemical and pharmaceutical industry and at recycling plants for solvent recovery.

Example of solvent recovery in refrigerator recycling[36,37]

In refrigerator recycling plants R11 or pentane is released from the insulating foam of the refrigerator during shredding. Figure 21.1.22. shows the Rekusolv process as it is used by a refrigerator recycling company. At this plant, around 25 refrigerators per hour are recycled thereby generating 8 kg/h of polluting gases. The Rekusolv plant is capable of condensing almost all of this. The unit is designed to operate for 10 to 12 hours before it has to be defrosted. The plant is operated during the day and is automatically defrosted at

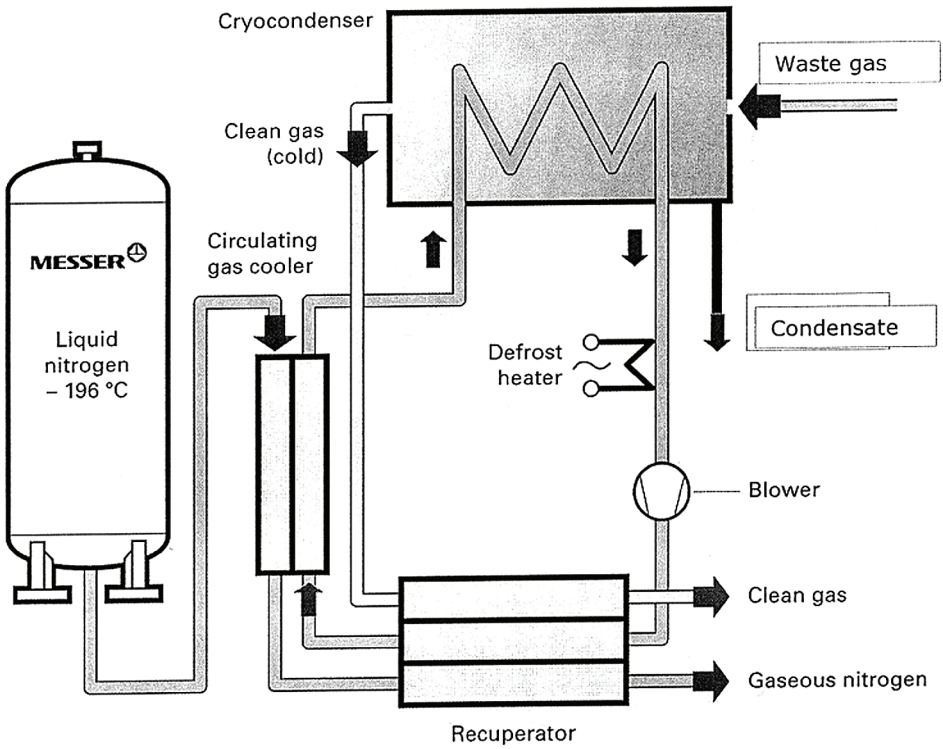


Figure 21.1.22. Block diagram of the Rekusolv process [After references 36,37].

night. The concentration of pollutants in the exhaust gas is reduced from 20 to 40 g/m^3 to 0.1 g/m^3 – a recovery rate of more than 99.5%.

21.1.5.5 Petrochemical industry and tank farms

Vapor recovery units are installed at petrochemical plants, tank farms and distribution terminals of refineries. Tank venting gases are normally small in volume, discharged intermittently at ambient temperature and pressure and loaded with high concentrations of organic vapors.[2]

Processes used for the cleanup of such waste air streams with organic vapor up to saturation point are often combined processes:[2,38,39]

- absorption and pressure-swing adsorption
- membrane permeation and pressure-swing adsorption
- condensation and adsorption

Adsorption on activated carbon and vacuum regeneration

Figure 21.1.23 represents the basic principle of the systems which are used to recover vapors displaced from tank farms and loading stations and blend them back into the liquids being loaded. The plant consists of two fixed-bed adsorbers packed with acti-

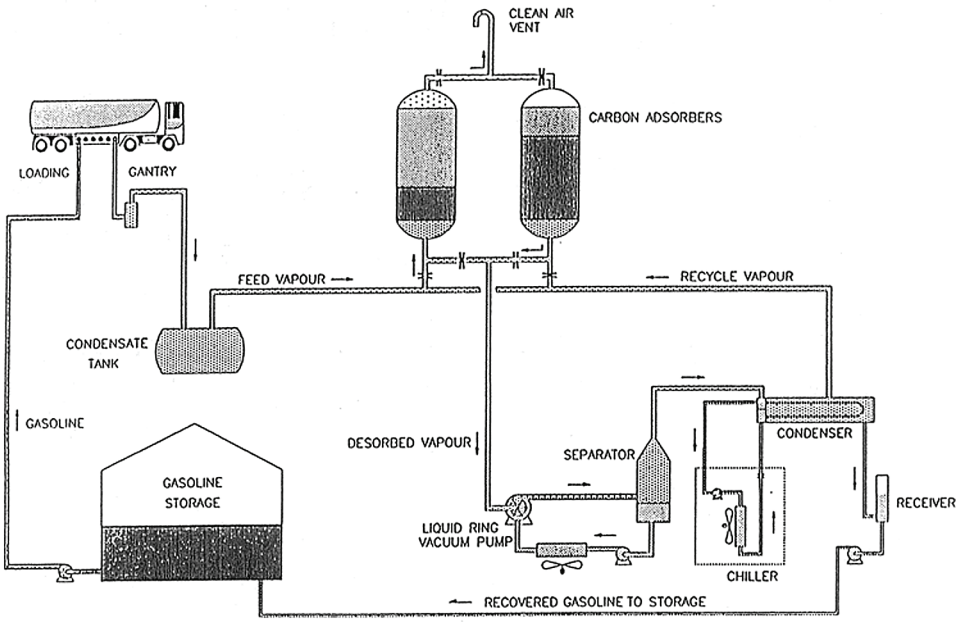


Figure 21.1.23. Vapor recovery by adsorption and vacuum regeneration [After reference 39].

vated carbon which operate alternatively. The vapor pressure gradients required as a driving force for desorption is generated by vacuum pumps. As the raw gas entering the adsorber is saturated with hydrocarbon vapors, the heat of adsorption causes local heating of the well-insulated adsorbent bed. The higher temperature of the spent activated carbon supports subsequent desorption as the pressure is being lowered by means of a vacuum pump.

The desorbed vapor is transported from the adsorption bed *via* a vacuum pump. A liquid ring pump using water for the seal fluid is normally applied for safety purposes in operations where the air is allowed to enter the adsorbers.

The desorption stream is processed through a cooler and absorber. The absorber uses gasoline (or the recovered solvent) as a sorbent and serves as a hydrocarbon reduction stage for the entire system. Loading facilities with the inlet vapor concentrations of over 10% by volume can demonstrate recovery efficiencies of over 99%.

21.1.5.6 Chemical industry

In the chemical industry, a variety of solvents and solvent mixtures are in use. For many gas cleaning operations, special adsorption processes are required.

Two-stage adsorption[40]

In many cases, a two-stage process offers significant advantages. This process makes use of two adsorbers that are operating alternately in series. Four-way reverse valves ensure safe changeover. During operation, the air passages of the valves are always open so that any blocking of the flow is impossible. Solvent laden air first passes into one of the

adsorbers. Purified air is released into the atmosphere only during the time when the second adsorber is being steamed. During this phase of the process, the on-line adsorber is only slightly charged with a solvent which means that it will be completely adsorbed. In general, the time required for steaming an adsorber is at most 50% of the time provided for adsorption.

After the adsorber has been steamed, the outlet valve is switched over. The steamed adsorber is then dried with solvent-free air taken from the laden adsorber. A feature of this process is that the steamed adsorber is always dried with solvent-free air. An advantage of this two-stage process is that the laden adsorber can be loaded beyond the breakthrough capacity since the second adsorber is unladen and can, therefore, accept any excess solvent.

The condensation phase and reprocessing of the desorbate are carried out in the same manner as described for the single-stage plant. For example, a two-stage adsorption plant for the recovery of dichloromethane is able to clean a gas stream of 3000 m^3/h to a residual solvent content of less than 20 mg/m^3.

REFERENCES

1 J.W. Leatherdale, **Air Pollution Control by Adsorption, Carbon Adsorption Handbook**, *Ann Arbor Science Publisher Inc.*, Michigan, 1978 P.N. edited by Cheremisinoff, F. Ellerbusch.

2 VDI 3674, **Waste gas cleaning by adsorption, Process and waste gas cleaning**, *Beuth Verlag GmbH*, April, 2013.

3 H. Menig, **Luftreinhaltung durch Adsorption, Absorption und Oxidation**, *Deutscher Fachschriften-Verlag*, Wiesbaden, 1977.

4 H. von Kienle, E. Bäder, **Aktivkohle und ihre industrielle Anwendung**, *Ferdinand Enke Verlag*, Stuttgart, 1980.

5 **Test methods for activated carbon**. *European Council of Chemical Manufacturers` Federations*/CEFIC Brussels (1986) 7.

6 A. Yehaskel, **Activated Carbon, Manufacture and Regeneration**, *Noyes* DATA Corporation, Park Ridge, New Jersey, USA, 1978.
T. Bandosz, **Activated Carbon Surfaces in Environmental Remediation**, *Elsevier*, 2006.

7 M. Smisek, S. Cerny, **Activated Carbon.** *Elsevier Publishing Company*, Amsterdam-London-New York, 1970.
H. Marsh, F. Rodriguez-Reinoso, **Activated Carbon**, *Elsevier*, 2006.

8 R.Ch. Bansal, J.-B. Donnet and F. Stoeckli, **Acitvated Carbon**, *Marcel Dekker Inc.*, New York, 1988.

9 H. Jüntgen, **Grundlagen der Adsorption**, *Staub-Reinhaltung Luft*, **36**, (1976) No. 7, pp. 281-324.

10 H. Seewald, **Technische verfügbare Adsorbentien. Vortragsveröffentlichung Haus der Technik**, H. 404, pp. 24-34, *Vulkan-Verlag*, Essen, 1977.

11 W. Kast, **Adsorption aus der Gasphase**. *VCH-Verlag*, Weinheim, 1988.

12 H. Krill, **Adsorptive Abgasreinigung - eine Bestandsaufnahme**, *VDI-Berichte* 1034, pp. 339-371, VDI-Verlag, Düsseldorf, 1993.

13 K.-D. Henning, **Activated Carbon for Solvent Recovery**, Company booklet *CarboTech Aktivkohlen GmbH*, D-45307 Essen, Germany.

14 A. Mersmann, G.G. Börger, S. Scholl, Abtrennung und Rückgewinnung von gasförmigen Stoffen durch Adsorption, *Chem.-Ing.-Techn*., **63**, No. 9, pp. 892-903.

15 H. Jüntgen, **Physikalisch-chemische und verfahrenstechnische Grundlagen von Adsorptionsverfahren, Vortragsveröffentlichung Haus der Technik**, H. 404, pp. 5-23, *Vulkan-Verlag*, Essen, 1977.

16 K.-D. Henning, **Science and Technology of Carbon**, Eurocarbon, Strasbourg/France, July 5-9, 1998.

17 K.-D. Henning, S. Schäfer, Impregnated activated carbon for environmental protection, *Gas Separation & Purification*, 1993, Vol. **7**, No. 4, p. 235.

18 P.N. Cheremisinoff, **Volatile Organic Compounds**, *Pollution Engineering*, March 1985, p.30

19 C.S. Parmele, W.L. O`Connell, H.S. Basdekis, **Vapor-phase cuts**, *Chemical Engineering*, Dec. 31, 1979, p. 59.

20 M.G. Howard, Organic solvents recovered efficiently by dry processes, *Polymers Paint Colour Journal,* May 18, 1983, p. 320.
21 W.D. Lovett, F.T. Cunniff, Air Pollution Control by Activated Carbon, *Chemical Engineering Progress*, Vol. **70**, No. 5, May 1974, p. 43.
22 H.L. Barnebey, Activated Charcoal in the Petrochemical Industry, *Chemical Engineering Progress*, Vol. **67**, No. 11, Nov. 1971, p. 45.
23 K.-D. Henning, W. Bongartz, J. Degel, Adsorptive Removal and Recovery of Organic Solvents, VfT Symposium on Non-Waste Technology, Espo/Finnland, June 20-23, 1988.
24 G.G. Börger, A. Jonas, Bessere Abflugtreinigung in Aktivkohle-Adsorben durch weniger Wasser, *Chem.-Ing.-Techn.*, **58** (1986), p. 610-611, Synopse 15.12.
25 K.-D. Henning, W. Bongartz, J. Degel, Adsorptive Recovery of problematic solvents, Paper presented at Nineteenth Biennial Conference on Carbon, June 25-30, 1989, Pennstate University/Pennsylvaia/USA.
26 A.A. Naujokas, *Loss Preventation*, **12** (1979) p. 128.
27 G. Konrad, G. Eigenberger, Rotoradsorber zur Abluftreinigung und Lösemittelrückgewinnung. *Chem.-Ing.-Techn.*, **66** (1994) No. 3, pp. 321-331.
28 H.W. Bräuer, **Abluftreinigung beim Flugzeugbau, Lösemittelrückgewinnung in der Wirbelschicht**, UTA *Umwelt Technologie Aktuell* (1993), No. 2, pp. 115-120.
29 W.N. Tuttle, Recent developments in vacuum regenerated activated carbon based hydrocarbon vapour recovery systems, Port Technology International, **1**, pp. 143-146, 1995.
30 Exhaust air purification and solvent recovery by the Supersorbon(r) Process, Company booklet, Lurgi Aktivkohlen GmbH, D-60388 Frankfurt, Gwinnerstr. 27-33, Germany.
31 G. Caroprese, Company booklet, Dammer s.r.l., I-20017 Passirana die Rhol (Mi), Italy.
32 R. Peinze, Company booklet, Air Engineering, CH-5465 Mellikon, Switzerland.
33 Environmental Technology, Company booklet, Eisenmann, D-71002 Böblingen, Germany.
34 Exhaust air purification and CS_2 recovery by the Supersorbon® process with front- and H_2S absorption, Company booklet, Lurgi Aktivkohlen GmbH, D-60388 Frankfurt, Germany.
35 U. Stöcker, Abgasreinigung in der Viskose-Herstellung und -Verarbeitung, *Chem.-Ing.-Techn.*, **48**, 1976, No. 10.
36 Exhaust gas purification, Company booklet, Messer Griesheim GmbH, D-47805 Krefeld, Germany.
37 F. Herzog, J. Busse, S. Terkatz, Refrigerator recycling - how to deal with CFCs and pentane, Focus on gas 13, Company booklet, Messer Griesheim GmbH, D-47805 Krefeld, Germany.
38 C.J. Cantrell, Vapour recovery for refineries and petrochemical plants, CEP, October 1982, pp. 56-60.
39 Kaldair Vapor Recovery Process, Company booklet, Kaldair Ltd., Langley Berks SL3 6EY, England.

21.2 RECOVERY VERSUS INCINERATION

*Danilo Alexander Figueroa Paredes, **Antonio Amelio, *José Espinosa
***INGAR (CONICET), Avellaneda 3657, S3002GJC Santa Fe, Argentina**
**** Department of Environment, Land and Infrastructure Engineering (DIATI), Politecnico di Torino, Corso Duca degli Abruzzi 24, 10129 Torino, Italy**

21.2.1 INTRODUCTION

Organic solvents are widely used in the pharmaceutical industry when performing, among several tasks, the reaction, separation, and purification steps involved in the manufacture of a drug product. As demonstrated by Luis *et al*.,[1] life cycle assessment (LCA) can be used as a tool to determine the best waste solvent technology from an environmental point of view and even as an *a priori* decision making tool.[2]

Incineration is the most obvious option when considering the use of waste solvents as fuels for steam and electricity production. Waste solvent incineration and incineration in a cement kiln are alternatives that deserve attention in such a case.[3,4]

Solvent recovery, on the other hand, minimizes the usage of raw materials. Batch distillation is the key recovery operation because high recovery and purity can typically be achieved. In addition, solvents from different waste streams can be recovered using the same column turning the recovery system both financially advantageous as well as environmentally friendly.[5] However, it is noteworthy that hybrid processes comprising distillation and membrane separation technologies like pervaporation are emerging as suitable choices, mostly due to the independence of the separation performance of membrane technologies from the phase equilibrium. Hence, the hybrid process is able to break azeotropes of azeotrope-forming waste streams while reducing the energy demand of the distillation task. Moreover, separations by distillation that are controlled by tangent pinch points are also candidates to be replaced by a hybrid process since recovering the solvent in high purity by distillation alone would require not only high instantaneous reflux ratios but also demand a significantly high number of theoretical trays. In such a case, distillate purity control is also an issue due to the occurrence of a zone of constant composition near the rectifier top.[6] Urtiaga *et al*.[7] demonstrated the technical feasibility of isopropyl alcohol recovery with the hybrid distillation/pervaporation. Koczca *et al*.[8] performed economic comparisons between the state-of-the-art and hybrid alternatives in the recovery of tetrahydrofuran from binary and ternary mixtures demonstrating the economic benefits of hybrid processes including pervaporation. Slater *et al*.[9] proposed the integration of pervaporation with a constant volume distillation for the recovery and reuse of tetrahydrofuran. The aforementioned authors assessed the effectiveness of the hybrid technology resorting to an analysis taking into account both economic and environmental aspects. Applied to the mixture THF-methanol, Luis *et al*.[10] performed a thorough analysis of the alternatives pressure swing distillation, distillation/pervaporation, and incineration in terms of their environmental impact (LCA) and energy consumption (simulation), concluding that the hybrid process can be considered a real alternative to the other technolo-

gies due to the saving in materials and energy in an overall scenario. Investment costs were not included, however, in their analysis.

In this chapter, the economic and environmental performance of the alternatives distillation/incineration and distillation/pervaporation for the treatment of the azeotropic mixture isopropyl alcohol-water, whose separation by distillation is characterized by an energy demand controlled by the tangent pinch points, are summarized.[11] The incineration alternative, either in a conventional waste solvent incineration plant or in a cement kiln, resorts to a pre-concentration step by distillation. The recovery alternative, on the other hand, considers a hybrid process consisting of a distillation column followed by a pervaporation unit. Quasi-optimal designs taking into account both operating and investment costs for each technological alternative were obtained resorting to the conceptual models of the units involved.[12,13] Optimal values for the operation variables obtained at the conceptual design level were used as input data of the life cycle analysis to consider all impacts on humans and the environment during the entire life cycle of the solvent.[5,14,15]

21.2.2 DESCRIPTION OF THE TREATMENT ALTERNATIVES FOR A CASE STUDY

Two process alternatives for the treatment of 5 t/day of a binary mixture isopropyl alcohol-water with 27 wt% of isopropyl alcohol (IPA) will be analyzed.

For alternative A1, whose operating sequence is depicted in Figure 21.2.1(a),[16] the fresh feed is concentrated *via* batch distillation to obtain a distillate with a composition near that of the azeotrope IPA-water. After that, while the distillate is sent to off-site incineration in a cement plant, the column residue is diverted to a biological disposal facility

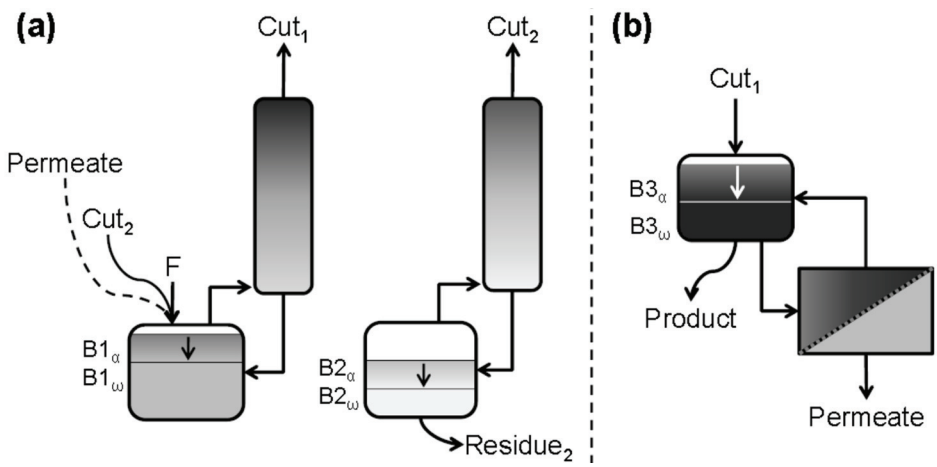


Figure 21.2.1. Operation sequence corresponding to: (a) Alternative A1, the first cut is sent to off-site incineration, while the second cut is recycled to the next batch, (b) Alternative A2, the first cut is treated in the pervaporation unit while both the second cut and the permeate of the membrane unit are recycled to the batch rectifier in the next batch. [Adapted, by permission, from A. Amelio, D.A. Figueroa Paredes, J. Degrève, P. Luis, B. Van der Bruggen, and J. Espinosa, Conceptual Model-Based Design and Environmental Evaluation of Waste Solvent Technologies: Application to the separation of the mixture acetone-water, *Sep. Sci. Technol.*, **53** (11), 1791, (2018).]

on-site. For this alternative, it is considered that the optimal process consists of concentrating the fresh feed up to a concentration near the azeotropic composition (88.5 wt% IPA) to obtain a mixture with a lower calorific value above 5500 kcal/kg. In this way, support fuel is avoided in the incineration task, and savings are expected in haulage costs due to the decreased volume to be transported from the pharmaceutical plant to the cement kiln.[6]

It is assumed that the distillation column can operate 20 hours a day, consuming the remaining 4 hours for filling, starting-up and emptying the column. The primary optimization variable is the "per-pass" recovery of alcohol, σ_{IPA}^{D}. in the first cut. Table 21.2.1 shows the lower calorific value corresponding to a mixture with 83 wt% of isopropyl alcohol, which is adopted as the target distillate composition during the first cut. The first cut, which is commonly operated at a variable reflux policy, is followed by a second cut operated at a constant reflux ratio policy (i.e., 0.5) to achieve an IPA concentration below 1 wt% in the boiler at the end of the batch. The second cut is recycled to the next batch to avoid IPA losses, as shown in Figure 21.2.1(a). Main process specifications for alternative A1 are summarized in Table 21.2.2.

Table 21.2.1. Lower calorific value of the concentrated feed (83 wt% IPA). [Data from reference 11].

Heat of combustion IPA [Kcal/kg]	7201
Latent heat W [kcal/kg]	539
Lower calorific value 83% IPA	5976.83
Lower calorific value 17% W	-91.63
Lower calorific value 83:17 Mixture	5882.20

Table 21.2.2. Process specifications for the treatment alternatives.

Treatment alternatives	Distillation/incineration (A1)	Distillation/pervaporation (A2)
Fresh feed amount and IPA weight percent	5 t/day, 27 wt%	5 t/day, 27 wt%
Average distillate composition (first cut)	mixture with a lower calorific value above 5500 Kcal/Kg	value subject to optimization taking into account operating and investment costs
IPA weight percent in the boiler at the end of the distillation task	< 1 wt%	< 1 wt%
IPA weight percent in the product tank at the operation end	-	> 99.8 wt%

For alternative A2, on the other hand, the alcohol is recovered in a two-step process comprised by a distillation column and a hydrophilic pervaporation unit, both units operated in batchwise mode. As in alternative A1, the residue of the column is sent to biological treatment and discharge. Figure 21.2.1(b) shows the operating sequence corresponding to alternative A2. The sequence for the distillation column is similar to that of alternative

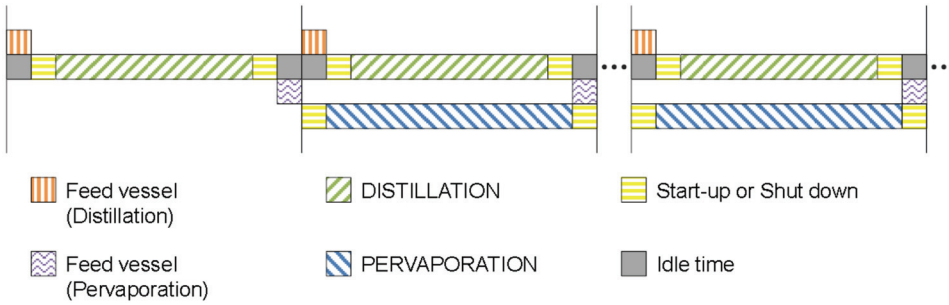


Figure 21.2.2. "Scheduling" corresponding to alternative A2.

A1. The first cut is sent to the membrane unit, which is also operated in batchwise mode. The isopropyl alcohol-rich distillate stored in the product tank is enriched in its IPA concentration until achieving an alcohol composition above 99.8 wt%. In this case, the dehydrated IPA can be recycled to the main pharmaceutical process thus minimizing the use of a fresh solvent. Note that both the second cut and the permeate from the membrane unit must be recycled to the batch rectifier in the next batch to avoid isopropyl alcohol losses.

Obtaining a quasi-optimal design for this alternative is more complex than for the alternative distillation/incineration since values for an increased number of optimization variables must be determined. Main optimization variables are: i) "per-pass" recovery of alcohol σ^{D}_{IPA} in the first cut, ii) distillate mole fraction, x^{D}_{IPA}, in the first cut, iii) distillation processing time, t_D, iv) pervaporation processing time, t_M, and v) permeate pressure, P_p.

Note that by parametrically varying the distillate mole fraction of the first cut, which is operated at a variable reflux policy, allows capturing the economic trade-offs between distillation and membrane tasks. To narrow the search space, it is assumed that the reflux ratio of the second cut is 0.5. The permeate pressure is 1.5 kPa.[7] Operating times for distillation and dehydration tasks are set to 16 and 20 hours, respectively, according to the tasks schedule shown in Figure 21.2.2.[16] The cycle time is 24 hours with a time-horizon of 360 days/year. Pseudo-steady state of the process is typically achieved after a relatively low number of cycles. Main process specifications for alternative A2 are summarized in Table 21.2.2.

21.2.3 CONCEPTUAL MODELING OF THE TREATMENT ALTERNATIVES

In the context of optimization-based design, Marquardt *et al.*[17] proposed a three-step approach for the design of hybrid processes: (i) generation of flow-sheet alternatives, (ii) evaluation of the alternatives with the aid of shortcut methods; (iii) rigorous optimization of the most promising alternatives to obtain the best flow-sheet. In this line, Caballero *et al.*[18] successfully applied the last two steps of the mentioned approach in the optimization of a hybrid separation system composed of a distillation column and a vapor permeation unit. Considering detailed rate-based models for distillation and pervaporation, Koch *et al.*[19] optimized a superstructure of the hybrid process using evolutionary algorithms for the simultaneous determination of the optimal process configuration, equipment design,

and operating conditions. To bridge the gap between shortcut calculations and detailed engineering design, Skiborowski *et al*.[20] proposed an efficient and robust approach for the optimal design of membrane-assisted distillation processes. Meyer *et al*.[11] and Amelio *et al*.[16] applied the second step of the approach proposed by Marquardt *et al*.[17] to the evaluation of alternatives for the treatment of solvents.

Given that flow-sheets for alternatives A1 and A2 are defined according to Figure 21.2.1, the methodology considered in this chapter intends to show how the economic and environmental performance of both waste solvent technologies can be evaluated from the conceptual design of each process. This task was performed resorting to conceptual models or shortcuts for each operation unit involved, models that are characterized by their abilities to capture the essence of the process at low computational cost. Considering an additional cost model including both investment and operating costs, this approach is suitable for the optimization-based design of waste solvent technologies. Quasi-optimal values for the utilities, that is, cooling water, electricity, and steam for distillation and pervaporation are, on the other hand, the input data necessary to perform the environmental assessment.[5,11,16]

Main issues in the conceptual modeling of each unit are highlighted in the following sections.

21.2.3.1 Conceptual model for the distillation task

For the case study under consideration, the quasi-optimal operation of the batch rectifier was estimated based on a conceptual model of the operation. The main assumptions of the conceptual model are: (i) the rectifier has an infinite number of stages, and (ii) the instant variations of the molar hold-up in the trays are negligible. Under these assumptions, the following relationships apply for every component in the mixture:[21]

$$\frac{d\sigma_i^D}{d\eta} = \frac{x_i^D}{x_{i0}^B} \qquad [21.2.1]$$

$$x_i^B = x_{i0}^B \frac{(1-\sigma_i^D)}{(1-\eta)} \qquad [21.2.2]$$

where:

σ_i^D fractional recovery of component i in the distillate
η rectification advance
x_i^D mole fraction of component i in the distillate
x_{i0}^B initial mole fraction of component i in the still

Equation [21.2.1] above has the advantage of considering the component recoveries and the rectification advance instead of the component mole fractions. This choice is appropriate at the design level considering that the design specifications in batch distillation are normally given in terms of component recoveries and that the vapor flow rate does not need to be specified at this level. Note that for given instantaneous values of the rectification advance and the recovery of each component in the distillate, it is possible to calculate the instantaneous still composition from Equation [21.2.2]. This equation gives the

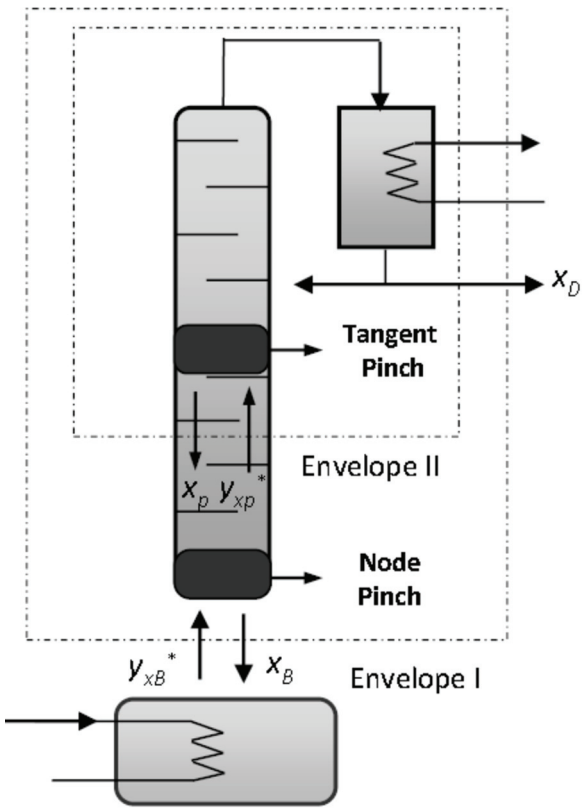


Figure 21.2.3. Schematics of an instantaneous separation with two controlling pinch points: a node pinch at the bottom and a saddle tangent pinch in the "middle" of the rectifier. [Data from reference 22].

instant still composition needed for calculating the instant distillate composition (if the column is operated at constant reflux) or for calculating the instantaneous reflux ratio (if the column is operated at constant distillate composition).

Focusing our attention on the operation at constant reflux ratio, the conceptual model must predict the instantaneous distillate composition with the aid of pinch theory.[22] The composition of the controlling pinch point must be determined to perform the mass balance around an envelope relating either a node pinch (Figure 21.2.3, Envelope I) or a tangent pinch (Figure 21.2.3, Envelope II) with the unknown distillate composition. Although Figure 21.2.3 shows a special case where two pinch points control the separation, the analysis of the Figure enhances comprehension of the basics of the conceptual model. As usual, equimolal overflow is assumed, and hence, the operating lines take the form of straight lines in the y-x diagram.

At pinch situation the mass balance around either Envelope I or II becomes:

$$-y^*_{x_p} + \frac{r}{r+1}x_p + \frac{x_D}{r+1} = 0 \qquad [21.2.3]$$

where:

x_p	pinch point lying on the y-x equilibrium curve
y^*_{xp}	vapor in phase equilibrium with x_p
x_D	distillate composition
r	reflux ratio

In the case of a node pinch controlling the separation, $x_p = x_D$ and hence, Equation [21.2.3] may be solved for the mole fraction of the distillate composition x_D from known values of the pinch x_p and the reflux ratio r. Otherwise, there is an additional constraint on the slope of the equilibrium curve at the tangent pinch that must be taken into account:[23]

$$\left.\frac{dy}{dx}\right|_{x = x_p} = \frac{r}{r+1} \qquad [21.2.4]$$

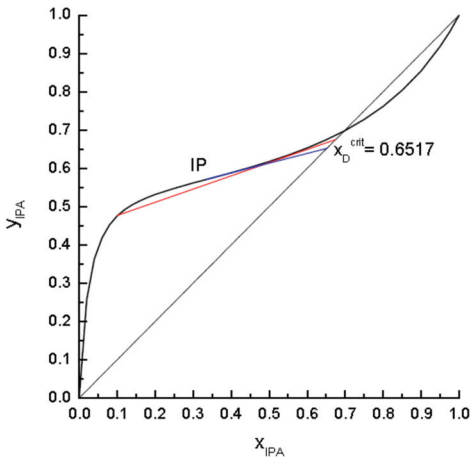


Figure 21.2.4. Diagram y vs. x for IPA-water mixture at 101.3 kPa. IP represents the inflection point of the equilibrium curve. [Adapted, by permission, from R. Meyer, D.A. Figueroa Paredes, M. Fuentes, A. Amelio, B. Morero, P. Luis, B. Van der Bruggen, and J. Espinosa, Conceptual model-based optimization and environmental evaluation of waste solvent technologies: Distillation/incineration versus distillation/pervaporation, *Sep. Purif. Technol.*, **158**, 238 (2016)].

with the right-hand side of Equation [21.2.4] representing the slope of the operating line of the rectifier.

In this case, Equations [21.2.3] and [21.2.4] have to be solved simultaneously for the mole fraction of the distillate composition x_D and the tangent pinch composition x_p. Different algorithms needed for estimating the instantaneous rectifier performance at different reflux policies can be found in Torres and Espinosa.[22] Note that for the case study, the equilibrium curve shows both an azeotrope and an inflexion point **IP**, which is typical in systems where the energy demand is controlled by tangent pinch points for certain separations, as is shown in Figure 21.2.4. In the case of starting compositions at the left of the inflection point, the choice of distillate compositions lower than x_D^{crit} will result in instantaneous separations for which the energy demand is controlled by the composition in the boiler; that is, operations with similar behavior to ideal mixtures. For distillate compositions higher than x_D^{crit}, the instantaneous minimum reflux can be controlled either by a "pinch" at the bottom of the column, a tangent pinch located somewhere in the “middle”, or both.[22]

It is noteworthy that the conceptual model of the batch rectifier decouples the variation of compositions from the variation of flows and batch size. As stated by Bernot *et al.*,[24] this kind of approach can be used to estimate batch sizes, operating times, equipment sizes, utility loads, and costs for the batch distillation. For given values of the batch size M_0 [kmol] and operating time t_D, the only variable that must be determined is the vapor flow rate V [kmol/h], which can be iteratively obtained from the results obtained at the conceptual model level and the mass balance around the condenser from:

$$V = \frac{1}{t_D}\int_0^{t_D} D(t)(R(t)+1)dt = \frac{1}{t_D}\int_0^{\eta} M_0(R(\eta)+1)d\eta \qquad [21.2.5]$$

where:

V	vapor flow rate
t_D	operating time
M_0	batch size

For integrating Equation [21.2.5] the instantaneous reflux ratio was calculated from:

$$R = f \times r \qquad [21.2.6]$$

where:

f factor

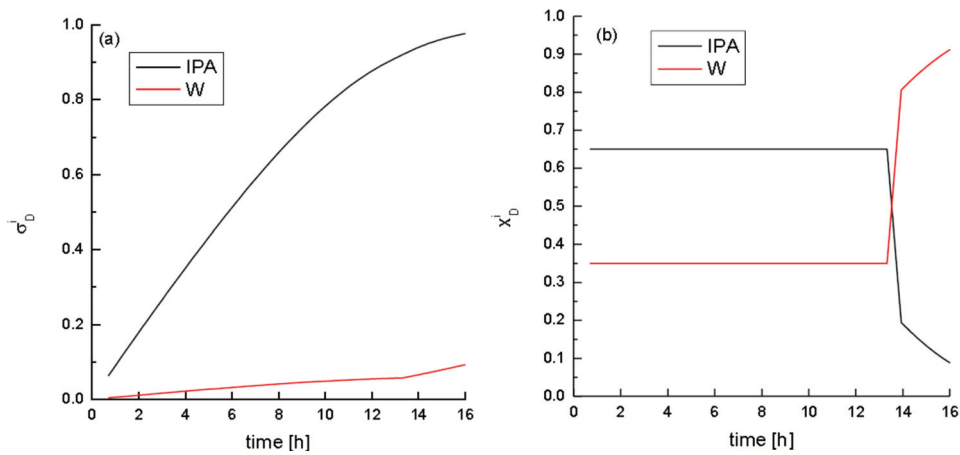
In all studied cases, the value of f was about 1.2. The number of trays was estimated with the aid of DISTIL[25] from (x_B^0, R(0)) to achieve the selected distillate composition x_D for the first cut at the column top. The simulation of the instantaneous separation in ASPEN Hysys[26] for the initial conditions was also used to determine both the column diameter and the type of internals. The tool Try Sizing (Aspen Hysys) recommended the adoption of a packing column with a diameter of 0.3048 m considering the relatively low vapor flow rates involved in all studies. Equation [21.2.5] was iteratively solved for different values of V until achieving the desired value of the operation time t_D.

Figure 21.2.5 depicts the time evolution of the primary variables calculated with the conceptual model for an IPA mole fraction of 0.65 in the first cut. The operation cycle of the batch rectifier is 16 h with a vapor flow rate of 5.359 kmol/h. The rectifier has 13 theoretical stages and a column diameter of 0.3048 m.

For a case study analyzed in Amelio *et al.*,[16] Figure 21.2.6 shows the time evolution of the reflux ratio obtained from rigorous simulation of the distillation task with ASPEN Batch Distillation.[26]

Whether the conceptual modeling approach, the rigorous simulation of the task or a combination of both approaches is used, two main issues must be taken into account: i) the selected model must be run until achieving pseudo-steady state and, ii) liquid-vapor equilibrium must be properly represented.

The main advantage of the conceptual modeling approach is that the vapor flow rate and column diameter needed to perform the desired separation in the operating time t_D are outputs of the model. Modeling the distillation task resorting to rigorous simulation, on the other hand, allows including the trays and condenser hold-up issue.[27]



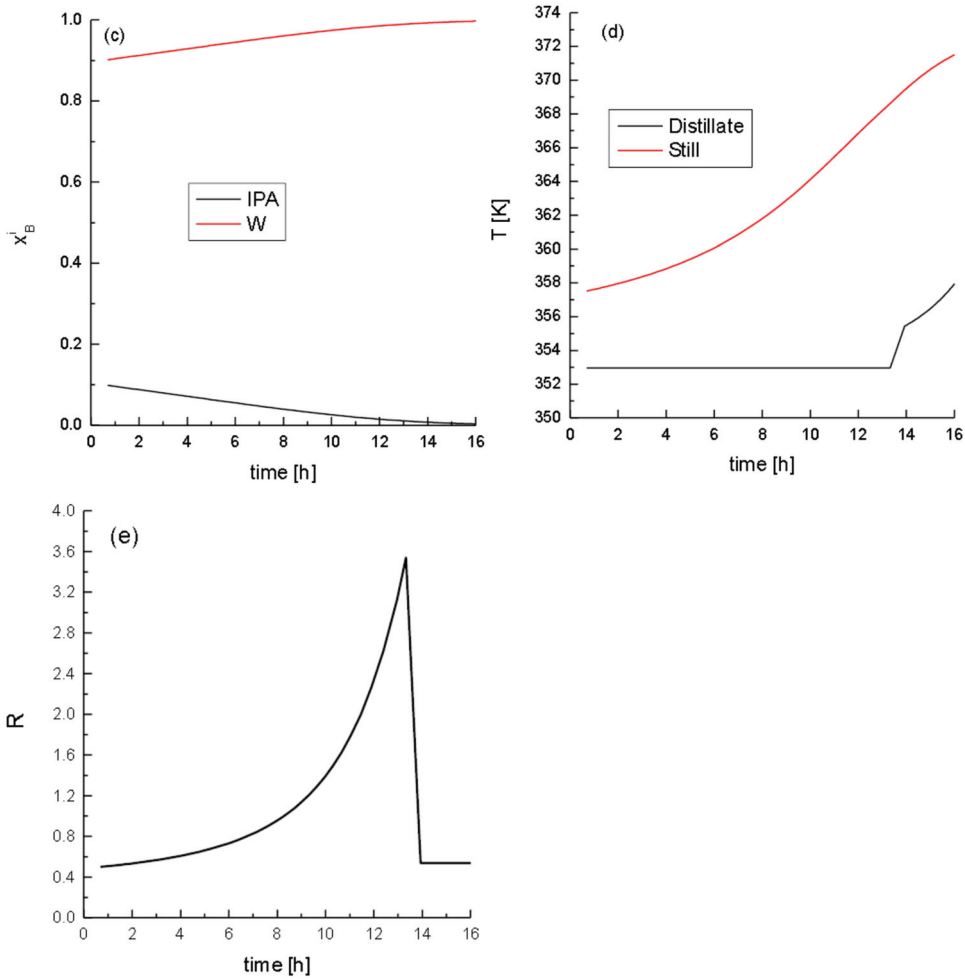
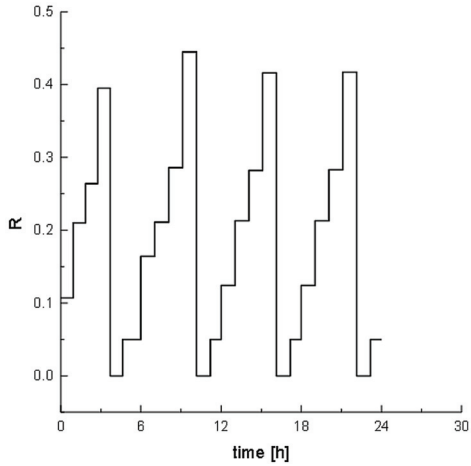


Figure 21.2.5. Time variation of (a) component recovery, (b) distillate composition, (c) still composition, (d) still and distillate temperatures, and (e) reflux ratio V = 5.359 kmol/h. $x_D^{Cut1} = 0.65$. $x_{IPA}^{Cut1} = 0.92$. [Data from reference 11].

21.2.3.2 Conceptual model for the pervaporation task

The process of pervaporative separation consists of two steps: selective dissolution and diffusion of the components of a liquid charge through a dense membrane and its consequent partial evaporation. The driving force for permeation is the difference in chemical potential of components at the two sides of the membrane – a difference which is generally accomplished by lowering the pressure at the permeate side. A common dense membrane consists of a dense layer oriented towards the feed/retentate side in the



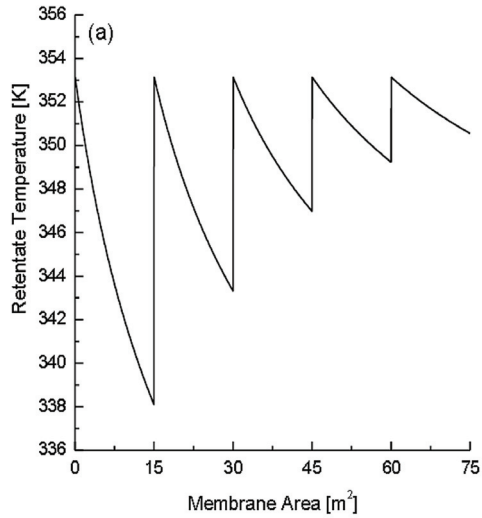
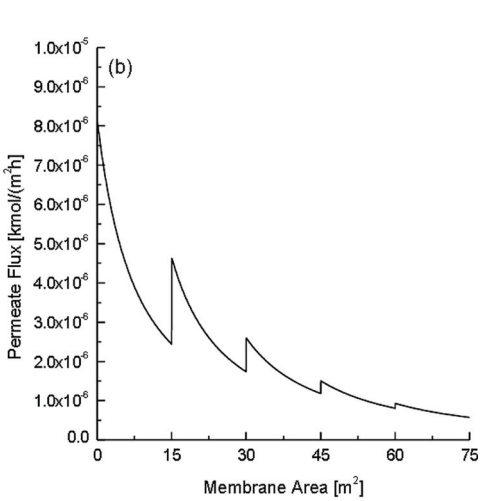


Figure 21.2.6. Time evolution of the reflux ratio obtained from rigorous simulations in Aspen Batch Distillation.[26] [Data from reference 16].



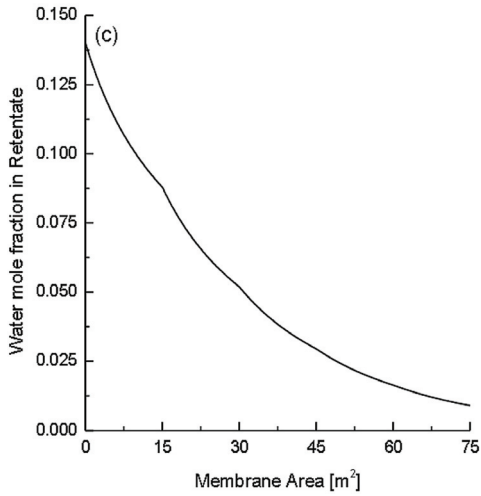


Figure 21.2.7. Variation across the membrane of (a) retentate temperature, (b) permeate flux and, (c) water mole fraction in the retentate side for a quasi-optimal design. Mixture isopropyl alcohol-water. [Adapted, by permission, from M.A. Sosa, and J. Espinosa, Feasibility Analysis of Isopropanol Recovery by Hybrid Distillation/ Pervaporation Process with the Aid of Conceptual Models, *Sep. Purif. Technol*., **78**, 237 (2011)].

pervaporation cell on top of a porous supporting layer oriented towards the permeate side in which vaporization occurs.[28]

In the typical arrangement of a staged pervaporation process, a heat exchanger is placed after either a constant temperature drop of the liquid mixture or a constant membrane area. The decrease in the temperature, which results in a decrease of the driving

force for the permeation process, is due to the change of state of the permeating components, which take their vaporization heat from the retentate liquid. An additional drop in the driving force for the separation is caused by a concentration decrease along the module of the preferentially permeating component in the liquid mixture.[29] The concepts above can be understood with the aid of Figure 21.2.7(a)-(c) that shows, for the mixture IPA-water, the variation of the retentate temperature, permeate flux, and water mole fraction in the retentate across a membrane unit composed by 5 modules of 15 m^2 each, respectively.[30]

Results shown in Figure 21.2.7(a)-(c) were obtained from integration of a model of the membrane unit which incorporates the semi-empirical mass transfer model based on Fick's law with concentration dependent diffusivity parameters developed by Urtiaga *et al.*[7] for the commercial membrane CMC-CF-23 (cm-celfa Membrantrenntechnik AG). Table 21.2.3 shows the steps that must be followed to solve both mass and energy balances around the unit. Parameters needed to run the model can be found in Urtiaga et al.[7]

Table 21.2.3. Algorithm to solve mass and energy balances in the membrane unit. Mixture IPA-water.[7,30]

Step 1. Calculate components activities $a^{f}_{i,\,353.14} = x^{f}_{i}\gamma^{f}_{i,\,353.14}$ [21.2.7]
Step 2. Calculate the water flux [kg/(m^2h)] $J_{w,\,353.14} = A_1[\exp((A_2 a^{f}_{w}) - 1)]$ [21.2.8]
Step 3. Calculate the ratio of partial fluxes q and then the IPA flux [kg/(m^2h)] $q = \frac{J_{w,\,353.14}}{J_{IPA353.14}} = \frac{A_3}{a^{f}_{IPA}}[\exp(A_4 a^{f}_{w} - 1)]$ [21.2.9]
Step 4. Use the Arrhenius-type equation to account for the dependence of water and isopropyl alcohol fluxes [kg/(m^2h)] with temperature $J_{i,\,T} = J_{i,\,T_0}\exp\left(-\frac{E_{a,\,i}}{RT}\right)$ [21.2.10] where: $\ln J_{i,\,T_0} = \ln J_{i,\,353.14} + \frac{E_{a,\,i}}{353.14R}$ [21.2.11]
Step 5. Calculate the molar fluxes [kmol/(m^2h)] $J^{mol}_{i,\,T} = \frac{J_{i,\,T}}{MW_i}$ [21.2.12] and then solve the mass balance corresponding to a differential area element from: $d[Lx_i] = -J^{mol}_{i,\,T}dA$ [21.2.13]
Step 6. Solve the energy balance corresponding to a differential area element from: $Lc_p dT = -\Delta H_{vap} J^{mol}_{T} dA$ [21.2.14]
Step 7. Update values for the retentate flow rate, retentate mole fraction for each component and temperature and go to Step 1. Integrate the model until the selected module area is achieved.

Focusing our attention on the case study under consideration, the membrane system is formed by a feed tank, the membrane unit itself and a recirculation pump. For the sake of simplicity, the vacuum-refrigeration system is not shown in Figure 21.2.1(b). However, it must be optimized for each purification task; i.e., for different amounts and compositions of the first cut of the distillation task.

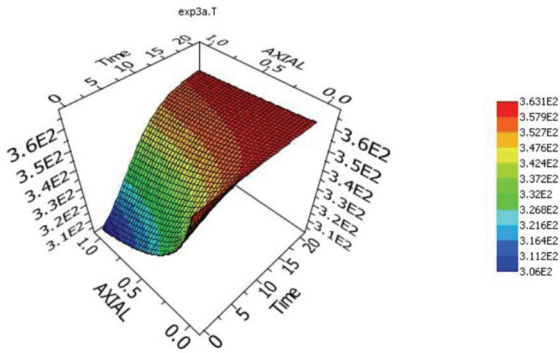


Figure 21.2.8. Evolution of the temperature along the retentate side of the membrane unit. Maximum operation temperature was set at 90ºC. [Adapted, by permission, from R. Meyer, D.A. Figueroa Paredes, M. Fuentes, A. Amelio, B. Morero, P. Luis, B. Van der Bruggen, and J. Espinosa, Conceptual model-based optimization and environmental evaluation of waste solvent technologies: Distillation/incineration versus distillation/pervaporation, *Sep. Purif. Technol*., **158**, 238 (2016)].

While the mass balance in the feed tank is modeled through a set of differential equations, the performance of the pervaporation unit of a given membrane area is calculated by integrating the spatially one-dimensional model shown in Table 21.2.3. The volumetric flow rate of the recirculation pump is fixed according to Reynolds numbers achievable in the module geometry chosen.[11,16] The final product is obtained in the feed tank at the operation end. As long as the feed to the membrane unit increases its alcohol content with time, the driving force for separation decreases as shown in Figure 21.2.8.[11] Therefore, pervaporation modules should be arranged in parallel to maximize the driving force during the batch cycle. The model was implemented in the equation-oriented simulation software gPROMS (Process Systems Enterprise).[31]

21.2.3.3 Conceptual model for the vacuum production task

Relevant aspects of the conceptual modeling of two different vacuum systems; namely, vacuum pump/refrigeration and steam-jet ejector systems, are briefly summarized in this section.

21.2.3.3.1 Vacuum pump/refrigeration system

The vacuum pump/refrigeration system is formed by a condenser and a vacuum pump. The aim of this system is to recover the significant part of permeate as a liquid while decreasing the charge of the gas evacuated by the vacuum pump. The permeate stream entering to the condenser is first cooled from the operating membrane temperature to the dew point and then condensed until reaching the bubble point of the mixture, points which are a function of the pressure and the instantaneous composition of the permeate mixture. Given the relatively low value of the permeate pressure, the low temperature required for the permeate condensation is usually reached by using a refrigerant as a cooling service fluid. In this case, the condenser is coupled with a vapor compression refrigeration cycle using propane as refrigerant.

Note that, inevitably, there is an inward leakage of air into the equipment under vacuum; namely, the membrane unit and the condenser. Given that the air remains always in the vapor phase, its mole fraction increases along the condenser. Particularly, at the condenser end, the vapor-liquid equilibrium is strongly affected by the presence of air so that the bubble point of the mixture is lower than that of the binary mixture. Another technical relevant aspect is the freezing point of the binary mixture, which depends on its composi-

tion and acts as the lower bound of the operating temperature in the condenser to avoid solids accumulation in the heat-transfer area.[32]

For proper design of both the condenser and the vacuum pump, an appropriate description of the phase change of the mixture is performed by considering a multi-node model for the condenser.[33] Given that inward leakage of air depends on the volume of the equipment under vacuum an iterative procedure is required to solve the material and energy balance together with the design equations for the condenser area and volume (including the membrane module).[32]

Optimal design of this sub-system is obtained by minimizing the overall annual cost of the process. In the objective function, a cost item accounting for the loss of non-condensed solvent is also considered. The optimization variables are the condensation temperature at the end of the condenser, and the refrigerant pressures in the vapor compression refrigeration cycle.

21.2.3.3.2 Steam-jet ejector system

If the permeate stream has a low solvent content as is the case of highly selective pervaporation membranes it is not necessary to recover the solvent in the next batch of the distillation task.[16] However, the vacuum level must still be maintained to allow the separation of the first cut of the distillation task into a solvent-rich product and a water-rich permeate. For this purpose, a conventional steam-jet ejector system can be adopted as an alternative with a lower investment cost than that of the vacuum pump/refrigeration system. Note, however, that the steam diluted permeate stream requires a biological treatment before discharge. To this end, it must be mixed with the still content at the end of the distillation task in the next batch.

To model this system with the aid of shortcut models, the feed must be converted into an air equivalent in standard conditions.[34] The data presented by Coker[34] for steam and cooling water consumption must be correlated for a system formed by n ejectors with n-1 inter-condensers.[16]

21.2.4 ECONOMIC ANALYSIS

The economic analysis can be done by applying the methodology explained in Seider *et al*.[35] For the case study under consideration, it was performed by calculating the annualized investment cost and the annual operating cost of alternatives A1 and A2 for different values of the corresponding optimization variables (e.g., the "per-pass" recovery of IPA in the first cut of the distillation task for alternative A1 or the mole fraction of isopropyl alcohol in the first cut of the distillation task for alternative A2) until achieving the economic optimum for each treatment technology, expressed as an overall cost in U$S/t IPA.

Table 21.2.4 shows the design and operation variables obtained at the conceptual design level for the alternative distillation/incineration, which in turn are the input data of the economic model described in detail in Meyer *et al*.[11] Among the operating costs, the costs involved in transporting the concentrated distillate (Cut1 in Figure 21.2.1(a)) to the cement plant were estimated from parameters given in Table 21.2.5.[11] Costs for both the incineration of the distillate and the biological disposal of the column residue (Residue2 in Figure 21.2.1(a)) together with costs related to the purchase of isopropyl alcohol and the consumption of utilities are shown in Table 21.2.6. Input data needed to estimate the eco-

nomic performance of the recovery alternative are summarized in Table 21.2.7, where design and operation variables corresponding to distillation and pervaporation tasks are taken into account.

Note that the total capital investment for each alternative is annualized taking ten years as a lifetime with 10% interest rate. The annual utility consumption is calculated by considering the operating cycle time of each process unit in a time-horizon of 360 days/ year.

Table 21.2.4. Design and operation variables for Alternative A1: Distillation/incineration.

Condenser area [m^2]	Packed diameter [m]
Evaporator area [m^2]	Cooling water [m^3/year]
Horizontal vessel volume [m^3]	Steam [kg/year]
Packed height [m]	

Table 21.2.5. Parameters used to calculate the transport cost. [Adapted, by permission, from R. Meyer, D.A. Figueroa Paredes, M. Fuentes, A. Amelio, B. Morero, P. Luis, B. Van der Bruggen, and J. Espinosa, Conceptual model-based optimization and environmental evaluation of waste solvent technologies: Distillation/incineration versus distillation/pervaporation**,** *Sep. Purif. Technol.***, 158,** 238 (2016)].

Truck capacity [m^3/trip]	25	Load/Unload time of products [h]	1
Distance per trip [km/trip]	2 x220	Driver wage [U$S/h]	10
Fuel economy [km/L]	5	Maintenance expenses [U$S/km]	0.0976
Fuel price [U$S/L]	0.85	General expenses [U$S/d]	8.22
Average Truck Speed [km/h]	60	Truck: Purchase cost [U$S]	2E+05

Table 21.2.6. Costs for raw material, utilities, incineration and biological disposal.

IPA [U$S/t]	1200	Electricity [U$S/MWh]	122.6
Cooling water [U$S/$m^3$]	0.091	Incineration in cement kiln [U$S/t]	150
Steam (1 barg) [U$S/kg]	0.025	Biological disposal [U$S/t O2]	650

Table 21.2.7. Design and operation variables for Alternative A2: Distillation/pervaporation.

Column	Membrane Unit
Condenser area [m^2]	Vessel [m^3]
Evaporator area [m^2]	Vacuum pump duty [kW]
Horizontal vessel volume [m^3]	Compressor duty [kW]
Packed height [m]	Recirculation pump flow rate [m^3/h]
Packed diameter [m]	Permeate condenser area [m^2]
Cooling water [m^3/year]	Retentate heater area [m^2]
Steam [kg/year]	Propane condenser area [m^2]

Table 21.2.7. Design and operation variables for Alternative A2: Distillation/pervaporation.

Column	Membrane Unit
	Membrane area [m^2]
	Vacuum vessel volume [m^3]
	Cooling water [m^3/year]
	Steam [kg/year]
	Electricity [kWh/year]

Applied to the case of acetone-water described in detail in Amelio *et al.*,[16] Tables 21.2.8 and 21.2.9 show the costs obtained from the optimization of alternatives A1 and A2 using the conceptual modeling approach together with a cost model. While for alternative A1 off-site incineration either in a cement kiln or a conventional waste solvent incinerator is considered, two different vacuum systems are taken into account for alternative A2. Note that in Table 21.2.9, the payback period and the internal rate of return IRR after ten years was calculated using a 35% income tax rate and a 10% interest rate to determine operating cost savings from solvent recovery.[5]

Table 21.2.8. Annualized investment and operating costs [10^3 U$S/year] for two variants of distillation/incineration. [Data from reference 16].

	Variant	
	Incineration in cement kiln	Conventional waste solvent incineration
Column investment cost	52	52
Column utilities cost	6.1	6.1
Column residue disposal cost	4.4	4.4
Transportation cost	10.7	1.7
Incineration cost	71.8	120
General cost	62	62
Overall cost	208	256
Acetone to incineration [t/year]	454	454
Overall cost [U$S/t Acetone]	457	563

Table 21.2.9. Annualized investment and operating costs [10^3 U$S/year] for two variants of distillation/pervaporation. [Data from reference 16].

	Vacuum system variant	
	Vacuum pump/refrigeration system	**Steam-jet ejector system**
Pervaporation unit investment cost	96.1	85.1
Column investment cost	52.7	52.2
Column utilities cost	6.4	6.1
Column residue disposal cost	5.8	7.1
Pervaporation unit utilities cost	1.9	5.4
Membrane replacement cost	3.9	3.9
General cost	116	110
Overall cost	283	270
Acetone recovered [t/year]	453	452
Overall recovery cost [U$S/t Acetone]	625	597
Payback period* [year]	3	3
Internal return rate* [%]	26	24

*annual earnings consider savings due to the avoided purchase of fresh solvent and the avoided disposal cost of the spent solvent.

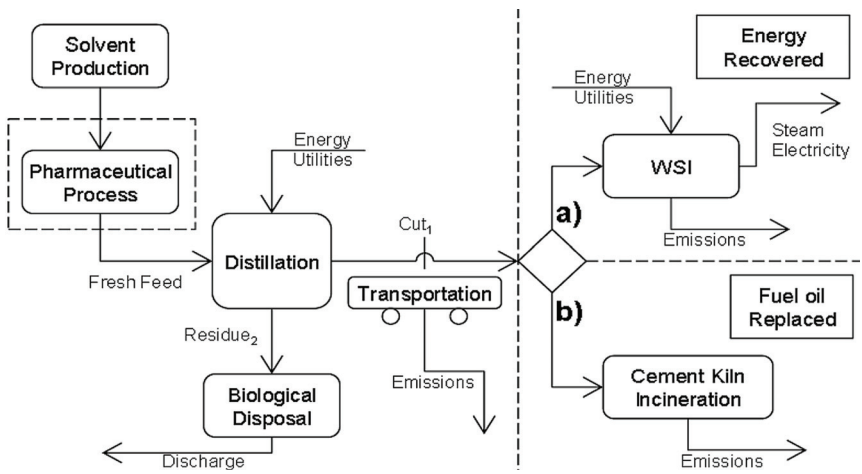


Figure 21.2.9. System boundaries for the alternative distillation/incineration considering two incineration variants: (a) a Waste Solvent Incineration plant and (b) a cement kiln. [Adapted, by permission, from A. Amelio, D.A. Figueroa Paredes, J. Degrève, P. Luis, B. Van der Bruggen, and J. Espinosa, Conceptual Model-Based Design and Environmental Evaluation of Waste Solvent Technologies: Application to the separation of the mixture acetone-water, *Sep. Sci. Technol*., **53** (11), 1791, (2018).]

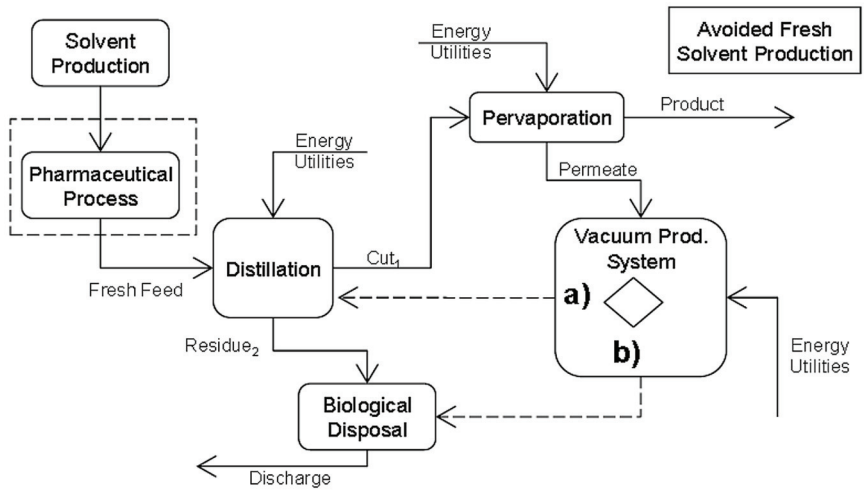


Figure 21.2.10. System boundaries for the alternative distillation/pervaporation considering two vacuum production variants: (a) a vacuum pump/refrigeration system and (b) a steam-jet ejector system. [Adapted, by permission, from A. Amelio, D.A. Figueroa Paredes, J. Degrève, P. Luis, B. Van der Bruggen, and J. Espinosa, Conceptual Model-Based Design and Environmental Evaluation of Waste Solvent Technologies: Application to the separation of the mixture acetone-water, *Sep. Sci. Technol.*, **53** (11), 1791, (2018)].

21.2.5 ENVIRONMENTAL ANALYSIS

Life cycle assessment will be used to evaluate the environmental impact of the alternatives studied for one year of operation. Figure 21.2.9(a)-(b) shows the boundaries between the technological system and nature for alternative A1.[16] Impacts related to the following tasks are considered for the distillation/incineration alternative: i) solvent production, ii) pre-concentration step, iii) transportation, iv) biological disposal and v) incineration either in a waste solvent incineration plant or in a cement kiln.

All these steps bring a burden to the environment. It is noteworthy that for the waste solvent incineration variant benefits due to steam and electricity production must be taken into account. For the case of incineration in a cement kiln, on the other hand, benefits due to substituted fuels and their corresponding avoided emissions must be considered.

Figure 21.2.10(a)-(b) shows the system boundaries for alternative A2.[16] Impacts related to the following tasks are considered for the distillation/pervaporation alternative: i) solvent production, ii) pre-concentration step, iii) pervaporation, iv) biological disposal and v) vacuum production either with a vacuum pump/refrigeration system or a steam-jet ejector system.

In this case, credits to the environment are given with the avoided production and incineration of the recovered solvent.

The environmental burden related to the construction and installation of equipment is not within the LCA boundaries for none of the alternatives analyzed in this chapter, and, therefore, not included in the overall assessment.[5]

The environmental impact assessment was undertaken using the ReCiPe 2008[36] method from SimaPro 7.3[37] software package. ReCiPe 2008[36] includes eighteen midpoint categories and three endpoint categories as shown in Tables 21.2.10 and 11, respectively. While midpoints categories are accounted with their characterization factors (e.g., kt CO_2 equivalent for the midpoint category climate change in Table 21.2.10), endpoints categories are presented regarding a single score.[36,38]

Table 21.2.10. Category indicators at the midpoint level.[36]

(1) climate change	(10) freshwater ecotoxicity
(2) ozone depletion	(11) marine ecotoxicity
(3) terrestrial acidification	(12) ionizing radiation
(4) freshwater eutrophication	(13) agricultural land occupation
(5) marine eutrophication	(14) urban land occupation
(6) human toxicity	(15) natural land transformation
(7) photochemical oxidant formation	(16) water depletion
(8) particulate matter formation	(17) mineral resource depletion
(9) terrestrial ecotoxicity	(18) fossil fuel depletion

Table 21.2.11. Category indicators at the endpoint level.[36]

(a) damage to human health
(b) damage to ecosystem diversity
(c) damage to resource availability

It must be emphasized that in order to carry out the environmental impact assessment, life cycle inventories corresponding to the tasks involved in alternatives A1 and A2 must be calculated from the results obtained at the conceptual modeling level on an annual basis and LCA software tools like Ecosolvent[15] and SimaPro.[37] Quasi-optimal values of the utilities; i.e., cooling water, electricity and steam needed for distillation and pervaporation, and travelled distance by the truck are key data input to estimate life cycle inventories. For the sake of comprehension, Tables 21.2.12 and 13 reproduce life cycle inventories obtained in Savelski *et al*.[5] for the production and incineration of 1 kg of isopropyl alcohol, respectively. For the case study under consideration, SimaPro[37] was used to calculate most of the life cycle inventories with the exception of the inventories corresponding to the incineration and biological disposal tasks, which were calculated with the aid of Ecosolvent.[15] Once the life cycle inventories are estimated, the ReCiPe 2008[36] method can be used for estimating the environmental burdens of the alternatives considered in terms of the human health, ecosystem, and natural resources as will be shown in the Results section. For more details, the interested reader is referred to the papers of Meyer *et al.*[11] and Amelio *et al*.[16]

Table 21.2.12. Life cycle inventory for IPA manufacture on a 1 kg basis. [Data from reference 5].

Cumulative energy demand [MJ-Eq]	6.26E+01
Air emissions [kg]	1.66E+00
CO_2 [kg]	1.63E+00
CO [kg]	2.28E-03
CH_4 [kg]	1.03E-02
NO_x [kg]	3.04E-03
NMVOC [kg]	1.78E-03
Particulates [kg]	1.27E-03
SO_2 [kg]	4.91E-03
Water emissions [kg]	5.80E-01
VOCs [kg]	9.01E-07
Soil emissions [kg]	2.44E-04
Total emissions [kg]	2.24E+00

Table 21.2.13. Life cycle inventory for the incineration of 1 kg of IPA. [Data from reference 5].

CO_2 [kg]	2.20E+00
CO [kg]	2.26E-05
NO_x [kg]	2.59E-04
NMVOC [kg]	3.09E-06
Particulates [kg]	3.78E-05
Total emissions [kg]	2.21E+00

21.2.6 RESULTS

21.2.6.1 Optimization of Alternative A1: Distillation/incineration

As mentioned in Section 21.2.2, the main optimization variable of this alternative is the recovery of isopropyl alcohol in the first cut. The conceptual model for the distillation task was repeatedly solved until achieving the corresponding pseudo-steady state for "per-pass" recoveries of IPA in the interval [84-98%]. In all cases, the concentration of IPA in the first cut was set to 83 wt% (Table 21.2.1).

Equation 21.2.5 was iteratively solved in each case for the vapor flow rate V at the given value of the distillation processing time t_D of 20 h. Figure 21.2.11 graphically depicts the behavior of the vapor flow rate with the optimization variable. The minimum value for V corresponds to a "per-pass" recovery of IPA in the first cut of around 96%.

While Table 21.2.14 shows the design and operation variables obtained at the conceptual model level, Table 21.2.15 reports the corresponding investment and operation costs calculated from the cost model on a yearly basis. Among the operating costs, the

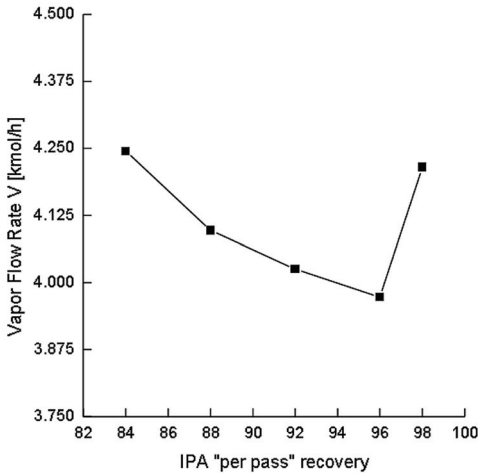


Figure 21.2.11. Vapor flow rate as a function of the "per-pass" recovery of IPA in the first cut. In all cases, t_D = 20 h and pseudo-steady state is achieved. [Adapted, by permission, from R. Meyer, D.A. Figueroa Paredes, M. Fuentes, A. Amelio, B. Morero, P. Luis, B. Van der Bruggen, and J. Espinosa, Conceptual model-based optimization and environmental evaluation of waste solvent technologies: Distillation/incineration versus distillation/pervaporation, Sep. Purif. Technol., **158**, 238 (2016)].

costs involved in transporting the concentrated distillate to the cement plant were estimated from parameters given in Table 21.2.5. Twenty-nine trips with a total traveled distance of 12760 km are required to cover the distance from the pharmaceutical plant to the cement kiln. Parameters needed to estimate the costs associated with the incineration of the distillate and with the biological disposal of the column residue are given in Table 21.2.6.

Table 21.2.14. Design and operation variables of the batch rectifier for different values of the "per-pass" recovery of IPA in the first cut. AlternativeA1: Distillation/incineration. [Adapted, by permission, from R. Meyer, D.A. Figueroa Paredes, M. Fuentes, A. Amelio, B. Morero, P. Luis, B. Van der Bruggen, and J. Espinosa, Conceptual model-based optimization and environmental evaluation of waste solvent technologies: Distillation/incineration versus distillation/pervaporation, *Sep. Purif. Technol*., **158**, 238 (2016)].

	IPA "per-pass" recovery [%]				
	84	**88**	**92**	**96**	**98**
Condenser area [m^2]	1.839	1.775	1.744	1.721	1.826
Evaporator area [m^2]	1.402	1.353	1.329	1.312	1.392
Horizontal vessel volume [m^3]	7.9	7.7	7.5	7.3	7.2
Packed height [m]	5.0	5.0	5.0	5.0	5.0
Packed diameter [m]	0.3048	0.3048	0.3048	0.3048	0.3048
Cooling water [m^3/year]	15213	14682	14424	14238	15105
Steam [kg/year]	578661	558486	548671	541583	574571

Table 21.2.15. Annualized investment and operating costs [U$S/year] for different values of the "per-pass" recovery of IPA in the first cut. Alternative A1: Distillation/incineration. [Adapted, by permission, from R. Meyer, D.A. Figueroa Paredes, M. Fuentes, A. Amelio, B. Morero, P. Luis, B. Van der Bruggen, and J. Espinosa, Conceptual model-based optimization and environmental evaluation of waste solvent technologies: Distillation/incineration versus distillation/pervaporation, *Sep. Purif. Technol.*, **158**, 238 (2016)].

	IPA "per-pass" recovery [%]				
	84	**88**	**92**	**96**	**98**
Column investment cost	64897	64613	64348	64084	64030
Column utilities cost	16079	15519	15247	15050	15966
Column residue disposal cost	19186	19186	19186	19186	19186
Transportation cost	10756	10756	10756	10756	10756
Incineration cost in cement kiln	85500	85500	85500	85500	85500
General cost	102580	102420	102270	102130	102100
Overall cost	298998	297994	297307	296706	297538
IPA to incineration [t/year]	473.8	473.8	473.8	473.8	473.8
Overall cost [U$S/t IPA]	631	629	627.5	626.2	628

Consistent with the results shown in Figure 21.2.11, the optimal recovery of isopropyl alcohol per batch is around 96%. However, as it is shown in Table 21.2.15, any of the design alternatives can be implemented since the differences in annualized costs are rather small. Note that for a batch time of 20 hours, the value that is large enough for the separation of the given feed amount, the rectifier processing capacity measured as its cross-sectional area could accommodate vapor flow rates as high as the double of the actual values. In other words, the separation could be accomplished in less time maintaining the same column. The cost of 296700 U$S/year is equivalent to a cost of 626 U$S/t IPA. Table 21.2.16 shows the mass balance in the pseudo-steady state, achieved after three days, corresponding to the optimal design. The feed charge is 5074 kg, and the amount of isopropyl alcohol sent to incineration is about 97.5% of the solvent contained in the fresh feed.

Table 21.2.16. Mass balance in the pseudo-steady state for the optimal design. Alternative A1: Distillation/incineration. [Adapted, by permission, from R. Meyer, D.A. Figueroa Paredes, M. Fuentes, A. Amelio, B. Morero, P. Luis, B. Van der Bruggen, and J. Espinosa, Conceptual model-based optimization and environmental evaluation of waste solvent technologies: Distillation/incineration versus distillation/pervaporation, *Sep. Purif. Technol.*, **158**, 238 (2016)].

	Column charge	**Cut_1**	**$Residue_1$**	**Cut_2 (Recycle)**	**$Residue_2$**
Overall amount [kmol]	228.28	36.57	191.71	3.26	188.45
IPA [mol/mol]	0.1001	0.6000	0.0048	0.1077	0.0030
Water [mol/mol]	0.8999	0.4000	0.9952	0.8923	0.9970

21.2.6.2 Optimization of Alternative A2: Distillation/pervaporation

According to the scheduling proposed in Figure 21.2.2, different separations were simulated with operation times for distillation and dehydration by pervaporation of 16 and 20 hours, respectively. The "per-pass" recovery of isopropyl alcohol in the batch rectifier was set at 92%, and variants with an IPA mole fraction in the first cut in the range [0.6-0.675] were analyzed. The composition of the distillate was selected as the main optimization variable to properly capture the cost trade-offs between the distillation column and the membrane unit.

Regarding the distillation task, Figure 21.2.5 depicts the time evolution of the primary variables calculated at the conceptual model level for an IPA mole fraction in the first cut of 0.65; that in turn is the optimal value from an economic point of view. The vapor flow rate V necessary to accomplish the desired separation in 16 hours is 5.359 kmol/h. The required number of theoretical stages and diameter of the rectifier are 13 and 0.3048 m, respectively. Table 21.2.17 shows the mass balances in the pseudo-steady state corresponding to this variant. Note that the charge to the column boiler (5568 kg) is composed by the fresh feed, the second cut and the condensed permeate from the membrane unit. Table 21.2.18 shows the corresponding mass balances in the pseudo-steady state for the IPA dehydration step in the membrane unit. The amount of isopropyl alcohol recovered in the product tank represents an overall recovery of 97.3% of the solvent contained in the fresh feed.

Table 21.2.17. Mass balance in the pseudo-steady state for the optimal design corresponding to the distillation step. Alternative 2: Distillation/pervaporation. [Adapted, by permission, from R. Meyer, D.A. Figueroa Paredes, M. Fuentes, A. Amelio, B. Morero, P. Luis, B. Van der Bruggen, and J. Espinosa, Conceptual model-based optimization and environmental evaluation of waste solvent technologies: Distillation/incineration versus distillation/pervaporation, *Sep. Purif. Technol*., **158**, 238 (2016)].

	Column charge	Cut_1	$Residue_1$	Cut_2 (Recycle)	$Residue_2$
Overall amount [kmol]	248.77	36.54	212.22	9.34	202.88
IPA [mol/mol]	0.1038	0.6500	0.0097	0.1543	0.0030
Water [mol/mol]	0.8962	0.3500	0.9903	0.8457	0.9970

Table 21.2.18. Mass balance in the pseudo-steady state for the optimal design corresponding to the purification step in the membrane unit. Alternative 2: Distillation/pervaporation. [Adapted, by permission, from R. Meyer, D.A. Figueroa Paredes, M. Fuentes, A. Amelio, B. Morero, P. Luis, B. Van der Bruggen, and J. Espinosa, Conceptual model-based optimization and environmental evaluation of waste solvent technologies: Distillation/incineration versus distillation/pervaporation, *Sep. Purif. Technol.*, **158**, 238 (2016)].

	Retentate vessel charge = Cut_1	Product	Permeate (Recycle)
Overall amount [kmol]	36.54	22.00	14.54
IPA [mol/mol]	0.6500	0.9949	0.1281
Water [mol/mol]	0.3500	0.0051	0.8719

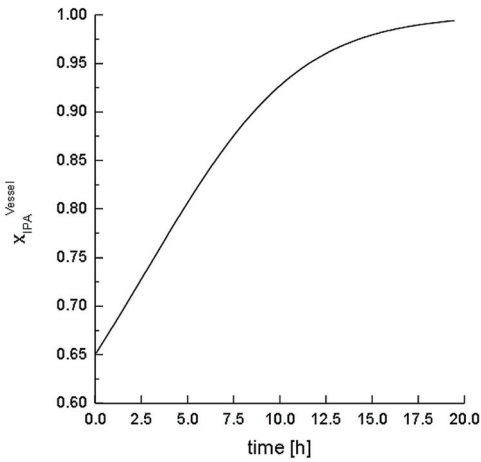


Figure 21.2.12. Evolution of the mole composition of isopropyl alcohol in the product tank corresponding to the optimal design. Alternative 2: Distillation/pervaporation. [Adapted, by permission, from R. Meyer, D.A. Figueroa Paredes, M. Fuentes, A. Amelio, B. Morero, P. Luis, B. Van der Bruggen, and J. Espinosa, Conceptual model-based optimization and environmental evaluation of waste solvent technologies: Distillation/incineration versus distillation/pervaporation, *Sep. Purif. Technol.*, **158**, 238 (2016)].

Figure 21.2.12 shows the simulation results of the purification step in the membrane unit corresponding to the feed charge reported in Table 21.2.18. Simulations in gPROMS[31] were done for different values of the membrane area until achieving an IPA purity equal to or greater than 99.4 mole percent (99.8 wt%) in a pervaporation processing time equal or lower than 20 hours. For the optimum variant the required area was 87.5 m^2. Modules of 17.5 m^2 each working in parallel were considered in order to maximize the driving force through the membrane along the batch time. Figure 21.2.8 in Section 21.2.3.2 shows the evolution of the temperature along the retentate side of the membrane unit corresponding to the optimal design.

Tables 21.2.19 and 20 show the results obtained at the conceptual model level and the cost model level, respectively. As mentioned above, the optimal IPA mole fraction in the first cut is about 0.65. At higher values there is a substantial increase in operating and investment costs of the column that does not outweigh the savings in membrane area caused by feeds with higher alcohol composition and lower amounts to be processed with respect to the rest of the designs studied. The cost of recovery for the optimal composition amounts to 856 U$S/t IPA, below the current purchase cost of IPA of 1200 U$S/t IPA reported in Table 21.2.6.

Table 21.2.19. Design and operation variables for different values of the IPA mole fraction in the first cut. Alternative A2: Distillation/pervaporation. [Adapted, by permission, from R. Meyer, D.A. Figueroa Paredes, M. Fuentes, A. Amelio, B. Morero, P. Luis, B. Van der Bruggen, and J. Espinosa, Conceptual model-based optimization and environmental evaluation of waste solvent technologies: Distillation/incineration versus distillation/pervaporation, *Sep. Purif. Technol.*, **158**, 238 (2016)]**.**

	IPA mole fraction			
	0.6	**0.625**	**0.65**	**0.675**
Column				
Condenser area [m^2]	2.351	2.355	1.693	1.645
Evaporator area [m^2]	1.792	1.795	1.290	1.254
Horizontal vessel volume [m^3]	7.36	7.36	7.36	7.36

Table 21.2.19. Design and operation variables for different values of the IPA mole fraction in the first cut. Alternative A2: Distillation/pervaporation. [Adapted, by permission, from R. Meyer, D.A. Figueroa Paredes, M. Fuentes, A. Amelio, B. Morero, P. Luis, B. Van der Bruggen, and J. Espinosa, Conceptual model-based optimization and environmental evaluation of waste solvent technologies: Distillation/incineration versus distillation/pervaporation, *Sep. Purif. Technol.*, **158**, 238 (2016)]**.**

	IPA mole fraction			
	0.6	**0.625**	**0.65**	**0.675**
Packed height [m]	5.0	5.5	8.0	14.0
Packed diameter [m]	0.3048	0.3048	0.3048	0.3048
Cooling water [m^3/year]	15556	15582	15364	16473
Steam [kg/year]	591720	592701	584413	626616
Membrane Unit				
Vessel [m^3]	3	2.95	2.9	2.86
Vacuum pump duty [kW]	1.60	1.59	1.46	1.44
Compressor duty [kW]	7.75	7.50	6.03	6.80
Permeate condenser area [m^2]	8.4	8.1	6.5	6.2
Retentate heater area [m^2]	1.05	1.01	0.81	0.77
Propane condenser area [m^2]	4.4	4.2	3.4	3.2
Membrane area [m^2]	105	105	87.5	87.5
Vacuum vessel volume [m^3]	5.3	5.3	4.7	4.7
Cooling water [m^3/year]	17776	16568	14851	13678
Steam [kg/year]	136577	124887	112790	101700
Energy consumption [kWh/year]	37846	35056	33529	30828

Table 21.2.20. Annualized investment and operating costs [U$S/year] for different values of the IPA mole fraction in the first cut. Alternative 2: Distillation/pervaporation. [Data from reference 11].

	IPA mole fraction			
	0.6	**0.625**	**0.65**	**0.675**
Pervaporation unit investment cost	126678	125938	113874	113139
Column investment cost	64585	66070	72674	87271
Column utilities cost	16442	16470	16239	17412
Column residue disposal cost	19188	19188	19188	19188
Pervaporation unit utilities cost	5084	4677	4214	3826
Pervaporation unit electricity cost	4640	4298	4110	3779

Table 21.2.20. Annualized investment and operating costs [U$S/year] for different values of the IPA mole fraction in the first cut. Alternative 2: Distillation/pervaporation. [Data from reference 11].

	IPA mole fraction			
	0.6	**0.625**	**0.65**	**0.675**
Membrane replacement cost	5308	5308	4423	4423
General cost	173077	173493	170448	178181
Overall cost	415002	415442	405170	427219
IPA recovered [t/year]	473	473	473	473
Overall recovery cost [U$S/t IPA]	877.4	878.3	856.6	903.2

21.2.6.3 Comparison between the treatment alternatives from an economic standpoint

Table 21.2.21 summarizes the economic figures obtained at the corresponding optimum for alternatives A1 and A2, respectively. The overall cost of each alternative, taking into account the cost of virgin solvent needed in each case, is also reported.

Annual earnings of the alternative A2 with respect to the alternative A1, considering savings due to the avoided purchase of fresh solvent and the avoided disposal cost of the spent solvent, amount 459000 U$S/year. Thus, considering an income tax rate of 35% and a 10% interest rate, a payback period of 2.2 years and an internal return rate of 33% is calculated for the recovery alternative. From these results, it is clear that the recovery alternative is financially advantageous.

Table 21.2.21. Overall costs [U$S/t IPA] for alternatives distillation/incineration and distillation/pervaporation at optimal designs including the purchase cost of virgin solvent. [Data from reference 11].

A1: Distillation/incineration	
Investment cost [U$S/year]	64084
Utilities cost [U$S/year]	34236
Transport cost [U$S/year]	10756
Incineration cost in cement kiln [U$S/year]	85500
General cost [U$S/year]	102130
Overall cost [U$S/year]	296706
Virgin solvent requirement [t IPA/year]	486
Overall cost including the purchase cost of virgin solvent [U$S/t IPA]	1810.5
A2: Distillation/pervaporation	
Investment cost [U$S/year]	186548
Utilities cost [U$S/year]	48175

Table 21.2.21. Overall costs [U$S/t IPA] for alternatives distillation/incineration and distillation/pervaporation at optimal designs including the purchase cost of virgin solvent. [Data from reference 11].

General cost [U$S/year]	170448
Overall cost [U$S/year]	405170
Virgin solvent requirement [t IPA/year]	13
Overall cost including the purchase cost of virgin solvent [U$S/t IPA]	865.8

21.2.6.4 Comparison between the treatment alternatives from environmental considerations

For alternative A1, Table 21.2.22 shows the input data necessary to estimate the environmental impacts corresponding to i) the production of virgin solvent, ii) the distillation task, iii) the biological disposal of the column residue, iv) the transportation of the distillate from the pharmaceutical plant to the cement kiln and v) the incineration task.

Table 21.2.23, on the other hand, summarizes the input data needed to calculate the environmental burden of alternative A2. Data for the following tasks are considered for the distillation/pervaporation alternative: i) virgin IPA production, ii) distillation, iii) pervaporation, iv) biological disposal and v) vacuum production with a vacuum pump/refrigeration system.

Table 21.2.22. Input data for LCA. Alternative A1: Distillation/incineration.
[Data from reference 11]

Overall mass balance per batch, one batch of 20 hours per day, 360 batches/year			
	Feed	*Distillate*	*Residue*
Overall Amount (kg/batch)	5000	1582.2	3417.8
Isopropyl alcohol (mass fraction)	0.27	0.8334	0.0092
Water (mass fraction)	0.73	0.1666	0.9908
Energy balance per batch, one batch of 20 hours per day, 360 batches/year			
Steam at 2 bar (kg/batch)	1504.4		
Cooling water (m^3/batch)	39.5		
Virgin solvent requirement (t/year)	486		
Transportation of the distillate from Pharmaceutical plant to Cement kiln			
Number of trips/year	29		
Distance/trip (km/trip)	440		
Fuel economy (km/L)	5		
Fuel consumption (L)	2552		

Table 21.2.23. Input data for LCA. Alternative A2: Distillation/pervaporation.
[Data from reference 11].

Overall mass balance per batch, one batch per day, 360 batches/year			
	Feed	*Product*	*Residue*
Overall Amount (kg/batch)	5000	1317.4	3682.6
Isopropyl alcohol (mass fraction)	0.27	0.9985	0.0094
Water (mass fraction)	0.73	0.0015	0.9906
Energy balance per batch, one batch per day, 360 batches/year			
Distillation Column (18 h/batch)			
Steam at 2 bar (kg/batch)	1623.4		
Cooling water (m^3/batch	42.7		
Membrane unit (19.45 h/batch)			
Steam at 2 bar (kg/batch)	313.3		
Cooling water (m^3/batch)	41.3		
Compressor electricity consumption (kWh/batch)	66.8		
Vacuum pump electricity consumption (kWh/batch)	25.1		
Circulating pump electricity consumption (kWh/batch)	1.2		
Virgin solvent requirement (t/year)	13		

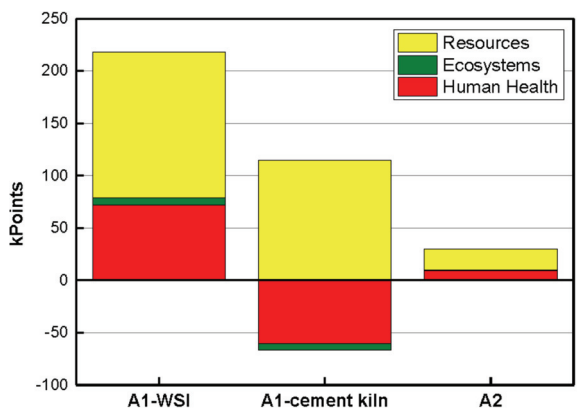


Figure 21.2.13. Environmental impact (ReCiPe 2008)[36] caused in endpoints categories human health, ecosystem and resources by alternatives A1 and A2. [Data from reference 11].

Figure 21.2.13 shows the environmental impact caused by the two treatment technologies considered at the endpoint level in category indicators damage to human health, damage to ecosystem diversity and damage to resource availability. The environmental burden associated with variant A1-WSI (i.e., distillation followed by off-site incineration in a conventional waste solvent incinerator) is also reported.

The results show that alternative A1-WSI generates the most significant impact. Alternative A1-cement kiln shows a burden on the availability of resources while bringing benefits for endpoints human health and ecosystem quality. On the other hand, alternative A2 does not show any benefit. However, its burden, in particular on resources availability, is rather small whether it is compared with those corresponding to both incineration alternatives mainly due to the almost complete recovery of IPA using the hybrid process distillation/pervaporation. For this alternative, the burden corresponding to the production of IPA is calculated from a virgin solvent requirement of 13 t IPA/year while burdens for the incineration variants must be estimated

from an IPA requirement amounting 486 t IPA/year. According to Table 21.2.12, a significant reduction in the cumulative energy demand is observed for the production of IPA in alternative A2 with respect to those in alternatives A1, as it is reduced in 29.6 E06 MJ/year.

For alternative A1-cement kiln, the burden on midpoint fossil fuel depletion is lower than that of alternative A1-WSI because in conventional incinerators additional energy is needed to burn the solvent. Moreover, a definite difference in results in favor of alternative A1-cement kiln can also be found in the category indicators at midpoint level climate change, human toxicity, and particulate matter formation. In line with these results, a positive effect on the environment is expected for this alternative because heavy fuel, hard coal, and their corresponding emissions are avoided.

Regarding the decision-making process, alternative A2 is the best choice from an environmental perspective if the designer is interested in minimizing the use of resources even when the hybrid process distillation/pervaporation produces a small impact regarding human health and ecosystem quality. On the other hand, when ecosystem quality and, in particular, human health are paramount, alternative A1 with incineration in a cement kiln is the best option. For the case study under consideration, we emphasize the importance of using and developing solvent recovery technologies to minimize the impact associated with solvent manufacture as noticed in several recent works in this field.[1,2,5,11,16]

21.2.7 DISCUSSION

Focusing the attention on the mixture isopropyl alcohol-water, quasi-optimal designs for the alternatives distillation/incineration and distillation/pervaporation were obtained from the conceptual design of the two waste solvent technologies. The main advantage of the conceptual design approach is that both process trade-offs and thermodynamic constraints of the mixture can be properly captured at a low computational cost. Indeed, pseudo-steady state solutions, which are normally neglected when the process is modeled by rigorous simulation, are easily handled in the conceptual modeling framework. Optimal values for “per-pass” recovery of isopropyl alcohol and distillate composition were determined for the first and second alternative, respectively. From the analysis of the economic figures, it was concluded that solvent recovery through the hybrid process is the best option mainly due to the savings in the purchase of virgin solvent.

The economic analysis was complemented by a life cycle assessment, with input data from the conceptual design step, as a tool to determine which technology is the most appropriate for the treatment of the waste solvent from an environmental standpoint. From the life cycle analysis, it was observed that the main impact on the environment was caused by the solvent production. The environmental impact caused by solvent recovery showed the lowest values regarding a total score indicating that the hybrid process the best option if minimization of the use of resources is paramount.

Regarding the performance assessment approach, it was concluded that life cycle analysis is enriched by input data obtained from the conceptual model-based process optimization of each alternative studied, especially regarding process knowledge and reliability of results.

However, a step forward must be taken in the proposed approach to incorporate in the analysis the recovery of different low-volume waste streams generated from multiple production campaigns with the same recovery system. Also, not only sharp but also sloppy splits considering partial recovery of solvents and, consequently, the incineration of the non-recovered fractions must be taken into account. In this way, implementation of the recovery system will become economically feasible while reducing the environmental impact of the pharmaceutical process. Table 21.2.24 summarizes the encouraging results recently obtained in this field by Savelski *et al*.[5]

Table 21.2.24 Economic evaluation of solvent recovery in selamectin, nelfinavir, and hydrocortisone processes. [Adapted, by permission, from M.J. Savelski, C.S. Slater, P.V Tozzi, and C.M. Wisniewski, On the simulation, economic analysis, and life cycle assessment of batch-mode organic solvent recovery alternatives for the pharmaceutical industry, *Clean Techn. Environ. Policy*, **19** (10), 2467 (2017)]**.**

Recovery scenario	Operating cost savings with respect to the current process using incineration as a mean of disposal (U$S/year)*	Payback period (year)	Internal return rate (%)
Selamectin (alone)	215000	8.8	8.7
Nelfinavir (alone)	80000	n/a	-1.3
Hydrocortisone (alone)	252000	7.9	11
Selamectin + Nelfinavir	314000	6.9	14.5
Selamectin + Hydrocortisone	486000	5.1	23.2
Selamectin + Nelfinavir + Hydrocortisone	584000	4.5	27.9

* Annual maintenance cost included in operating cost savings

21.2.8 ACKNOWLEDGEMENTS

José Espinosa dedicates this chapter to therapists and personnel of the Research and Rehabilitation Center “Doctor Esteban Laureano Maradona" for their outstanding work during his rehabilitation therapy from a cerebrovascular accident.

REFERENCES

1 P. Luis, A. Amelio, S. Vreysen, V. Calabro, and B. Van der Bruggen, Life cycle assessment of alternatives for waste-solvent valorization: batch and continuous distillation vs incineration, *Int. J. Life Cycle Assess*., **18**, 1048 (2013).

2 A. Amelio, G. Giuseppe, S. Vreysen, P. Luis, and B. Van der Bruggen, Guidelines based on life cycle assessment for solvent selection during the process design and evaluation of treatment alternatives, *Green Chem*., **16**, 3045 (2014).

3 C. Seyler, S. Hellweg, M. Monteil, and K. Hungerbühler, Life cycle inventory for use of waste solvent as fuel substitute in the cement industry: a multi-input allocation model, *Int. J. Life Cycle Assess.*, **10** (2), 120 (2004).

4 C. Seyler, T.B. Hofstetter, and K. Hungerbühler, Life cycle inventory for thermal treatment of waste solvent from chemical industry: a multi-input allocation model, *J. Clean Prod*., **13**, 1211 (2005).

5 M.J. Savelski, C.S. Slater, P.V Tozzi, and C.M. Wisniewski, On the simulation, economic analysis, and life cycle assessment of batch-mode organic solvent recovery alternatives for the pharmaceutical industry, *Clean Techn. Environ. Policy,* **19** (10), 2467 (2017).
6 I.M. Smallwood, **Solvent Recovery Handbook**, Second edition, *CRC Press*, Boca Raton, 2002.
7 A.M. Urtiaga, E.D. Gorri, and I. Ortiz, Pervaporative recovery of isopropanol from industrial effluents, *Sep. Purif. Technol*., **49**, 245 (2006).
8 K. Koczka, J. Manczinger, P. Mizsey, and Z. Fonyo, Novel hybrid separation processes based on pervaporation for THF recovery, *Chem. Eng. Process.*, **46**, 239 (2007).
9 C.S. Slater, M.J. Savelski, T.M. Moroz, and M.J. Raymond, Pervaporation as a green drying process for tetrahydrofuran recovery in pharmaceutical synthesis, *Green Chemistry Letters and Reviews*, **5** (1), 55 (2012).
10 P. Luis, A. Amelio, S. Vreysen, V. Calabro, and B. Van der Bruggen, Simulation and environmental evaluation of process design: Distillation vs. hybrid distillation–pervaporation for methanol/ tetrahydrofuran separation, *Applied Energy*, **113**, 565 (2014).
11 R. Meyer, D.A. Figueroa Paredes, M. Fuentes, A. Amelio, B. Morero, P. Luis, B. Van der Bruggen, and J. Espinosa, Conceptual model-based optimization and environmental evaluation of waste solvent technologies: Distillation/incineration versus distillation/pervaporation, *Sep. Purif. Technol*., **158**, 238 (2016).
12 M. Skiborowski, A. Harwardt, and W. Marquardt, Conceptual design of distillation based hybrid separation processes, *Annu. Rev. Chem. Biomol. Eng*., **4**, 45 (2013).
13 M.A. Sosa, D.A. Figueroa Paredes, J.C. Basílico, B. van der Bruggen, and J. Espinosa, Screening of pervaporation membranes with the aid of Conceptual Models: an application to bioethanol production, *Sep. Purif. Technol*., **146**, 326 (2015).
14 T.B. Hofstetter, C. Capello, and K. Hungerbühler, Environmentally preferable treatment options for industrial waste solvent management, a case study of a toluene containing waste solvent, *TransIchemE*, **81** (Part B), 189 (2003).
15 C. Capello, S. Hellweg, B. Badertscher, H. Betschart, and K. Hungerbühler, Environmental assessment of waste-solvent treatment options. Part I: The Ecosolvent tool, *J. Ind. Ecol*., **11** (4), 26 (2007).
16 A. Amelio, D.A. Figueroa Paredes, J. Degrève, P. Luis, B. Van der Bruggen, and J. Espinosa, Conceptual Model-Based Design and Environmental Evaluation of Waste Solvent Technologies: Application to the separation of the mixture acetone-water, *Sep. Sci. Technol*., **53** (11), 1791, (2018).
17 W. Marquardt, S. Kossack, and K. Kraemer, A Framework for the Systematic Design of Hybrid Separation Processes, *Chinese J. Chem. Eng*., **16**, 333 (2008).
18 J.A. Caballero, I.E. Grossmann, M. Keyvani, and E.S. Lenz, Design of hybrid distillation-vapor membrane separation systems, *Ind. Eng. Chem. Res.,* **48**, 9151 (2009).
19 K. Koch, D. Sudhoff, S. Kreiß, A. Górak, and P. Kreis, Optimisation-based design method for membrane-assisted separation processes, *Chem. Eng. Process. Process Intensif*., **67**, 2 (2013).
20 M. Skiborowski, J. Wessel, and W. Marquardt, Efficient Optimization-Based Design of Membrane-Assisted Distillation Processes, *Ind. Eng. Chem. Res*., **53**, 15698 (2014).
21 J. Espinosa, and J.L. Marchetti, Conceptual modeling and referential control applied to batch distillations, *Ind. Eng. Chem. Res.*, **46**, 6000 (2007).
22 K.A. Torres, and J. Espinosa, The influence of tangent pinch points on the energy demand of batch distillations: development of a conceptual model for binary mixtures, *Ind. Eng. Chem. Res*., **50**, 6260 (2011).
23 M.F. Doherty, and M.F. Malone, **Conceptual Design of Distillation Systems**, *McGraw-Hill Higher Education*, New York, 2001.
24 C. Bernot, M.F. Doherty, and M. F.; Malone, Design and operating targets for nonideal multicomponent batch distillation, *Ind. Eng. Chem. Res.*, **32**, 293 (1993).
25 Distil User Manual, *Hyprotech Ltd*., Calgary, Canada, 1999.
26 Aspen Batch Distillation & Aspen Hysys User Manual, Version 8, 2014.
27 I.M Mujtaba, and S. Macchietto, Holdup issues in batch distillation-binary mixtures, *Chem. Eng. Sci*., **53** (14), 2519 (1998).
28 G. Genduso, P. Luis, and B. Van der Bruggen, Overcoming any configuration limitation: an alternative operating mode for pervaporation and vapour permeation, *J. Chem. Technol. Biotechnol*., (2015)
29 T. Melin, and R. Rautenbach, **Membranverfahren: Grundlagen der Modul- und Anlagenauslegung**, 2nd ed., *Springer-Verlag*, Berlin, Heidelberg, New York, 2004.
30 M.A. Sosa, and J. Espinosa, Feasibility Analysis of Isopropanol Recovery by Hybrid Distillation/ Pervaporation Process with the Aid of Conceptual Models, *Sep. Purif. Technol*., **78**, 237 (2011).

31 gPROMS User Manual, *Process Systems Enterprise Ltd.*, 1998.
32 A. Fahmy, Membrane Processes for the Dehydration of Organic Compounds, Ph. D. Thesis, University of Hannover, Germany (2002).
33 G.L. Ding, Recent developments in simulation techniques for vapour-compression refrigeration systems. *Int. J. Refrig.*, **30**, 1119 (2007).
34 A.K. Coker, **Ejectors and Mechanical Vacuum Systems, Ludwig's Appl. Process Des. Chem. Petrochemical Plants**, 4th ed., *Elsevier*, Burlington, 2007.
35 W.D. Seider, J.D. Seader, and D.R. Lewin, **Product and Process Design Principles: Synthesis, Analysis, and Evaluation**, 2nd intern, *John Wiley & Sons*, New York, 2004.
36 M. Goedkoop, R. Heijungs, M. Huijbregts, A. De Schryver, J. Struijs, and R. Van Zelm, ReCiPe 2008: a life cycle impact assessment method which comprises harmonised category indicators at the midpoint and the endpoint level. Report I: Characterisation (2009).
37 SimaPro User Manual, Version 7.3, *PréConsultants*, 2001.
38 A.W. Sleeswijk, L.F. van Oers, J.B. Guinée, J. Struijs, and M.A. Huijbregts, Normalisation in product life cycle assessment: An LCA of the global and European economic systems in the year 2000. *Sci. Total Environ.,* **390**, 227 (2008).

21.3 SOLVENT RECOVERY, RECYCLING, AND INCINERATION

George Wypych
ChemTec Laboratories, Toronto, Canada

Distillation is a millennia old technology of solvent recovery used for various compositions of materials, including modern chemical processes. To take full advantage of natural resources distillation has to be carefully analyzed considering energy input required and costs and benefits of recovery. Optimal design of advanced distillation configuration for enhanced energy efficiency of waste solvent recovery process in semiconductor industry is one of the examples of developments.[1] A distillation process was used to recover waste solvent, reduce the production-related costs, and protect environment from the semiconductor industrial waste.[1] The conventional sequence of distillation columns was optimized using the Box and sequential quadratic programming method for the minimum energy use.[1] A heat pump-assisted distillation was implemented to improve the distillation performance achieving a significant energy savings of 40.5% compared to the conventional column sequence.[1] Figure 21.3.1 shows a complexity of the system.[1] The thermally coupling of columns 3 and 5 helped to enhance energy efficiency further improved by application of heat integration and heat pump to column 4.[1] The distillation technique was used to recover monoisopropanolamine, methyl diglycol, N-methylformamide, and 1-piperazine ethanol from the wastes of a photoresist stripper in the thin-film transistor light emitting diodes industry.[1]

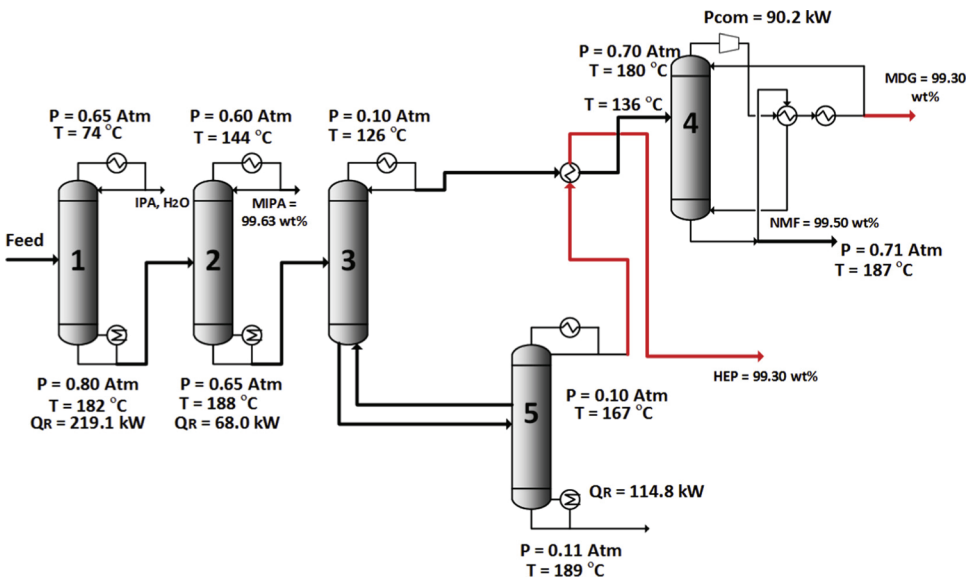


Figure 21.3.1. Solvent recovery from semiconductor wastes using heat integration and heat pump assisted distillation. [Adapted, by permission, from Y. D. Chaniago, L. Q. Minh, M. S. Khan, K.-K. Koo, A. Bahadori, M. Lee, *Ener. Conversion Manag.*, **102**, 92-103, 2015.]

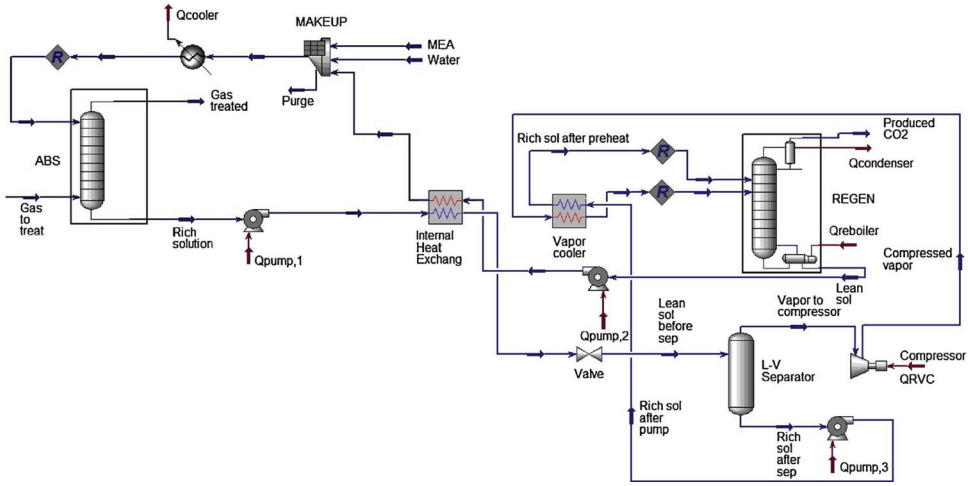


Figure 21.3.2. Aspen Hysys™ flow sheet for the Rich Vapor Compression (RVC) process configuration. [Adapted, by permission, from L. Dubois, D. Thomas, *Int. J. Greenhouse Gas Control,* **69**, 20-35, 2018.]

Carbon dioxide absorption is an integral part of many processes, such as natural gas or biogas to achieve heating value requirements, to prevent freezing in the low-temperature chillers in the production of liquefied natural gas, to avoid catalyst poisoning in the manufacture of ammonia, decrease global warming potential caused by carbon dioxide emissions, and obtaining supercritical liquid carbon dioxide.[2] Chemical absorption columns are most frequently implemented for this purpose.[2] Ammonia, monoethanolamine, diethanolamine, triethanolamine, 2-aminoethoxyethanol, diisopropanolamine, diethanolmethylamine use and recovery have been studied.[2] The higher the concentration of CO_2 absorbed, the lower the amount of solvent required.[2] The carbon dioxide diffusion in the aqueous solvent is related to the size of the absorption column required.[2]

The post-combustion CO_2 capture process in cement producing plants by absorption-regeneration is the more mature technology but its cost reduction is still required.[3] Three different solvents, namely monoethanolamine, piperazine, and piperazine-methyldiethanolamine blend have been studied. The heat pump modifications, namely LVC and RVC lead to the higher regeneration energy savings (from 11% to 18% depending on the solvent) while also reducing significantly the condenser cooling energy.[3] The best results in terms of the regeneration energy were obtained with the blend of 10 wt% monoethanolamine + 30 wt% piperazine using RVC configuration (Figure 21.3.2).[3]

A solvent for recovery of carbon dioxide from gaseous mixture contains alkanolamine, reactive amines acting as promoter or activators, sulfolane, and a carbonate buffer.[4]

Success of electric vehicles requires reduction of the cost of the lithium-ion battery. Drying the coated cathode layer and subsequent recovery of the solvent for recycle is a vital step in the lithium-ion battery manufacturing.[5] The energy demand for the process is very significant at 10.2 kWh per kg of n-methyl pyrrolidone vaporized, and 421 kWh per 10 kWh battery pack.[5] The overall energy demand is 45 times of the heat needed to vapor-

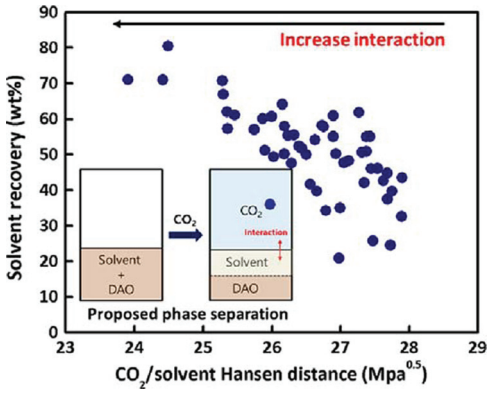


Figure 21.3.3. Solvent recovery improvement. [Adapted, by permission, from S. I. Im, S. Shin, J. W. Park, H. J. Yoon, K. S. Go, N. S. Nho, K B. Lee, *Chem. Eng. J*., **331**, 389-94, 2018.]

ize the n-methyl pyrrolidone.[5] The large energy demand is a result of the large quantity of air that has to be heated and cooled.[5] The cost of solvent recovery consists 3.4% of the total cost of production of battery.[5]

The solvent deasphalting process is a heavy oil upgrading process in which deasphalted oil is extracted from heavy oil feedstock by precipitating asphaltene using an excess amount of alkane solvent.[6] After the extraction, solvent recovery is carried out to separate the solvent from the deasphalted oil to recycle the expensive solvent.[6] Carbon dioxide was applied to selectively separate solvent from deasphalted oil at a relatively low temperature.[6] The temperature was decreased from 200°C to 40°C when using CO_2 compared to the conventional method.[5] The increase in the interaction between CO_2 and solvent causes the separation of solvent from deasphalted oil, leading to an increase in solvent recovery as can be deduced from verification based on Hansen distance calculations (Figure 21.4.3).[6] The numerical simulations indicate the possibility of continuous operation of solvent recovery using carbon dioxide.[6]

Oils and fats contain wide variety of chemical building blocks, including fatty acids, fatty acid esters, and fatty alcohols which can be used as a feedstock for the production of renewable materials.[7] An efficient recovery of non-polar extraction solvents is possible for a wide range of low-quality oils.[7] Commercially available PDMS membranes enable high solvent fluxes and rejection of triglyceride and fatty acids.[7] In deacidification experiments, a highly-selective separation of free fatty acids from triglycerides for long-chain and medium-chain oils can be achieved using polar solvents and available polyimide-based membranes.[7] A membrane performance can be accurately described by a (reduced) solution-diffusion model with imperfections, for which mass transfer of solvents and fatty acids is described by the convective contribution, while mass transfer of triglycerides is described by the diffusive contribution.[7]

A membrane vapor extraction efficiently recovers butanol from a dilute aqueous solution, such as, for example, from a fermentation broth.[8] In the membrane vapor extraction, feed and solvent liquids are not in contact; they are separated by vapor.[8] A semi-volatile aqueous solute, such as butanol vaporizes at the upstream side of a membrane, diffuses as a vapor through the membrane pores, and subsequently condenses and dissolves into a high-boiling nonpolar solvent, favorable to the solute but not to water.[8] Compared to the traditional distillation, the energy consumption with the membrane vapor extraction is minimal owing to essential cancellation of the enthalpies of feed vaporization and absorption by solvent.[8] Because transport across the membrane occurs in the vapor

phase rather than in the liquid phase, membrane-transport resistance is significantly reduced.[8]

A three-stage organic solvent nanofiltration process has been presented which comprises of a two-stage membrane cascade for separation with a third membrane stage added for integrated solvent recovery, i.e., solvent recycling.[9] The two-stage cascade gives an increased separation selectivity whereas the integrated solvent recovery stage mitigates the otherwise large solvent consumption of the purification.[9] This operation attains a purity of 98.7% through semi-continuous process with two washes of the solvent recovery stage.[9]

Extraction of vegetable oils results in a mixture of 70-75 wt% hexane and 25-30 wt% oil.[10] The organic solvent nanofiltration can be used to recover hexane from the crude mixture of soybean oil and hexane.[10] The fluoropolymer-based membranes are promising candidates in aliphatic solvent separation which permit oil rejection above 98%.[10]

The recycling and recovery of ionic liquids after the extraction of metal ions were investigated for trioctylmethyl ammonium camphorate and trioctylmethyl ammonium dodecanedioate.[11] The metal ions extracted were cadmium, copper, and lead with initial concentrations of 50 and 100 ppm.[11] The extraction percentage was above 90%.[11] The ionic liquid used was water immiscible.[11] The ionic liquids were successfully recovered by using solvents with polarity indices between 5.1 and 4.3 (ethanol, acetone).[11]

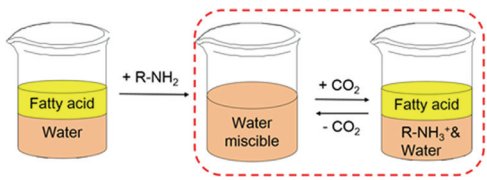


Figure 21.3.4. Illustration of the mechanism of action of a switchable solvent. [Adapted, by permission, from Q. Chen, L. Wang, G. Ren, Q. Liu, Z. Xu, D. Sun, *J. Colloid Interface Sci*., **504**, 645-51, 2017.]

The possibility of reusing an ionic liquid for the pretreatment of biomass has been investigated.[12] The presence of lignin and water within a pretreatment solvent resulted in a far less effective pretreatment process.[12] Ethyl-3-methylimidazolium acetate/ethanolamine (60/40 vol%) provided multiuse process with deterioration of the ionic liquid observed from considerably low sugar conversions and lignin extraction after using the 5th and 7th batch, respectively.[12]

Ion-pair interactions were explored to design a fatty acid solvent of switchable miscibility with water.[13] Fatty acids of medium-length chains are immiscible with water but become miscible when ion pairs are formed with amines.[13] The ion pairs become phase separated after bubbling CO_2 into the solution due to the dissociation of the fatty acid-amine complexes.[13] The switchable solvent mechanism was used in removing and recovering oily contaminants. Figure 21.3.4 illustrates the mechanism of action of a switchable solvent.[13]

Chlorinated volatile organic compounds, including polychloromethanes, polychloroethanes and polychloroethylenes, are or were used as solvents, degreasing agents in a variety of commercial products.[14] These compounds are ubiquitous contaminants that can be found in the contaminated soil, air, and any kind of fluvial medium such as groundwater, river, and lake.[14] The review article discusses various remediation technologies including thermal incineration, biodegradation, phytoremediation, ozonation, photocatalytic

oxidation, Fenton oxidation, electrochemical oxidation, zero valent metal and bimetal reduction, catalytic dehydrochlorination, and electrochemical reduction.[14]

Waste solvents are frequently incinerated for a partial recovery of their combustion heat.[15] The large chemical sites often have in-house waste incineration facilities but smaller enterprises outsource the treatment of their residuals which requires the special transfer of information about the contents of wastes.[15] A waste classification system developed in Switzerland is based on a heating value and on both water and pollutant content of the residues.[15] The generated knowledge is a crucial step in the design and operation of sustainable industrial waste incineration network, aimed at maximizing the energy efficiency while fulfilling technical and regulatory constraints.[15]

The substitution of combustion fuels in cement plants is increasing throughout many countries, and its individual performance is constantly assessed against strict regulatory standards.[16] The waste co-incineration reduced health-critical congeners of dioxins and dioxin-like polychlorinated biphenyls whilst providing the necessary energy and calcination needs.[16]

REFERENCES

1 Y. D. Chaniago, L. Q. Minh, M. S. Khan, K.-K. Koo, A. Bahadori, M. Lee, *Ener. Conversion Manag*., **102**, 92-103, 2015.
2 C. Mendez-Alvarez, V. Plesu, A. E. Bonet Ruiz, J. Bonet Ruiz, P. Iancu, J. Llorens, Proceedings of the 26th European Symposium on Computer Aided Process Engineering – ESCAPE 26, Portorož, Slovenia.
3 L. Dubois, D. Thomas, *Int. J. Greenhouse Gas Control,* **69**, 20-35, 2018.
4 P. B. R. K. Ausula, A. Sharma, **WO2014118633A3**, *Carbon Clean Solutions Pvt, Ltd*, Feb. 19, 2015.
5 S. Ahmed, P. A. Nelson, K. G. Gallagher, D. W. Dees, *J. Power Sources*, **322**, 169-78, 2016.
6 S. I. Im, S. Shin, J. W. Park, H. J. Yoon, K. S. Go, N. S. Nho, K B. Lee, *Chem. Eng. J*., **331**, 389-94, 2018.
7 K. Werth, P. Kaupenjohann, M. Knierbein, M. Skiborowski, *J. Membrane Sci.*, **528**, 369-80, 2017.
8 J. Chen, N. Razdan, T. Field, D. E. Liu, P. Wolski, X. Cao, J. M. Prausnitz, C. J. Radke, *J. Membrane Sci.,* **528**, 103-11, 2017.
9 M. Schaepertoens, C. Didaskalou, J. F. Kim, A. G. Livingston, G. Szekely, *J. Membrane Sci*., **514**, 646-58, 2016.
10 X. Li, W. Cai, T. Wang, Z. Wu, J. Wang, X. He, J. Li, *Separation Purification Technol*., **181**, 223-9, 2017.
11 M. A. Valdes Vergara, I. V. Lijanova, N. V. Likhanova, O. O. Xometl, D. Jaramillo Vigueras, A. J. Morales Ramirez, *Separation Purification Technol.*, **155**, 110-7, 2015.
12 P. Weerachanchai, J.-M. Lee, *Bioresource Technol*., **169**, 336-43, 2014.
13 Q. Chen, L. Wang, G. Ren, Q. Liu, Z. Xu, D. Sun, *J. Colloid Interface Sci*., **504**, 645-51, 2017.
14 B. Huang, C. Lei, C. Wei, G. Zeng, *Environ. Int.*, **71**, 118-38, 2014.
15 V. Bolis, E. Capon-García, O. Weder, K. Hungerbühler, *J. Cleaner Prod.*, **183**, 1228-40, 2018.
16 G. Richards, I. E. Agranovski, *J. Hazard. Mater.*, **323**, 698-709, 2017.

21.4 APPLICATION OF SOLAR PHOTOCATALYTIC OXIDATION TO VOC-CONTAINING AIRSTREAMS

K. A. Magrini, A. S. Watt, L. C. Boyd, E. J. Wolfrum, S. A. Larson, C. Roth, G. C. Glatzmaier
National Renewable Energy Laboratory, Golden, CO, USA

21.4.1 SOLVENT DEGRADATION BY PHOTOCATALYTIC OXIDATION

Photocatalytic solvent oxidation had been demonstrated at the pilot scale in two field tests located at McClellan Air Force Base (AFB) in Sacramento, California and at the Fort Carson U. S. Army Installation in Colorado Springs, Colorado (Watt *et al*., 1999; Magrini *et al*., 1998). The objective of the tests was to determine the effectiveness of solar-powered photocatalytic oxidation (PCO) treatment units for destroying emissions of chlorinated organic compounds (trichloroethylene and dichloroethylenes) from an air stripper at ambient temperature and destroying paint solvent emissions (toluene and MEK) from a painting facility at higher temperatures. Goals for field testing these solar-driven systems were to gather real-world treatability data and establish that the systems maintained performance during the duration of the testing.

The photocatalytic oxidation process can effectively destroy hazardous organic pollutants in air and water streams. Although treatment systems will vary depending on the type of stream being treated, the basic process remains the same. The key ingredient is the photoactive catalyst titanium dioxide (TiO_2), which is an inexpensive, non-toxic material commonly used as a paint pigment. When TiO_2 is illuminated with lamps or natural sunlight, powerful oxidizing species called hydroxyl radicals form. These radicals then react with the organic pollutant to tear it apart and ultimately form carbon dioxide (CO_2) and water (Phillips and Raupp, 1992). When halogenated organics are treated, dilute mineral acids like HCl form. The process works at both ambient and mildly elevated temperatures (>200°C) (Fu *et. al.*, 1995; Falconer and Magrini, 1998).

Researchers throughout the world have been investigating PCO as an advanced oxidation technology for treating air and water streams contaminated with a variety of organic and inorganic compounds (Blake, 1996; Cummings *et al.*, 1996). The susceptibility of an organic species to complete oxidation is typically reported in terms of photoefficiency, defined as the number of molecules of contaminant oxidized to carbon dioxide, water, and simple mineral acids divided by the number of photons incident on the catalyst. These values vary widely, depending on the reactor design, catalyst geometry and the compound of interest.

Much of the work on photocatalytic oxidation focuses on treating the halogenated organics trichloroethylene (TCE) and perchloroethylene, contaminants commonly found in ground water sources. These compounds and other chlorinated ethylenes typically react rapidly with TiO_2 and photons at efficiencies greater than 100%. These rates are likely due to chain reactions propagated by chlorine radicals (Luo and Ollis, 1996; Nimlos *et. al.* 1993; Yamazaki-Nishida, 1996). Paint solvent emissions generally consist of toluene,

xylenes, ketones and acetate vapors. Measured photoefficiencies for benzene and other aromatic compounds like toluene are typically less than 5% (Gratson *et. al.*, 1995; d'Hennezel and Ollis, 1997). Besides exhibiting low photoefficiencies, aromatic species tend to form less reactive, nonvolatile intermediates during gas phase PCO. These intermediates build up on the catalyst surface and block or inhibit the active catalytic sites for further reaction (Larson and Falconer, 1997). The addition of heat and small amounts of platinum to the TiO_2 catalyst overcome these problems (Falconer and Magrini, 1998; Fu *et. al.*, 1996). Oxygenated organics such as ethanol and acetone have photoefficiencies typically around 1-10% (Peral and Ollis, 1992).

Several field demonstrations of PCO using sunlight to treat groundwater contaminated with TCE have been reported (Mehos and Turchi, 1993; Goswami *et. al.*, 1993). These field tests found that nontoxic constituents in the water can non-productively react with or "scavenge" the photogenerated hydroxyl radicals and reduce the rate of the desired reaction. Common scavengers such as humic substances and bicarbonate ions increase treatment costs for the technology (Bekbolet and Balcioglu, 1996). Turchi and co-workers, (1994) found that by air stripping the volatile contaminants from the water stream, the regulated compounds at many contaminated sites could be transferred to the air, leaving the radical scavengers behind. The water can then be safely discharged and the air effectively treated with PCO. The improved photoefficiency reduces treatment costs and more than offsets the added cost of air stripping these contaminants from water. Read *et. al.*, (1996) successfully field tested a lamp-driven, PCO system on chloroethylene vapors from a soil vapor extraction well located at DOE's Savannah River Site. Magrini *et al.*, 1996, and Kittrell *et al.*, 1996, both used modified TiO_2 catalysts and lamp-driven reactors to treat VOCs representative of semiconductor manufacturing and contact lens production, respectively. 1,2-dichloroethane, stripped from contaminated groundwater, was successfully treated in a pilot scale PCO demonstration at Dover AFB (Rosansky *et al.*, 1998).

The second field test assessed PCO to treat paint solvent vapors. Painting operations for military and civilian vehicles are conducted in ventilated enclosures called paint booths. Filters in the exhaust ducts trap paint droplets from the paint overspray while the VOC-laden air is typically exhausted through roof vents. The vent emissions can contain several hundred parts per million (ppm) of the paint solvents, which continue to evaporate from the vehicle after painting is complete. Most types of paint generally contain significant amounts of VOCs such as toluene, a suspected carcinogen, as well as other hazardous solvents such as methyl ethyl ketone, methyl isobutyl ketone, hexanes, xylenes, n-butyl acetate, and other components in lesser amounts.

Current technologies for treating these emissions include catalytic combustion of the vapors over supported Cu and Cr-oxides at temperatures of 350°C (Estropov *et. al,* 1989); air-flow reduction and recirculation strategies (Ayer and Darvin, 1995); and regenerative thermal oxidation at near incineration temperatures (Mueller, 1988). The use of platinized TiO_2 and temperatures of 180-200°C provide significant energy savings in treating these emissions. Our goals for testing the paint booth emissions was to gather real-world treatability data and establish that the system maintained performance during the duration of the testing.

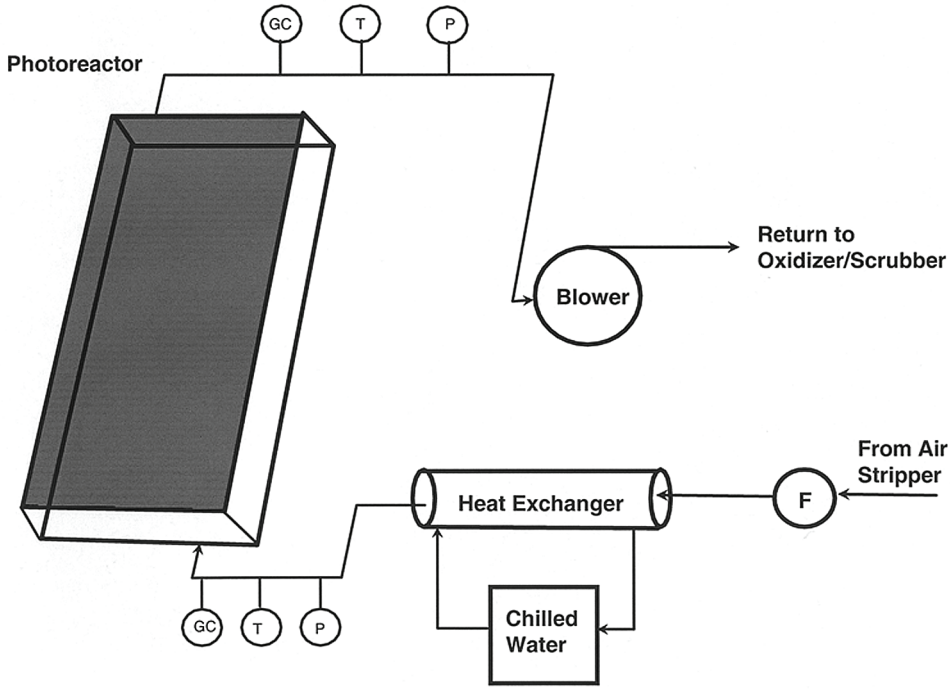


Figure 21.4.1. Schematic of the 10 SCFM solar photoreactor system used at McLellan AFB.

21.4.2 PCO PILOT SCALE SYSTEMS

21.4.2.1 Air stripper application

Figure 21.4.1 shows a schematic of the pilot-scale system used at McClellan AFB. This system, scaled from an optimized laboratory reactor, was fabricated by Industrial Solar Technology Corporation (Golden, CO). The reactor, 1.22 m wide by 2.44 m, consisted of a fiberglass-reinforced plastic I-beam frame. A transparent fluoropolymer film, treated to accept adhesives, formed the front and back windows of the reactor. The film windows were attached to the reactor frame with foam tape coated on both sides with an acrylic adhesive. The catalyst, titanium dioxide (Degussa P25), was coated onto a structured, perforated polypropylene tubular packing commonly used in oil-water separators. The TiO_2 was suspended in water as a slurry and sprayed onto the tubular supports with a new paint sprayer until the supports were opaque. Fluid modeling of airflow through the reactor showed that a 5.1 cm PVC manifold, located at the inlet and outlet of the reactor, would provide an even flow distribution. Small (0.6 cm) holes, drilled into the manifold at one inch intervals, provided the even flow distribution required for efficient contact of the contaminated air with the catalyst.

A two-inch diameter pipe from the outlet of the air stripper supplied the contaminated air stream to the reactor. The air stream was first passed through to a tube-in-shell

heat exchanger for partial dehumidification. A chiller circulated 2°C ethylene glycol through the tube side of the heat exchanger. Chilling, which reduced the relative humidity of the air stream from near saturation to less than 20% at 20°C, was required because high humidity reduces the TCE destruction rate, likely because of competitive adsorption between moisture and TCE molecules at the catalyst surface (Fan and Yates, 1996). By lowering the humidity to less than 20% at 20°C, the reaction rate was sufficient to ensure complete TCE destruction. This effect was observed by Hung and Marinas (1997) in a lamp-illuminated annular reactor in which TCE conversion was not affected by relative humidity up to 20%; conversion deteriorated as the humidity level reached saturation. Laboratory tests of the system demonstrated that at TCE concentrations of near 100 ppmv, less than 15% of the TCE in the airstream transferred to the condensate formed in the heat exchanger. The condensate (approx. 1-2 liters per day) could be fed back into the air stripper for treatment.

On the reactor, GC sample ports and temperature and pressure sensors provided monitoring of reactor inlet and outlet VOC concentrations and temperature and pressure drop throughout the system. A portable gas chromatograph provided on-line VOC organic analysis of the inlet and outlet air streams. A portable light intensity monitor was used to measure the global horizontal light intensity at the surface of the photoreactor. The calibrated radiometer was mounted on the reactor framework which faced south at an angle of 40° to the horizon. Two blowers in series were used to draw contaminated air into the system. The blowers were located at the end of the air handling system so that the entire system was maintained under slight negative pressure. Because TCE oxidation can produce intermediates such as phosgene, (Nimlos *et. al,* 1993; Read *et. al.,* 1996; Fan and Yates, 1996), keeping the system under vacuum prevented release of any toxic vapors. The exhaust gases from the blower were returned for final treatment by a caustic contacting tower. Any hydrochloric acid and phosgene formed from TCE oxidation were neutralized and hydrolyzed respectively by the caustic scrubber.

The contaminated airstream provided by the air stripper unit contained volatile organic compounds as analyzed from Summa canister tests by Air Toxics, Ltd. using EPA method TO-14. These compounds, listed in Table 21.4.1, consisted primarily of trichloroethylene and trace quantities of dichloromethane, 1,1-dichloroethene, cis-1,2-dichloroethane, chloroform, carbon tetrachloride, and benzene. The other compounds present in the outlet presumably formed during treatment.

Table 21.4.1. Results from the Summa canister tests of inlet and outlet reactor air streams during the McClellan tests. The two inlet and two outlet samples were taken sequentially and represent approximately replicate samples.

Compound	Inlet 1, ppbv	Inlet 2, ppbv	Outlet 1, ppbv	Outlet 2, ppbv	Detection limit, ppbv
Chloromethane	ND	ND	4.8	4.1	1.5-30
Dichloromethane	36	36	30	32	1.5-30
1,1-Dichloroethane	ND	ND	17	17	1.5-30
1,1-Dichloroethene	200	200	ND	ND	1.5-30

Table 21.4.1. Results from the Summa canister tests of inlet and outlet reactor air streams during the McClellan tests. The two inlet and two outlet samples were taken sequentially and represent approximately replicate samples.

Compound	Inlet 1, ppbv	Inlet 2, ppbv	Outlet 1, ppbv	Outlet 2, ppbv	Detection limit, ppbv
cis-1,2-Dichloroethane	220	240	6	2.2	1.5-30
Chloroform	250	260	280	280	1.5-30
Carbon tetrachloride	700	730	790	790	1.5-30
Benzene	170	190	120	110	1.5-30
1,2-Dichloroethane	ND	ND	12	ND	1.5-30
Trichloroethylene	13,000	13,000	660	280	1.5-30
Acetone	ND	ND	84	69	9.8-120
1,4-Dioxane	ND	ND	10	ND	9.8-120

21.4.2.2 Paint booth application

For the paint solvent application, a slipstream of a paint booth vent located at Fort Carson was analyzed to determine the components present with rapid scan gas chromatograph. On any operational day, several paint types are sprayed. The solvent emissions content thus varies during painting operations. In general, the amounts and types of solvent emissions from the Fort Carson paint booth are listed in Table 21.4.2.

Table 21.4.2. Breakdown of solvent emissions from painting operations at Fort Carson in 1994. VOC refers to volatile organic compounds, HAP to hazardous air pollutants, MEK to methyl ethyl ketone, and MIBK to methyl isobutyl ketone

Paint type	Total usage lbs/yr	VOC lbs/yr	HAP lbs/yr	MEK lbs/yr	Toluene lbs/yr	MIBK lbs/yr	Xylene lbs/yr
Solvent base	19,656	110,074	5,405	3,931	491	0	983
Thinner	983	7,235	722	552	0	174	0

A small field test system, consisting of a photoreactor packed with Degussa TiO_2-coated glass beads, was used to assess treatability of the slipstream and provide design data for the pilot scale system. The small reactor operated with a flow rate of 20 liters/minute provided by a pump connected to the paint booth exhaust vent line and variable reactor temperature (ambient to 200°C). Inlet and outlet VOC concentrations were simultaneously measured by two gas chromatographs directly connected to both lines. This arrangement provided real time monitoring of the inlet and outlet VOC concentrations during painting operations.

The resultant treatability data was used to size a 5-SCFM pilot-scale system (Figure 21.4.2) also built by Industrial Solar Technologies. This system consists of a parabolic trough reflector to focus incident sunlight onto a receiver tube containing the catalyst. The trough has a 91 cm aperture width and is 243 cm long. The reflective surface is covered

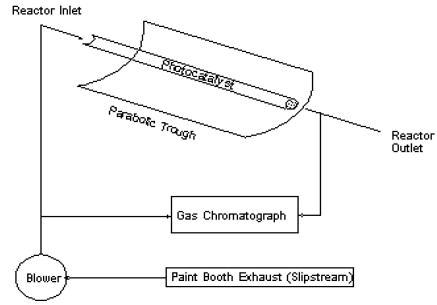


Figure 21.4.2. Schematic of the 10 SCFM parabolic trough, solar photoreactor system used at Fort Carson U. S. Army Installation.

with SA-85 (3M Company), a polymer film that reflects greater than 90% of the incident radiation onto the catalyst tube, providing both heat and light for reaction. The catalyst-containing receiver tube is a 3.81 cm I.D. borosilicate tube packed with 1.9 cm ceramic berl saddles coated with 2.0 wt% platinum on TiO_2. A higher weight loading of platinum was used in the field test because of the variable VOC composition of the paint booth stream. Operating temperatures of 200°C were obtained, depending on cloud cover, during most of the day. Note that a thermally heated, lamp-illuminated system will provide similar performance as the solar-based system described here. The reflective trough rotates around the fixed receiver tubes by means of a gear motor. A control and photodiode arrangement activate the gear motor, permitting the trough to track the sun throughout the day. Paint booth emissions were sampled directly from the exhaust stream via 10.1 cm aluminum ducting. On-line analysis of the inlet and outlet concentrations was provided by sample lines connected to the MTI gas samplers. Reactor temperature and inlet flows were measured continuously.

21.4.3 FIELD TEST RESULTS

21.4.3.1 Air stripper application

The field test at McClellan AFB took place during a 3-week period in April, 1997. System operating conditions included two flow rates (10 and 20 SCFM) and variable light intensity. The photoreactor system, designed to perform optimally at 10 SCFM with natural sunlight, was also operated at 20 SCFM to challenge the system. Because of varying solar illumination levels during the day, the system can operate for longer periods at lower flow rates. Residence times in the reactor at 10 and 20 SCFM were 0.50 sec and 0.25 sec, respectively.

Figure 21.4.3 shows TCE conversion and UV intensity versus illumination time at 10 SCFM for two days of operation. UV intensities were measured with a UV radiometer (UHP, San Gabriel, CA, Model UHX). TCE inlet concentrations varied from 10-15 ppmv. Detection limits for the gas chromatograph were measured at 0.5 ppmv. Figure 21.4.3 indicates that conversions greater than 95% at 10 SCFM are achieved with UV intensities at or greater than 1.5 mW/cm^2. At 10 SCFM, continuous destruction greater than 95% was achieved for at least 6 hours per day on two clear days in April at this latitude (37°N). The

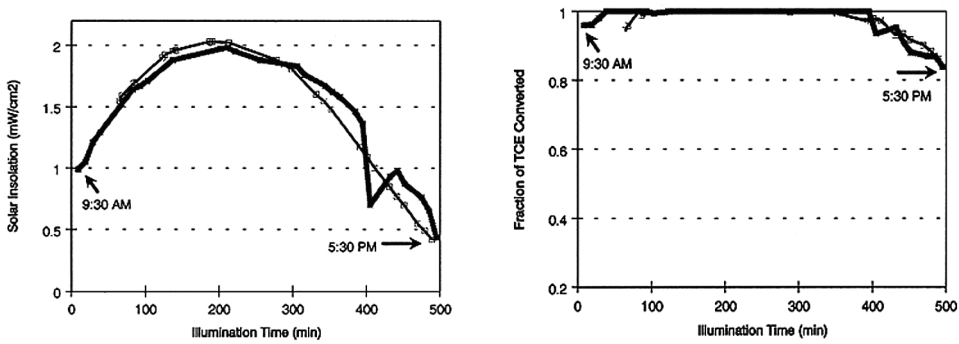


Figure 21.4.3. Solar insolation (left) and fractional TCE conversion (right) versus illumination time. Flow rate and relative humidity of the incoming air stream was 10 SCFM at 20% RH. Data taken on April 8-9, 1997.

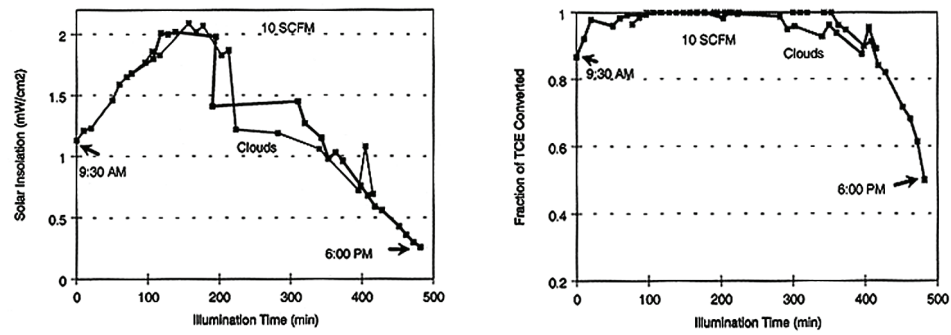


Figure 21.4.4. Solar insolation (left) and fractional TCE conversion (right) versus illumination time during periods of partial cloud cover. Flow rate and relative humidity of the incoming stream was 10 SCFM and 20% RH. Data taken on April 7 and April 16, 1997.

length of operation for a solar-driven system will vary with time of year, latitude, and altitude due to the effect each parameter has on available solar-UV intensity.

Figure 21.4.4 shows the effect of clouds on solar insolation (left) and TCE conversion (right) as a function of illumination time at 10 SCFM for two separate days. Again TCE conversions greater than 95% were obtained when the insolation levels were greater than 1.5 mW/cm^2. In general, clear skies had UV intensities of 2 mW/cm^2 or better. Haze and high clouds reduced the intensity to 1.5 mW/cm^2, and thicker clouds reduced available intensity to about 1 mW/cm^2. Conversions greater than 90% were still achievable during periods of significant cloud cover due to the photoreactor's ability to use global horizontal (diffuse) UV illumination.

TCE conversion versus solar insolation for three days of operation at 20 SCFM is shown in Figure 21.4.5. Doubling the flow rate halves the residence time of the gas in the photoreactor. Conversions greater than 95% are achieved with UV intensities greater than 2.0 mW/cm^2. The reproducibility of TCE conversion indicates that the little or no catalyst deactivation occurred during the three weeks of testing.

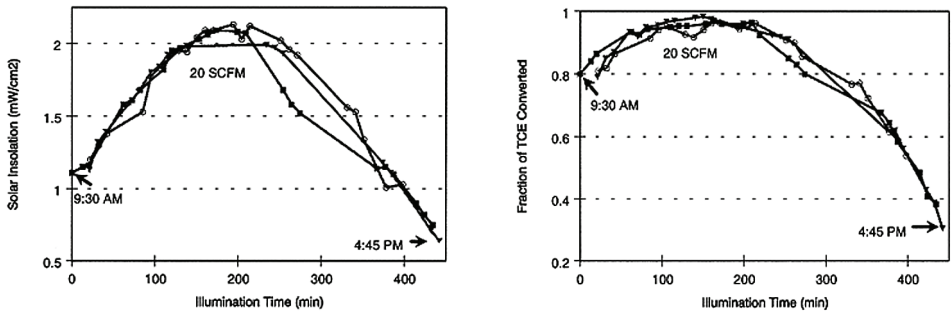


Figure 21.4.5. Solar insolation (left) and fractional TCE conversion (right) versus illumination time. Flow rate and relative humidity of the incoming air stream was 20 SCFM at 20% RH. Data taken on April 10, 14, and 15, 1997.

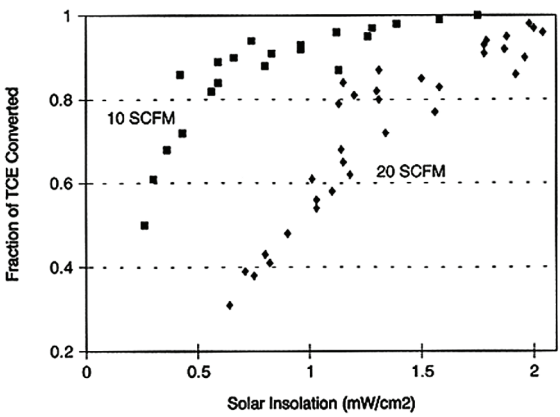


Figure 21.4.6. Pooled UV intensity versus TCE conversion data for all 10 SCFM and 20 SCFM runs.

Pooling all of the data taken at the two flow rates provides a relation between TCE conversion and UV intensity (Figure 21.4.6). Significant scatter, which exists for both flow rates, is likely due to the rapidly varying UV intensity levels during cloud events. The variable illumination makes it difficult to establish a precise correlation between an isolated UV measurement and the UV exposure received by the gas as it flows through and reacts with the photocatalyst bed. The 10 SCFM data suggests a square root relationship between UV intensity and conversion. The square root dependence was observed in a continuous flow reactor when TCE concentrations were less than 60 ppmv (Nimlos *et. al*., 1993). Higher concentrations yielded an approximately linear dependence.

On the last day of testing, grab samples were collected in Summa canisters and delivered to a local analytical laboratory (Air Toxics, Ltd., Folsom, CA) for TO-14 analysis to confirm the analyses provided by the MTI gas chromatographs and to provide outlet TCE concentrations that were below our GCs detection limits. Replicate samples were reported as 13,000 ppbv for TCE in inlet air, and 280 and 660 ppbv TCE in the outlet (Table 21.4.1). This corresponds to 97.8% and 94.9% removal of TCE.

The reactor outlet airstream contained most of the dichloromethane and carbon tetrachloride present in the inlet stream. This result was expected, as single carbon haloorganics do not easily photooxidize (Jacoby *et. al*, 1994). Nearly all of the 1,1-dichloroethene and *cis*-1,2-dichloroethane were destroyed (destruction efficiencies of 97.3% and 99.1%

respectively). This too was expected, as dichlorinated ethanes and ethenes photooxidize almost as rapidly as TCE.

Small amounts (<20 ppbv) of chloromethane, 1,1-dichloroethane, 1,2-dichloroethane and acetone, and 1,4-dioxane appeared in the reactor outlet and are likely reaction intermediates from TCE oxidation.

About 40% of the benzene in the inlet stream did not come out of the reactor. This result is in line with recent results in which benzene was oxidized with a sol-gel TiO_2 catalyst (Fu, X. *et. al.*, 1995). Though not all of the benzene reacted, that which did formed only CO_2 and H_2O. Adding platinum to the TiO_2 sol significantly improved benzene oxidation. Transient reaction studies of benzene and Degussa TiO_2 thin films indicate that benzene oxidizes rapidly at 300K to form strongly bound surface intermediates that oxidize very slowly (Larson and Falconer, 1997). Other work with thin films of TiO_2 and benzene shows that benzene does not form intermediates when water vapor is present. In the absence of water, acetone forms and the catalyst becomes coated with a durable brown material (Sitkiewitz, S. and Heller, A., 1996). Because these tests were run at an average of 20% RH and the catalyst exhibited stable activity, it is likely that benzene was oxidized. Thus, since the catalyst activity did not deteriorate over the course of testing, it may be possible that low concentrations of aromatic species can be tolerated and treated in a solar photocatalytic reactor. It is also possible that the benzene was absorbed by the catalyst support material.

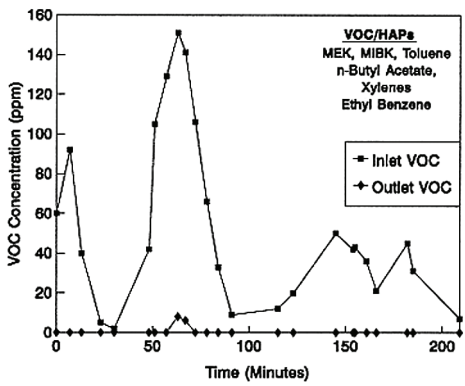


Figure 21.4.7. Inlet and outlet VOC concentrations from the Fort Carson paint booth using the small, lamp-driven, field test reactor.

21.4.3.2 Paint booth application

Figure 21.4.7 shows the real time test results using the lamp-driven, small field scale reactor for treating VOC emissions from painting operations at Fort Carson. The inlet and outlet VOC concentrations are given in ppm. Test data begins at 8:10 AM on June 25, 1996 and ended at 11:55 for this run. The painting operations are conducted in a batch mode. Vehicles are placed in the paint booth, painted, then removed from the booth to the parking area, where they dry. The mixture of VOCs emitted from the aliphatic polyurethane green military paint being sprayed consisted of methyl ethyl ketone, methyl isobutyl ketone, toluene, n-butyl acetate, xylenes, and ethyl benzene. When the reactor reached an operating temperature of 170°C, complete VOC destruction was achieved for the entire run except for a period of peak VOC emissions beginning at 9:30 and ending at 9:45. Thus, during this four hour period, the PCO process destroyed virtually all of the VOCs in the slip stream from the paint booth exhaust. The total time averaged conversion is estimated to be greater than 95%. These data were used to design the solar-driven, photothermal reactor system.

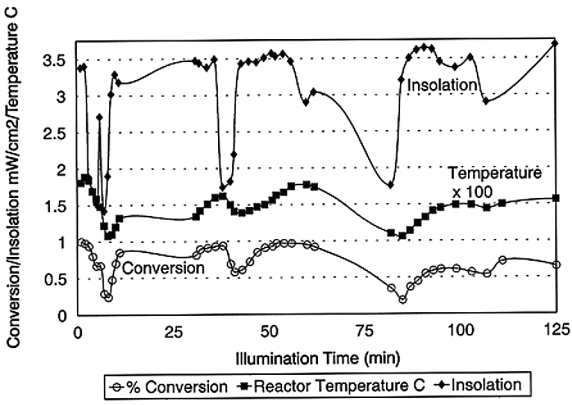


Figure 21.4.8. The effect of sunlight fluctuations on the photothermal destruction of methyl ethyl ketone in the parabolic trough, photothermal reactor. MEK conversion, insolation level, and reactor temperature are plotted as a function of continuous outdoor illumination time.

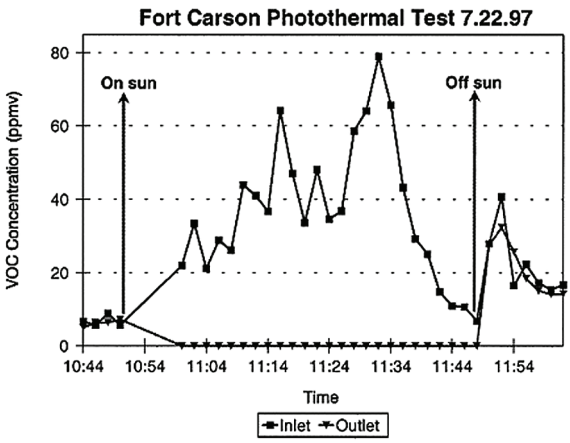


Figure 21.4.9. VOC concentration from paint solvents as a function of illumination time during photocatalytic treatment with a concentrating, parabolic trough, solar photoreactor.

Based on the lamp tests, the 5-SCFM thermal photoreactor system was tested with methyl ethyl ketone (MEK), a paint solvent surrogate. Figure 21.4.8 shows the results of on-sun testing with this system. The Y-axis plots three factors: temperature in ^{o}Cx100 MEK, conversion as a fraction with 1 equaling 100% conversion, and solar insolation as mW/cm^2. The X-axis plots illumination time in minutes. This test was performed on a hazy day with numerous clouds to evaluate the system under challenging conditions. Though conversion and reactor temperature parallel the insolation, they do so in a less than 1:1 ratio. This is likely due to the square root dependence of reaction rate on light intensity and to the heat transfer (insulative) characteristics of the ceramic support. 100% conversion was achieved when insolation levels were above 3.5 mW/cm^2 and reactor temperatures above 175°C.

The photothermal reactor was tested in July, 1997 for three weeks on paint booth emissions using natural sunlight. A representative data set for July 22, 1997 is shown in Figure 21.4.9 in which the total VOC concentration for the inlet and the outlet of the parabolic trough, photothermal reactor is plotted against illumination time. The solvent stream, which varied with time, generally contained about 140 ppmv of toluene, methyl ethyl ketone, methyl isobutyl ketone, xylenes, butyl acetate and ethyl benzene. The operating temperature was from 190 to 208°C, dependent on available illumination. On-sun refers to turning the concentrating receiver into the sun, which initiates heating and photoreaction. Off-sun refers to turning the receiver away from the sun (photoreaction and heating stops). Inlet and outlet VOC concentrations, which matched closely when the reactor was off-sun, were taken to ensure that thermal reaction as the

reactor cooled and adsorption of contaminants onto the catalyst surface were not significant. No attempt was made to decouple photoreaction from thermal reaction because of rapid temperature changes when the trough was rotated off-sun and the difficulty of thermally heating the catalyst.

The results of 3 weeks of testing demonstrated that the photothermal treatment system has destruction and removal efficiencies (DREs) in excess of 95% under conditions where incident UV irradiation provided operating temperatures from 150 to 200°C. No loss of performance of the catalyst occurred.

Significant results from these pilot-scale field tests:

- A non-tracking, ambient-temperature, solar-powered photocatalytic reactor consistently achieved greater than 95% destruction of 10-15 ppmv TCE for 4 to 6 hours of operation per day during April at a latitude of 37°N. Catalyst performance remained constant during three weeks of testing.
- 95% destruction was achieved at 10 SCFM with UV intensities greater than 1.5 mW/cm^2 and at 20 SCFM at UV intensities greater than 2.0 mW/cm^2.
- Greater than 95% destruction of a variable paint solvent stream (140 ppm total VOC) was achieved with a concentrating solar photoreactor operated with ambient sunlight at temperatures of 180-200°C. These operating temperatures were achievable for 4-8 hours of operation per day in July at a latitude of 39.5°N. Catalyst performance remained constant during three weeks of testing.

21.4.4 COMPARISON WITH OTHER TREATMENT SYSTEMS

The design and fabrication of the photocatalytic reactor system used in the McLellan field test was provided by NREL engineers and the Industrial Solar Technology Corporation (IST), Golden, CO. IST estimates that the cost for a 200-SCFM system is about $14,000.00, depending on the site requirements for hours of operation per day and the site solar potential. Costs to construct the reactors could be significantly reduced through economies of scale and large scale production likely could reduce reactor costs by half. Other purchased equipment costs for the photoreactor include a condenser/chiller and an instrumented blower/scrubber skid system for air handling. The level of instrumentation on the skid directly affects cost. The system described here was instrumented more than would be required for a commercial system. Equipment and installation costs for comparably sized carbon adsorption and thermal oxidation systems were calculated using EPAs HAPPRO v.2.1 software. Thus, total direct costs for the three systems are very close and range from an estimate of $131K for thermal oxidation, $119K for PCO, to $97K for carbon adsorption. Indirect costs were estimated using a factor of 0.28 x total purchased equipment cost. This value includes engineering, construction fee, and start-up costs. (Vatavuk, 1994) Total capital required for all three systems is approximately equal and ranges from $121K to $164K. Operating costs are also similar and range from $23 to $28K and total annual costs range from $37K for thermal oxidation to nearly equivalent values for carbon adsorption and PCO at $32K and $33K, respectively. No fuel is required for PCO and carbon adsorption. Details of the calculations are provided in the footnotes following Table 21.4.3.

Table 21.4.3. Comparison of estimated costs for similarly sized PCO, carbon adsorption, and thermal oxidation VOC treatment systems.

Direct Costs	Solar PCO non-concentrating	Carbon Adsorption	Thermal Oxidation
Purchased Equipment (PE)			
Photoreactor[1]			
Condenser/Chiller[2]	14,000		
Instrumented	10,625		
Blower/Scrubber Skid[3]	60,000		
Total PE (TPE)[4]	91,395	74,500[5]	100,500[5]
Installation	27,419	22,350	30,150
Total Direct Costs	118,814	96,850	130,650
Indirect Costs	29,923	24,391	32,904
Indirect Installation Costs[7]			
Total Capital Required[8]	148,736	121,241	163,554
Operating Costs[9]			
Electricity	2,880	1,440	1,440
Fuel[10]	0	0	5,000
Maintenance, Labor and Material	20,376	19,308	20,952
Direct Annual Costs	23,256	25,748	27,392
Indirect Annual Costs	8,664	7,063	9,527
Total Annual Costs	31,920	32,811	36,919
Levelized Cost[12]	56,135	25,549	63,456
Levelized Cost/CFM	281	263	318

[1]IST Corp., Golden, CO. Non-concentrating reactor cost is current and estimated price reductions anticipated from
[2]Peters and Timmerhaus, 1991.
[3]Zentox Corp., Ocala, FL. Concentrating vs. non-concentrating is primarily a function of instrumentation level.
[4]Includes 0.08 x PE for taxes and freight (Vatavuk, 1994).
[5]Calculated using EPAs HAPPRO v.2.1 software.
[6]0.38 x PE (Vatavuk, 1994).
[7]0.28 x TPE, including engineering costs, construction fee, and start-up costs (Vatavuk, 1994)
[8]Includes 6% contingency.
[9]Based on $0.08/kWh, 10 kW blower and chiller costs.
[10]Based on $0.33/ccf natural gas.
[11]0.06 x Total Capital Required for taxes, insurance, and administration.
[12]Based on 10% interest rate, 10 year depreciation.

REFERENCES

Ayer, J. and Darvin, C. H., 1995, “Cost Effective VOC Emission Control Strategies for Military, Aerospace, and Industrial Paint Spray Booth Operations: Combining Improved Ventilation Systems with Innovative, Low-Cost Emission Control Technologies”, Proceedings of the 88th Annual Meeting of the Air and Waste Management Association, Vol. 4B, 95-WA77A.02.

Blake, D.M., 1996, Bibliography of Work on the Heterogeneous Photocatalytic Removal of Hazardous Compounds from Water and Air, Update Number 2 to October 1996. NREL/TP-430-22197. Golden, CO: National Renewable Energy Laboratory.
Bekbolet, M. and Balcioglu, I., 1996, *Water Sci. Techn.*, **34**, No. 9, pp. 73-80.
Cummings, M. and Booth, S. R., Proc. Int. Conf. Incineration Therm.Treat. Technol. (1996), pp. 701-713. d'Hennezel, O. and Ollis D. F., 1997, *J. Catalysis*, **167**, No. 1, pp. 118-126.
Evstropov, A. A., Belyankin, I. A., Krainov, N. V., Mikheeva, T. Ya., Kvasov, A. A., 1989, "Catalytic Combustion of Gas emissions from A Spray-Painting Chamber", Lakokras. Mater. Ikh. Primen, Issue 1, pp. 115-118. Falconer, J. L. F. and Magrini-Bair, K. A., 1998, "Photocatalytic and Thermal Catalytic Oxidation of Acetaldehyde on Pt/TiO_2", accepted for publication in the *J. Catalysis*.
Fan, J. and Yates, J. T., *J. Am. Chem. Soc.*, **118**, pp. 4686-4692.
Fu, X., Clark, L. A., Zeltner, W. A., Anderson, M. A., 1996, "Effects of Reaction Temperature and Water Vapor Content on the Heterogeneous Photocatalytic Oxidation of Ethylene", *J. Photochem. Photobiol. A*, **97**, No. 3, pp. 181-186.
Fu, X., Zeltner, W. A., and Anderson, M. A., 1995, *Applied Catalysis B: Environmental*, Vol. **6**, pp. 209-224.
Gratson, D.A.; Nimlos, M.R.; Wolfrum, E.J., 1995, Proceedings of the Air and Waste Management Association.
Hung, C.-H. and Marinas, B. J., 1997, *Environ. Sci. Techn.,* **31**, pp. 1440-1445.
Jacoby, W.A.; Nimlos, M.R.; Blake, D.M.; Noble, R.D.; Koval, C.A., 1994, *Environ. Sci. Techn.*, **28**, No. (9), pp. 1661-1668.
Kittrell, J. R., Quinlan, C. W., Shepanzyk, J. W., "Photocatalytic Destruction of Hexane Eliminates Emissions in Contact Lens Manufacture", Emerging Solutions in VOC Air Toxics Control, Proc. Spec. Conf. (1996), pp. 389-398.
Larson, S. A. and Falconer J. L., 1997, *Catalysis Lett.*, **44**, No. 9, pp. 57-65.
Luo, Y. and Ollis, D. F., 1996, *J. Catalysis*, **163**, No. 1, pp. 1-11.
Magrini, K. A., Watt, A. S., Boyd, L. C., Wolfrum, E. J., Larson, S. A., Roth, C., and Glatzmaier, G. C., "Application of Solar Photocatalytic Oxidation to VOC-Containing Airstreams", ASME Proceedings of the Renewable and Advanced Energy Systems for the 21st Century, pp. 81-90, Lahaina, Maui, April 1999.
Magrini, K. A., Rabago, R., Larson, S. A., and Turchi, C. S., "Control of Gaseous Solvent Emissions using Photocatalytic Oxidation", Proc. Annu. Meet. Air Waste Manage. Assoc., 89th, (1996) pp. 1-8.
Mueller, J. H., (1988), "Spray Paint Booth VOC Control with a Regenerative Thermal Oxidizer", Proceedings-APCA Annual Meeting 81st(5), Paper 88/84.3, 16 pp.
Nimlos, M. R., Jacoby, W. A., Blake, D. M. and Milne, T. A., 1993, *Environ. Sci. Techn.*, **27**, p. 732.
Peral, J. and Ollis, D.F., 1992, *J. Catalysis*, **136**, pp. 554-565.
Phillips, L.A.; Raupp, G.B., 1992, *J. Molec. Catalysis*, **7**, pp. 297-311.
Read, H. W., Fu, X., Clark, L. A., Anderson, M. A., Jarosch, T., 1996, "Field Trials of a TiO_2 Pellet-Based Photocatalytic Reactor for Off-Gas Treatment at a Soil Vapor Extraction Well", *J. Soil Contamination,* **5**, No. 2, pp. 187-202.
Rosansky, S. H., Gavaskar, A. R., Kim, B. C., Drescher, E., Cummings, C. A., and Ong, S. K., "Innovative Air Stripping and Catalytic Oxidation Techniques for Treatment of Chlorinated Solvent Plumes", Therm. Technol., Int. Conf., Rem. Chlorinated Recalcitrant Compounds., 1st (1998) pp. 415-424.
Sitkiewitz, S. and Heller, A., 1996, *New J. Chemistry*, **20**, No. 2, pp. 233-241.
Turchi, C.S., Wolfrum, E., Miller, R.A., 1994, Gas-Phase Photocatalytic Oxidation: Cost Comparison with Other Air Pollution Control Technologies, NREL/TP-471-7014. Golden, CO: National Renewable Energy Laboratory.
Watt, A. S., Magrini, K. A., Carlson-Boyd, L. C., Wolfrum, E. J., Larson, S. A., Roth, C., and Glatzmaier, G. C., "A Pilot-Scale Demonstration of an Innovative Treatment for Vapor Emissions", *J. Air Waste Management*, November, 1999.
Yamazaki-Nishida, S., Fu, X., Anderson, M. A. and Hori, K., 1996, *J. Photochem. Photobiol. A: Chem.*, **97**, pp. 175-179.

ADDENDUM

Overview

Since the 2nd edition of the Handbook of Solvents was published in 2014, the use of semiconductor photocatalysis *via* photocatalytic oxidation (PCO) to remove chlorinated organics from air and water streams has further developed as an emerging industry consisting of indoor air cleaning systems, water treatment systems, waste treatment systems, more efficient visible light activated catalysts, and more efficient and varied materials that include

self-cleaning including textiles, ceramics, and mirrors (Ragesh *et al.,* 2014). The range of compounds that are treatable by PCO in water have further expanded from chlorinated organics to include taste and odor compounds, pharmaceuticals including endocrine disruptors (bisphenol A), pesticides, dyes, paints, CECs (contaminants of emerging concern) and microorganisms including pathogenic bacteria (E-coli), fungi, algae and viruses. Photocatalysts continue to evolve from the original photocatalyst, titanium dioxide (TiO_2), to novel materials comprising nanoparticles of TiO_2, varied metal addition to TiO_2 and ZnO, varied types of carbon-doped TiO_2, 2-dimensional photocatalysts based on metal oxides, metal chalcogenides and metal free materials such as graphene, and MOFs (metal oxide frameworks) with an emphasis on increasing both ultraviolet and visible light utilization. Nitrogen-doping confers strong visible light responses in TiO_2, ZnO and perovskite photocatalysts. Other visible light activated catalysts comprise Nb_2O_5, plasmonic catalysts based on Au, Ag and Cu supported on metal oxides, and polymeric graphitic carbon nitrides. Combining heterogeneous photocatalysis with molecular photocatalysts offers a new approach to broadening visible-light activated organic transformation. Novel reactor configurations include combinations of photocatalysts with membrane reactors for water treatment and the combination of selective removal of either contaminants or catalyst foulant prior to photocatalytic treatment. Several comprehensive reviews of photocatalysis have been published recently and interestingly conclude that TiO_2-based photocatalysts remain the material of choice for varied applications due to its low cost, high oxidizing power and broad applicability to varied contaminants. The following sections describe the significant advances that have occurred in the last five years.

Chlorinated organic destruction in air and water streams

Photocatalytic water treatment remains at the forefront of PCO research because of the ability of titania and other heterogenous photocatalysts to mineralize/oxidize a wide range of compounds efficiently using low cost reactor designs and facile integration with other advances oxidation processes (AOPs). Several recent reviews catalog progress in destroying chlorinated organics in air and water streams beginning with an expanded compendium of priority water pollutants defined in Directive 2013/39/EU in which AOPs combined with photocatalytic treatment provide an efficient process to destroy persistent pesticides and chlorinated organics (Ribeiro *et al*., 2015). An emerging aqueous pollutant of concern widely found in the ambient environment is bisphenol A (BPA), which is broadly used as a precursor for epoxy and polycarbonate resins used to coat water containers and medical devices. It is found in water, air and soil and is classified as an endocrine disruptor. Reddy *et al*. (2018) surveyed the literature on PCO of BPA and concluded that titania performs the best with no production of aqueous toxic intermediates. BPA contaminated water is expected to increase in the coming decades. The dominance of TiO_2 for water treatment is interpreted as a focus on bandgap values by the research community and a lack of implementation of modeling tools to design more active photocatalysts (Shaham-Waldman, 2016). Other work reviews modifying ZnO photocatalysts to absorb in the visible spectrum with a focus on destroying persistent dyes and phenols in natural water resources from textile manufacture (Lee *et al*., 2016). Metal addition, anionic, cationic,

and rare earth dopants have been used to reduce recombination and photo-corrosion and improve efficiency by using ZnO nanoparticles.

Taste and odor compounds in drinking water supplies are a current problem that can be addressed by PCO though toxicity of intermediates is not well known and interference by natural organic matter can impact catalyst activity. Non-toxic geosmin and 2-methylisoborneol are drinking water contaminants derived from cyanobacteria and actinomyces that are prevalent and at low concentrations (ng/L) that make treatment difficult. AOPs that treat these species are detailed in a recent review by Antonopoulou *et al*., 2014.

Concern about the presence of biohazards in water supplies such as harmful microorganisms that can lead to epidemic outbreaks and the efficiency of PCO to disinfect these organisms is described in a recent review by Reddy *et. al*., 2017. TiO_2-produced hydroxyl radicals attach to bacterial cell walls and induce cellular damage by rapid leakage of potassium ions. Additionally, peroxide radicals and free metal ions that also form can be effective by damaging the phospholipid layer of bacterial cell walls. Modifications to TiO_2 *via* metal addition and particle size manipulation have treated *E. coli, S. aureus*, *P. aeroginosa* and *L. monocytogens* with treatment times ranging from 1-8 hours. Other aquatic species treatable by TiO_2 PCO include the fungi *Candia albicans*, a virus *Bacteriophage MS2* with Ag/TiO_2, the protozoa *Cryptosporidium* and *Giardia lamblia*, and the algae *Chlorella* with treatment times of hours and efficiencies of > 80%. Improving catalyst efficiency, designing and deploying larger scale systems, identifying catalyst regeneration and cycle times, and understanding destruction mechanisms still require development if these systems are to be used reliably at larger scales. Nanoparticulate zinc oxide (ZnO) as well has been modified and evaluated for its bactericidal photoactivity. Modifications similar to those applied to TiO_2 (metal and non-metal doping, noble metal deposition, and coupling with semiconductors and carbon heterojunction addition) have been evaluated for PCO of aqueous organics and bacteria (*S. aureus* and *E. coli*) with nanoparticulate (NP) ZnO exhibiting excellent bactericidal activity *via* reactive oxygen species generation, Zn^{+2} release, membrane disfunction and NP internalization though these mechanisms are not completely understood at the cellular level (Qi *et al*., 2017).

New photocatalysts

Modifying titania remains a primary research focus to improve its intrinsic photoactivity by doping to extend the photoactive zone. Nanoparticulate titania is becoming more used specifically since it can be immobilized on support systems (Mahlambi *et al*., 2015) for use in water treatment. Other modification to titania to improve its performance include manipulating catalyst morphology to tune the bandgap to the visible spectrum while reducing recombination (Xu *et al*., 2014). Anion doping is more effective than cation doping, which generates destructive electron-hole recombination centers (Wang *et al*., 2018). Nitrogen doping has been successfully used to achieve a high visible light response. Parameters that impact visible light activity include the band gap, available nitrogen doping sites and amounts, defect amounts, and TiO_2 particle morphology. Controlling these variables through preparation provides control over the visible light response. Other photocatalysts that benefit from nitrogen doping include ZnO, Ga_2O_3, and GeO_2. Perovskites respond to nitrogen doping as well by forming photoactive perovskite oxynitrides. Reduc-

ing the bandgap of TiO_2 and ZnO by metal addition is a straightforward method to increasing visible light activation. Adding nanoparticles of Ag, Fr, Mo and Cu reduces the effective bandgaps of both materials with Ag strongly enhancing photoactivity (Khaki *et al.,* 2017). Doping carbon into the titania structure produces a visible light activated catalyst with carbon replacing oxygen sites and forming oxygen vacancies. At >400 nm illumination, 23% NO destruction was achieved compared with 60% at 290 nm illumination (Wu *et al*., 2013). Graphite doping into titania achieved a similar result with visible light activation at 420 nm greater than pure anatase TiO_2 for methyl orange destruction, 35.8 vs. 21.3%. respectively (Jia *et al*., 2016). Other work used low cost starch as a carbon source to dope pure anatase to produce a 2.79 eV, which is within the visible portion of the spectrum. Rhodamine B dye destruction with the doped material was more efficient than either undoped titania or Degussa P-25 titania (Warkhade *et al.*, 2017). Another novel carbon doping approach uses an *in-situ* synthetic strategy to produce carbon-TiO_2 nanotubes by calcining surface sulfonated polystyrene nanofibers/TiO_2 composites. The resulting 200 nm diameter tubes were more active under visible and UV light than the base titania with the tube morphology more applicable to waste water treatment applications (Ji *et al*., 2017). Zinc oxide nanostructure development as an inexpensive alternative to titania is a current research focus with dopant addition (nonmetals comprising N, C, and S; metals including transition, rare-earth and aluminum which substitutes for Zn and red shifts the band gap) used to improve visible light activity (Samadi *et al.*, 2016; Lee *at al*., 2016). Interestingly, most of these studies evaluated PCO activity with model compounds; not much work has been done with actual waste streams.

Another type of new photocatalysts are two dimensional (2D) materials consisting of three primary types: metal oxides, metal chalcogenides, and metal free photocatalysts tailored for PCO. Photoactive metal oxide examples include TiO_2, WO_3, titanoniobate, and perovskite oxides; chalcogenide nanosheets of MoS_2, SnS_2, TiS_2, WS_2, $MoSe_2$; and metal-free materials based on light-weight elements comprising carbon, phosphorous, binary carbon nitride, hexagonal boron nitride and boron carbide. Graphene additionally is of interest because of its high carrier mobility (Luo *et al*., 2016). Further development of these PCO candidates are required before they are useable in actual applications. Silver orthophosphate (Ag_3PO_4) is a new visible light activated photocatalyst that due to its low bandgap utilizes >90% of wavelengths >420 nm. This catalyst however requires a sacrificial agent as it can photo decompose. Adding Ag nanoparticles overcomes this tendency (Dewil *et al.,* 2017).

New applications

Pharmaceuticals as emerging pollutants have become a major concern not only because of the threat to health and safety of aquatic species but also due to their continuous accumulation in aqueous environments and the development of antibiotic-resistant microbial strains (Ganiyu 2015). Single water treatment techniques are largely ineffective but combining processes like membrane separation with AOPs including PCO can be completely effective as each process overcomes the challenges of the other. Coupling PCO with membranes is attractive because of simultaneous separation and destruction of pollutants, self-cleaning/anti-fouling properties by foulant destruction, and flexibility for commercial

applications. Generally, PCO combined with membrane technology can either be a pre- or post-treatment stage or a hybrid/one-pot process (Zheng *et al*., 2017). An example is the complete destruction of the drugs Tamoxifen and Gemfibrozil in a side pressurized and submerged membrane photocatalytic reactor with crystalline TiO_2 after 20 minutes with >90% total organic carbon (TOC) removal in 120 minutes. An economic disadvantage to large scale deployment of these hybrid reactors is UV-light source cost.

Perspectives on AOPs

Dewil *et al.*, 2017 provide a succinct review of advanced oxidation processes including PCO and notes "AOPs should not and cannot do the "full monty" in that they must select specific treatment targets in which they excel: microcontaminant removal, pathogen destruction, and polishing treated industrial streams". Also required is taking the next step from academic and laboratory scale studies to large-scale, fully operational applications. Byrne *et al.*, 2018 also review recent advances in photocatalysis for environmental applications. Coupling AOPs with renewable energy is critical for simultaneous water treatment and energy production. Additionally, waste valorization coupled with AOPs can reduce process costs; an example is using red mud, a process waste solid from bauxite processing, as an AOP catalyst as it contains useable titania, alumina and iron oxides. A recent review of chlorinated volatile organics (VOCs) destruction by AOPs (Dai *et al.*, 2018) determined that PCO works well at total VOC contents < 500 ppm. Advancements in applying PCO to mitigate VOCs in indoor air environments (Huang *et al*., 2014, 2016) environments highlight the need to develop visible light activated materials and efficient regeneration mechanisms as products of incomplete oxidation can be more toxic than the parent species and deactivate catalyst surfaces that in turn reduce performance.

In summary, significant progress has been made in the development of PCO for treating chlorinated and other organics in water streams since the last update in 2013. Of note is the development of efficient visible light absorbing photocatalysts, two dimensional catalysts, nanomaterials, and coupling with other processes that either provide targeted destruction of specific compounds or separation of recalcitrant species that can be treated with other methods. Bactericidal activity continues to expand with viruses, algae, fungi found to be amenable to photocatalytic oxidation as are persistent odor compounds in drinking water. Numerous recent reviews catalog PCO development with most noting that the time has come to develop applications for actual use in larger-scale systems.

REFERENCES

Antonopoulou, M., Evgenidou, E., Lambropoulou, D., Konstantinou, I., "A review on advanced oxidation processes for the removal of taste and odor compounds from aqueous media", *Water Research* 53 (2014) 215-234.

Byrne, C., Subramanian, G., Pillai, S. G., "Recent advances in photocatalysis for environmental applications", J. of *Environmental Chemical Engineering* **6** (2018) 3531-3555.

Dai, C., Zhou, Y., Peng, H., Huang, S., Qin, P., Zhang, J., Yang, Y., Luo, L., Zhang, X., "Current progress in remediation of chlorinated volatile organic compounds: A review", *J. of Ind. And Eng. Chem.* **62** (2018) 106-119.

Dewil, R., Mantzavinos, D., Poulios, I., Rodrigo, M. A., "New perspectives for advanced oxidation processes", *J. of Environmental Management* **195** (2017) 93-99.

Ganiyu, S. O., van Hullebusch, E. D., Cretin, M., Esposito, G., Oturan, M. A., Coupling of membrane filtration and advanced oxidation processes for removal of pharmaceutical residues: A critical review", *Separation and Purification Technology* **156** (2015) 891-914.

Huang, B., Lei, C., Wei, C., Zeng, G., "Chlorinated volatile organic compounds (Cl-VOCs) in environment - sources, potential human health impacts, and current remediation technologies", *Environment International* **71** (2014) 118-138.
Huang, Y., Ho, S. S. H., Lu, Y., Niu, R., Xu, L., Cao, J., Lee, S., "Removal of indoor volatile organic compounds via photocatalytic oxidation: A short review", *Molecules* **21** (56) (2016) 1-20.
Ji, L., Zhang, Y., Miao, S., Gong, M., Liu, X., "In situ synthesis of carbon doped TiO_2 nanotubes with an enhances photocatalytic performance under UV and visible light", *Carbon* **125** (2017) 544-550.
Jia, J., Li, D., Wan, J., Yu, X., "Characterization and mechanism analysis of graphite/C-doped TiO_2 composite for enhanced photocatalytic performance", *J. of Industrial and Engineering Chemistry* **33** (2016) 162-169.
Khaki, M., Shafeeyan, M., Raman A., Daud, W., "Application of doped photocatalysts for organic pollutant degradation - A review", *J. of Environmental Management* **108** (2017) 78-94.
Lee, K. M., Lai, C. W., Ngai. K. S., Juan. J. C., "Recent developments of zinc oxide based photocatalyst in water treatment technology: A review", *Water Research* **88** (2016) 428-448.
Luo, B., Liu, G., Wang, L., "Recent advances on 2D materials for photocatalysis", *Nanoscale* **8** (2016) 6904-6920.
Mahlambi, M. M., Ngila, C. J., Mamba, B. B., "Recent developments in environmental photocatalytic degradation of organic pollutants: The case of titanium dioxide nanoparticles - A review", *J. of NanoE.*, (2015) 1-29.
Qi, K., Cheng, B., Yu, J., Ho, W., "Review on the improvement of the photocatalytic and antibacterial activities of ZnO", *J. of Alloys and Compounds* 727 (2017) 792-820.
Ragesh, P., Ganesh, V. A., Nair, S. V., Nair, a. s., "A review on self-cleaning and multifunctional materials", *J. Materials Chemistry* **A2**, (2014) 14773-14797.
Reddy, P. (a), Kavitha, B., Reddy, P., Kim, K-H., "TiO_2-based photocatalytic disinfection of microbes in aqueous media: A review", *Environmental Research* **154** (2017) 296-303.
Reddy, P. (b), Reddy, P, Kwon, E., Kim, K-H., Akter, T., Kalagara, S., "Recent advances in photocatalytic treatment of pollutants in aqueous media", *Environment International* **91** (2016) 94-103.
Reddy, P.(c), Kim, K-H., Kavitha, B., Kumar, V., Raza, N., Kalagara, S., "Photocatalytic degradation of bisphenol A in aqueous media: a review", *J. of Environmental Management* **213** (2018) 189-205.
Ribeiro, A. R., Nunes, O. C., Pereira, M. F. R., Silva, A. M. T., "An overview on the advanced oxidation processes applied for the treatment of water pollutants defined in the recently launched directive 2013/39/EU", *Environment International* **75** (2015) 33-51.
Samadi, M., Zirak, M., Naseri, A., Korashadizade, E., Moshfegh, A., "Recent progress on doped ZnO nanostructures for visible-light photocatalysis", *Thin Solid Films* **605** (2016) 2-19.
Shaham-Waldmann, N. and Paz, Y., "Away from TiO_2: A critical minireview on the developing of new photocatalysts for degradation of contaminants in water", *Materials Science in Semiconductor Processing* **42** (2016) 72-80.
Warkhade, S., Gaikwad, G. S., Zodape, S. P., Pratap, U., Maldhure, A. V., Wankhade, A. V., "Low temperature synthesis of pure anatase carbon doped titanium dioxide: An efficient visible light active photocatalyst", *Materials Science in Semiconductor Processing* **63** (2107) 18-24.
Wang, W., Tade, M. O., Shao, Z., "Nitrogen-doped simple and complex oxides for photocatalysis: A review", *Progress in Materials Science* **92** (2018) 33-63.
Wu, X., Yin, S., Dong, Q., Guo, C., Li, H., Kimura, T., Sato, T., "Synthesis of high visible light active carbon doped TiO2 photocatalyst by a facile calcination assisted solvothermal method", *App. Cat. B: Environmental* **142-143** (2013) 450-457.
Xu, H., Ouyang, S., Liu, L., Reunchan, P., Umezawa, N., Ye, J., "Recent advances in TiO_2-based photocatalysis", *J. of Materials Chemistry* **A 2** (2014) 12642-12661.
Zheng, X., Shen, Z-P., Shi, L., Cheng, R., Yuan, D-H., "Photocatalytic membrane reactors (PMRs) in water treatment: Configurations and influencing factors", *Catalysts* **7** (2017) 224

22

Natural Attenuation of Chlorinated Solvents in Ground Water

Hanadi S. Rifai, Charles J. Newell*, and Todd H. Wiedemeier**
Civil and Environmental Engineering, University of Houston, Houston, Texas, USA
***Groundwater Services, Inc., Houston, Texas, USA**
****T.H. Wiedemeier and Associates, Conifer, Colorado, USA**

22.1 INTRODUCTION

Chlorinated solvents were first produced some 100 years ago and came into common usage in the 1940's. Chlorinated solvents are excellent degreasing agents and they are nearly nonflammable and noncorrosive. These properties have resulted in their widespread use in many industrial processes such as cleaning and degreasing rockets, electronics and clothing (used as dry-cleaning agents). The most commonly used chlorinated solvents are perchloroethene (PCE), trichloroethene (TCE), 1,1,1-trichloroethane (TCA), and carbon tetrachloride (CT) (Wiedemeier *et al*., 1999, Scherr *et al*. 2011). After their release into the environment, these compounds, which are toxic and some of them are human carcinogens, can interact physically and chemically, form non-aqueous phases while moving downward into aquifer systems, sorbing with soil organic materials and finally dissolving into the aquifer (Ferguson and Pietari 2000). Chlorinated solvent compounds and their natural degradation or progeny products have become some of the most prevalent organic contaminants found in the shallow groundwater of the United States and other countries worldwide.

Chlorinated solvents (CS) undergo the same natural attenuation processes as other ground water contaminants such as advection, dispersion, sorption, volatilization and biodegradation. In addition CS is subject to abiotic degradation *via* pathways such as hydrolysis, dehydrohalogenation, hydrogenolysis, and dihaloelimination. Over the past decade,

researchers have expanded their understanding of the microbial degradation of chlorinated solvents and have identified degradation pathways for these compounds that were not previously known. Unlike petroleum hydrocarbons, which can be oxidized by microorganisms under either aerobic or anaerobic conditions, most chlorinated solvents are degraded only under specific ranges of oxidation-reduction potential. For example, PCE is biologically degraded through use as a primary growth substrate only under strongly reducing anaerobic conditions.

This chapter is focused on the natural attenuation behavior of CS at the field scale. The first part of the chapter reviews many of the physical, chemical and abiotic natural attenuation processes that attenuate CS concentrations in ground water. Some of these processes have been described in more detail in previous chapters in the handbook and are therefore only reviewed in brief. In the second part of this chapter, the biological processes that bring about the degradation of the most common chlorinated solvents are reviewed and conceptual models of chlorinated solvent plumes are presented as are summaries of data from field studies with chlorinated solvent contamination.

22.2 NATURAL ATTENUATION PROCESSES AFFECTING CHLORINATED SOLVENT PLUMES

Many abiotic mechanisms affect the fate and transport of organic compounds dissolved in ground water. Physical processes include advection and dispersion while chemical processes include sorption, volatilization and hydrolysis. Advection transports chemicals along ground water flow paths and in general does not cause a reduction in contaminant mass or concentration. Dispersion or mixing effects, on the other hand, will reduce contaminant concentrations but will not cause a reduction in the total mass of chemicals in the aquifer. Sorption or partitioning between the aquifer matrix and the ground water, much like dispersion, will not cause a reduction in contaminant mass. Volatilization and hydrolysis both will result in lower concentrations of the contaminant in ground water. Most of these processes, with the exception of hydrolysis and dehydrohalogenation chemical reactions, do not break down or destroy the contaminants in the subsurface.

Chlorinated solvents are advected, dispersed, and sorbed in ground water systems. They also volatilize although their different components have varying degrees of volatility. Chlorinated solvents additionally hydrolize and undergo other chemical reactions such as dehydrohalogenation or elimination and oxidation and reduction. These abiotic reactions, as will be seen later in the chapter, are typically not complete and often result in the formation of an intermediate that may be at least as toxic as the original contaminant.

22.2.1 ADVECTION

Advective transport is the transport of solutes by the bulk movement of ground water. Advection is the most important process driving dissolved contaminant migration in the subsurface and is given by:

$$v_x = -\frac{K}{n_e}\frac{dH}{dL} \qquad [22.1]$$

where:

v_x	seepage velocity [L/T]
K	hydraulic conductivity [L/T]
n_e	effective porosity [L^3/L^3]
dH/dL	hydraulic gradient [L/L]

Typical velocities range between 10^{-7} and 10^3 ft/day (Newell *et al*., 1990) with a median national average of 0.24 ft/day. The seepage velocity is a key parameter in natural attenuation studies since it can be used to estimate the time of travel of the contaminant front:

$$t = \frac{x}{v_x} \qquad [22.2]$$

where:

x	travel distance (ft or m)
t	time

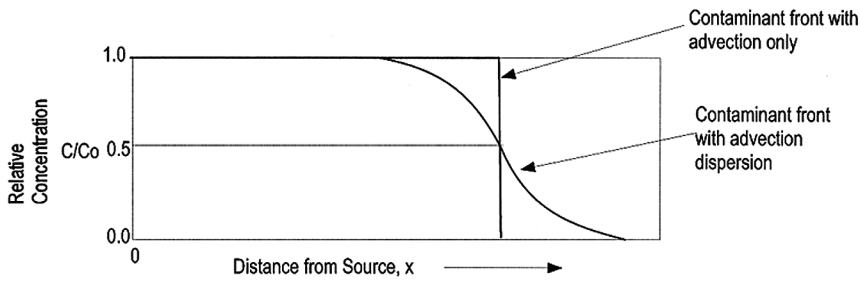


Figure 22.1 Breakthrough curve in one dimension showing plug flow with continuous source resulting from advection only and from the combined processes of advection and hydrodynamic dispersion. [Adapted, by permission, from T. H. Wiedemeier, H. S. Rifai, C. J. Newell and J. T. Wilson, **Natural Attenuation of Fuels and Chlorinated Solvents in the Subsurface,** *John Wiley & Sons, Inc.*, New York, NY, 1999.]

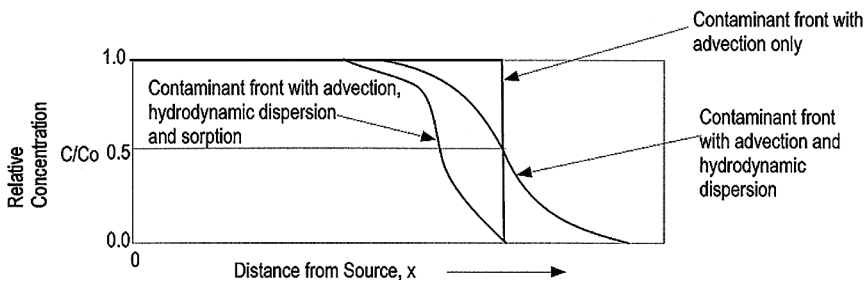


Figure 22.2 Breakthrough curve in one dimension showing plug flow with continuous source resulting from advection only; from the combined processes of advection and hydrodynamic dispersion; and from the combined processes of advection, hydrodynamic dispersion, and sorption. [Adapted, by permission, from T. H. Wiedemeier, H. S. Rifai, C. J. Newell and J. T. Wilson, **Natural Attenuation of Fuels and Chlorinated Solvents in the Subsurface,** *John Wiley & Sons, Inc.*, New York, NY, 1999.]

Solute transport by advection alone yields a sharp solute concentration front as shown in Figure 22.1. In reality, the advancing front spreads out due to the processes of dispersion and diffusion as shown in Figure 22.1, and is retarded by sorption (Figure 22.2) and biodegradation.

22.2.2 DISPERSION

Hydrodynamic dispersion causes a contaminant plume to spread out from the main direction of ground water flow. Dispersion dilutes the concentrations of the contaminant, and introduces the contaminant into relatively pristine portions of the aquifer where it mixes with more electron acceptors cross gradient to the direction of ground-water flow. As a result of dispersion, the solute front travels at a rate that is faster than would be predicted based solely on the average linear velocity of the ground water. Figure 22.1 illustrates the effects of hydrodynamic dispersion on an advancing solute front. Mechanical dispersion is commonly represented by the relationship:

$$\text{Mechanical dispersion} = \alpha_x v_x \qquad [22.3]$$

where:

v_x average linear ground-water velocity [L/T]
α_x dispersivity [L]

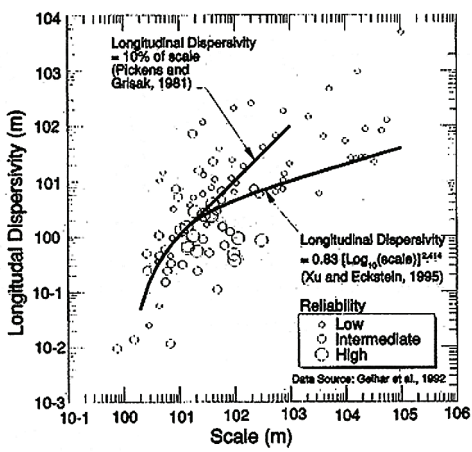


Figure 22.3 Relationship between dispersivity and scale. [Adapted, by permission, from T. H. Wiedemeier, H. S. Rifai, C. J. Newell and J. T. Wilson, **Natural Attenuation of Fuels and Chlorinated Solvents in the Subsurface,** *John Wiley & Sons, Inc.*, New York, NY, 1999.]

Dispersivity represents the spreading of a contaminant over a given length of flow and is characteristic of the porous medium through which the contaminant migrates. It is commonly accepted that dispersivity is scale-dependent, and that at a given scale, dispersivity may vary over three orders of magnitude (Gelhar *et al.*, 1985 and 1992) as shown in Figure 22.3.

Several approaches can be used to estimate longitudinal dispersivity, x, at the field scale. One technique involves conducting a tracer test but this method is time consuming and costly. Another method commonly used in solute transport modeling is to start with a longitudinal dispersivity of 0.1 times the plume length (Lallemand-Barres and Peaudecerf, 1978; Pickens and Grisak, 1981; Spitz and Moreno, 1996). This assumes that dispersivity varies linearly with scale. Xu and Eckstein (1995) proposed an alternative approach. They evaluated the same data presented by Gelhar *et al*. (1992) and, by using a weighted least-squares method, developed the following relationship for estimating dispersivity:

$$\alpha_x = 0.83(\log_{10} L_p)^{2.414} \qquad [22.4]$$

where:

α_x	longitudinal dispersivity [L]
L_p	plume length [L]

Both relationships are shown on Figure 22.3.

In addition to estimating longitudinal dispersivity, it may be necessary to estimate the transverse and vertical dispersivities (α_T and α_Z, respectively) for a given site. Commonly, α_T is estimated as 0.1 α_x (based on data from Gelhar *et al*., 1992), or as 0.33 α_x (ASTM, 1995; US EPA, 1986). Vertical dispersivity (α_Z) may be estimated as 0.05 α_x (ASTM, 1995), or as 0.025 α_x to 0.1 α_x (US EPA, 1986).

22.2.3 SORPTION

Many organic contaminants, including chlorinated solvents, are removed from solution by sorption onto the aquifer matrix. Sorption of dissolved contamination onto the aquifer matrix results in slowing (retardation) of the contaminant relative to the average advective ground-water flow velocity and a reduction in dissolved organic concentrations in ground water. Sorption can also influence the relative importance of volatilization and biodegradation (Lyman *et al*., 1992). Figure 22.2 illustrates the effects of sorption on an advancing solute front. Sorption is a reversible reaction; at given solute concentrations, some portion of the solute is partitioning to the aquifer matrix and some portion is also desorbing and reentering solution.

Sorption can be determined from bench-scale experiments. These are typically performed by mixing water-contaminant solutions of various concentrations with aquifer materials containing various amounts of organic carbon and clay minerals. The solutions are then sealed with no headspace and left until equilibrium between the various phases is reached. The amount of contaminant left in solution is then measured.

The results are commonly expressed in the form of a sorption isotherm or a plot of the concentration of chemical sorbed (µg/g) versus the concentration remaining in solution (µg/L). Sorption isotherms generally exhibit one of three characteristic shapes depending on the sorption mechanism. These isotherms are referred to as the Langmuir isotherm, the Freundlich isotherm, and the linear isotherm (a special case of the Freundlich isotherm). The reader is referred to Wiedemeier *et al*. (1999) for more details on sorption isotherms.

Since sorption tends to slow the transport velocity of contaminants dissolved in ground water, the contaminant is said to be “retarded.” The coefficient of retardation, R, is defined as:

$$R = \frac{v_x}{v_c} \qquad [22.5]$$

where:

R	coefficient of retardation
v_x	average linear ground-water velocity parallel to ground-water flow
v_c	average velocity of contaminant parallel to ground-water flow

The ratio v_x/v_c describes the relative velocity between the ground water and the dissolved contaminant. The coefficient of retardation for a dissolved contaminant (for satu-

rated flow) assuming linear sorption is determined from the distribution coefficient using the relationship:

$$R = 1 + \frac{\rho_b K_d}{n} \qquad [22.6]$$

where:

R	coefficient of retardation [dimensionless]
ρ_b	bulk density of aquifer [M/L^3]
K_d	distribution coefficient [L^3/M]
n	porosity [L^3/L^3]

The bulk density, ρ_b, of a soil is the ratio of the soil mass to its field volume. In sandy soils, ρ_b can be as high as 1.81 gm/cm^3, whereas, in aggregated loams and clayey soils, ρ_b can be as low as 1.1 gm/cm^3.

The distribution coefficient is a measure of the sorption/desorption potential and characterizes the tendency of an organic compound to be sorbed to the aquifer matrix. As the distribution coefficient increases, the potential for sorption to the aquifer matrix also increases. The distribution coefficient, K_d, is given by:

$$K_d = \frac{C_a}{C_l} \qquad [22.7]$$

where:

K_d	distribution coefficient (slope of the sorption isotherm, ml/g).
C_a	sorbed concentration (mass contaminant/mass soil or µg/g)
C_l	dissolved concentration (mass contaminant/volume solution or µg/ml)

Several researchers have found that if the distribution coefficient is normalized relative to the aquifer matrix total organic carbon content, much of the variation in observed K_d values between different soils is eliminated (Dragun, 1988, Bailey and White, 1970; Karickhoff *et al*., 1979; Kenaga and Goring, 1980; Brown and Flagg, 1981; Schwarzenbach and Westall, 1981; Hassett *et al*., 1983; Chiou *et al*., 1983). Distribution coefficients normalized to total organic carbon content are expressed as K_{oc}. The following equation gives the expression relating K_d to K_{oc}:

$$K_{oc} = \frac{K_d}{f_{oc}} \qquad [22.8]$$

where:

K_{oc}	soil sorption coefficient normalized for total organic carbon content
K_d	distribution coefficient
f_{oc}	fraction total organic carbon (mg organic carbon/mg soil)

Table 22.1 presents calculated retardation factors for several LNAPL and DNAPL related chemicals as a function of the fraction of organic carbon content of the soil. It can be seen from Table 22.1 that R can vary over two orders of magnitude at a site depending on the chemical in question and the estimated value of porosity and soil bulk density.

Table 22.1. Calculated retardation factors for several chlorinated solvent-related chemicals.

Compound	log(K_{oc})	Fraction of organic compound to aquifer (f_{oc})			
		0.0001	0.001	0.01	0.1
Carbon tetrachloride	2.67	1.2	3.3	24.0	231.2
1,1,1-TCA	2.45	1.1	2.4	14.9	139.7
PCE	2.42	1.1	2.3	13.9	139.7
1,1- or 1,2-DCA	1.76	1.0	1.3	3.8	29.3
trans 1,2-DCE	1.42	1.0	1.1	2.3	13.9
cis 1,2-DCE	1.38	1.0	1.1	2.2	12.8
TCE	1.26	1.0	1.1	1.9	10.0
Chloroethane	1.25	1.0	1.1	1.9	9.8
Dichloromethane	1.23	1.0	1.1	1.8	9.4
Vinyl chloride	0.06	1.0	1.0	1.1	1.6

22.2.4 ONE-DIMENSIONAL ADVECTION-DISPERSION EQUATION WITH RETARDATION

In one dimension, the advection-dispersion equation is given by:

$$R\frac{\partial C}{\partial t} = D_x\frac{\partial^2 C}{\partial x^2} - v_x\frac{\partial C}{\partial x} \qquad [22.9]$$

where:

v_x	average linear velocity ground-water velocity [L/T]
R	coefficient of retardation [dimensionless]
C	contaminant concentration [M/L^3]
D_x	hydrodynamic dispersion [L^2/T]
t	time [T]
x	distance along flow path [L]

22.2.5 DILUTION (RECHARGE)

Ground water recharge can be defined as the entry into the saturated zone of water made available at the water-table surface (Freeze and Cherry, 1979). Recharge may therefore include precipitation that infiltrates through the vadose zone and water entering the ground-water system due to discharge from surface water bodies (i.e., streams and lakes). Recharge of a water table aquifer has two effects on the natural attenuation of a dissolved contaminant plume. Additional water entering the system due to infiltration of precipitation or from surface water will contribute to dilution of the plume, and the influx of relatively fresh, electron-acceptor-charged water will alter geochemical processes and in some cases facilitate additional biodegradation.

Wiedemeier *et al*. (1999) present the following relationship for estimating the amount of dilution caused by recharge:

$$C_L = C_0 \exp - \left(\frac{RW\left(\frac{L}{V_D}\right)}{WThV_D} \right) \quad [22.10]$$

Eliminating the width and rearranging, gives:

$$C_L = C_0 \exp\left(\frac{RL}{Th(V_D)^2} \right) \quad [22.11]$$

where:

C_L	concentration at distance L from origin assuming complete mixing of recharge with groundwater (mg/L)
C_0	concentration at origin or at distance L = 0 (mg/L)
R	recharge mixing with groundwater (ft/yr)
W	width of area where recharge is mixing with groundwater (ft)
L	length of area where recharge is mixing with groundwater (ft)
Th	thickness of aquifer where groundwater flow is assumed to completely mix with recharge (ft)
V_D	Darcy velocity of groundwater (ft/yr)

22.2.6 VOLATILIZATION

Volatilization causes contaminants to transfer from the dissolved phase to the gaseous phase. In general, factors affecting the volatilization of contaminants from ground water into soil gas include the contaminant concentration, the change in contaminant concentration with depth, the Henry's Law constant and diffusion coefficient of the compound, mass transport coefficients for the contaminant in water and soil gas, sorption, and the temperature of the water (Larson and Weber, 1994).

The Henry's Law constant of a chemical determines the tendency of a contaminant to volatilize from ground water into the soil gas. Henry's Law states that the concentration of a contaminant in the gaseous phase is directly proportional to the compound's concentration in the liquid phase and is a constant characteristic of the compound (Lyman *et al*., 1992):

$$C_a = HC_l \quad [22.12]$$

where:

H	Henry's Law Constant (atm m^3/mol)
C_a	concentration in air (atm)
C_l	concentration in water (mol/m^3)

Values of Henry's Law constants for selected chlorinated solvents and the BTEX compounds are given in Table 22.2. As indicated on the table, values of H for chlorinated compounds also vary over several orders of magnitude. Chlorinated solvents have low Henry's Law constants, with the exception of vinyl chloride. Volatilization of chlorinated solvents compounds from ground water is a relatively slow process that generally can be neglected when modeling biodegradation.

Table 22.2. Physical properties of chlorinated compounds.

Constituent	CAS #	Molecular weight		Diffusion coefficient				$\log K_{oc}$ (@20-25°C)	
				in air		in water			
		M_x, g/mol	Ref	D_{air}, cm^2/s	Ref	D_{wat}, cm^2/s	Ref	L/kg	Ref
Bromodichloromethane	75-27-4	163.8	a	2.98E-2	a	1.06E-5	a	1.85	a
Carbon tetrachloride	56-23-5	153.8	a	7.80E-2	a	8.80E-6	a	2.67	a
Chlorobenzene	108-90-7	112.6	a	7.30E-2	a	8.70E-6	a	2.46	a
Chloroethane	75-00-3	64.52	a	1.50E-1	a	1.18E-5	a	1.25	a
Chloroform	67-66-3	119.4	a	1.04E-1	a	1.00E-5	a	1.93	a
Chloromethane	74-87-3	51	a	1.28E-1	a	1.68E-4	b	1.40	c
Chlorophenol, 2-	95-57-8	128.6	a	5.01E-2	a	9.46E-6	a	2.11	a
Dibromochloromethane	124-48-1	208.29	a	1.99E-2	a	1.03E-5	a	2.05	a
Dichlorobenzene, (1,2)(-o)	95-50-1	147	a	6.90E-2	a	7.90E-6	a	3.32	a
Dichlorobenzene, (1,4)(-p)	106-46-7	147	a	6.90E-2	a	7.90E-6	a	3.33	a
Dichlorodifluoromethane	75-71-8	120.92	a	5.20E-2	a	1.05E-5	a	2.12	a
Dichloroethane, 1,1-	75-34-3	98.96	a	7.42E-2	a	1.05E-5	a	1.76	a
Dichloroethane, 1,2-	107-06-2	98.96	a	1.04E-1	a	9.90E-6	a	1.76	a
Dichloroethene, *cis*-1,2	156-59-2	96.94	a	7.36E-2	a	1.13E-5	a	1.38	f
Dichloroethene, *trans*-1,2	156-60-5	96.94	a	7.07E-2	a	1.19E-5	a	1.46	a
Dichloromethane	75-09-2	85	a	1.01E-1	a	1.17E-5	a	1.23	a
Tetrachloroethane, 1,1,2,2-	79-34-5	168	a	7.10E-2	a	7.90E-6	a	0.00	a
Tetrachloroethene	127-18-4	165.83	a	7.20E-2	a	8.20E-6	a	2.43	c
Trichlorobenzene, 1,2,4-	120-28-1	181.5	a	3.00E-2	a	8.23E-6	a	3.91	a
Trichloroethane, 1,1,1-	71-55-6	133.4	a	7.80E-2	a	8.80E-6	a	2.45	a
Trichloroethane, 1,1,2-	79-00-5	133.4	a	7.80E-2	a	8.80E-6	a	1.75	c
Trichloroethene	79-01-6	131.4	d	8.18E-2	e	1.05E-4	b	1.26	g
Trichlorofluoromethane	75-69-4	137.4	a	8.70E-2	a	9.70E-6	a	2.49	a
Vinyl chloride	75-01-4	62.5	a	1.06E-1	a	1.23E-5	a	0.39	h

[a]U.S.E.P. Agency, Hazardous Waste Treatment, Storage, and Disposal Facilities (TSDF), EPA-450/3-87-026, USEPA, OAQPS, Air Emission Models, 1989.
[b]Calculated diffusivity using the method of Hayduk and Laudie (W. Hayduk, H. Laudie, *AIChE J.*, **20**, 3, 611-15, 1974) and W. J. Lyman, **Handbook of Chemical Property Estimation Methods**, *McGraw-Hill*, New York, 1982.
[c]J. H. Montgomery, **Groundwater Chemicals Desk Reference**, 3rd Ed., *Lewis Publisher*s, Chelsea, MI, 1990
[d]NIOSH, Pocket Guide to Chemical Hazards, Ed., U.S. Dept. of Health & Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, 1990.
[e]Calculated diffusivity using the method of Fuller, Schettler, and Giddings [W. J. Lyman, **Handbook of Chemical Property Estimation Methods**, *McGraw-Hill*, New York, 1982]
[f]Calculated using Kenaga and Goring K_{ow}/solubility regression equation from W. J. Lyman, **Handbook of Chemical Property Estimation Methods**, *McGraw-Hill*, New York, 1982 and K^{ow} data from J. H. Montgomery, **Groundwater Chemicals Desk Reference**, 3rd Ed., *Lewis Publisher*s, Chelsea, MI, 1990, $\log(S, mg/L) = 0.922 \log(K_{ow}) + 4.184$ d

[g]Back calculated from solubility [Based on K_{ow} from J. H. Montgomery, **Groundwater Chemicals Desk Reference**, 3rd Ed., *Lewis Publisher*s, Chelsea, MI, 1990 and method from T. M. Vogel, C. S. Criddle and P. L. McCarty, *Environ. Sci. Tech*., **21**, 722-736 (1987)., $\log(K_{oc}) = 0.00028 + 0.938 \log(K_{ow})$]
[h]RBCA Chemical Database. Ground Water Services, Inc.

22.2.7 ABIOTIC DEGRADATION PATHWAYS

Hydrolysis, dehydrohalogenation, hydrogenolysis, and dihaloelimination are the main abiotic attenuation reaction mechanisms. Abiotic reactions are very dependent on the environmental circumstances, and in general, temperature has the most significant t effect on the rate of natural abiotic reactions (Vogel *et al*., 1987; Vogel, 1994; Tobiszewski and Namiesnik 2012).

Hydrolysis is a substitution reaction with very slow rate, and half-lives of days to centuries in ground water conditions (especially at low temperatures) in which a compound reacts with water, and a halogen substituent is replaced with a hydroxyl (OH^-) group resulting in the formation of alcohols and alkenes (Knox *et al*., 1993 after Johnson *et al*., 1989):

$$RX + HOH \rightarrow ROH + HX \qquad [22.13]$$

The likelihood that a halogenated solvent will undergo hydrolysis depends in part on the number of halogen substituents. More halogen substituents on a compound will decrease the chance for hydrolysis reactions to occur, and will therefore decrease the rate of the reaction. (Vogel *et al*., 1987). McCarty (1996) lists TCA (1, 1, 1-trichloroethane) as the only major chlorinated solvent that can be transformed chemically through hydrolysis (as well as elimination) leading to the formation of 1, 1-DCE (1, 1-dichlorethene) and acetic acid.

Locations of the halogen substituent on the carbon chain may also have some effect on the rate of reaction. The rate also may increase with increasing pH; however, a rate dependence upon pH is typically not observed below a pH of 11 (Mabey and Mill, 1978; Vogel and Reinhard, 1986). Rates of hydrolysis may be increased by the presence of clays, which can act as catalysts (Vogel *et al*., 1987). Other factors that impact the level of hydrolysis include dissolved organic matter, and dissolved metal ions. Hydrolysis rates can generally be described using first-order kinetics, particularly in solutions in which water is the dominant nucleophile (Vogel *et al*., 1987). A listing of half-lives for abiotic hydrolysis and dehydrohalogenation of some chlorinated solvents is presented on Table 22.3. Note that no distinctions are made in the table as to which mechanism is operating; this is consistent with the references from which the table has been derived (Vogel *et al*., 1987; Butler and Barker, 1996).

Table 22.3. Approximate half-lives of abiotic hydrolysis and dehydrohalogenation reactions involving chlorinated solvents.

Compound	Half-Life (years)	Products
Chloromethane	no data	
Dichloromethane	704	
Chloroform	3500, 1800	

Table 22.3. Approximate half-lives of abiotic hydrolysis and dehydrohalogenation reactions involving chlorinated solvents.

Compound	Half-Life (years)	Products
Carbon tetrachloride	41	
Chloroethane	0.12	ethanol
1,1-Dichloroethane	61	
1,2-Dichloroethane	72	
1,1,1-Trichloroethane	1.7, 1.1 2.5	acetic acid 1,1-DCE
1,1,2-Trichloroethane	140, 170	1,1-DCE
1,1,1,2-Tetrachloroethane	47, 380	TCE
1,1,2,2-Tetrachloroethane	0.3 0.4, 0.8	1,1,2-TCA TCE
Tetrachloroethene	0.7*, 1.3E-06	
Trichloroethene	0.7*, 1.3E-06	
1,1-Dichloroethene	1.2 x 10	
1,2-Dichloroethene	2.1 x 10	

*Butler and Barker (B. J. Butler and J. F. Barker in **Dense Chlorinated Solvents and other DNAPLs in Ground Water: History, Behavior, and Remediation**, J. F. Pankow and J. A. Cherry, Ed., *Waterloo Press,* Waterloo, Canada, 1996, pp.) indicate that these values may reflect experimental difficulties and that the longer half life [as calculated by Jeffers et al. (P. M. Jeffers, L. M. Ward, L. M. Woytowitch and N. L. Wolfe, *Environ. Sci. Tech.*, **23**, 965-969 (1989) should be used.

One common chlorinated solvent for which abiotic transformations have been well-studied is 1,1,1-TCA. 1,1,1-TCA may be abiotically transformed to acetic acid through a series of substitution reactions, including hydrolysis. In addition, 1,1,1-TCA may be reductively dehalogenated to form 1,1- DCA and then chloroethane (CA), which is then hydrolyzed to ethanol (Vogel and McCarty, 1987) or dehydrohalogenated to vinyl chloride (Jeffers *et al*., 1989).

Dehydrohalogenation is an elimination reaction (not a redox reaction) involving halogenated alkanes in which a halogen is removed from one carbon atom, followed by the subsequent removal of a hydrogen atom from an adjacent carbon atom. In this two-step reaction, less halogenated and less saturated compounds including an alkene, and a hydrochloric acid (HCl) are produced as follows (Tobiszewski and Namiesnik 2012):

$$RHCCl - CRH_2 \rightarrow RHC = CHR + HCl \qquad [22.14]$$

Contrary to the patterns observed for hydrolysis, the likelihood that dehydrohalogenation will occur increases with the number of halogen substituents. It has been suggested that under normal environmental conditions, monohalogenated aliphatics apparently do not undergo dehydrohalogenation, and these reactions are apparently not likely to occur (March, 1985; Vogel *et al*., 1987). However, Jeffers *et al*. (1989) report on the dehydrohalogenation of CA to VC. Polychlorinated alkanes have been observed to undergo dehydro-

halogenation under normal conditions and extremely basic conditions (Vogel *et al*., 1987). As with hydrolysis, bromine substituents are more reactive with respect to dehydrohalogenation.

Dehydrohalogenation rates may also be approximated using pseudo-first-order kinetics. The rates will not only depend upon the number and types of halogen substituent, but also on the hydroxide ion concentration. Under normal pH conditions (i.e., near a pH of 7), interaction with water (acting as a weak base) may become more important (Vogel *et al*., 1987). Transformation rates for dehydrohalogenation reactions are presented in Table 22.3.

The organic compound 1,1,1-TCA is also known to undergo dehydrohalogenation (Vogel and McCarty, 1987). In this case, TCA is transformed to 1,1-DCE, which is then reductively dehalogenated to VC. The VC is then either reductively dehalogenated to ethene or consumed as a substrate in an aerobic reaction and converted to CO_2. In a laboratory study, Vogel and McCarty (1987) reported that the abiotic conversion of 1,1,1-TCA to 1,1-DCE has a rate constant of about 0.04 $year^{-1}$. Jeffers *et al*. (1989) reported that the tetrachloroethanes and pentachloroethanes degrade to TCE and PCE via dehydrohalogenation, respectively. Jeffers *et al*. (1989) also report that CA may degrade to VC.

Hydrogenolysis, a reductive process that includes the simple replacement of a chlorine (or another halogen) by a hydrogen by adding two electron to the molecule as follows:

$$RCl + H^+ + 2e^- \rightarrow RH + Cl^- \qquad [22.15]$$

Nobre and Nobre (2004) reported hydrogenolysis as the main abiotic degradation pathway for highly chlorinated ethene derivatives (Nobre and Nobre, 2004).

Dihaloelimination, on the other hand, is the removal of two chlorines (or other halogens) accompanied by the formation of a double carbon-carbon bond. Therefore the final products of this process are less saturated aliphatic hydrocarbons and two chloride ions. The reaction is as follows:

$$RCCl - CClR + 2e^- \rightarrow RC{=}CR + 2Cl^- \qquad [22.16]$$

While these two reactions are thermodynamically possible under reducing conditions, they often do not take place in the absence of biological activity (Butler and Barker (1996), Criddle *et al*. (1986), Jafvert and Wolfe (1987), Reinhard *et al*. (1990), Acton (1990), Nobre and Nobre (2004), and Tobiszewski and Namiesnik (2012)). In general, microbes may produce reductants that facilitate such reactions in conjunction with minerals in the aquifer matrix. Moreover, the reducing conditions necessary to produce such reactions are most often created as a result of microbial activity. It is therefore not clear if some of these reactions are truly abiotic, or if because of their reliance on microbial activity to produce reducing conditions or reactants, they should be considered to be a form of cometabolism. In some cases, truly abiotic reductive dechlorination has been observed (Gillham and O'Hannesin, 1994; Wang and Tan, 1990), however, the conditions that favor such reactions may not occur naturally.

Recent studies show that zero-valent metals (e.g., iron, zinc, and palladium), sulfide minerals (like FeS and FeS_2), and green rust can act as abiotic agents and increase the reductive dechlorination rates of chlorinated ethanes and ethenes. For example, in the presence of zero-valent iron, β-elimination is the main degradation pathway of chlorinated ethenes. In the β-elimination pathway, chlorines in vicinal carbon atoms are eliminated and a third C–C bond will be formed (Tobiszewski and Namiesnik, 2012; Brown *et al*., 2009; and Ma and Wu, 2008). Hara *et al*. (2005) reported that with β-elimination, TCE, c-DCE, and t-DCE reduction occurred 40, 10, 100 times faster, respectively, in comparison to hydrogenolysis (Hara *et al*. 2005).

22.3 BIODEGRADATION OF CHLORINATED SOLVENTS

The biodegradation of organic chemicals can be grouped into two broad categories:

1. Use of the organic compound as a primary growth substrate; and
2. Cometabolism.

The use of chlorinated solvents as a primary growth substrate (meaning the mediating organism uses energy for growth) is probably the most important biological mechanism affecting them in the subsurface. Biodegradation of chlorinated solvents can occur *via* both reductive and oxidative processes depending on the degree of chlorination and the site conditions. Oxidative processes (CS is used as an electron donor) encompass aerobic and anaerobic biodegradation reactions.

When chlorinated solvents are used as electron acceptors, reduction occurs *via* an anaerobic reductive dechlorination process called halorespiration. Generally, there is a direct relationship between the number of chlorine substituents and the reduction tendency of chlorinated solvents. Conversely, when chlorinated solvents are used as electron donors, oxidative degradation occurs under aerobic or anaerobic conditions. In contrast with reductive dechlorination, as the numbers of chlorine substituents decrease, the oxidation rate of chlorinated solvent increases (Gossett and Zinder, 1996;Tiehm and Schmidt, 2011; and Mattes *et al*., 2010).

It is important to note that not all chlorinated solvents can be degraded *via* all of these reactions. In fact, vinyl chloride is the only chlorinated solvent known to degrade *via* all of these pathways.

Chlorinated solvents can also be degraded *via* cometabolic pathways. During cometabolism, microorganisms gain carbon and energy for growth from metabolism of a primary substrate, and chlorinated solvents are degraded fortuitously by enzymes present in the metabolic pathway. Cometabolism reactions can be either oxidation or reduction reactions (under aerobic or anaerobic conditions), however based on data from numerous field sites, it does not appear that cometabolic oxidation will be a significant process in plumes of chlorinated solvents. Anaerobic reductive dechlorination can also occur *via* cometabolism. The process of cometabolic reductive dechlorination, however, is “sufficiently slow and incomplete that a successful natural attenuation strategy typically cannot completely rely upon it” (Gossett and Zinder, 1996).

The types of biodegradation reactions that have been observed for different chlorinated solvents are presented in Table 22.4. The remainder of this section will focus on describing the various mechanisms shown in Table 22.4.

Table 22.4. Biological degradation processes for selected chlorinated solvents.

Compound	HR	DAeO	DAnO	AeC	AnC
PCE	x				x
TCE	x			x	x
DCE	x	x	x	x	x
Vinyl chloride	x	x	x	x	x
1,1,1-TCA	x			x	x
1,2-DCA	x	x		x	x
Chloroethane		x		x	
Carbon tetrachloride	x				x
Chloroform	x			x	x
Methylene chloride		x	x	x	

HR=Halorespiration, DAeO=Direct aerobic oxidation, DAnO=Direct anaerobic oxidation, AeC=Aerobic cometabolism, AnC=Anaerobic cometabolism

22.3.1 REDUCTIVE DECHLORINATION OR HALORESPIRATION

Reductive dechlorination is a reaction in which a chlorinated solvent acts as an electron acceptor and a chlorine atom on the molecule is replaced with a hydrogen atom. When this reaction is biological, and the organism is utilizing the substrate for energy and growth, the reaction is termed halorespiration. The electron donor in this process can be labile organic carbon or the hydrogen molecule which is produced *via* the fermentation process (Holliger and Schumacher, 1994; Brown *et al*., 2009; Kennedy *et al*., 2006). Dehalogenating bacteria such as *Dehalococcides, Sulfurospirillum mulivorans*, and *Dehalobacter restictus* can biodegrade CS in the presence of adequate electron donors (Schumacher and Holliger, 1996; Major *et al*., 2002; Löffler and Edwards, 2006; Amos *et al*., 2008; Brown *et al*. 2009; and Robinson *et al*., 2009).

In general, reductive dechlorination of ethenes occurs by sequential dechlorination from PCE to TCE to DCE to VC and finally to ethene. A summary of key biotic and abiotic reactions for chlorinated ethenes, ethanes, and methanes first developed by Vogel *et al*. (1987) is shown in Figure 22.4.

When the hydrogen molecule is the electron donor, the generalized reaction can be represented as follows:

$$H_2 + C\text{-}Cl \rightarrow C\text{-}H + H^+ + Cl^- \qquad [22.17]$$

Where C–Cl represents a carbon-chloride bond in a chlorinated solvent. In this reaction, H_2 is the electron donor which is oxidized and the chlorinated solvent is the electron

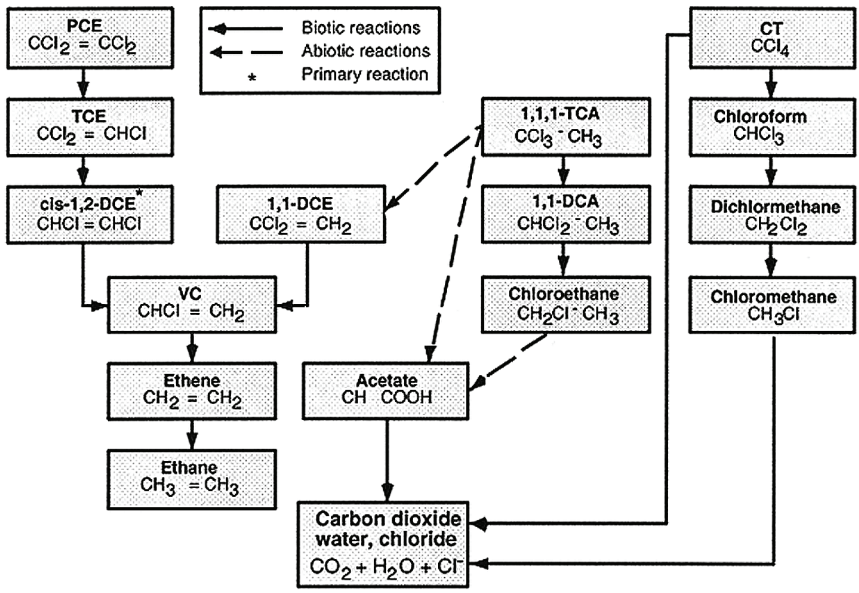


Figure 22.4 Abiotic and biological transformation pathways for selected chlorinated solvents. [Adapted, by permission, from T. H. Wiedemeier, H. S. Rifai, C. J. Newell and J. T. Wilson, **Natural Attenuation of Fuels and Chlorinated Solvents in the Subsurface,** *John Wiley & Sons, Inc.*, New York, NY, 1999.]

acceptor which is reduced. In addition to other electron donors (also called fermentation products) that have been identified, the importance of hydrogen as an electron donor in the reductive dechlorination of PCE and TCE was recognized in studies by Holliger *et al.* (1993), Gossett and Zinder (1996), Smatlak *et al.* (1996), and Ballapragada *et al.* (1997).

The hydrogen is produced in the subsurface by the fermentation of a wide variety of organic compounds including petroleum hydrocarbons and natural organic carbon. Because of its importance in the microbial metabolism of the halorespirators, the relative supply of hydrogen precursors compared to the amount of chlorinated solvent that must be degraded is an important consideration when evaluating natural attenuation. For halorespiration to occur using the hydrogen molecule as the electron donor, Wiedemeier *et al.* (1999) conclude that the following conditions must exist: "1) the subsurface environmental condition must be anaerobic and have a low oxidation-reduction potential (based on thermodynamic considerations, reductive dechlorination reactions will occur only after both oxygen and nitrate have been depleted from the aquifer); 2) chlorinated solvents amenable to halorespiration must be present; and 3) there must be an adequate supply of fermentation substrates for production of dissolved hydrogen."

Fermentation, the process that generates hydrogen, is a balanced oxidation-reduction reaction, in which different portions of a single substrate are oxidized and reduced, yielding energy. Fermentation yields substantially less energy per unit of substrate compared to oxidation reactions which utilize an external electron acceptor; thus, fermentation gener-

ally occurs when these external electron acceptors are not available. Bacterial fermentation which can be important in anaerobic aquifers includes primary and secondary fermentation.

Primary fermentation refers to the fermentation of primary substrates such as sugars, amino acids, and lipids yields acetate, formate, CO_2 and H_2, but also yields ethanol, lactate, succinate, propionate, and butyrate.

Secondary fermentation, on the other hand, refers to the fermentation of primary fermentation products such as ethanol, lactate, succinate, propionate, and butyrate yielding acetate, formate, H_2, and CO_2. Bacteria which carry out these reactions are called obligate proton reducers because the reactions must produce hydrogen in order to balance the oxidation of the carbon substrates. These secondary fermentation reactions are energetically favorable only if hydrogen concentrations are very low (10^{-2} to 10^{-4} atm or 8,000 nM to 80 nM dissolved hydrogen, depending on the fermentation substrate). Thus, these fermentation reactions occur only when the produced hydrogen is utilized by other bacteria, such as methanogens which convert H_2 and CO_2 into CH_4 and H_2O. However, in the presence of external electron acceptors (halogenated organics, nitrate, sulfate, etc.), other products will be formed (Wiedemeier *et al*., 1999).

There are a number of compounds besides the ones listed above that can be fermented to produce hydrogen. Sewell and Gibson (1991) noted that petroleum hydrocarbons support reductive dechlorination. In this case, the reductive dechlorination is driven by the fermentation of biodegradable compounds such as the BTEX compounds in fuels. Metabolism of BTEX compounds to produce hydrogen likely requires the involvement of several strains of bacteria.

As hydrogen is produced by fermentative organisms, it is rapidly consumed by other bacteria. The utilization of H_2 by non-fermentors is known as interspecies hydrogen transfer and is required for fermentation reactions to proceed. Although H_2 is a waste product of fermentation, it is a highly reduced molecule which makes it an excellent, high-energy electron donor. Both organisms involved in interspecies hydrogen transfer benefit from the process. The hydrogen-utilizing bacteria gain a high-energy electron donor, and, for the fermentors, the removal of hydrogen allows additional fermentation to remain energetically favorable.

A wide variety of bacteria can utilize hydrogen as an electron donor: denitrifiers, iron reducers, sulfate reducers, methanogens, and halorespirators. Thus, the production of hydrogen through fermentation does not, by itself, guarantee that hydrogen will be available for halorespiration. For dechlorination to occur, halorespirators must successfully compete against the other hydrogen utilizers for the available hydrogen. Smatlak *et al*. (1996) suggest that the competition for hydrogen is controlled primarily by the Monod half-saturation constant $K_s(H_2)$, the concentration at which a specific strain of bacteria can utilize hydrogen at half the maximum utilization rate. Ballapragada *et al*. (1997), however, provide a more detailed discussion of halorespiration kinetics and point out that competition for hydrogen also depends on additional factors including the bacterial growth rate and maximum hydrogen utilization rate.

Smatlak *et al*. (1996) have suggested that the steady-state concentration of hydrogen will be controlled by the rate of hydrogen production from fermentation. Both laboratory results and field observations have suggested, however, that the steady-state concentration of hydrogen is controlled by the type of bacteria utilizing the hydrogen and is almost completely independent of the rate of hydrogen production (Fennell et. al, 1997; Ballapragada et. al, 1997; Chapelle *et al*., 1995; Carr and Hughes, 1997). Under nitrate reducing conditions, steady-state H_2 concentrations were <0.05 nM; under iron reducing conditions, they were 0.2 to 0.8 nM; under sulfate reducing conditions, they were 1-4 nM, and under methanogenic conditions, they were 5-14 nM (Lovley and Goodwill, 1988; Lovley *et al*., 1994, and Chapelle *et al*., 1995). Finally, Carr and Hughes (1997) show that dechlorination in a laboratory column is not impacted by competition for electron donor at high hydrogen concentrations. Thus, it is clear that an increased rate of hydrogen production will result in increased halorespiration without affecting the competition between bacteria for the available hydrogen.

When labile organic carbon is the electron donor, the process is termed Microbial Reductive Dechlorination (MRD) or biostimulation. In this process, bacteria use chlorinated aliphatic compounds (CAHs) like perchloroethene (PCE), trichloroethene (TCE), and dichlororoethene isomers (DCE) as electron acceptors to oxidize labile organic carbon which can be available naturally or introduced to the site. Reduced aquifer conditions in the presence of organic carbon can facilitate the MRD process (Kennedy *et al*., 2006; Scow and Hicks, 2005).

The reduced environment is provided by the consumption of electron acceptors such as oxygen, nitrate and SO_4^{2-} by heterotrophic bacteria during the process of labile organic carbon oxidation. Under reduced conditions, MRD converts TCE to DCE as follows:

$$4C_2HCl_3 + CH_3COOH + H_2O \rightarrow 4C_2H_2Cl_2 + 2CO_2 + 4H^+ + 4Cl^- \qquad [22.18]$$

As can be seen in this reaction, a parent chlorinated solvent is converted to one or more chlorinated progeny products. In this way, CAHs will be eliminated; this process faces some difficulty to commence and can lead to the production of detrimental chlorinated daughter products (Kennedy *et al*., 2006).

22.3.1.1 Stoichiometry of reductive dechlorination

Under anaerobic conditions, the reductive dehalogenation of the chlorinated ethenes occurs as a series of consecutive irreversible reactions. In this case, by adding one mole hydrogen (produced through fermentation of the organic carbon source), one mole of parent compound is converted to one mole of daughter product (ITRC, 2005). Thus, the theoretical minimum hydrogen requirement for dechlorination can be calculated on a mass basis as shown below:

1 mg H_2 will dechlorinate 21 mg of PCE to ethene
1 mg H_2 will dechlorinate 22 mg of TCE to ethene
1 mg H_2 will dechlorinate 24 mg of DCE to ethene
1 mg H_2 will dechlorinate 31 mg of VC to ethene [22.19]

Complete fermentation of BTEX compounds is expected to yield 0.25 to 0.4 mg H_2 per mg BTEX. Therefore, for each mg of BTEX consumed, 4.5 to 7 mg of chloride could be released during reductive dechlorination (Gossett and Zinder (1996)).

However, the utilization of hydrogen for dechlorination will never be completely efficient because of the competition for hydrogen in the subsurface. As a result, the minimum dose for electron donor should be enough to reduce all electron acceptors present in groundwater including oxygen, nitrate, dissolved iron, sulfate and chloroethenes. One rule of thumb that has been proposed is the following: for reductive dechlorination to completely degrade a plume of dissolved chlorinated solvents, organic substrate concentrations greater than 25 to 100+ times that of the chlorinated solvent are required (McCarty, 1997; ITRC, 2005)

Recently, novel *in-situ* methods like Biogeochemical Reductive Dechlorination (BiRD) have been introduced. BiRD requires less organic substrate and can commence after consumption of oxygen, nitrate, and dissolved iron, while in MRD the chlorinated solvent's reduction starts after sulfate depletion (Kennedy *et al*., 2006).

22.3.1.2 Chlorinated solvents that are amenable to halorespiration

As shown in Table 22.4, all of the chlorinated ethanes (PCE, TCE, DCE, VC) and some of the chlorinated ethanes (TCA, 1,2 DCA) can be degraded *via* halorespiration; however, methylene chloride has not yet been shown to be degraded by this process. The oxidation state of a chlorinated solvent affects both the energy released by halorespiration and the rate at which the reaction occurs. In general, the more oxidized a compound is (more chlorine atoms on the organic molecule), the more amenable it is for reduction by halorespiration.

As with the ethenes, chlorinated ethanes will also undergo halorespiration. Dechlorination of 1,1,1-TCA has been described by Vogel and McCarty (1987) and Cox *et al*. (1995), but understanding this pathway is complicated by the rapid hydrolysis reactions (e.g., half-life is 0.5-2.5 yrs) that can affect TCA (Vogel, 1994; see Chapter 3).

Finally, halorespiration has been observed with highly chlorinated benzenes such as hexachlorobenzene, pentachlorobenzene, tetrachlorobenzene, and trichlorobenzene (Holliger *et al*., 1992; Ramanand *et al*., 1993; Suflita and Townsend, 1995). In anaerobic conditions, highly chlorinated benzenes can be easily reductively dechlorinated and product lower chlorinated benzenes. Bacteria from the genus *Dehalococcoides* are known for having the main role in this process. Conversely, lower chlorinated benzenes have a lower tendency for reductive dechlorination, and finally mono-chlorinated benzene is the most resistant in this anaerobic process (Field and Sierra-Alvarez, 2008).

As discussed by Suflita and Townsend (1995), halorespiration of aromatic compounds has been observed in a variety of anaerobic habitats, including aquifer materials, marine and freshwater sediments, sewage sludges, and soil samples. However, isolation of specific microbes capable of these reactions has been difficult.

22.3.1.3 Limitations of reductive dechlorination

The behavior of chlorinated ethanes and ethenes in natural waters is variable and depends strongly on environmental conditions. For example, at some TCE-contaminated sites, a rapid decrease in concentration from high to negligible levels is observed, whereas at oth-

ers the level of contamination remains constant (Chapman *et al*., 2007). Inadequate electron donors, high concentration of other electron acceptors like oxygen, nitrate, dissolved iron and sulfate, short contact time, absence of indigenous bacteria capable of dechlorination, and low pH in the subsurface are the most important factors affecting the natural attenuation of chlorinated solvents (Robinson *et al*. 2009; Löffler and Edwards 2006).

As mentioned previously, reductive dechlorination occurs in different steps and in each step one chlorine atom is removed. This chlorine atom can form hydrochloric acid (HCl) which is a strong acid. HCl production and formation of organic acids during the fermentation process reduces the pH. Based on laboratory studies, the optimum pH range for the dechlorinating bacteria is between 6.8 and 7.8, and conditions below this range can decrease the dechlorination rate. To overcome this problem, adding an alkalinity source like sodium or potassium bicarbonate is suggested in different studies (Robinson *et al*., 2009; AFCEE, 2004; and Cope and Hughes 2001).

22.3.1.4 Interaction between abiotic pathways and reductive biotic pathways

As mentioned previously, treatment of chlorinated solvents in groundwater can occur via biotic and abiotic reductive processes. In the past, it was assumed that biotic and abiotic reductive pathways are independent. As a result, the research in these two areas was undertaken independently such that biotic dechlorination focused on microbiology, and abiotic chemical reduction focused on electron transfers.

Recent research, however, has focused on the interaction between biological and abiotic processes. There are two types of biological-abiotic interactions including causative and synergistic relationships. In a causative relationship, the goal focuses on producing reducing minerals like iron sulfides, and reduced-iron oxides *via* biological reactions. In a synergistic relationship biological processes are used to enhance the efficiency of the abiotic processes (Brown *et al*., 2009).

An example of a process based on the causative relationship is one referenced earlier in this chapter, named Biogeochemical Reductive Dechlorination (BiRD). This method can be viewed as an alternative method to MRD for destructing CAHs (Brown *et al*., 2009; Kennedy *et al*., 2006). The main concept in BiRD is based on this fact that carbon is used by bacteria for growth and for producing energy *via* different reductive metabolic pathways that can affect the abiotic processes. Reduced minerals, in this case, mostly iron sulfides (FeS and FeS_2) are produced through bacterial respiration; these minerals aid the abiotic reductive dechlorination process (Kennedy *et al*., 2006; Lee and Batchelor, 2002). BiRd occurs *via* three steps:

•1 Microbiological sulfate respiration. Sulfate-reducing bacteria can cause biological oxidation of an organic carbon and produce hydrogen sulfide (H_2S), for example:

$$2CH_2O + SO_4^{2-} \rightarrow 2HCO_3^- + H_2S(g) \qquad [22.20]$$

- Geochemical FeS respiration. The produced H_2S can combine with Fe minerals in oxide/hydroxide form that are sufficiently found in most sediments to create iron sulfide, for example:

$$2FeOOH(s) + 3H_2S(aq) \rightarrow 2FeS(s) + S^\circ + 2H_2O \quad [22.21]$$

This is a very fast abiotic reaction, and over time, FeS_2 can be generated as follows:

$$FeS(s) + S^\circ \rightarrow 2FeS_2 \quad [22.22]$$

As can be seen, if all reactions occur completely, the half of the reduced SO_4^{2-} will appear as FeS and the other half will be FeS_2. FeS can also be generated by the reaction between iron minerals and hydrogen sulfide as:

$$2Fe(OH)_2(s) + H_2S(aq) \rightarrow FeS(s) + 2H_2O \quad [22.23]$$

Kennedy and Everett (2001) reported that in common native sediments, FeS and FeS_2 can be produced in the presence of organic carbon and SO_4^{2-}.

An increase in iron sulfide mineral concentrations have been reported in a number of environments with rich organic carbons like marine or lake sediments and also in aquifers with organic carbon or hydrocarbon contamination.

- Chemical dechlorination. Both reduced iron and sulfur in iron sulfide can cause reduction of some oxidized compounds like CAHs. Butler and Hayes (1999) reported that TCE and PCE can be swiftly reduced to acetylene by FeS under laboratory conditions. They also emphasize the short half life of acetylene (19 days), and insignificant chlorinated daughter products as the benefits of using FeS. Reasonable dechlorination rates for PCE, cDCE, and VC in reaction with FeS_2 also reported by Lee and Batchelor (2002).

  A proposed chemical reaction for TCE dechlorination by FeS oxidation can be shown as follows:

$$4FeS + 9C_2HCl_3 + 28H_2O \rightarrow 4Fe(OH)_3 + 4SO_4^{2-} +$$

$$+ 4C_2H_2 + 27Cl^- + 35H^+ \quad [22.24]$$

It should be noted that microbial degradation of chlorinated solvents in groundwater (including MRD and BiRD) can occur naturally or by human activities through enhanced or engineered bioremediation methods (Scow and Hicks, 2005). In engineered methods, using BiRD has some theoretical advantages in comparison with MRD including:

1. In MRD, the organic carbon source introduced to the site should mix with both the chlorinated solvent and the bacteria, while in BiRD, the pathway for the introduced organic carbon and the chlorinated solvent is the same and FeS is present within the aquifer matrix.
2. In MRD, to provide long term dechlorination, viscous organic carbon may be used that can decrease the aquifer permeability and lead to some difficulty in contaminant movement through the aquifer. For BiRD, simply degradable and solvable organic carbon can be used such that the aquifer permeability will not be affected.
3. In MRD, most of the introduced carbon can be used by other types of heterotrophic bacteria which are in competition with chlororespiring bacteria. In BiRD, most of the introduced carbon is used for reduction of SO_4^{2-} because of the low concentration of oxygen and nitrite and also the inhibiting effect of SO_4^{2-} presence on methanogenesis activities.

4. At some sites, there are no indigenous bacteria capable of MRD or the presented bacteria have a long time lag so bioaugmentation would be needed. In contrast, because dechlorination occurs through abiotic pathways in BiRD, choosing the introduced organic carbon can be done in a way that facilitates biodegradation by common sulfate reducing bacteria.
5. BiRD generates little dechlorinated daughter products, whereas the production of daughter products like vinyl chloride (VC) is a problem in MRD (Kennedy and Everett, 2001; Kennedy *et al*., 2006).

22.3.2 OXIDATION OF CHLORINATED SOLVENTS

In contrast to halorespiration, direct oxidation of some chlorinated solvents can occur biologically in groundwater systems. In this case, the chlorinated compound serves as the electron donor, and oxygen, sulfate, ferric iron or other compounds serve as the electron acceptor.

22.3.2.1 Direct aerobic oxidation of chlorinated compounds

Under direct aerobic oxidation conditions, the facilitating microorganism uses oxygen as an electron acceptor and obtains energy and organic carbon from the degradation of the chlorinated solvent. In general, the more-chlorinated aliphatic chlorinated solvents (e.g., PCE, TCE, and TCA) have not been shown to be susceptible to aerobic oxidation, while many of the progeny products (e.g., vinyl chloride, 1,2-DCA, and cDCE) are degraded *via* direct aerobic oxidation. A number of studies have showed direct aerobic oxidation for cDCE and VC (Giddings *et al*. 2010, Jin and Mattes 2008, Gossett 2010, Tiehm and Schmidt 2011) but only few studies like the one conducted by Olaniran *et al*. (2008) reported tDCE direct oxidation in contaminated sites in Africa.(Olaniran *et al*. 2008)

Hermans *et al*. (1985) and Hartmans and de Bont (1992) show that vinyl chloride can be used as a primary substrate under aerobic conditions, with vinyl chloride being directly mineralized to carbon dioxide and water. Direct vinyl chloride oxidation has also been reported by Davis and Carpenter (1990), McCarty and Semprini (1994), and Bradley and Chapelle (1998). Aerobic oxidation is rapid relative to reductive dechlorination of dichloroethene and vinyl chloride. Recent research demonstrated that during direct aerobic oxidation, the interaction among different chloroethenes can be an important factor (Zhao *et al*., 2010).

Although direct DCE oxidation has not been verified (Bradley and Chapelle, 1998), studies have suggested that DCE isomers may be used as primary substrates (Klier *et al*., 1998). In these experiments, it was observed that *cis*-1,2-DCE degraded more rapidly than the other isomers and that DCE degradation was much slower in aquifer microcosms than in surface soil microcosms.

Of the chlorinated ethanes, only 1,2-dichloroethane has been shown to be aerobically oxidized. Stucki *et al*. (1983) and Janssen *et al*. (1985) show that 1,2-DCA can be used as a primary substrate under aerobic conditions. In this case, the bacteria transform 1,2-DCA to chloroethanol, which is then mineralized to carbon dioxide. McCarty and Semprini (1994) describe investigations in which 1,2-dichloroethane (DCA) was shown to serve as primary substrates under aerobic conditions.

In general, the highly chlorinated ethenes (e.g., PCE, TCE, and TCA) are not likely to serve as electron donors for aerobic microbial degradation reactions. To date, no micro-

organisms have been identified that can use PCE, TCE, or TCA as primary substrates under aerobic conditions. This is because the highly chlorinated compounds tend to be much more oxidized than most organic carbon present in a groundwater system.

Chlorobenzene and polychlorinated benzenes (up to and including tetrachlorobenzene) have been shown to biodegrade under aerobic conditions. Several studies have shown that bacteria are able to utilize chlorobenzene (Reineke and Knackmuss, 1984), 1,4-DCB (Reineke and Knackmuss, 1984; Schraa *et al*., 1986; Spain and Nishino, 1987), 1,3-DCB (de Bont *et al*., 1986), 1,2-DCB (Haigler *et al*., 1988), 1,2,4-TCB (van der Meer *et al*., 1987; Sander *et al*., 1991), and 1,2,4,5-TeCB (Sander *et al*., 1991) as primary growth substrates in aerobic systems. Nishino *et al*. (1994) note that aerobic bacteria able to grow on chlorobenzene have been detected at a variety of chlorobenzene-contaminated sites but not at uncontaminated sites. Spain (1996) suggests that this provides strong evidence that the bacteria are selected for their ability to derive carbon and energy from chlorobenzene degradation *in situ*. The pathways for all of these reactions are similar, bearing resemblance to benzene degradation pathways (Chapelle, 1993; Spain, 1996).

22.3.2.2 Aerobic cometabolism of chlorinated compounds

Degradation of chlorinated compounds under aerobic cometabolic degradation can occur fortuitously and that is because the implicated enzymes in this process can be used for auxiliary substrates that are bacterial growth substrates (Tiehm and Schmidt, 2011). It has been reported that under aerobic conditions, chlorinated ethenes, with the exception of PCE, are susceptible to cometabolic oxidation (Murray and Richardson, 1993; Vogel, 1994; McCarty and Semprini, 1994; Adriaens and Vogel, 1995).

Vogel (1994) further elaborates that the oxidation rate increases as the degree of chlorination decreases. Aerobic cometabolism of ethenes may be characterized by a loss of contaminant mass, the presence of intermediate degradation products (e.g., chlorinated oxides, aldehydes, ethanol, and epoxides), and the presence of other products such as chloride, carbon dioxide, carbon monoxide, and a variety of organic acids (Miller and Guengerich, 1982; McCarty and Semprini, 1994). Cometabolism requires the presence of a suitable primary substrate such as toluene, phenol, or methane. For cometabolism to be effective, the primary substrate must be present at higher concentrations than the chlorinated compound, and the system must be aerobic. Because the introduction of high concentrations of oxidizable organic matter into an aquifer quickly drives the groundwater anaerobic, aerobic cometabolism typically must be engineered.

22.3.2.3 Anaerobic oxidation of chlorinated compounds

Anaerobic oxidation occurs when anaerobic bacteria use the chlorinated solvent as an electron donor by utilizing an available electron acceptor such as ferric iron (Fe(III)). Anaerobic oxidation has been mostly described in laboratory studies. Bradley and Chapelle (1996) show that vinyl chloride can be oxidized to carbon dioxide and water *via* Fe(III) reduction. In microcosms amended with Fe(III)-EDTA, reduction of vinyl chloride concentrations closely matched the production of carbon dioxide. Slight mineralization was also noted in un-amended microcosms. The rate of this reaction apparently depends on the bioavailability of Fe(III). In a subsequent paper, Bradley and Chapelle (1997) reported “significant” anaerobic mineralization of both DCE and VC in microcosms con-

taining creek bed sediments. The sediments were taken from a stream where groundwater containing chlorinated ethenes continually discharges. Anaerobic mineralization was observed in both methanogenic and Fe(III) reducing conditions.

Knowledge regarding anaerobic oxidation has not been completed yet, and there remain a number of uncertainties related to anaerobic oxidation occurring in groundwater. In some field sites, for example, the assumption of anaerobic oxidation, has been changed into a possibility for occurring aerobic oxidation with very low concentrations of oxygen (Gossett 2010).

22.4 BIODEGRADATION RATES FOR CHLORINATED SOLVENTS

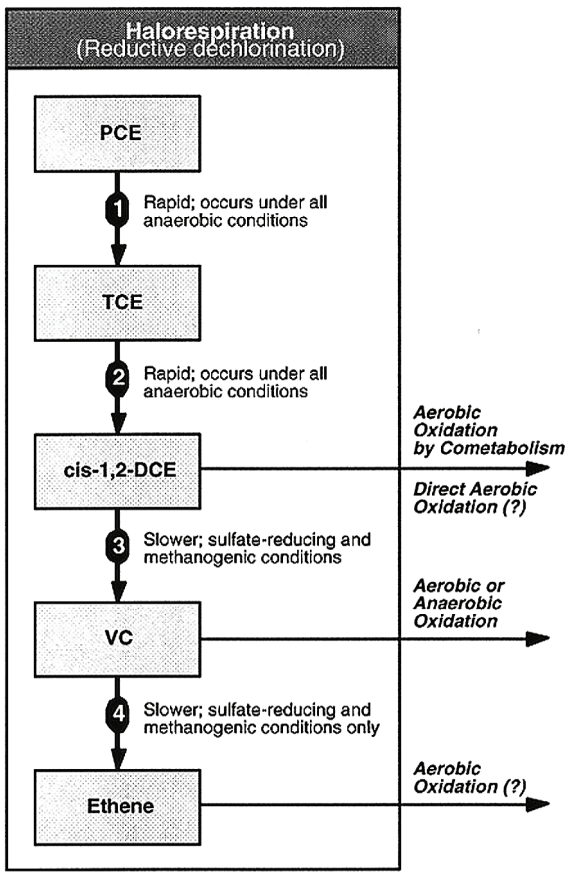


Figure 22.5 Reaction sequence and relative rates for halorespiration of chlorinated ethenes, with other reactions shown. [Adapted, by permission, from T. H. Wiedemeier, H. S. Rifai, C. J. Newell and J. T. Wilson, **Natural Attenuation of Fuels and Chlorinated Solvents in the Subsurface,** *John Wiley & Sons, Inc.*, New York, NY, 1999.]

Overall, dechlorination is more rapid for highly chlorinated compounds than for compounds that are less chlorinated (Vogel and McCarty, 1985; Vogel and McCarty, 1987; Bouwer, 1994). Figure 22.5 qualitatively shows the reaction rate and required conditions for halorespiration of PCE to ethene. PCE (four chlorines) degrades the fastest under all anaerobic environments, while VC (single chlorine) will degrade only under sulfate-reducing and methanogenic conditions, with a relatively slow reaction rate.

At many chlorinated ethene sites, concentrations of *cis*-1,2-DCE are often higher than any of the parent chlorinated ethene compounds. The reason for the accumulation of 1,2-DCE may be due to either slower rates of DCE halorespiration, or the prevalence of organisms that reduce PCE as far as *cis*-1,2-DCE over ones that can reduce PCE all the way to ethene (Gossett and Zinder, 1996). Although many researchers have commented that reductive dechlorination will result in the accumulation of VC (e.g., see Bradley and

Chapelle, 1996 and Weaver *et al*., 1995), at many field sites VC accumulation is much lower than *cis*-1,2-DCE. This may occur because the vinyl chloride in many chlorinated solvent plumes can migrate to zones that can support direct oxidation of VC oxidation, either aerobically and/or anaerobically.

Suarez and Rifai (1999) analyzed data from 138 studies (field and laboratory) to estimate biodegradation coefficients for chlorinated compounds. Suarez and Rifai (1999) found a total of thirteen studies that reported Michaelis-Menten kinetics, 28 studies that reported zero-order rates, and 97 studies that reported first-order constants. The reader is referred to Chambon *et al*. (2013) for a detailed description of the different kinetic models that have been proposed for chlorinated solvent biotransformations.

22.4.1 MICHAELIS-MENTEN RATES

The data in Table 22.5 present the Michaelis-Menten kinetic data from Suarez and Rifai (1999). Half-saturation constants varied from 0.6 mg/L to 29.5 mg/L for TCE and from 0.17 mg/L to 28 mg/L for DCE. Maximum specific degradation rates were within the ranges 0.038-478.59 $mg_{compound}/mg_{protein}$-day for TCE, and 0-11,115 $mg_{compound}/mg_{protein}$-day for DCE.

Table 22.5. Michaelis-Menten parameters for chlorinated solvents.

Compound	Type of study	Redox environ	Culture	μ_{max}, day^{-1}	K_s, mg/L	Y, mg/mg	MSDR	IC, mg/L	Ref
1,1,1-TCA	continuous reactor	aerobic	methylosinus trichosporium OB3b		28.46		4.60	>93.1	1
1,1-DCE	growth reactor	aerobic cometabolism (methane)	mixed methanotropic culture	1.37	0.43		0-11115	0.01	2
	continuous reactor	aerobic	methylosinus trichosporium OB3b		0.48		0.84	1.94-2.91	1
1,2-DCA	continuous reactor	aerobic	methylosinus trichosporium OB3b		7.62		9.26	4.95-6.93	1
cis-1,2-DCE	growth reactor	aerobic cometabolism (phenol)	filamenous phenol oxidizers				0.27-1.5		3
	continuous reactor	aerobic	methylosinus trichosporium OB3b		2.91		25.4	12.6-25.2	1
	methanogenic fluidized bed reactor	anaerobic			28.0				4
trans-1,2-DCE	continuous reactor	aerobic	methylosinus trichosporium OB3b		14.34		46.19	8.72-14.74	1
	growth reactor	aerobic cometabolism (methane)	mixed methanotropic culture	0.68	0.17		0.00-0.44	4.7	2
PCE	methanogenic fluidized bed reactor	anaerobic			12.0				4
	biofilm reactor						0.00	0.99	5
	fed-batch reactor	anaerobic		0.47					6

Table 22.5. Michaelis-Menten parameters for chlorinated solvents.

Compound	Type of study	Redox environ	Culture	μ_{max}, day^{-1}	K_s, mg/L	Y, mg/mg	MSDR	IC, mg/L	Ref
TCE	growth reactor	aerobic			0.37		0.53	14.7	7
	growth reactor	aerobic cometabolism (formate)			8.2		7.6	10.1	7
	growth reactor	aerobic cometabolism (methane)	mixed methanotropic culture	1.07	0.13		0.00-1.13	1.0	2
	methanogenic fluidized bed reactor	anaerobic			19.0				4
	growth reactor	aerobic cometabolism (phenol)	filamenous phenol oxidizers				0.1-0.25		3
	microcosm	aerobic cometabolism (toluene)		0.77-1.65		0.52	1.5	0.66	8
	microcosm	aerobic cometabolism (phenol)		0.88-1.43		0.4	3.0	0.66	8
	growth reactor	aerobic cometabolism (propane)	propane oxidizing culture		0.6		0.04	3.0	9
	batch	aerobic	methylomas methanic 68-1		29.48	0.1	438.59		10
	batch		methylosinus trichosporium OB3b		16.51	0.08	187.7		10
	continuous reactor	aerobic	methylosinus trichosporium OB3b		19.0		54.71	9.17-13.1	1
	continuous reactor	aerobic cometabolism (methane)	mixed methanotropic culture			0.01			11
Vinyl chloride	methanogenic fluidized bed reactor	anaerobic			23.0				11
	small column microcosm	aerobic cometabolism (methane)				1.0-3.5		1.0-17.0	12

K_s=half saturation, Y=yield, MSDR=maximum specific degradation rate, IC=initial concentration, S_0

1 J. E. Anderson and P. L. McCarty, *Environ. Sci. Tech*., **30**, 3517-3524 (1996).

2 A. R. Bielefeldt, H. D. Stensel and S. E. **Strand in Bioremediation of Chlorinated Solvents**, R. E. Hinchee, A. Leeson and L. Semprini, Ed., *Battelle Press,* Columbus, Ohio, 1994, pp. 237-244.

3 B. Z. Fathepure and J. M. Tiedje, *Environ. Sci. Tech*., **28**, 746-752 (1994).

4 B. S. Ballapragada, H. D. Stensel, J. A. Puhakka and J. F. Ferguson, *Environ. Sci. Tech.*, **31**, 1728-1734 (1997).

5 J. Gao, R. S. Skeen and B. S. Hooker in **Bioremediation of Chlorinated Solvents**, R. E. Hinchee, A. Leeson and L. Semprini, Ed., *Battelle Press*, Columbus, Ohio, 1995, pp. 53-59.

6 L. Alvarez-Cohen and P. L. McCarty, *Environ. Sci. Tech*., **25**, 1381-1387 (1991).

7 U. Jenal-Wanner and P. L. McCarty, *Environ. Sci. Tech*., **31**, 2915-2922 (1997).

8 J. E. Keenan, S. E. Strand and H. D. Stensel in **Bioremediation of Chlorinated and Polycyclic Aromatic Hydrocarbon Compounds**, R. E. Hinchee, A. Leeson, L. Semprini and S. K. Ong, Ed., *Lewis Publishers*, Boca Raton, Florida, 1994, pp. 1-13.

9 S.-C. Koh, J. P. Bowman and G. S. Sayler in **Bioremediation of Chlorinated and Polycyclic Aromatic Hydrocarbon Compounds**, R. E. Hinchee, A. Leeson, L. Semprini and S. K. Ong, Ed., *Lewis Publishers*,

Boca Raton, Florida, 1994, pp. 327-332.
10 S. E. Strand, G. A. Walter and H. D. Stensel in **Bioremediation of Chlorinated Solvents**, R. E. Hinchee, A. Leeson and L. Semprini, Ed., *Battelle Press*, Columbus, Ohio, 1994, pp. 161-167.
11 M. E. Dolan and P. L. McCarty, *Environ. Sci. Tech.*, **29**, 1892-1897 (1995).
12 D. Aronson and P. H. Howard, **Anaerobic Biodegradation of Organic Chemicals in Groundwater**: A Summary of Field and Laboratory Studies, SRC TR-97-0223F, *American Petroleum Institute*, Washington, D.C., 1997.

22.4.2 ZERO-ORDER RATES

A summary of more than 40 studies reporting zero-order rates is included in Table 22.6. The reported zero-order rates ranged from 0 to 19.8 mg/L/day with mean values for anaerobic rates of 0.04, 2.14, 1.80, 1.74, and 0.11 mg/L/day for carbon tetrachloride, DCE, PCE, TCE, and vinyl chloride, respectively. TCE appeared to be reductively dechlorinated at the fastest rate coefficient, with a median equal to 0.76 mg/L/day. In contrast, vinyl chloride exhibited the slowest rate coefficient of reductive dechlorination with a median value of 0.01 mg/L/day.

Table 22.6. Summary of zero-order decay rates for reductive dechlorination obtained from laboratory studies (mg/L-day).

	CCl_4	*cis*-12-DCE	DCE (all other isomers)	PCE	TCE	Vinyl chloride
number of rates[a]	8	18	8	29	7	9
minimum	0.022	0.013	0.009	0.013	0.314	0.002
25th percentile	0.024	0.183	0.023	0.288	0.511	0.006
median	0.029	0.511	0.250	0.577	0.760	0.011
75th percentile	0.042	1.318	1.385	1.040	1.297	0.075
90th percentile	0.049	3.348	2.021	2.801	3.798	0.379
maximum	0.054	16.958	3.470	19.800	7.490	0.495
mean	0.034	1.854	0.850	1.863	1.740	0.107
standard deviation	0.012	3.939	1.213	4.162	2.567	0.184
geometric mean[b]	0.000	15.513	1.471	17.323	6.590	0.034

[a]All the zero order rates provided were calculated by the authors of the respective studies [b]To calculate the geometric mean, values equal to zero were included as 10^{-10}. [From M.P. Suarez and H.S Rifai, Bioremediation J., 3, 337-62.]

22.4.3 FIRST-ORDER RATE CONSTANTS

Table 22.7 summarizes the first order decay coefficients from both field and laboratory studies. As can be seen in Table 22.7, first-order rate constants for chlorinated solvents varied from 0 to 1.03 day^{-1} in the 90% of the cases, with mean values equal to 0.11, 0.02, 0.14, 0.05, 0.26, 0.17, and 0.23 day^{-1} for carbon tetrachloride, DCA, DCE, PCE, TCA, TCE, and vinyl chloride, respectively. The range minimum-90th percentile for aerobic rates was 0-1.35 day^{-1} while for anaerobic rates it was 0-1.11 day^{-1}. Field rates from aerobic/anaerobic studies ranged from 0 to 1.96 day^{-1}. The compound that showed the highest mean value under aerobic conditions was vinyl chloride (1.73 day^{-1}), while TCA exhibited the highest mean anaerobic rate coefficient (0.35 day^{-1}).

Table 22.7. Summary of first-order decay rate for chlorinated solvents (day^{-1}).

	Number of rates	Number of reported rates	Number of calculated rates[b]	Mean	Standard deviation	90th percentile	Geometric mean[c]	Range reported rates
Carbon tetrachloride								
All studies	13	0	13	0.108	0.134	0.216	0.054	0.0037-0.49
Aerobic oxidation *In situ* & laboratory *In situ* studies[a] Laboratory	 1 1	 0 0	 1 1					
Aerobic cometabolism Field & laboratory *In situ* studies Laboratory	 1 1	 0 0	 1 1					
Overall aerobic	2	0	2	0.019				0.016-0.022
Aerobic/anaerobic (field studies)								
Reductive dechlorination Field & laboratory Field/*in situ* studies[a] Laboratory	 11 7 4	 0 0 0	 11 7 4	 0.124 0.141 0.093	 0.140 0.174	 0.230 0.334	 0.065 0.060 0.075	 0.004-0.49 0.004-0.49 0.023-0.16
Anaerobic oxidation Field & laboratory Field/*in situ* studies[a] Laboratory								
DCA (all isomers)								
All studies	25	16	9	0.017	0.036	0.046	0.001	0-0.131
Aerobic oxidation *In situ* & laboratory *In situ* studies[a] Laboratory	 2 2	 2 2	 0 0				 0.000 0.000	
Aerobic cometabolism Field & laboratory *In situ* studies Laboratory	 5 5	 0 0	 5 5	 0.067 0.067	 0.056 0.056	 0.128 0.128	 0.046 0.046	 0.014-0.131 0.014-0.131
Overall aerobic	7	2	8	0.048	0.056	0.126	0.000	0-0.131
Aerobic/anaerobic (field studies)								
Reductive dechlorination Field & laboratory Field/*in situ* studies[a] Laboratory	 18 16 2	 14 14 0	 4 2 2	 0.005 0.002 0.036	 0.012 0.003	 0.016 0.004	 0.001 0.001 0.035	 0-0.044 0-0.011 0.028-0.044
Anaerobic oxidation Field & laboratory Field/*in situ* studies[a] Laboratory								
***cis*-1,2-DCE**								
All studies	34	24	10	0.004	0.395	0.257	0.004	0-1.96
Aerobic oxidation *In situ* & laboratory *In situ* studies[a] Laboratory								

Table 22.7. Summary of first-order decay rate for chlorinated solvents (day^{-1}).

	Number of rates	Number of reported rates	Number of calculated rates[b]	Mean	Standard deviation	90th percentile	Geometric mean[c]	Range reported rates
Aerobic cometabolism Field & laboratory *In situ* studies Laboratory	5 3 2	2 2 0	3 1 2	0.476 0.885 0.187	0.787 0.843 0.250	1.680 1.820 0.399	0.476 0.885 0.187	0.081-1.96 0.281-1.96 0.081-0.434
Overall aerobic								
Aerobic/anaerobic (field studies)	4	4	0	0.000	0.003	0.006	0.000	0-0.008
Reductive dechlorination Field & laboratory Field/*in situ* studies[a] Laboratory	25 17 8	18 13 5	7 4 3	0.004 0.002 0.014	0.048 0.031 0.069	0.069 0.013 0.117	0.004 0.002 0.014	0-0.2 0-0.13 0.001-0.2
Anaerobic oxidation Field & laboratory Field/*in situ* studies[a] Laboratory								
DCE (all other isomers)								
All studies	27	14	13	0.149	0.302	0.666	0.003	0-1.15
Aerobic oxidation *In situ* & laboratory *In situ* studies[a] Laboratory								
Aerobic cometabolism Field & laboratory *In situ* studies Laboratory	8 4 4	2 0 2	6 4 2	0.458 0.720 0.196	0.416 0.316 0.347	0.845 1.012 0.521	0.002 0.670 0.000	0-1.15 0.39-1.15 0-0.714
Overall aerobic								
Aerobic/anaerobic (field studies)								
Reductive dechlorination Field & laboratory Field/*in situ* studies[a] Laboratory	19 16 3	12 12 0	7 4 3	0.019 0.003 0.101	0.061 0.001 0.147	0.012 0.005 0.220	0.004 0.003 0.039	0.001-0.27 .001-.006 0.01-0.27
Anaerobic oxidation Field & laboratory Field/*in situ* studies[a] Laboratory								
PCE								
All studies	50	31	19	0.051	0.084	0.153	0.000	0-0.41
Aerobic oxidation *In situ* & laboratory *In situ* studies[a] Laboratory	10 3 7	5 3 2	5 0 5	0.001 0.000 0.001	0.001 0.002	0.003 0.003	0.000 0.000	0-0.004 0.000 0-0.004
Aerobic cometabolism Field & laboratory *In situ* studies Laboratory	3 3	1 1	2 2	0.025 0.025			0.000 0.000	0-0.054 0-0.054
Overall aerobic	13	6	7	0.006	0.015	0.017	0.000	0-0.054
Aerobic/anaerobic (field studies)	1	1	0					
Reductive dechlorination Field & laboratory Field/*in situ* studies[a] Laboratory	36 13 23	23 9 14	13 4 9	0.068 0.010 0.101	0.093 0.022 0.101	0.185 0.022 0.212	0.002 0.000 0.024	0-0.41 0-0.08 0-0.41
Anaerobic oxidation Field & laboratory Field/*in situ* studies[a] Laboratory								

Table 22.7. Summary of first-order decay rate for chlorinated solvents (day^{-1}).

	Number of rates	Number of reported rates	Number of calculated rates[b]	Mean	Standard deviation	90th percentile	Geometric mean[c]	Range reported rates
TCA								
All studies	47	27	20	0.261	0.502	1.026	0.000	0-2.33
Aerobic oxidation								
In situ & laboratory	11	7	4	0.002	0.007	0.009	0.000	0-0.022
In situ studies[a]	2	2	0					
Laboratory	9	5	4	0.003	0.007	0.005	0.000	0-0.022
Aerobic cometabolism								
Field & laboratory	5	1	4	0.247	0.522	0.723	0.001	0-1.18
In situ studies								
Laboratory	5	1	4	0.27	0.522	0.723	0.001	0-1.18
Overall aerobic	16	8	8	0.079	0.294	0.030	0.000	0-1.8
Aerobic/anaerobic (field studies)								
Reductive dechlorination								
Field & laboratory	31	19	12	0.355	0.562	1.110	0.003	0-2.33
Field/*in situ* studies[a]	10	3	7	0.029	0.039	0.058	0.000	0-0.125
Laboratory	21	16	5	0.511	0.629	0629	0.007	0-2.33
Anaerobic oxidation								
Field & laboratory								
Field/*in situ* studies[a]								
Laboratory								
TCE								
All studies	86	52	34	0.173	0.475	0.636	0.001	0-3.13
Aerobic oxidation								
In situ & laboratory	12	6	6	0.005	0.010	0.025	0.000	0-0.028
In situ studies[a]	2	2	0					
Laboratory	10	0	10	0.006	0.011	0.026	0.000	0-0.028
Aerobic cometabolism								
Field & laboratory	17	7	10	0.586	0.566	1.418	0.309	0.024-1.65
In situ studies	3	2	1	0.948			0.582	0.105-1.41
Laboratory	14	5	9	0.509	0.524	1.265	0.269	0.024-1.65
Overall aerobic	29	13	16	0.346	0.517	1.354	0.001	0-1.65
Aerobic/anaerobic (field studies)	1	1	0					
Reductive dechlorination								
Field & laboratory	56	38	18	0.086	0.434	0.022	0.001	0-3.13
Field/*in situ* studies[a]	32	26	6	0.003	0.005	0.006	0.000	0-0.023
Laboratory	24	12	12	0.196	0.654	0.337	0.012	0-3.13
Anaerobic oxidation								
Field & laboratory								
Field/*in situ* studies[a]								
Laboratory								
Vinyl chloride								
All studies	26	8	18	0.229	0.476	0.946	0.023	0-1.96
Aerobic oxidation								
In situ & laboratory	4	0	4	0.087			0.080	0.043-0.125
In situ studies[a]								
Laboratory	4	0	4	0.087			0.080	0.043-0.125
Aerobic cometabolism								
Field & laboratory	4	0	4	1.023			0.552	0.055-1.96
In situ studies	2	0	2	1.730			1.715	1.5-1.96
Laboratory	2	0	2	0.316			0.178	0.055-0.576
Overall aerobic	8	0	8	0.555	0.756	0.107	0.211	0.043-0.12
Aerobic/anaerobic (field studies)	3	2	1	0.004			0.002	0.001-0.009

Table 22.7. Summary of first-order decay rate for chlorinated solvents (day^{-1}).

	Number of rates	Number of reported rates	Number of calculated rates[b]	Mean	Standard deviation	90th percentile	Geometric mean[c]	Range reported rates
Reductive dechlorination								
Field & laboratory	8	5	3	0.153	0.228	0.499	0.007	0-0.52
Field/*in situ* studies[a]	4	4	0	0.003			0.001	0-0.007
Laboratory	4	1	3	0.303			0.036	0-0.52
Anaerobic oxidation								
Field & laboratory	7	1	6	0.042	0.048	0.104	0.018	0.001-0.12
Field/*in situ* studies[a]	1	1	0					
Laboratory	6	0	6	0.049	0.048	0.107	0.028	0.008-0.12

[a]*In situ* studies include in situ microcosms and in situ columns [b]When enough information was provided by the authors of a study, the authors of this paper calculated the rate coefficient assuming first order kinetics [c]To calculate the geometric mean, values equal to zero were included as 10-t°.

The biodegradability under different electron acceptors for each one of the chlorinated solvents was also analyzed by Suarez and Rifai (1999). As summarized in Table 22.8, DCA presented very high potential for biodegradation *via* aerobic cometabolism and reductive dechlorination with none of the studies reporting recalcitrance. Median half-lives for this compound were 1,260 days and 15 days for reductive dechlorination and cometabolism, respectively. DCE exhibited high potential for aerobic cometabolism with 11% of the studies showing recalcitrance and a very short median half-life (1 day). None of the 44 studies on reductive dechlorination of DCE reported recalcitrance, which leads to the conclusion that DCE may undergo this process though with a relatively slow rate (median half-life equal to 234 days).

Table 22.8. Biodegradability of chlorinated solvents.

	All studies	Process			
		Aerobic oxidation	Cometabolism	Reductive dechlorination	Anaerobic oxidation
Carbon tetrachloride					
# rates	13	1	1	11	
# rates-recalcitrant	0	0	0	0	
half-life (days)[a]	14	NC	NC	9	
% rates recalcitrant	0%	0%	0%	0%	
potential for biodegradation[b]	almost always	NA	NA	almost always	
DCA (all isomers)					
# rates	25	2	5	18	
# rates-recalcitrant	2	2	0	0	
half-life (days)[a]	990	NC	15	1260	
% rates recalcitrant	8%	100%	0%	0%	
potential for biodegradation[b]	almost always	NA	almost always	almost always	
DCE (all isomers)					
# rates	61		13	44	
# rates-recalcitrant	3		2	0	
half-life (days)[a]	173		2	234	
% rates recalcitrant	5%		15%	0%	
potential for biodegradation[b]	almost always		frequently	almost always	
PCE					
# rates	50	10	3	36	
# rates-recalcitrant	14	6	1	5	
half-life (days)[a]	80	NC	35	32	
% rates recalcitrant	28%	60%	35%	14%	
potential for biodegradation[b]	sometimes	barely	NA	frequently	

Table 22.8. Biodegradability of chlorinated solvents.

	All studies	Process			
		Aerobic oxidation	Cometabolism	Reductive dechlorination	Anaerobic oxidation
TCA					
# rates	47	11	5	31	
# rates-recalcitrant	14	8	1	5	
half-life (days)[a]	68	NC	53	24	
% rates recalcitrant	30%	73%	20%	16%	
potential for biodegradation[b]	sometimes	barely	frequently	frequently	
TCE					
# rates	85	11	17	56	
# rates-recalcitrant	12	6	0	5	
half-life (days)[a]	151	NC	3	201	
% rates recalcitrant	14%	55%	0%	9%	
potential for biodegradation[b]	frequently	barely	almost always	almost always	
Vinyl chloride					
# rates	27	4	5	15	7
# rates-recalcitrant	0	0	0	0	0
half-life (days)[a]	14	8	0.462	80	58
% rates recalcitrant	0	0%	0%	0%	0%
potential for biodegradation[b]	almost always	almost always	almost always	almost always	almost always

[a]Median value from the reported studies; [b]Quantitative estimation based on % occurrence of recalcitrance; NA Insufficient information; NC Not calculable (λ=0); Scale % recalcitrance – biodegradability: < 10% – Almost always, 10%-25% – Frequently, 25%-50% – Sometimes, 50%-75% – Barely, >75% – Almost never.
[From M.P. Suarez and H.S. Rifai, *Bioremediation J.*, **3**, 337-362. Copyright © 1999 *Battelle Memorial Institute*. Reprinted with permission.]

The process that exhibited the highest potential for biodegradation of PCE and TCA was reductive dechlorination with 86% and 84% of the analyzed studies showing biotransformation. Median half-lives for reductive dechlorination of PCE and TCA were 34 days and 24 days, respectively. With respect of TCE, none of the 17 studies reporting aerobic cometabolism (most of them laboratory studies) showed recalcitrance and the median half-life was very short (3 days). Reductive dechlorination also appeared to be a very good alternative for biotransformation of TCE with only 9% of 56 studies reporting recalcitrance and median half-life equal to 201 days. Finally, vinyl chloride exhibited very high potential for biodegradation under aerobic conditions with no studies showing recalcitrance and median half-lives of 8 days and 0.462 days for oxidation and cometabolism, respectively.

In addition to the data reported above by Suarez and Rifai (1999), a groundwater anaerobic biodegradation literature review was performed by Aronson and Howard (1997). Based on their review, Aronson and Howard (1997) developed a range of "recommended values" for the anaerobic biodegradation first order decay rate coefficients. For many of the chlorinated solvents, the authors defined the low-end rate coefficient based on the lowest measured field value, and defined the high-end value as the mean rate coefficient for all the field/*in-sit*u microcosm studies. Table 22.9 shows the resulting recommended ranges for first order anaerobic biodegradation rate coefficients for several chlorinated solvents along with the mean value of the field/*in-situ* microcosm studies (note that some minor discrepancies exist between the reported high-end rates and the mean value for the field/*in-situ* microcosm studies).

Table 22.9. Mean and recommended first-order rate coefficients for selected chlorinated solvents [Data from D. Aronson and P. H. Howard, **Anaerobic Biodegradation of Organic Chemicals in Groundwater: A Summary of Field and Laboratory Studies**, SRC TR-97-0223F, *American Petroleum Institute*, Washington, D.C., 1997.]

Compound	Mean of field/*in-situ* studies			Recommended 1st order rate coefficients				Comments
	1st order rate		#	low-end		high-end		
				1st order rate				
	C	HL		C	HL	C	HL	
PCE	0.0029	239	16	0.00019	3,647	0.0033	210	Lower limit was reported for a field study under nitrate-reducing conditions
TCE	0.0025	277	47	0.00014	4,950	0.0025	277	Lower limit was reported for a field study under unknown redox conditions
Vinyl chloride	0.0079	88	19	0.00033	2,100	0.0072	96	Lower limit was reported for a field study under methanogenic/sulfate-reducing conditions
1,1,1-TCA	0.016	43	15	0.0013	533	0.01	69	Range not appropriate for nitrate-reducing conditions. Expect lower limit to be much less
1,2-DCA	0.0076	91	2	0.0042	165	0.011	63	Range reported from a single field study under methanogenic conditions
CCl_4	0.37	1.9	9	0.0037	187	0.13	5	Range not appropriate for nitrate-reducing conditions. Expect lower limits to be much less
Chloroform	0.030	23	1	0.0004	1,733	0.03	23	Only one field study available. Biodegradation under nitrate-reducing conditions expected
Dichloromethane	0.0064	108	1	0.0064	108	–	–	Rate constant reported from a single field study under methanogenic conditions
Trichlorofluoromethane	–	–	–	0.00016	4,311	0.0016	433	All studies with very low concentrations of this compound
2, 4-Dichlorophenol	0.014	50	2	0.00055	1,260	0.027	26	Range may not be appropriate for nitrate reducing conditions

C=coefficients, day^{-1}; HL=half lives, day; #=number of studies used for mean. [From T.H. Wiedemeier, H. S. Rifai, C. J. Newell and J.T. Wilson, **Natural Attenuation of Fuels and Chlorinated Solvents in the Subsurface**. Copyright © 1999 *John Wiley & Sons, Inc*. Reprinted by permission of *John Wiley & Sons, Inc*.]

22.5 GEOCHEMICAL EVIDENCE OF NATURAL BIOREMEDIATION AT CHLORINATED SOLVENT SITES

22.5.1 ASSESSING REDUCTIVE DECHLORINATION AT FIELD SITES

Assessing biological activity at a field site based on monitoring data can be difficult. However, there are a number of monitoring parameters that can be indicative of halorespiration. First, the presence of methane in the groundwater indicates that fermentation is occurring and that the potential for halorespiration exists. Second, the transformation of

PCE and TCE has been studied intensely and many researchers report that of the three possible DCE isomers, 1,1-DCE is the least significant intermediate and that *cis*-1,2-DCE predominates over *trans*-1,2-DCE (Barrio-Lage *et al*., 1986; Parsons *et al*., 1984; Parsons and Lage, 1985). Third, because chlorinated ethenes are 55 to 85% chlorine by mass, the degradation of these compounds releases a large mass of chloride. Therefore, elevated chloride concentrations also indicate reductive dechlorination.

Recent studies have developed innovative methods to link geochemical data to bioremediation, for example:

- Push-pull testing: in this direct method an isotope is injected into the site (aquifer), and then immediately taken out and tested. For example, Hageman *et al*. (2004) estimated the dechlorination of TCE by using the reduction of the fluorinated analog trichlorofluoroehene (Hageman *et al*., 2004).
- Interaction with aquifer geochemistry: in this indirect method, multivariable statistics or artificial neural network method is used to analyze and link geochemical data to bioremediation or microbial community data.
- Using isotopes: In this method, evidence of bioremediation at the field scale can be collected by using stable isotopes of carbon and hydrogen via a fractionation approach or as tracer (Scow and Hicks, 2005)

22.5.2 PLUME CLASSIFICATION SCHEMES

Wiedemeier *et al*. (1996) proposed a classification system for chlorinated solvent plumes based on the amount and origin of fermentation substrates that produce the hydrogen that drives halorespiration. Three types of groundwater environments and associated plume behavior, Type 1, Type 2, and Type 3, are described below. While the classification system can be used to represent entire plumes, it can also be used to define different zones within a chlorinated solvent plume.

22.5.2.1 Type 1

For highly chlorinated solvents to biodegrade, anaerobic conditions must prevail within the contaminant plume. Anaerobic conditions are typical at sites contaminated with fuel hydrocarbons, landfill leachate, or other anthropogenic carbon because these organics exert a tremendous electron-acceptor demand on the system. This condition is referred to as a *Type 1 environment*. In a Type 1 environment, anthropogenic carbon is fermented to produce hydrogen which drives halorespiration.

The geochemistry of groundwater in a Type 1 environment is typified by strongly reducing conditions. This environment is characterized by very low concentrations of dissolved oxygen, nitrate, and sulfate and elevated concentrations of Fe(II) and methane in the source zone (Figure 22.6). The presence of methane is almost always observed and confirms that fermentation has been occurring at the site, generating hydrogen. If measured, hydrogen concentrations are typically greater than 1 nanomolar. Importantly, a Type 1 environment results in the rapid and extensive degradation of the more highly-chlorinated solvents such as PCE, TCE, and DCE:

$$\text{PCE} \rightarrow \text{TCE} \rightarrow \text{DCE} \rightarrow \text{VC} \rightarrow \text{Ethene} \rightarrow \text{Ethane}$$

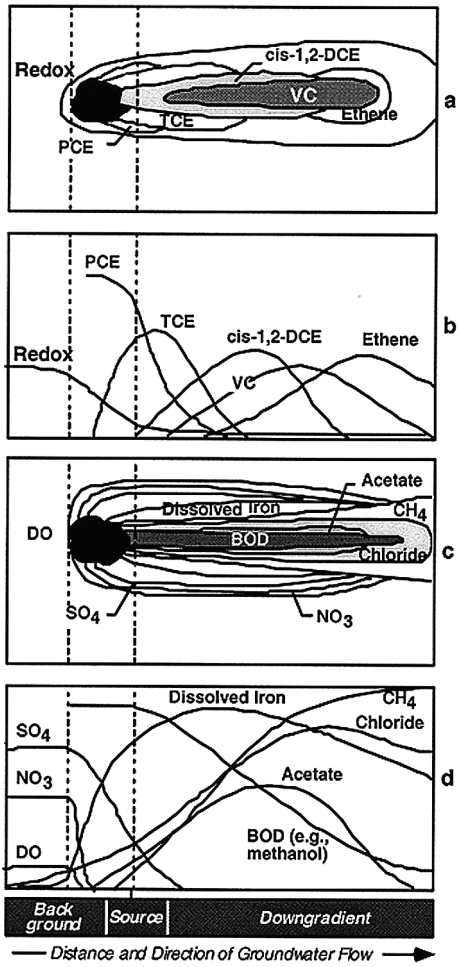


Figure 22.6. Conceptual model of Type 1 environment for chlorinated solvent plumes. [From T.H. Wiedemeier, H. S. Rifai, C. J. Newell and J.T. Wilson, **Natural Attenuation of Fuels and Chlorinated Solvents in the Subsurface**. Copyright © 1999 *John Wiley & Sons, Inc.* Reprinted by permission of *John Wiley & Sons, Inc.*]

In this type of plume, *cis*-1,2-DCE and VC degrade more slowly than TCE; thus, they tend to accumulate and form longer plumes (Figure 22.6a). In Figure 22.6b, the PCE declines to zero and is replaced, in sequence, by a peak in TCE concentrations, followed by a peak in *cis*-1,2-DCE, VC, and ethene. Fermentation constituents (BOD and acetate) and inorganics are shown in Figure 22.6.c and 22.6d. Figure 22.6d illustrates how the fermentation substrate (represented by BOD) extends beyond the source before being consumed. Both panels show long chloride and methane plumes extending far downgradient from the plume area, because chloride is conservative and methane cannot be biodegraded in an anaerobic environment. The **acetate** curve indicates where active primary fermentation is occurring; declining acetate concentrations are due to consumption by methanogens in the plume area.

In a recent study, Newell and Aziz (2004) studied the sustainability of biodegradation reactions at Type I chlorinated solvent sites. They presented a framework that classified Type I sites based on the relative amounts and depletion rates of electron donors and the chlorinated solvents (the electron acceptor in this case). Their study evaluated 13 chlorinated solvent sites and estimated the median and maximum mass discharge rates for dissolved oxygen, nitrate and sulfate flowing into chlorinated solvent plumes. These values were then converted to hydrogen equivalents and potential for lost perchloroethylene (PCE).

22.5.2.2 Type 2

The classification system of Wiedemeier *et al.* (1996) recognized that anaerobic conditions may also result from the fermentation of naturally-occurring organic material in the groundwater that flows through chlorinated solvent source zones. This *Type 2 environment* occurs in hydrogeologic settings that have inherently high organic carbon concentrations, such as coastal or stream/river deposits with high concentrations of organics, shallow

aquifers with recharge zones in organic-rich environments (such as swamps), or zones impacted by natural oil seeps. A Type 2 environment generally results in slower biodegradation of the highly chlorinated solvents compared to a Type 1 environment. However, given sufficient organic loading, this environment can also can result in rapid degradation of these compounds. A Type 2 environment typically will not occur in crystalline igneous and metamorphic rock (see discussion of likely hydrogeologic settings for Type 3 environments).

22.5.2.3 Type 3

A Type 3 environment is characterized by a well-oxygenated groundwater system with little or no organic matter. Concentrations of dissolved oxygen typically are greater than 1.0 mg/L. In such an environment, halorespiration will not occur and chlorinated solvents such as PCE, TCE, TCA, and CT will not biodegrade. In this environment, very long dissolved-phase plumes are likely to form. The most significant natural attenuation mechanisms for PCE and TCE will be advection, dispersion, and sorption. However, VC (and possibly DCE) can be rapidly oxidized under these conditions. A Type 3 environment is often found in crystalline igneous and metamorphic rock (fractured or unfractured) such as basalt, granite, schist, phyllite, glacial outwash deposits, eolian deposits, thick deposits of well-sorted, clean, beach sand with no associated peat or other organic carbon deposits, or any other type of deposit with inherently low organic carbon content if no anthropogenic carbon has been released.

Two conceptual models are provided for environments in which Type 3 behavior occurs. For sources with PCE and TCE, the major natural attenuation processes are dilution and dispersion alone (no biodegradation). As shown in Figure 22.7, the PCE and TCE plumes extend from the source zone and concentrations are slowly reduced by abiotic processes. Chloride concentrations and oxidation-reduction potential will not change as groundwater passes through the source zone and forms the chlorinated ethene plume. If TCA is the solvent of interest, significant abiotic hydrolysis may occur, resulting in a more rapid decrease in TCA concentrations and an increase in chloride concentrations.

In Figure 22.7, a source releases VC and 1,2-DCA into the groundwater at a Type 3 site (an unlikely occurrence as more highly chlorinated solvents are typically released at sites). Because the VC and 1,2-DCA can be degraded aerobically, these constituents decline in concentration at a significant rate. Chloride is produced, and a depression in dissolved oxygen concentration similar to that occurring at fuel sites, is observed.

22.5.2.4 Mixed environments

As mentioned above, a single chlorinated solvent plume can exhibit different types of behavior in different portions of the plume. This can be beneficial for natural biodegradation of chlorinated solvent plumes. For natural attenuation, this may be the best scenario. PCE, TCE, and DCE are reductively dechlorinated with accumulation of VC near the source area (Type 1); then, VC is oxidized (Type 3) to carbon dioxide, either aerobically or *via* Fe(III) reduction further downgradient and does not accumulate. Vinyl chloride is removed from the system much faster under these conditions than under reducing conditions.

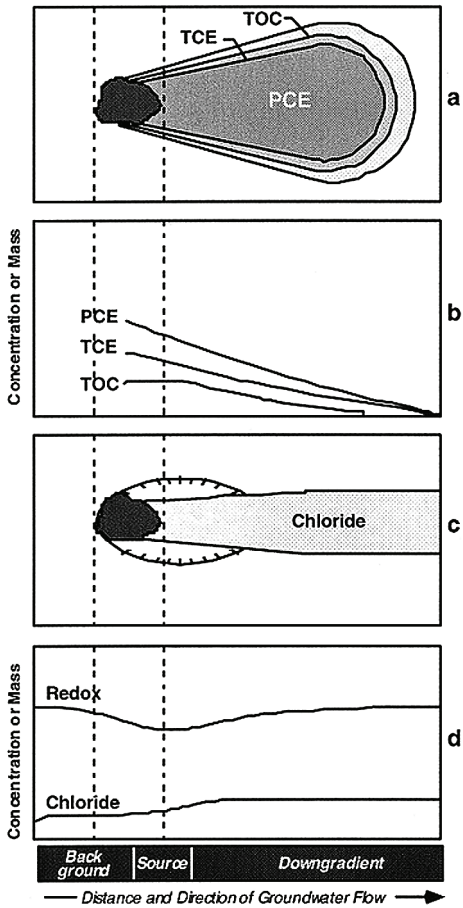


Figure 22.7. Conceptual model of Type 3 environment for chlorinated solvent plumes. [From T.H. Wiedemeier, H. S. Rifai, C. J. Newell and J.T. Wilson, **Natural Attenuation of Fuels and Chlorinated Solvents in the Subsurface**. Copyright © 1999 *John Wiley & Sons, Inc*. Reprinted by permission of J*ohn Wiley & Sons, Inc*.]

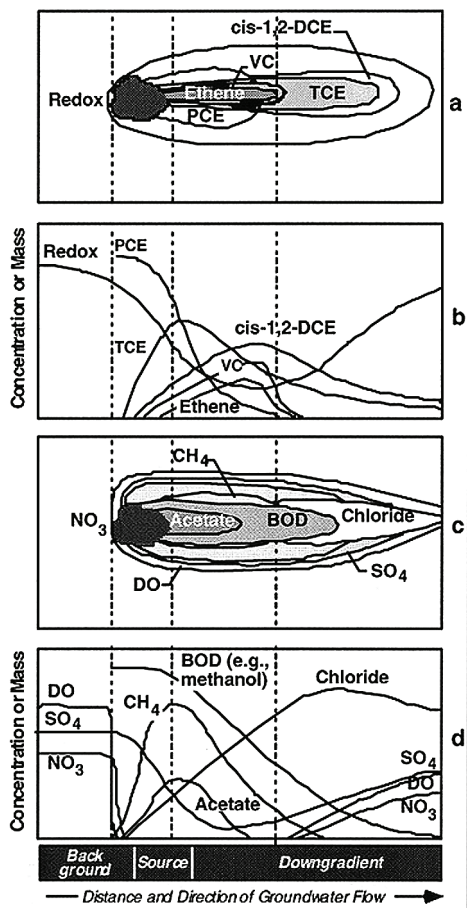


Figure 22.8. Conceptual model of mixed environments with Type 1 environment in source zone and Type 3 environment downgradient of source. [From T.H. Wiedemeier, H. S. Rifai, C. J. Newell and J.T. Wilson, **Natural Attenuation of Fuels and Chlorinated Solvents in the Subsurface**. Copyright © 1999 *John Wiley & Sons, Inc.* Reprinted by permission of *John Wiley & Sons, Inc*.]

A less ideal variation of the mixed Type 1 and Type 3 environments is shown in the conceptual model in Figure 22.8. An extended TCE and 1,2-DCE plume results because insufficient fermentable carbon results in an anaerobic zone which is too short for complete biodegradation. Therefore, TCE extends well into the aerobic zone where no biodegradation occurs. A long DCE plume also extends into the aerobic zone, indicating insignificant direct aerobic biodegradation was assumed. While a long chloride plume will

be observed, the short anaerobic zone means much less methane is produced, allowing dilution/dispersion to limit the extent of the methane plume.

22.6 CHLORINATED SOLVENT PLUMES – CASE STUDIES OF NATURAL ATTENUATION

22.6.1 PLUME DATABASES

Three different databases provided chlorinated solvent site data. The first database, the Hydrogeologic Database (HGDB) (Newell *et al*., 1990), provided information on plume length, plume width, plume thickness, and highest solvent concentration for 109 chlorinated solvent sites. The second database condensed extensive site characterization data from 17 Air Force chlorinated solvent sites, with information on parent compounds vs. progeny product concentrations, competing electron acceptors, hydrogen, and metabolic by-products. The third database, provided by McGuire *et al*. (2004), was from 45 chlorinated solvent plumes in the United States and Europe (35 sites in United States, 9 in Netherlands and one in Italy) where MNA (monitored natural attenuation) was applied as sole or a part of the treatment plan.

The data in the HGDB were broken into two groups: the chlorinated ethenes, where one or more of the chlorinated ethenes (PCE, TCE, DCE, or VC) was reported to be the major contaminant, and other chlorinated solvent sites, where all other chlorinated solvents besides the ethenes (e.g., TCA, DCA, chlorobenzene) were lumped together. As shown in Table 22.10, the median length of the 75 chlorinated ethene plumes was 1000 ft, with one site reporting a plume length of 13,200 ft. These median lengths are longer than those reported for fuel hydrocarbon plumes and this may be attributed to the competition for hydrogen during halorespiration.

Table 22.10. Characteristics of chlorinated solvent plumes from HGDB database

	Plume length, ft	Plume width, ft	Vertical penetration, ft	Highest concentration, mg/L
Chlorinated ethenes (e.g., PCE, TCE, etc.)				
Maximum	13,200	4,950	500	28,000
75th percentile	2,500	1,000	100	72
Median	1,000	500	40	8.467
25th percentile	600	200	25	0.897
Minimum	50	15	5	0.001
n	75	75	78	81
Other chlorinated solvents (e.g., TCA, DCA)				
Maximum	18,000	7,500	150	2,500
75th percentile	2,725	1,000	51	13.250
Median	575	350	35	3.100
25th percentile	290	188	24	0.449
Minimum	100	100	8	0.016
n	24	24	24	28

Note: Highest concentration for chlorinated ethenes (28,000 mg/L) was for TCE, which is above the solubility limit. The highest concentration for.other chlorinated solvents. (2500 mg/L) was for chloromethane and toluene.
[From T.H. Wiedemeier, H. S. Rifai, C. J. Newell and J.T. Wilson, **Natural Attenuation of Fuels and Chlorinated Solvents in the Subsurface**. Copyright © 1999 *John Wiley & Sons, Inc*. Reprinted by permission of *John Wiley & Sons, Inc*.]

The other category, "other chlorinated solvent sites," had shorter plumes, with a median plume length of 575 ft compared to 1000 ft for the chlorinated ethene sites. Twelve of the 24 plumes were comprised of TCA, which is degraded biologically via halorespiration and other mechanisms and abiotically by hydrolysis (half life of 0.5 to 2.5 years). Despite the degradability of TCA, the TCA plumes had a median length of 925 ft. The shorter plumes in this database of 24 sites were reported to be comprised of either a general indicator, such as Total Organic Halogens, or individual compounds such as 1,1-dichloroethane, methylene chloride, or chlorobenzene. The median highest concentration at these "other chlorinated solvent sites" was 3.1 mg/L (see Table 22.10).

Data compiled from 17 Air Force sites using the AFCEE (Air Force Center for Environmental Excellence) natural attenuation protocol (Wiedemeier, *et al.* 1996) showed a median plume length of 750 ft (based on 14 plumes). There were significant differences in plume length for different plume classes, with Type 1 plumes (sites with available man-made fermentation substrates such as BTEX) being shorter than Type 3 plumes (sites without available fermentation substrates). Twelve of the sites exhibiting Type 1 plumes had a median plume length of 625 ft, while the two sites with Type 3 plumes had lengths of 1100 and 5000 ft. Four mixed plumes (Type 1 in source zone, Type 3 in the downgradient part of the plume) had a median length of 2538 ft.

Site-specific biodegradation rate information was developed using several methods, including one developed by Buscheck and Alcantar (1995), one based on the use of conservative tracers (the trimethylbenzenes), and other methods such as model calibration. Rates varied significantly, with half-lives ranging from over 300 years for a Type 3 site located in Utah to 0.2 years for a Type 1 site (see Table 22.11). The median first order half-life for the 14 chlorinated plumes was 2.1 years.

Table 22.11. Chlorinated solvent plume characteristics.

#	State	Type	PL	PW	PT	TCS	SV	FBR	HL	MCC
13	UT	Type 3	5000	1400	40	4.953	60	0.000006	316.4	Other
9	NY	Mixed	4200*	2050	60	774.721	139	0.001*	1.9*	Other
10	NE	Mixed	3500	1400	50	164.010	152	0.000001	1899	Other
8	MA	Type 1	1800	1200	50	4.340	106	0.0005	3.8	Other
11	FL	Mixed	1575*	400	15	1258.842	113	0.0009*	2.1*	Other
14	AK	Type 3	1100	250	25	4.899	260	0.0065	0.3	Other
1	SC	Type 1	750	550	5	328.208	1600	–	–	–
7	MA	Type 1	750	250	50	50.566	20.8	0.0095	0.2	Conserv. tracer
12	MS	Mixed	750	550	5	0.472	1500	0.01	0.2	Buscheck
4	NE	Type 1	650	450	30	47.909	6.7	0.0006	3.2	Buscheck
3	FL	Type 1	600	350	20	0.429	36	0.0007	2.7	Buscheck
5	WA	Type 1	550	300	10	3.006	32.9	0.001	1.9	Buscheck
2	MI	Type 1	375	100	10	0.397	292	–	–	–
6	OH	Type 1	100	60	10	15.736	25	–	–	–
Maximum			5,000	2,050	60	1,259	1,600	0.0095	316.4	

Table 22.11. Chlorinated solvent plume characteristics.

#	State	Type	PL	PW	PT	TCS	SV	FBR	HL	MCC
75th percentile			1,744	1,038	48	136	233	0.00375	3.5	
Median			750	425	22.5	10.3	109.5	0.0009	2.1	
25th percentile			613	263	10	3.3	34	0.00055	1.1	
Minimum			100	60	5	0.397	7	0.000006	0.2	
			14	14	14	14	14	11	11	

PL=plum length, ft; PW=plum width, ft; PT=plum thickness, ft; TCS=total chlorinated solvents, mg/L; SV=seepage velocity, ft/year; FBR=first-order biodegradation rate coefficient for solvents, day^{-1}; HL=half-life, years; MCC=method for calculating rate coefficient.
*Plume discharges into stream; may not represent maximum potential plume length.
Mixed refers to Type 1 conditions in source zone, Type 3 conditions in downgradient part of plume. Median length Type 1 sites: 625 ft, mixed sites 2538 ft, Type 3: 3050 ft (two sites). [From T.H. Wiedemeier, H. S. Rifai, C. J. Newell and J.T. Wilson, **Natural Attenuation of Fuels and Chlorinated Solvents in the Subsurface**. Copyright © 1999 *John Wiley & Sons, Inc*. Reprinted by permission of *John Wiley & Sons, Inc*.]

McGuire *et al*. (2004) reported, based on 45 chlorinated solvent sites, that at more than 80 percent of sites, the maximum concentration of total chlorinated solvents was over 1 mg/L; at almost 40 percent of sites, the total concentration was greater than 10 mg/L, and the concentration was more than 100 mg/L at 16 percent of sites. TCE at 47 percent of sites, PCE at 36 percent, and both TCA and DCA at 7 percent of sites were the dominant chlorinated solvents. Approximately, 96 percent of the studied plumes had less than 5000 feet length and less than 100 acres in aerial extent (McGuire *et al*., 2004).

22.6.2 MODELING CHLORINATED SOLVENT PLUMES

A few models exist (analytical or numerical) which are specifically designed for simulating the natural attenuation of chlorinated solvents in ground water. Ideally, a model for simulating natural attenuation of chlorinated solvents would be able to track the degradation of a parent compound through its daughter products and allow the user to specify differing decay rates for each step of the process. This may be referred to as a reactive transport model, in which transport of a solute may be tracked while it reacts, its properties change due to those reactions, and the rates of the reactions change as the solute properties change. Moreover, the model would also be able to track the reaction of those other compounds that react with or are consumed by the processes affecting the solute of interest (e.g., electron donors and acceptors).

Analytical models have been developed to simulate sequential reactions such as those involved in the biodegradation of chlorinated solvents (e.g., Sun *et al*., 1999; Lu *et al*., 2003; Sun *et al*., 2004; Quezada *et al*., 2004; Jones *et al*., 2006; Srinivasan and Clement, 2007; Hoehener and Atteia, 2010; Atteia and Hohener, 2012; Burnell *et al*., 2012). In general, these analytical solutions tend to be one-dimensional although some have been extended to 3-D using simplifying assumptions. Models such as BIOCHLOR, described here in more detail, are implemented in spreadsheet programs and rely in their implementation on an underlying analytical solution for reactive transport such as the ones referenced above.

Numerical models for reactive transport are less commonly developed due to their complexity and the lack of data to support their use at field sites. The RT3D model for the natural attenuation of chlorinated solvents is briefly discussed in this section. Other models such as SEAM3D (Widdowson, 2004) have been presented in the literature.

22.6.2.1 BIOCHLOR natural attenuation model

The BIOCHLOR Natural Attenuation Model (Newell *et al*., 1998) simulates chlorinated solvent natural attenuation using an Excel based interface. BIOCHLOR simulates the following reductive dechlorination process:

$$\mathrm{PCE} \xrightarrow{k_1} \mathrm{TCE} \xrightarrow{k_2} \mathrm{DCE} \xrightarrow{k_3} \mathrm{VC} \xrightarrow{k_4} \mathrm{ETH}$$

The equations describing the sequential first order biodegradation reaction rates are shown below for each of the components:

$$r_{PCE} = -k_1 C_{PCE} \quad [22.25]$$

$$r_{TCE} = k_1 C_{PCE} - k_2 C_{TCE} \quad [22.26]$$

$$r_{DCE} = k_2 C_{TCE} - k_3 C_{DCE} \quad [22.27]$$

$$r_{VC} = k_3 C_{DCE} - k_4 C_{VC} \quad [22.28]$$

$$r_{ETH} = k_4 C_{ETH} \quad [22.29]$$

where k_1, k_2, k_3, k_4 are the first order rate constants and C_{PCE}, C_{TCE}, C_{DCE}, C_{VC} and C_{ETH} are the aqueous concentration of PCE, TCE, DCE, vinyl chloride, and ethene, respectively. These equations assume no degradation of ethene.

To describe the transport and reaction of these compounds in the subsurface, one-dimensional advection, three-dimensional dispersion, linear adsorption, and sequential first order biodegradation are assumed as shown in the equations below. All equations, but the first, are coupled to another equation through the reaction term. [22.25] to [22.29]

$$R_{PCE}\frac{dC_{PCE}}{dt} = -v\frac{dC_{PCE}}{dx} + D_x\frac{d^2C_{PCE}}{dx^2} + D_y\frac{d^2C_{PCE}}{dy^2} + D_z\frac{d^2C_{PCE}}{dz^2} - k_1 C_{PCE}$$

$$R_{TCE}\frac{dC_{TCE}}{dt} = -v\frac{dC_{TCE}}{dx} + D_x\frac{d^2C_{TCE}}{dx^2} + D_y\frac{d^2C_{TCE}}{dy^2} + D_z\frac{d^2C_{TCE}}{dz^2} - k_1 C_{TCE} - k_2 C_{TCE}$$

$$R_{DCE}\frac{dC_{DCE}}{dt} = -v\frac{dC_{DCE}}{dx} + D_x\frac{d^2C_{DCE}}{dx^2} + D_y\frac{d^2C_{DCE}}{dy^2} + D_z\frac{d^2C_{DCE}}{dz^2} - k_2 C_{DCE} - k_3 C_{DCE}$$

$$R_{VC}\frac{dC_{VC}}{dt} = -v\frac{dC_{VC}}{dx} + D_x\frac{d^2C_{VC}}{dx^2} + D_y\frac{d^2C_{VC}}{dy^2} + D_z\frac{d^2C_{VC}}{dz^2} + k_3 C_{VC} - k_4 C_{VC}$$

$$R_{ETH}\frac{dC_{ETH}}{dt} = -v\frac{dC_{ETH}}{dx} + D_x\frac{d^2C_{ETH}}{dx^2} + D_y\frac{d^2C_{ETH}}{dy^2} + D_z\frac{d^2C_{ETH}}{dz^2} + k_4C_{ETH}$$

where R_{PCE}, R_{TCE}, R_{DCE}, R_{VC}, and R_{ETH} are the retardation factors, v is the seepage velocity, and D_x, D_y, and D_z are the dispersivities in the x, y, and z directions.

BIOCHLOR uses a novel analytical solution to solve these coupled transport and reaction equations in an Excel spreadsheet. To uncouple these equations, BIOCHLOR employs transformation equations developed by Sun and Clement (1998). The uncoupled equations were solved using the Domenico model, and inverse transformations were used to generate concentration profiles. Details of the transformation are presented elsewhere (Sun and Clement, 1998). Typically, source zone concentrations of *cis*-1,2-dichloroethythene (DCE) are high because biodegradation of PCE and TCE has been occurring since the solvent release.

BIOCHLOR also simulates different first-order decay rates in two different zones at a chlorinated solvent site. For example, BIOCHLOR is able to simulate a site with high dechlorination rates in a high-carbon area near the source that becomes a zone with low dechlorination rates downgradient when fermentation substrates have been depleted.

The BIOCHLOR model was used to reproduce the movement of the Cape Canaveral plume from 1965 to 1998. The Cape Canaveral site (Figure 22.9) is located in Florida and exhibits a TCE plume which is approximately 1,200 ft long and 450 ft wide. TCE concentrations as high as 15.8 mg/L have been measured recently at the site. The site characteristics used in the BIOCHLOR model are listed in Table 22.12. The hydraulic conductivity assumed in the model was $1.8x10^{-2}$ cm/sec and the hydraulic gradient was 0.0012. A porosity of 0.2 was assumed as well as the Xu and Eckstein model for longitudinal dispersivity. The lateral dispersivity was assumed to be 10% of the longitudinal dispersivity and vertical dispersion was neglected.

A median value for the retardation factor was used (R=5.3) since BIOCHLOR accepts only one value for this parameter. The site was modeled using one anaerobic zone with one set of rate coefficients as shown in Table 22.12. This is justified because the dissolved oxygen readings at the site were less than 0.7 mg/L at all monitoring points. The rate coefficients were calculated by calibrating the model to the 1997 field data. The source zone was simulated as a spatially-variable source and the source concentrations ranged from 0.001 to 98.5 mg/L for the various compounds as shown in Table 22.12. The source thickness was estimated by using the deepest point in the aquifer where chlorinated solvents were detected.

Centerline concentrations for all five species (PCE, TCE, c-DCE, VC and ETH) predicted by the model are shown in Figure 22.10. Figure 22.10 shows the centerline predictions for each chlorinated solvent and a no degradation curve for all of the chlorinated solvents as well as field data. The data in Figure 22.10 indicate that TCE concentrations discharging into the ocean will be less than 0.001 mg/L.

Lu *et al*. (2006) used BIOCHLOR to calculate dechlorination rate constants for six plumes and to determine the relationship between *Dehalococcoides* DNA in an aquifer

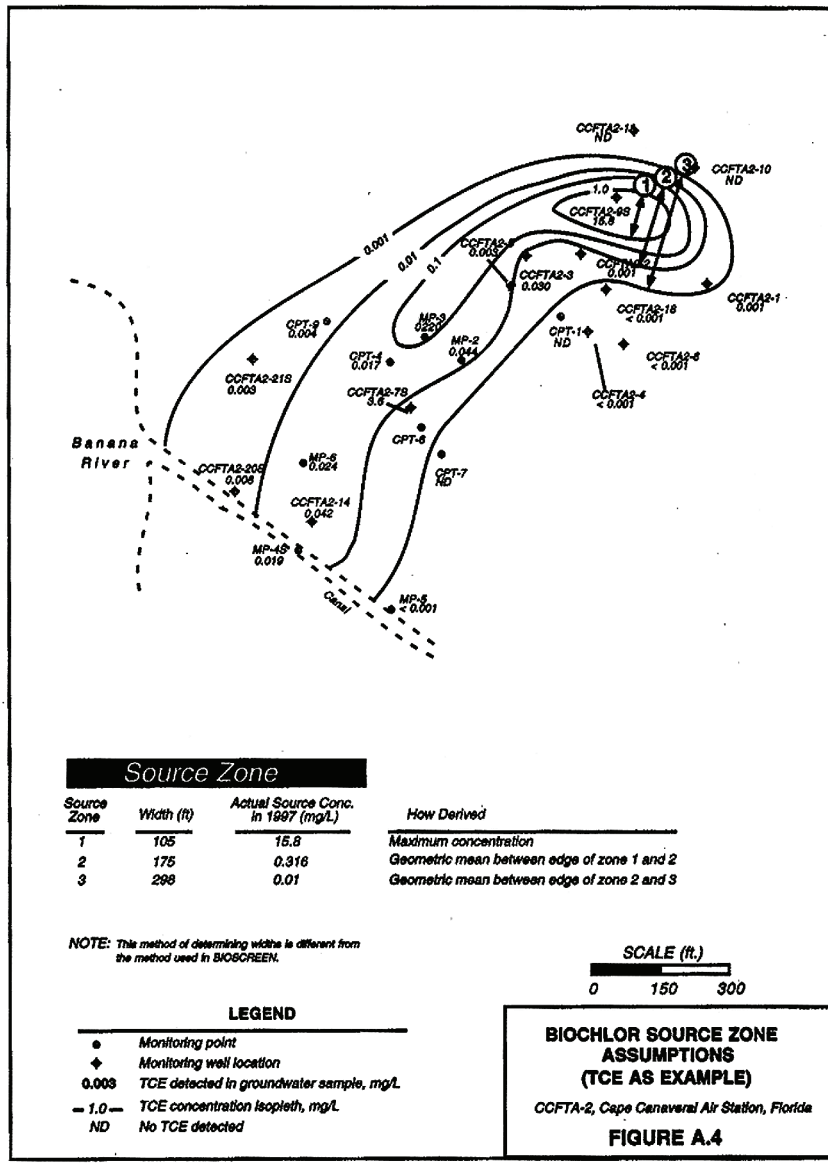


Figure 22.9. BIOCHLOR source zone assumptions (TCE as example), CCFTA-2, cape Canaveral Air Station, Florida [Adapted from C. E. Aziz, C. J. Newell, A. R. Gonzales, P. Haas, T. P. Clement and Y. Sun, BIOCHLOR Natural Attenuation Decision Support System User's Manual, prepared for the Air Force Center for Environmental Excellence, Brooks, AFB, San Antonio, 1999.].

and the dechlorination rate constant. Their results indicated greater dechlorination rates for *cis*-DCE and VC in the presence of detectable *Dehalococcoides* DNA.

Table 22.12. BIOCHLOR example, Cape Canaveral Air Station, Florida. [Data from C. E. Aziz, C. J. Newell, A. R. Gonzales, P. Haas, T. P. Clement and Y. Sun, BIOCHLOR Natural Attenuation Decision Support System User's Manual, prepared for the Air Force Center for Environmental Excellence, Brooks, AFB, San Antonio, 1999.]

Data type	Parameter	Value	Source
Hydrogeology	Hydraulic conductivity: Hydraulic gradient: Porosity:	1.8×10^{-2} cm/s 0.0012 ft/ft 0.2	Slug-tests results Static water level measurement Estimated
Dispersion	Original Longitudinal dispersivity: Transverse dispersivity: Vertical dispersivity:	 varies with x varies with x 0 ft	Based on estimated plume length of 1450 ft. Note: No calibration was necessary to match observed plume length
Adsorption	Individual retardation factors: Common retardation factor: Soil bulk density ρ_b: f_{oc}: K_{oc}: (L/kg)	PCE: 6.7 TCE: 2.8 c-DCE:2.8 VC: 5.6 ETH: 5.3 5.3 1.6 kg/L 0.184% PCE: 398 TCE: 126 c-DCE: 126 VC: 316 ETH: 302	Calculated Median value Estimated Lab analysis Literature correlation using solubilities at 20°C
Biodegradation	Biodegradation rate coefficients (1/year): PCE →TCE TCE →c-DCE c-DCE →VC C →ETH	 2.0 0.9 0.6 0.4	Based on calibration to field data using a simulation time of 32 yr. Started with literature values and then adjusted model to fit field
General	Modeled area length Modeled area width Simulation time	1085 ft 700 ft 33 yrs	Based on area of affected groundwater plume from 1965 (first release) to 1998 (present)
Source data	Source thickness Source widths, ft Source concentrations, mg/L PCE TCE c-DCE VC ETH	56 ft *Zone 1 Zone 2 Zone 3* 105 175 298 *Zone 1 Zone 2 Zone 3* 0.056 0.007 0.001 15.8 0.318 0.01 98.5 1.0 0.01 3.080 0.089 0.009 0.030 0.013 0.003	Based on geological logs and monitoring data. Source concentrations are aqueous concentrations

Table 22.12. BIOCHLOR example, Cape Canaveral Air Station, Florida. [Data from C. E. Aziz, C. J. Newell, A. R. Gonzales, P. Haas, T. P. Clement and Y. Sun, BIOCHLOR Natural Attenuation Decision Support System User's Manual, prepared for the Air Force Center for Environmental Excellence, Brooks, AFB, San Antonio, 1999.]

Data type	Parameter	Value	Source
Actual data	Distance from source, ft	*560 650 930 1085*	Based on observed
	PCE concentration, mg/L	<0.001 ND <0.001 <0.001	concentration
	TCE, mg/L	0.22 0.0165 0.0243 0.019	at site near centerline
	c-DCE, mg/L	3.48 0.776 1.200 0.556	of plume
	VC, mg/L	3.080 0.797 2.520 5.024	
	ETH, mg/L	0.188 ND 0.107 0.150	
Output	Centerline concentration	see Figure 22.10	

22.6.3 RT3D NUMERICAL MODEL

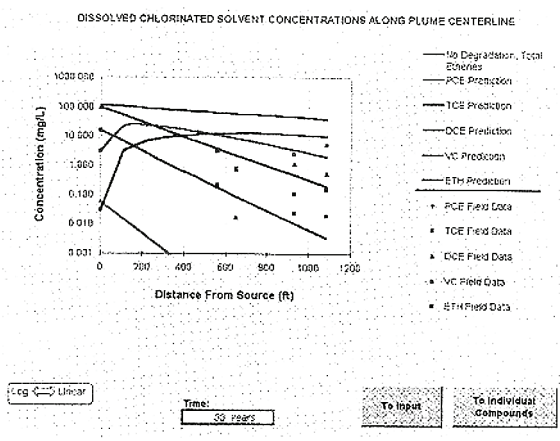


Figure 22.10. Centerline output. Cape Canaveral Air Force Base, Florida. [Adapted from C. E. Aziz, C. J. Newell, A. R. Gonzales, P. Haas, T. P. Clement and Y. Sun, BIOCHLOR Natural Attenuation Decision Support System User.s Manual, prepared for the Air Force Center for Environmental Excellence, Brooks, AFB, San Antonio, 1999.].

RT3D (Reactive Transport in 3 Dimensions, Sun *et al*., 1996) is a FORTRAN 90-based model for simulating 3D multi-species, reactive transport in groundwater. This model is based on the 1997 version of MT3D (DOD Version 1.5), but has several extended reaction capabilities. RT3D can accommodate multiple sorbed and aqueous phase species with any reaction framework that the user needs to define. RT3D can simulate different scenarios, since a variety of pre-programmed reaction packages are already provided and the user has the ability to specify their own reaction kinetic expressions. This allows, for example, natural attenuation processes or an active remediation to be evaluated. Simulations can be applied to modeling contaminants such as heavy metals, explosives, petroleum hydrocarbons, and/or chlorinated solvents.

RT3D's pre-programmed reaction packages include:

1. Two species instantaneous reaction (hydrocarbon and oxygen).
2. Instantaneous hydrocarbon biodegradation using multiple electron acceptors (O_2, NO_3^-, Fe^{2+}, SO_4^{2-}, CH_4).
3. Kinetically limited hydrocarbon biodegradation using multiple electron acceptors (O_2, NO_3^-, Fe^{2+}, SO_4^{2-}, CH_4).
4. Kinetically limited reaction with bacterial transport (hydrocarbon, oxygen, and bacteria).

5. Non-equilibrium sorption/desorption. It can also be used for non-aqueous phase liquid dissolution).
6. Reductive, anaerobic biodegradation of PCE, TCE, DCE, and VC.
7. Reductive, anaerobic biodegradation of PCE, TCE, DCE, and VC combined with aerobic biodegradation of DCE and VC.
8. Combination of #3 and #7.

RT3D represents a remarkable breakthrough in the development and solving of optimization models of bioremediation design. It is a modular, three-dimensional simulator capable of predicting multi-species (solutes and microbes), bio-reactive transport while understanding natural attenuation and active bioremediation processes.

Since its introduction, RT3D has been used in several studies for simulating the natural attenuation of chlorinated solvents. Ling and Rifai (2007), for example, used MODFLOW (to predict the flow field), and RT3D (to simulate the sequential decay reactions of chlorinated solvents) to model natural attenuation with source control at a chlorinated solvents dry-cleaner site located in northeastern Texas.

22.6.3 CS CASE STUDIES

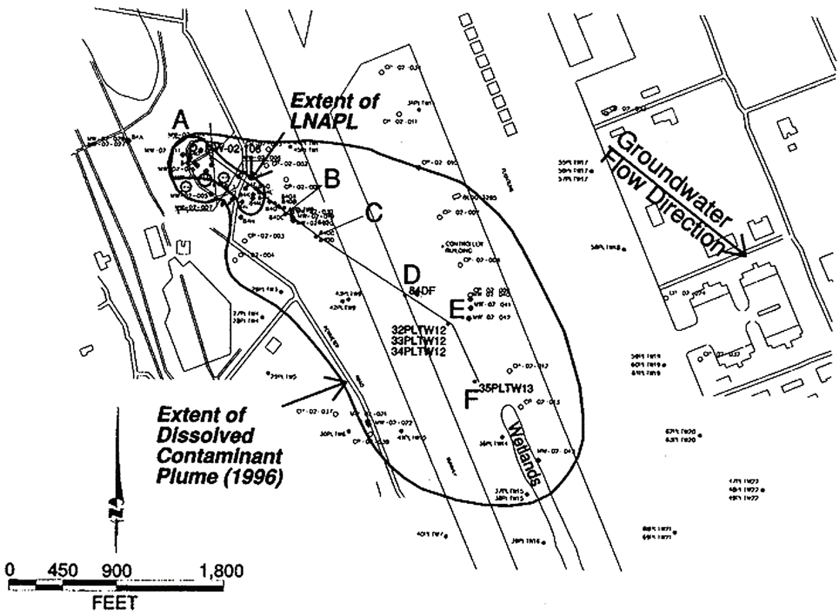


Figure 22.11. Site layout, Plattsburgh Air Force Base, New York. [From T.H. Wiedemeier, H. S. Rifai, C. J. Newell and J.T. Wilson, N**atural Attenuation of Fuels and Chlorinated Solvents in the Subsurface**. Copyright © 1999 *John Wiley & Sons, Inc*. Reprinted by permission of *John Wiley & Sons, Inc*.]

One of the earliest case studies of chlorinated solvent natural attenuation is the Plattsburgh Air Force Base (AFB) in New York, a former fire training facility (site FT-002). Activities at FT-002 (Figure 22.11) have caused contamination of shallow soils and groundwater with a mixture of chlorinated solvents and fuel hydrocarbons. Groundwater contaminants

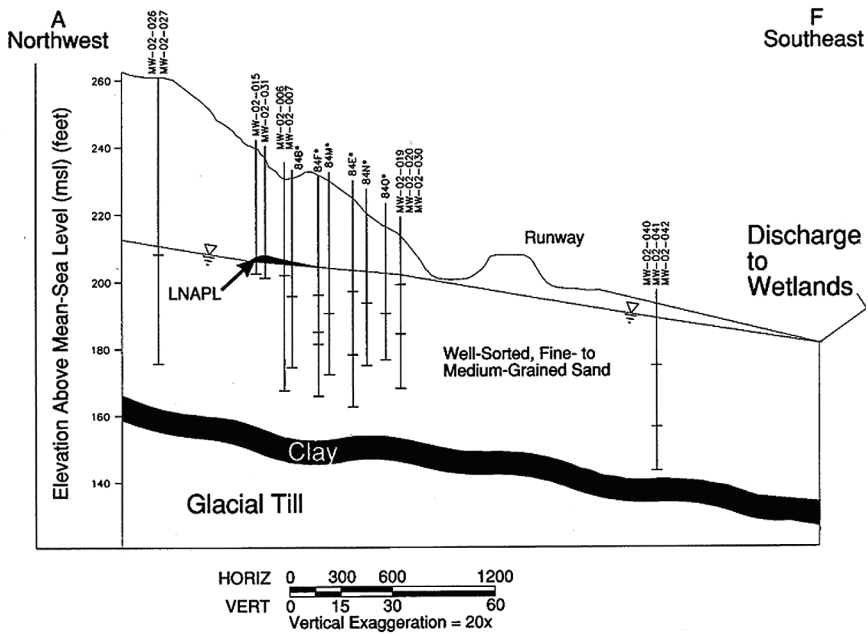


Figure 22.12. Hydrogeologic section, Plattsburgh Air Force Base, New York. [adapted from T.H. Wiedemeier, H. S. Rifai, C. J. Newell and J.T. Wilson, **Natural Attenuation of Fuels and Chlorinated Solvents in the Subsurface**. Copyright © 1999 *John Wiley & Sons, Inc*. Reprinted by permission of *John Wiley & Sons, Inc.*]

include TCE, *cis*-1,2-DCE, VC and BTEX. The site is underlain with 4 distinct stratigraphic units: sand, clay, till and carbonate bedrock. The depth to groundwater in the sand aquifer ranges from 45 ft below ground surface (BGS) on the west side of the site to zero on the east side of the runway (Figure 22.12). Groundwater flow is to the southeast and the average gradient is about 0.01 ft/ft (Wiedemeier *et al*., 1999) Hydraulic conductivity values for the unconfined san aquifer range from 0.059 to 90.7 ft/day. Wiedemeier *et al*. (1999) estimated an average velocity of 142 ft/yr for the sand aquifer.

The extent of Light Non-Aqueous Phase (LNAPL) contamination at Plattsburgh is shown in Figure 22.13. The LNAPL is a mixture of jet fuel and waste solvents from which BTEX and TCE dissolve into the ground water (DCE and VC are not present in the waste mixture). The dissolved BTEX plume (Figure 22.13) extends approximately 2000 ft downgradient from the site and has a maximum width of about 500 ft. BTEX concentrations as high as 17 mg/L were measured in the source area. Historical data from FT-002 indicate that the dissolved BTEX plume has reached a quasi-steady state and is no longer expanding.

The chlorinated solvent plumes (Figure 22.13) in groundwater extend about 4000 ft downgradient from FT-002. Concentrations of TCE, DCE and VC as high as 25, 51, and 1.5 mg/L, respectively, have been observed recently. Since DCE and VC were not measured in LNAPL samples from the source area, the presence of DCE and VC at the site can

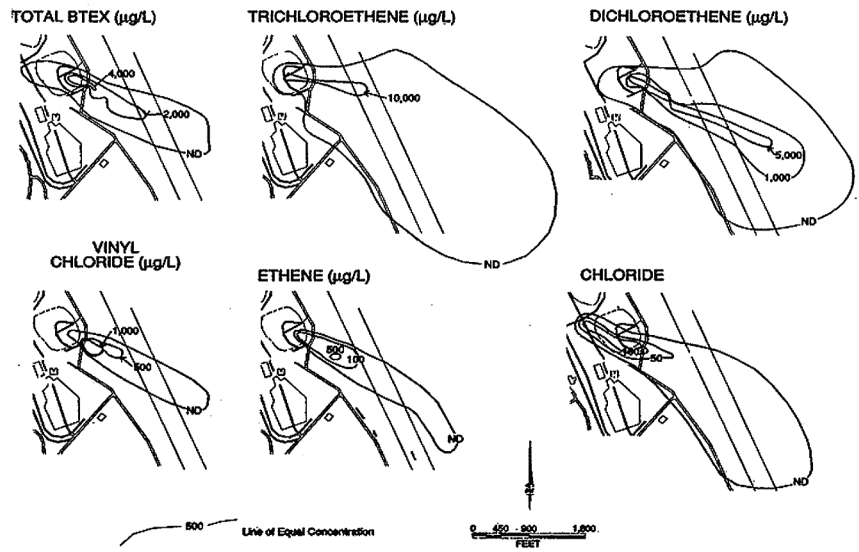


Figure 22.13. Chlorinated solvents and by-products, 1995, Plattsburgh Air Force Base, New York. [Adapted from T.H.Wiedemeier, H. S. Rifai, C. J. Newell and J.T. Wilson, **Natural Attenuation of Fuels and Chlorinated Solvents in the Subsurface**. Copyright © 1999 *John Wiley & Sons, Inc.* Reprinted by permission of *John Wiley & Sons, Inc*.]

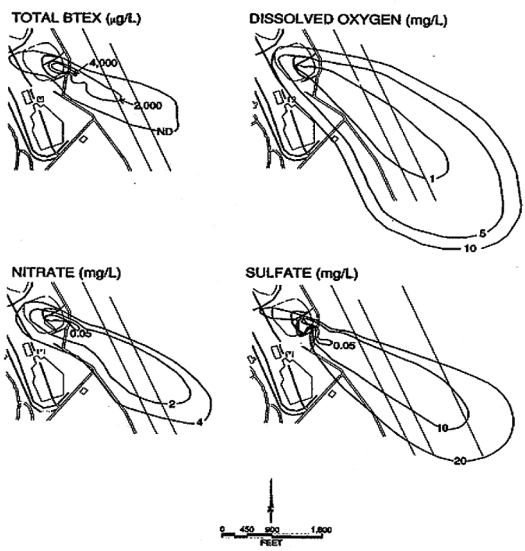


Figure 22.14. BTEX and electron acceptors, 1995, Plattsburgh Air Force Base, New York. [Adapted from T.H.Wiedemeier, H. S. Rifai, C. J. Newell and J.T. Wilson, **Natural Attenuation of Fuels and Chlorinated Solvents in the Subsurface**. Copyright © 1999 *John Wiley & Sons, Inc.* Reprinted by permission of *John Wiley & Sons, Inc*.]

be attributed to dechlorination. The data in Figure 22.14 show the distribution of electron acceptor concentrations observed at the site including dissolved oxygen, nitrate and sulfate. Background concentrations for these compounds are 10, 10 and 25 mg/L, respectively and their absence within the contaminated zones is an indication of biodegradation of BTEX and chlorinated solvents at the site.

Figure 22.15, on the other hand, shows the distribution of metabolic by-products of the biodegradation reactions including ferrous iron and methane. The presence of these by-products is further evidence of biological activity in the aquifer. Elevated chloride and ethene concentrations as shown in Figure 22.13 suggest that TCE, DCE and VC are being biode-

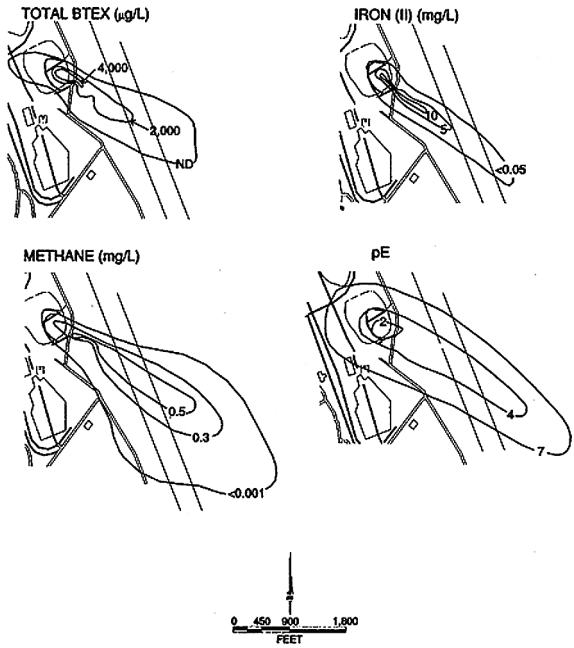


Figure 22.15. BTEX and metabolic by-products, 1995, Plattsburgh Air Force Base, New York. [Adapted from T.H.Wiedemeier, H. S. Rifai, C. J. Newell and J.T. Wilson, **Natural Attenuation of Fuels and Chlorinated Solvents in the Subsurface**. Copyright © 1999 *John Wiley & Sons, Inc.* Reprinted by permission of *John Wiley & Sons, Inc*.]

graded. Wiedemeier *et al*. (1999) calculated apparent biodegradation constants for FT-002 using trimethylbenzene as a conservative tracer. Their results are shown in Table 22.13. The data in Table 22.13 indicate biodegradation rates of the chlorinated solvents at the site ranging between 0 and 1.27 per yr.

Available geochemical data were analyzed by Wiedemeier *et al*. (1999) and they concluded that the geochemistry of the ground water near the source area and for about 1500 ft downgradient is significantly different from the groundwater further downgradient from the source (between 1500 and 4000 ft downgradient). This led the authors to conclude that Plattsburgh exhibits Type 1 behavior near the source and Type 3 behavior within the leading edge of the plume (see Section 22.5.2).

In the area extending to 1500 ft downgradient from the source, BTEX and TCE are comingled in the ground water. This area is characterized by anaerobic conditions that are strongly reducing. BTEX is being used as a primary substrate and TCE is being reductively dechlorinated to *cis*-1,2-DCE and VC. Between 1500 and 2000 ft downgradient from the source, however, the majority of the BTEX has been biodegraded and the system exhibits Type 3 behavior. These conditions are not optimal for reductive dechlorination, and it is likely that VC is being oxidized *via* ferric reduction or aerobic respiration.

Table 22.13. Approximate first-order biodegradation rate constants.

Compound	Correction method	A-B 0-970 ft, year^{-1}	B-C 970-1240 ft, year^{-1}	C-E 1240-2560 ft, year^{-1}
TCE	Chloride TMB Average	1.27 1.20 1.24	0.23 0.52 0.38	-0.30 NA -0.30
DCE	Chloride TMB Average	0.06 0.00 0.03	0.60 0.90 0.75	0.07 NA 0.07
VC	Chloride TMB Average	0.00 0.00 0.00	0.14 0.43 0.29	0.47 NA 0.47

Table 22.13. Approximate first-order biodegradation rate constants.

Compound	Correction method	A-B 0-970 ft, year^{-1}	B-C 970-1240 ft, year^{-1}	C-E 1240-2560 ft, year^{-1}
BTEX	Chloride TMB Average	0.13 0.06 0.10	0.30 0.60 0.45	0.39 NA 0.39

Other case studies have since been presented in the literature (e.g., Witt *et al*., 2002; An *et al*., 2004; Suarez *et al*., 2004; Rodriguez *et al*., 2004; Nobre and Nobre, 2004; Hausman and Rifai, 2005; Morrill *et al*., 2005; Kennedy *et al*., 2006; Kuchovsky and Sracek, 2007; Courbet *et al*., 2011; and Truex *et al*., 2007).

REFERENCES

AFCEE 2004. Principles and Practices of Enhanced Anaerobic Bioremediation of Chlorinated Solvents In: US Department of Defense, Afcfeeatestcpe (Ed.).

Amos BK, Suchomel EJ, Pennell KD and Löffler FE. 2008. Microbial activity and distribution during enhanced contaminant dissolution from a NAPL source zone. *Water Research* **42**: 2963-2974.

An, Y-J, D.H. Kampbell, J. W. Weaver, J. T. Wilson, and S-W Jeong, Natural attenuation of trichloroethene and its degradation products at a lake-shore site, *Environmental Pollution*, **130**: 325-335, 2004.

Atteia, O. and P. Hohener, Fast semi-analytical approach to approximate plumes of dissolved redox-reactive pollutants in heterogeneous aquifers. 2. Chlorinated Ethenes, *Advances in Water Resources*, **46**: 74-83, 2012.

Brown RA, Mueller JG, Seech AG, Henderson JK and Wilson JT. 2009. Interactions between biological and abiotic pathways in the reduction of chlorinated solvents. *Remediation Journal* **20**: 9-20.

Burnell, D. K., J.W. Mercer, and L. W. Sim, Analytical Models of Steady-State Plumes Undergoing Sequential First-Order Degradation, *Ground Water,* **50**(3): 394-411, 2012.

Cope N and Hughes JB. 2001. Biologically-Enhanced Removal of PCE from NAPL Source Zones. *Environmental Science & Technology* **35**: 2014-2021.

Courbet, C.,A. Riviere, S. Jeannottat, S. Rinaldi, D. Hunkeler, H. Bendjoudi, G. de Marsily, Complementing approach to demonstrate chlorinated solvent biodegradation in a complex pollution plume: Mass balance, PCR, and compound-specific stable isotope analysis, *Journal of Contaminant Hydrology*, **126**: 315-329, 2011.

Ferguson JF and Pietari JMH. 2000. Anaerobic transformations and bioremediation of chlorinated solvents. *Environmental Pollution* **107**: 209-215.

Field J and Sierra-Alvarez R. 2008. Microbial degradation of chlorinated benzenes. *Biodegradation* **19**: 463-480.

Giddings CGS, Liu F and Gossett JM. 2010. Microcosm Assessment of Polaromonas sp. JS666 as a Bioaugmentation Agent for Degradation of cis-1,2-dichloroethene in Aerobic, Subsurface Environments. *Ground Water Monitoring & Remediation* **30**: 106-113.

Gossett JM. 2010. Sustained Aerobic Oxidation of Vinyl Chloride at Low Oxygen Concentrations. *Environmental Science & Technology* **44**: 1405-1411.

Hara J, Ito H, Suto K, Inoue C and Chida T. 2005. Kinetics of trichloroethene dechlorination with iron powder. *Water Research* **39**: 1165-1173.

Hausman, S. S. and H. S. Rifai, Modeling remediation time using natural attenuation at a dry-cleaner site, *Remediation*, 5-31, 2005.

Hohener, P., and O. Atteia, Multidimensional analytical models for isotope ratio in ground water pollutant plumes of organic contaminants undergoing different biodegradation kinetics, *Advances in Water Resources*, **33**:740-751, 2010.

ITRC (Interstate Technology & Regulatory Council). 2005. Overview of In Situ Bioremediation of Chlorinated Ethene DNAPL Source Zones. BIODNAPL-1. Washington, D.C.: Interstate Technology & Regulatory Council, Bioremediation of Dense Nonaqueous Phase Liquids (Bio DNAPL) Team. www.itrcweb.org.

Jin YO and Mattes TE. 2008. Adaptation of Aerobic, Ethene-Assimilating Mycobacterium Strains to Vinyl Chloride as a Growth Substrate. *Environmental Science & Technology* **42**: 4784-4789.

Jones, N. L., T. P. Clement, and C. M. Hansen, A Three-Dimensional Analytical Tool for Modeling Reactive Transport, *Ground Water*, **44**(4): 613-617, 2006.

Kennedy LG and Everett JW. 2001. Microbial degradation of simulated landfill leachate: solid iron/sulfur interactions. *Advances in Environmental Research* **5**: 103-116.

Kennedy LG, Everett JW and Gonzales J. 2006. Assessment of biogeochemical natural attenuation and treatment of chlorinated solvents, Altus Air Force Base, Altus, Oklahoma. *Journal of Contaminant Hydrology* **83**: 221-236.
Kuchovsky, T. and O. Sracek, Natural attenuation of chlorinated solvents: a comparative study, *Environmental Geology*, **53**:147-157, 2007.
Lee W and Batchelor B. 2002. Abiotic Reductive Dechlorination of Chlorinated Ethylenes by Iron-Bearing Soil Minerals. 1. Pyrite and Magnetite. *Environmental Science & Technology* **36**: 5147-5154.
Ling, M., and H. S. Rifai, Modeling Natural Attenuation with Source Control at a Dry-Cleaner Site, *Groundwater Monitoring Review and Remediation,* **27**(1), 108-121, 2007
Löffler FE and Edwards EA. 2006. Harnessing microbial activities for environmental cleanup. *Current Opinion in Biotechnology* **17**: 274-284.
Lu, X., Y. Sun, and J. N. Petersen, Analytical solutions of TCE Transport with Convergent Reactions, *Transport in Porous Media*, **51**:211-225, 2003
Ma C and Wu Y. 2008. Dechlorination of perchloroethylene using zero-valent metal and microbial community. *Environ. Geol.,* **55**: 47-54.
Major DW, McMaster ML, Cox EE, Edwards EA, Dworatzek SM, Hendrickson ER, Starr MG, Payne JA and Buonamici LW. 2002. Field Demonstration of Successful Bioaugmentation to Achieve Dechlorination of Tetrachloroethene to Ethene. *Environmental Science & Technology,* **36**: 5106-5116.
Mattes TE, Alexander AK and Coleman NV. 2010. Aerobic biodegradation of the chloroethenes: pathways, enzymes, ecology, and evolution. *FEMS Microbiology Reviews* **34**: 445-475.
Morrill, P., Lacrampe-Couloume, G., Slater, G.F., Sleep, B.E., Edwards, E.A., McMaster, M.L., Major, D.W., and Sherwood Lollar, B. (2005). Quantifying chlorinated ethene degradation during reductive dechlorination at Kelly AFB using stable carbon isotopes. *Journal of Contaminant Hydrology*, **76**, 279-293.
Newell, C.J.and C. E. Aziz, Long-term sustainability of reductive dechlorination reactions at chlorinated solvent sites, *Biodegradation*, **15**:387-394, 2004.
Nobre RCM and Nobre MMM. 2004. Natural attenuation of chlorinated organics in a shallow sand aquifer. *Journal of Hazardous Materials* **110**: 129-137.
Olaniran AO, Pillay D and Pillay B. 2008. Aerobic biodegradation of dichloroethenes by indigenous bacteria isolated from contaminated sites in Africa. *Chemosphere* **73**: 24-29.
Quezada, C. R., T. P. Clement, and K-K Lee, GEneralized solution to multi-species transport equations coupled with a first-order reaction network involving distinct retardation factors, *Advances in Water Resources*, **27**: 507-520, 2004.
Robinson C, Barry DA, McCarty PL, Gerhard JI and Kouznetsova I. 2009. pH control for enhanced reductive bioremediation of chlorinated solvent source zones. *Science of The Total Environment* **407**: 4560-4573.
Rodriguez, E., K.A. McGuinness, and D. U. Ophori, A field evaluation of enhanced reductive dechlorination of chlorinated solvents in ground-water, New York Metropolitan Area, *Environmental Geology*, **45**: 623-632, 2004.
Scherr KE, Nahold MM, Lantschbauer W and Loibner AP. 2011. Sequential application of electron donors and humic acids for the anaerobic bioremediation of chlorinated aliphatic hydrocarbons. *New Biotechnology* **29**: 116-125.
Schumacher W and Holliger C. 1996. The proton/electron ration of the menaquinone-dependent electron transport from dihydrogen to tetrachloroethene in "*Dehalobacter restrictus*". *Bacteriology* **178**: 2328-2333.
Scow KM and Hicks KA. 2005. Natural attenuation and enhanced bioremediation of organic contaminants in groundwater. *Current Opinion in Biotechnology* **16**: 246-253.
Srinivasan, and, Analytical solutions for sequentially coupled one-dimensional reactive transport problems - Part I: Mathematical derivations, *Advances in Water Resources*, **31**: 203-218, 2008.
Suarez, M. P., H. S. Rifai, T. J. Rittaler, and S. Hausman, Natural Attenuation of Chlorinated Solvent Plumes at Texas Dry-Cleaners, *Remediation*, v. **14**, No. 3, 7 - 31, 2004.
Sun, Y., J.N. Petersen, and T. P. Clement, Analytical solutions for multiple species reactive transport in multiple dimensions, *Journal of Contaminant Hydrology*, **35**: 429-440, 1999.
Sun, Y., X. Lu, J. N. Petersen, and T. A. Buscheck, An Analytical Solution of Tetrachloroethylene Transport and Biodegradation, *Transport in Porous Media*, **55**: 301-308, 2004.
Tiehm A and Schmidt KR. 2011. Sequential anaerobic/aerobic biodegradation of chloroethenes-aspects of field application. *Current Opinion in Biotechnology* **22**: 415-421.
Tobiszewski M and Namiesnik J. 2012. Abiotic degradation of chlorinated ethanes and ethenes in water. *Environ. Sci. Pollut. Res.* **19**: 1994-2006.
Truex, M. J., C. D. Johnson, J. R. Spencer, T. P. Clement, and B. B. Looney, A deterministic approach to evaluate and implement monitored natural attenuation for chlorinated solvents, *Remediation*, 2007.

Widdowson, M.A., Modeling natural attenuation of chlorinated ethenes under spatially varying redox conditions, *Biodegradation* **15**: 435-451, 2004.
Witt, M. E., G.M. Klecka, E. J. Lutz, T. A. Ei, N. R. Grosso, and F. H. Chapelle, Natural attenuation of chlorinated solvents at Area 6, Dover Air Force Base: groundwater biogeochemistry, *Journal of Contaminant Hydrology*, **57**: 61-80, 2002.
Zhao H-P, Schmidt KR and Tiehm A. 2010. Inhibition of aerobic metabolic cis-1,2-di-chloroethene biodegradation by other chloroethenes. *Water Research* **44**: 2276-2282.

Index

Numerics
1,1,1-trichloroethane 1376, 1432-1433, 1729
1,2-dichloropropane 1431-1432, 1436
^{14}C labeling 920, 922
^{1}H-NMR 1186
1-octanol 917
2,5-hexanedione 1434
2-hexanoyl 1434
2-methylisoborneol 1724
3D printing mold 1008
3D printing technology 1008
4-methylpentan-2-one 1592

A
aberrant recombination 1412, 1418
abiotic
  degradation 1738
  hydrolysis 1738
  mechanism 1730
  pathway 1749
  reductive dechlorination 1740
abrasion resistance 1024
absorption 1636
  -regeneration 1706
acetate 949
acetone 902, 916, 945, 1039, 1317, 1364, 1592
acid
  deposition 1314
  pickling 998
  rain 1223
  -base properties 1539
acidity 1125-1126
acrylic 903, 945, 949
  acid ester 902
  fatty acid derivative 1027
  resin 1017, 1020
activated
  alumina 1642
  carbon 1636-1639, 1641-1642, 1645-1646, 1650, 1654, 1657-1661, 1667, 1670
    adsorption system 1638
    bed 1640, 1645-1646, 1652, 1663
    fiber 1650
    life 1660
    load 1654
    particles 1650
    pellets 1655
    quality 1652
    regeneration 1641
    schematic model 1642
    service life 1660
    system 1647
    type 1643
    deteriorated state 1661
  sludge treatment plant 1233
activation
  energy 1174
  model 1607
  volume 1474-1475, 1484, 1490
active compound 1033
active site 1637
activity
  coefficient 1061, 1063, 1069, 1589-1590, 1628
  model 1467
actylol 1566
acute
  exposure 1291
  leukemia 1394, 1411, 1418
  level 1363
  lymphoblastic leukemia 1393
  lymphocytic leukemia 1399
  myeloid leukemia 1393, 1396, 1399
  non-lymphocytic leukemia 1408, 1415
  oxalate nephropathy 1372
  renal failure 1371
acylation 1512
adenocarcinoma 1381
adenoma 1381, 1383
adhesion 904, 945
adhesive 901, 1276, 1380-1383, 1431, 1433
  bonding 911
  foaming 905
  industry 902
  manufacturing industry 902

pressure sensitive 901
production 902
reactive system 904
adipose tissue 1360
adsorbate 1637, 1640
adsorbent 1163, 1638
pore 1639
regeneration 1640, 1662
volume 1648
working capacity 1641, 1648
adsorber
bed 1639-1640
construction forms 1649
resin 1643
system 1640
adsorption 955, 1637, 1640
capacity 1638-1639, 1656-1657
cycle 1645-1646, 1652
enthalpy 1638
front 1656
fundamentals 1637
heat 1644, 1656, 1671
isotherm 1220, 1638, 1653-1654
kinetics 1637, 1639
plant 1637
process 1636
step 1663
system design 1647
technology 1654
temperature 1660
wheel 1665-1666
adsorptive
power 1638
solvent recovery 1644
advancing front 1732
advection 1729-1730, 1732, 1735, 1763
-dispersion
equation 1735
model 1222
adverse effect 1154
aerobic
bacteria 1750
biodegradation 1773
cometabolism 1758-1759
oxidation 1749
aerosol formulation 1381, 1430
aerospace 908, 911
industry 1383, 1427
manufacturing process 908
solvent 911
surface cleaning performance 912
workers 1385
Agency for Toxic Substances and Disease 1385
agricultural crops 1566
agrochemical solvent 1602, 1624
air
blasting 998
bubble 1020
contaminants standard 967
emission 1203, 1635
partition coefficient 1369
pollution 1257
abatement 1314
control 1641, 1643
quality 1241
standard 1313
airborne exposure level 1290
aircraft 1112
coating 908
element flexing 908
interior 911
refueling 1128
turbine 1128
worker 1376
airflow rate 1217
airshed model 1249
airstream 1710
airways 1156
albuminuria 1351
alcohol 1379
abuse 1349
consumption 1425
dehydrogenase 1545
alcoholism 1426
alcoholysis 1595
aldehyde 1607
aldol reaction 1545
algae 1723-1724
alginate membrane 1599
aliphatic
alcohol 1364
aldehyde 1364
hydrocarbon 1091, 1376

alkalinity 1125
alkane oxidation gene 917
alkene dimerization 1511
alkyd
  oil 1008
  resin 1017, 1080
  waterborne coating 1116
  lactate 1570
alkylating agents 1411
alkylation 1541
alkylsulfate chain length 1502
allergic
  dermatitis 1352
  effect 1352
  potential 1352
  reaction 1184
allylic fatty acid derivative 1027
alternative
  solvent 959
  substance 964
aluminosilicate 1643
aluminum trichloride 1511
alveolar
  air 1155, 1157-1158, 1160, 1164, 1166, 1168-1169
    concentration 1167
  basement membrane 1371
  blood vessels 1348
  duct 1156
  membrane 1158, 1369
  steady state 1159
  ventilation 1169, 1348
alveoli ventilation 1425
ambient
  air
    pollutant 1315
    sample 1206
  monitoring detector 1315
  water sample 1208
American
  Conference of Governmental Industrial Hygienists 1154, 1334, 1398
  Congress of Governmental Experts 1178
Ames assay 1353
amine 1041
amino acid 1584
aminocarbonylation 1549
ammonium lactate 1593
amniotic cavity 1359
amorphous phase 1042-1043, 1179
amphiprotic cosolvent 1066
anaerobic
  aquifer 1744
  biodegradation 1127, 1741
  condition 1730, 1761
  conditions 1745
  oxidation 1750-1751
  reductive dechlorination 1741
anemia 1417
anencephaly 1362
angiosarcoma 1395
aniline point 1128, 1139
animal studies 1381, 1410
anion
  asymmetry 1520
  doping 1724
  exchanger 997
anionic radius 1506
anode electrode paper 1089
anthropogenic carbon 1761
anti-acne properties 1592
antibiotic 1005, 1180, 1592
  resistance 922
  -resistant microbial strains 1725
antifouling coating 1102
antifungal formulation 1592
antigen 1372
  -antibody reaction 1371
antiglomerular basement membrane 1371
antihelminthic 1430
  agent 1381
antihistamine 1592
anti-hypertension drug 1384
antimicrobial
  activity 1624
  agent 930, 1005, 1110
antioxidant 1044
  activity 1619
anti-smudge surface 1107
anti-solvent
  effect 1581
  path 1492
  precipitation 1577

antistatic
compound 953
finishing 958
antiviral 1592
Antoine constant 1569, 1576
aortic stenosis 1364
aplastic anemia 1393-1394, 1410, 1416
apolar 951
solvent 935
apoptotic activity 1412
aprotic
equilibrium 1511
polar solvent 1005
aquatic species 1725
aqueous
environment 1725
phase 916, 1023
solution 952
aquifer 1729
matrix 1733-1734, 1740
Archimedes number 1477
architectural surface coating 1015-1016
aromatic solvent 902, 1020
Arrhenius law 1520
arterial
blood 1155, 1158, 1370
concentration 1158
aryl almidine 1602
asbestos 913
ash content 1128
asphalt 913, 1141
concrete 914
dispersion 913
mixture 914
plastic behavior 913
asphaltene precipitation 1707
asthma 1110, 1245, 1352
atherosclerosis 1183
atmospheric
emission 1643
pollution 1422
atomic force microscopy 1552
attenuation process 1729
attrition rate 1660
autoantibodies 1371
auto-body repair technician 1288
autoignition 1126
temperature 1126
autoimmune
disease 1352, 1371
mechanism 1371
automobile
exhaust 1240
mechanics 1377
automotive
application 906
door paneling 906
gasoline 1377
industry 905, 1009
solvent release 1010
manufacturer 1382, 1427
paint 1144
average airborne exposure 1292
aviation fuel 1128, 1131, 1377
axon swelling 1351
azeotrope 1680
formation 1574
azeotropic
composition 1676
mixture 1675
system 1576

B

bacteria 1005
bacterial
cell wall 1724
transport 1772
bactericidal photoactivity 1724
baggage area 911
balloon angioplasty 1183
bandgap 1724-1725
value 1723
barges 1112-1113
barotropic effect 1461
barrier function 920
basecoat 1028
batch
distillation 1674, 1678
reactor 1596
rectifier 1675
to batch inconsistency 1043
battery production cost 1707
beaded activated carbon 1650
Beckmann rearrangement 1611

beer 1566
bentonite 955
benzaldehyde lyase 1545-1546
benzene 947, 1003, 1035, 1080, 1348, 1363, 1376, 1379-1381, 1385, 1391, 1408-1409, 1426, 1718
  causation 1408
  concentration 1403
  cumulative dose 1392
  dermal absorption 1392
  exposure 1394, 1408
    level 1398
    limits 1397
  human carcinogen 1393
  level 1404
  metabolite 1395, 1413, 1419
benzothiazines 1606
Biginelli reaction 1542, 1544
bilaminar germ disc 1359
bile
  acid 1429
  excretion 1432
binary
  azeotropic system 1574
  interaction parameters 1467
  mixture 1580, 1685
  system 1459, 1463
binder 1017
binding
  agent 1258
  force 1637
Bingham pycnometer 1130
bioabsorbable stent 1005
bioactive compound 1557
bioavailability 1041, 1058, 1179
biocatalysis 931, 935, 1529
biocatalyst 935, 1544
biocatalytic
  organic reaction 1545
  process 916
  reaction 923, 1544
biochemical
  pathway 1426
  reactions 1490
biocide treatment 1108
biocompatible 1531
biocorrosion 930
biodegradability 1022, 1127, 1540
biodegradable 1531
  chelating agent 1592
  solvent 959
biodegradation 1222, 1708, 1729, 1732, 1741, 1764, 1772
  coefficient 1752
  potential 1127
  rate 1751
biodiesel 1557, 1593
  synthesis system 1544
biofilm
  matrix 930
  reactor 931
biofiltration 1085
biofouling 930
biofuel production 1483
biogas 1567, 1706
biogenic hydrocarbon emission 1245
biological
  change 1153
  condition 1154
  contamination 1493
  disposal 1690, 1699
    facility 1675
  exposure index 1154
  marker 1408
  monitoring 1154-1155
  patina 1108
  transformation 1743
  treatment 1636, 1676, 1686
biomarker 1413, 1415, 1419
biomass 1456, 1708
  conversion 1489
  crop 1567
  -based solvent 1602
biomedical 1458
biomedicine 1594
bio-oil 914
biopolymer 1494, 1594
bioproduction process 917
bioreactor 917
bioreduction 1545
biorefinery 1567, 1624
bioremediation 928, 931, 1760-1761
biorenewable 1540
  medium 1546

reaction media 1528
solvent 1551, 1555-1556, 1558, 1592
biosolvent 1601
biosphere 916
biostimulation 1745
biotechnological application 938
biotechnology 916, 931, 990, 1033
process 1034
biotic dechlorination 1747
biotransformation 917-918, 924, 928, 931, 933, 940, 1154, 1183-1184, 1349, 1515, 1543, 1759
process 1349
rate 1356
bitumen 914
bituminous
binder 914
material 914
blastocyst 1360
blastomere 1359
bleaching 982, 983, 1088
bleeding 1110
blister formation 1175
blistering 1004
mechanism 1175
blocking 1140
blood 1428
biochemical change 1436
brain barrier 1369
circulation 1156
collection 1155
malignancy 1400
pressure 1384
stream 1361, 1369, 1428
vessel 1592
/air partition coefficient 1157-1158, 1165
/gas partition coefficient 1159-1160
blushing 1099
body
fat 1425, 1428
fluid 1005
mass index 1384
bodywork repair 1287
bohemite 1107
boiling point 1004, 1026, 1036, 1079, 1127, 1134, 1255-1256, 1508, 1528, 1569, 1575, 1592
bomb calorimeter 1128
bond
line 911
performance 1002
strength 904
bonding 910
bone
marrow 1361, 1365, 1393, 1395-1396, 1410, 1412, 1415-1416, 1418
aplasia 1396
cell 1409, 1419
damage 1408
disease 1403
function 1363
suppression 1393
bookbinding 905, 1085
boric acid 1002
boundary conditions 1467
Bradford-Hill criteria 1376
brain 1369, 1440, 1442
development 1363
edema 1451
growth 1365
breakdown
metabolite 1375
voltage 1131
breakthrough
capacity 1672
curve 1639
breath
collection 1160
monitoring 1153, 1155, 1163-1164
sampling 1155
sampling methodology 1160
breathing 1369
discomfort 1245
frequency 1157
bromination 1091
bromine index 1128
bromobenzene toxicity 1422
bromobutyl rubber 1091
bronchioles 1156
bronchitis 1352
Brønsted acidity 1512
brushability 1099
brushing 909, 1017
bubble
coalescence 1020

formation 1175
nucleation 1175
point 1463, 1685
time 1142
velocity 1020
bubbling 1004
building
material 1257
product 905
Bunsen coefficient 1140
buoy 1092
butan-2-one 1592
butanol 916, 1707
button mushroom 1557
butyl
acetate 1132, 1289
alcohol 1374
rubber 1091

C

C reductase activity 1433
caffeic acid 1586-1587, 1590
caffeine 1587, 1590, 1620-1622
extraction 1622
recovery 1621
cage capacity 954
calcification 1183
calcium
carbonate 913
hydroxide 1110
oxalate monohydrate 1372
calibration 1270
California aerospace company 1385
calorific value 1128, 1676
calorimetric method 1128
camel hair 949
Camp Lejeune 1385
camphene 1003
cancer 1393, 1396, 1408, 1412
epidemiology 1429
incidence 1385
mortality 1386
risk 1378, 1381, 1397, 1430
cancerogenic properties 947
capillary
blood 1157
sample 1169
condensation 1638-1639, 1653
forces 1024
segment 1156
car
interior 1176
painter 1435
carbohydrate feedstock 1624
carboligation 1545
carbomer 1035
carbon
bed 1644, 1646
dioxide 959-960, 1114, 1477, 1707, 1710
absorption 1706
capture 999
process 1706
diffusion 1706
supercritical 910, 1457
disulfide 1079, 1080, 1443, 1666
hardness 1660
heterojunction 1724
monolith 1556
monoxide 1315
nanotube 1556
composite 1553
tetrachloride 1422, 1426-1427, 1436, 1602, 1729
carbonyl oxygen 1567
carbopol resin 1035
carboxyhemoglobin 1451
carboxymethyl cellulose 1597
carcinogen 1195, 1241, 1319, 1353, 1729
potential 1377
carcinogenesis 1291, 1408, 1415
carcinogenic 1383
component 914
effect 1120, 1392, 1395, 1426
exposure 1394
risk 1381
solvents 1353
carcinogenicity 1182, 1185, 1353, 1387, 1393
carcinoma 1383, 1430
cardiac
output 1159, 1369
toxicity 1184
cardiovascular disease 1183
Carnahan-Starling term 1569, 1627
carotene 1618
carotenoids 1052, 1617

carpet 905
carrier
  fluid 911
  gas 1638
  mobility 1725
cartilage tissue engineering 1086
cashmere 949
casting composition 1008
castor 965
  pomace 984
catalyst 1404, 1599, 1602
  activity 1484, 1488
  deactivation 1716
  geometry 1710
  life 1488
  manufacture 1494
  morphology 1724
  poisoning 1706
  surface 1720
catalytic
  action 935-936
  combustion 1650
  cycle 1413, 1419
  dehydrochlorination 1709
  extractive reaction 1600
    process 1601
  membrane 1596
    reactor 1624
  oxidation 1636
  reaction 1485-1486
  solvent 1513
catechin 1588, 1622-1623
catheter 1005
cation
  doping 1724
  exchange capacity 1236
  exchanger 997
  moiety 1235
  -anion combination 1228, 1233
causative factor 1411
cavitation 1140
ceiling limit 1310
cell
  architecture 1426
  culture 1408
  envelope 919
    structure 929
  growth 1222
  injury 1371
  lineage 1399
  maturation 1400
  membrane 1372, 1426
    structure 1352
  physiology 927
  surface 922
  wall 929
cellophane 1666
cellular
  antigen 1371
  genetic material 1415
  homeostasis 927
  hyperplasia 1348
  membrane 1159, 1370
  origin 1412
  repair mechanism 1153
  toxic effect 1392
cellulase 940, 1545
cellulose 1547
  acetate 1079
  acetate butyrate 945
    pervaporation membrane 1599
  depolymerization 1545
  ether 1080
  feedstock 1593
  nanofibril 1556
  nitrate 1258
cellulosic
  feedstock 1567
  fiber 949
cement 1106
  kiln 1674-1676, 1690, 1699-1700
  plant 1675, 1706, 1709
central nervous system 1350, 1360-1362, 1392
  depression 1292
centrifugal scrubber 1669
centrifuge 948
cephalin 982
ceramics 1723
cerebellar degeneration 1447
cerebral atrophy 1447
chain
  extension 913
  length 1235, 1506-1507, 1519
  transfer agent 1022

Chapman-Enskog-Wilke-Lee model 1471
charcoal 955
charcoal filter 948, 953
chelating extractant 997
chemical
  attack 1016
  bonding 911
  building blocks 1707
  change 1255
  compound 1272
  equilibrium 1599
  extraction 991
  hepatitis 1434
  industry 916, 1012, 1566, 1624
  interaction 1044, 1174
  intermediate 1430
  modification 1637
  oxygen demand 1127
  pulping 1088
  reaction 901, 1017, 1036, 1038
  reduction 1556
  resistance 1024
  stripping operation 910
  synthesis 1034
  teratogen 1360
  transformation 1038
chemisorption 1637
chemoenzymatic epoxidation 1546
chemoselective addition 1549
chemoselectivity 1542, 1601
chemotherapeutic agent 1411
childbearing age 1361
childhood acute lymphoblastic leukaemia 1363
childhood leukaemia 1363
chiller 1706
chip impact resistance 1132
chiral
  alcohol 939, 1549
  eutectic mixture 1548
  template 1592
chitosan 1597
chloral hydrate 1428
chloride ion 1108
chlorinated
  compound 1749, 1750
  fluorocarbon 1092
  hydrocarbon 1079, 1085, 1216
  organics 1723
  olyolefin 1011
  rubber 1015, 1017
  solvent 905, 914, 964, 1364, 1381-1382, 1427, 1566, 1742-1743, 1752, 1773
    plume 1762, 1764, 1767, 1774
  volatile organic compound 1708
chloroaluminate ionic liquid 1511
chlorofluorocarbon 1310
chloroform 1422, 1427, 1602
cholangiocarcinoma 1432
cholesterol 923
chromatid 1409
  aberration 1411
  fragment 1410
  gap 1409
chromatographic
  performance 1051
  reactor 1600
chromatography 1051
chromatoid 1415
  aberrations 1417
chromosomal
  aberration 1408-1410, 1412, 1415-1417, 1419
  abnormalities 1360
  analysis 1417
  change 1408, 1410, 1415
  damage 1411
  translocation 1408, 1412, 1415, 1419
chromosome 1408-1409
  break 1409
chronic
  end-stage kidney disease 1376
  exposure 1427-1428
  fatigue syndrome 1356
  glomerular disease 1372
  hepatitis 1428
  kidney disease 1373
  lymphocytic leukemia 1393, 1399, 1402
  myelocytic leukemia 1401
  myelogenous leukemia 1392
  myeloid leukemia 1393, 1399, 1412, 1419
  nephrotoxicology 1370
  renal failure 1373
Chung-Lee-Starling
  expression 1471
  model 1471

cigarette
  paper 1089
  smoking 1391
citrus essential oil 923
clathrate 1043, 1179
  formation 1045
Clausius-Clapeyron equation 1140
clay
  content 1236
  dispersion 1107
  products 1106
  thin film 1107
Clean
  Air Act 972, 1298
    amendment of 1990 1313
  Water Act 1325
cleaner 945, 1107
cleaning 910-911, 1007, 1729
  compound 911
  cycle 954
  efficiency 951
  formulation 1085
  operation 1030
  operations 1093
  performance 959
  process 1495
  product 1431
  solvent 1128
clear varnish 1115
clearcoat 1288, 1291
cleavage 1359
  plane 1042
Cleveland open cup 1133
Closed Bottle test 1232-1233
clothing 1729
cloud point 1463, 1584
cloudiness 1131
cluster formation 1530
coagulant 1079
coagulation 1079
  bath 1079
coal
  processing 1489
  tar 913
    distillation 1391
coalescence 1359
coalescent
  hydrolytic stability 1024
  migration 1028
  solvents 1027
coalescing
  agent 1024, 1026, 1028
  aid 1025
  efficiency 1025
  power 1024
  solvent 906, 1022, 1024, 1026, 1114
    classification 1028
  efficiency 1024
  role 1024
coated
  cathode layer 1706
  fabrics 1109
coating 905, 913, 1009, 1015, 1040, 1493
  adhesion 1018
  formulation 1022
  industry 1591, 1625
  material 1015, 1017
  mechanical movement 908
  quality 1005
  reflow 1005
  system 1015, 1017, 1026
  technique 1015
cocaine 1181
co-carcinogen 1353
coconut 965
coffee
  beans 1621
  consumption 1378
  roasting 1621
cognitive
  function 1011
  performance 1292
  test 1350
coherent film 1024
coil coating 942
  line 944
  production rate 942
  system 943
coke production 1391
cold wiping 911
collapsible bag 1163
collision repair 1287
  industry 1289, 1291

process 1288
colonized marble artifacts 1108
color depth 1129
colorimetric reaction 1162
column residue 1675, 1699
combustion
fuel 1709
heat 1709
cometabolic
pathway 1741
reductive dechlorination 1741
cometabolism 1740-1741, 1750
compatibilizing solvent 1116
complexation agent 1055
Compliance Sector Notebook 901
component recovery 1678
composite 911, 1556
compressability 1043
compressed rubber foam 905
computer
control 954
model 1249
concave nanocube 1557
concentration 1653
gradient 1158
conceptual
design 1701
model 1701
modeling 1678
approach 1681
level 1691
conceptus 1360-1361
concrete 1016, 1106
alkalinity 1016
coating material 1016-1017
primer 913
condensation 908, 1636, 1665
process 1669
unit 1666
condenser 953-954, 981
conductivity 1174
meter 1131
conformation 936
congenital malformation 1364
conjunctivitis 1352
constant volume distillation 1674
construction industry 1176
contact
adhesive 901-902
dermatitis 1352
time 1348
container 1044-1045, 1112
contamination 1079
control measure 1291, 1316
controlled
drug release 1183
evaporation 1024
morphology 1177
co-nucleation 1492
convective contribution 1707
conventional
adsorption system 1650
column sequence 1705
conversion 1596
rate 1597
convoluted tubule 1382
cooling
energy 1706
gas 1381
coordination polymer 1554
copper
catalyst 1604
removal 1592
corrosion
protection 908, 1093
material 1650
corrosiveness 1129
Cosden process 1511
cosmetic 1175
applications 1592
industry 1591
product 945
cosolvency 1054, 1061, 1066, 1072
cosolvent 953, 1002, 1028, 1055, 1060
effect 1057, 1074
flushing 1058
cotton 948, 949
cottonseed 965
oil extraction 985
Coulomb's law 936
coulometric titration 1128
coumarin 1608
counterfeit
medicine 1181

tablet 1177
coupling
agent 1107
reaction 1549, 1604
craze development 1132
crazing 1132
creams 1592
creasing 948-949
creatinine
clearance point 1374
correction 1155
creep recovery 906
critical
phenomena 1464
point 1456, 1463, 1466, 1469
pressure 1456
solubility temperature 999
temperature 1456, 1460, 1570
value 1495
volume 1570
cross
-aldol reaction 1550
-coupling reaction 1547
-dehydrogenative coupling 1549
-draft extraction 1291
-infection 1005
crosslinked polymer 1553
crosslinker 906
crosslinking 1116
polymer 943
crossover pressure 1461
crude oil 981, 1032
crust formation 1004
cryolite 1500
crystal
engineering strategy 1042
face 1042
growth rate 1042
hydrophilicity 1179
formation 1042
habit 1041, 1042
lattice 1043, 1179
plane 1042
shape 1042
structure 1041
surface 1179
wettability 1179
crystalline
defect 1042
form 1043
structure 1041-1042, 1174, 1179
crystallinity 1174
crystallization 1041, 1043, 1554
process 1034, 1036, 1041-1043
step 1045
cubic arrangement 1023
cultured
human lymphocyte 1409, 1416
lymphocyte 1409
cumulative exposure 1374, 1396, 1403
curable coating 1116
cutback asphalt 913
cut-off point 1050
cyanoacrylate 901
cyanobacteria 1724
cycloaddition 1548, 1557, 1608-1609
cyclohexane 1081, 1404
cyclohexanone 1651
surface reaction 1659
cyclopentanone 1660
cytochrome 1421-1422
C reductase activity 1433-1434
P450 1428, 1434
enzyme activity 1433
system 1426
system 1349
cytogenetic assay 1408
cytogenetics 1415
cytoplasmic membrane 920-921, 923, 926, 929
cytotoxicity 928, 1540

D

daily ethanol consumption 1435
damaged lymphocyte 1412
Darcy velocity 1736
Dawson-Khoury-Kobayashi correlation 1470
deacidification experiment 1707
dead space 1160
deasphalted oil 1707
deasphalting 1030
death 916
debromination 1058
debrominative transformations 1058
decamethylcyclopentasiloxane 959, 960

dechlorination 1744-1745, 1748-1749, 1770, 1775, 1747
decomposition temperature 1476, 1507
decorative
  foil 905
  purposes 1022
  textile 1257
deep
  eutectic
    mixture 1557, 1558
    solvent 928, 940, 1014, 1544, 1528-1529, 1532, 1551, 1553, 1557
  penetration 1592
defensive mechanism 922
degassing 1079
degradant 1041, 1044
degradation product 1258
degradative potential 916
degreaser 1107, 1433
degreasing 947, 1113, 1288, 1379, 1383 1391, 1426, 1729
degumming 982
dehulling 979
dehydration 1677, 1695
  process 1546
dehydrogenase 1370
dehydrohalogenation 1729, 1738-1739
de-icing fluid 908
delignification 1489
demineralization 1048
demographic factors 1379
denaturalization 1557
denaturing agent 1038
density 1130, 1521
dental adhesive 906
deodorization 982-983
depainting 909-910
depreciation 1636
dermal
  absorption 1391
  exposure 1154, 1289
dermatitis 945, 1350, 1352
derosination 1114
design specification 1678
designer solvent 1228
desolvate solvate 1045
desolvated solvate 1043
desorbate 1637
desorbed solvent 1186
desorption 1637
  cycle 1652
  efficiency 1645
  extent 1236
  step 1660
  time 1645
detector 1190
  tube 1162, 1267
detergent 949, 951
detoxification 1421
  enzyme 1422
  process 1183
developmental pathway 1361
dew point 1463
diabetes 1370
diabetic
  kidney 1375
  nephropathy 1375
diacetyl peroxide 1660
diagnostic tool 1408
dialysis system 1005
dianion 1514
diatomaceous earth 983
dibasic ester 1026
dichloroacetic acid 1428
dichloroethylene 1381
dichloromethane 909, 1431, 1436
die
  casting 1007
  flux 1007
  lubrication 1007
dielectric constant 936, 1485, 1570
Diels-Alder
  adduct 1543
  reaction 1485, 1514, 1549
diesel
  engine exhaust 1365
  fuel 1377
    exposure 1378
diether compound 1110
diethyl ether 1132
differential
  scanning calorimetry 1186
  thermal analysis 1186

diffusion 1157-1159, 1369, 1637, 1682
  coefficient 1518, 1637
  distance 1656
  process 1018, 1174
  rate 1158, 1352, 1579
  theory 1470
diffusive contribution 1707
diffusivity 1157
diglycosidase 1546
dihaloelimination 1729, 1738, 1740
dilatation 1274
diluent solution 1020
dilute solution 1212
dilution ratio 1130
dimer 1567
dimerization 1413, 1419
dimethyl sulfoxide 1108
dimethylacetamide 911, 1079, 1188
dimethylformamide 1036, 1188
dip coating 1004
dipole moment 936, 1062
dipping 909
dipropylene glycol ether 959
direct
  aldol reaction 1550
  current deposition 1552
  exposure 1242
  injection 1187
  steaming 1644
dirt pickup 1025
discoloration 1025
discrete film 1023
disease severity 1374
disinfection mechanism 1110
disintegration 1180
dispersion 1729, 1735
dispersity 1491
dispersivity 1732
display device 1107
dissertations 1457
dissimilar binary system 1460
dissipation time 1131
dissociation constant 1488
dissolution 1682
  properties 1179
dissolving power 1140
distillate
  composition 1676, 1701
  purity 1674
  temperature 1682
distillation 1048, 1080, 1477, 1675, 1677-1678, 1695, 1699, 1705
  column 1675-1676, 1705
  configuration 1705
  /incineration 1677, 1690, 1701
  /pervaporation 1674-1675, 1699, 1701
distilling vessel 949, 954
distribution coefficient 1621, 1734
diuretics 1384
d-limonene 1602
DNA 1557
  adduct 1413
  breakage 1412, 1419
  change 1408, 1415
  damage 1412, 1418
  metabolism 1409
  synthesis 1409, 1416, 1432
domestic environment 1026
door panel 905
dose 1396
  metrics 1396
  -effect response 1350
  -response 1373, 1374
dosimetry 1392
dosing
  equipment 954
  unit 953
double bond number 1579
Dow Method 1218-1219
downdraft extraction system 1288
down-stream separation 1484
drinking water 1048, 1724
  standard 1327
driveway sealer 913
drug 1039, 1557
  coated device 1005
  dissolution 1074
  eluting stent 1183
  product 1674
  release modulation 1005
  solubility 1055
  stability 1180
  substance 1033, 1179

/container interaction 1180
-active molecule 1602
-printing 1086
drum 1038
dry
cleaning 947, 959, 1110, 1166, 1362, 1364, 1377
detergent 949, 953, 959, 1729
machine 948, 953-955
relative humidity 950
process 953
laundry 947
point 1127, 1140
spinning 1079
drying 910, 1034, 1079, 1472, 1495
conditions 1180
process 1017, 1026, 1043
speed 1116
time 1174
duration of exposure 1379
dyeing 947, 1110
dyes-sensitized solar cell 1551
dynamic
adsorption 1639-1640
capacity 1657
drying 1043
headspace injection 1189
percolation extractor 985, 989
viscosity 1568

E

ear 1183
early pregnancy 1364
earnings 1698
ebulliometric method 1574
ecological
issues 1566
paint 1280-1281
risk 964
economic analysis 1686
ecosystem 1242
diversity 1700
quality 1700
eczema 1348
edible oil processing 980
effective pore size 1653
effluent limitation 1326
guidelines 1326
egioselective bioreduction 1546
elastic recoil 1183
electric
breakdown 1131
conductivity data 1275
stress 1131
conductivity 1131, 1174
resistance 1134
transformer 1381
electricity production 1674, 1690
electrochemical
oxidation 1709
properties 1515
reduction 1709
synthesis 1553
window 1515
electrochemistry 1529, 1538, 1551
electrodeposition 1009, 1516, 1538, 1540, 1551-1552
electroencephalograph 1447
electrokinetic
remediation 1058
technique 1058
electrolyte 1551
electrometric titration 1128
electron
acceptor 1732, 1741, 1744, 1747, 1749
beam curing 942
donor 1741, 1743, 1745, 1747, 1749
ionization mode 1190
-hole recombination center 1724
electronic
nose 1274, 1275
transition energy 1537
electronics 964, 1086, 1729
electroosmosis 1059
electrophilic substitution 1512, 1541
electropolishing 1551
electrospinning 1083
electrostatic
interaction 1221, 1234
solvation 1532
electrosynthesis 1518
embolic composition 1592
embolization 1592
embryo 1359
embryolethality 1361

embryonic period 1359
embryotoxic effect 1351
emerging industry 1722
emission 942, 1079, 1081, 1316
  control technology 1317
  limit 1103
  load 1270
  source 1241, 1347
  stationary source 1316
emissive limit 1266
emitting surface 1258
emollient effect 1592
emotional reaction 1274
emulsification 904-905
emulsion 952
  paint 1260, 1264
  system 1023
enaminone 1607
enantioface 938
enantiomer 938, 1567
enantiomeric
  excess 938
  ratio 938
enantiopure epoxide 918
enantioselective bioreduction 1545
enantioselectivity 938, 939, 1485, 1601
enantiotropic smectic mesophase 1507
encapsulation 1492
encephalopathy 1292, 1350
endocrine 1422
endocrine disruptors 1723
endometrial epithelium 1359
endometrium 1359
endoplastic reticulum 1434
endothermic
  desorption mechanism 1638
  reaction 1235
energetic materials 1492
energy 942
  consumption 1674
  demand 1674
  difference parameters 914
  efficiency 905, 1281, 1705, 1709
  input 1705
  parameters 1569
  state 1043
  storage 1500, 1515
  storage technology 1517
  transduction 920
  use 1705
engineering design 1639
enhancement factor 1466
enlarged liver 1434
enrichment condensation 1646
Enskog theory 1469, 1470-1471
enthalpy 1054
  of formation 1532
  of vaporization 1127
  value 1235
  -entropy relationship 1073
entrainer 1014, 1473, 1480, 1574, 1576
entropy 1054
  change 1532
Environment Canada 1335
environmental
  “smog” chamber 1249
  assessment 1678
  behavior 1057
  emission 1291
  exposure 1153, 1408, 1415
  hazard 1195
  impact 1566, 1674, 1700
    assessment 1691
  perspective 1701
  pollutant 931, 1383
  properties 1236
  Protection Agency 901, 1203, 1256, 1297, 1313, 1381, 1383, 1386, 1393, 1395, 1397 1429
    organizational structure 1313
    regional offices 1314
  protection requirements 1637
  regulation 911, 970, 1566
  requirement 1636
  science 1057
  stress cracking 1131-1132
environmentally-friendly
  reaction
    conditions 1549
    media 1553
  solvent 1547
enzymatic
  activity 1412, 1419
  esterification 1601

reaction 917, 933-934, 1490
toxicity 930
enzyme 927, 1544, 1601
activity 1490, 1599
amount 935
catalysis 933
enantioselectivity 939
lyophilization 934
specificity 940
stability 937
thermal stability 937
water content 935
epidemiological
data 1376
study 1413
epidemiology 1362
epilepsy 1364
epimembranous glomerulonephritis 1372
epithelial lining 1359
epoxide hydrolase 918
epoxy 901, 911, 1108
resin 1015, 1017, 1282
equation of state 1466, 1475
model 1468
equifugacity 1588
equilibrium condition 1590
equilibrium
curve 1680
load 1639
properties 1464
solubility limit 1479
equipment cleaning 909-910
equivalent conductivity 1520
erythrocyte 1401
erythroid 1395
erythroleukemia 1393
essential oil 1616
ester 1364
formation 1601
esterase 938
esterification 1594-1595, 1600, 1624
etching agent 1093
ethanol 916, 945
ethyl
2-hydroxypropanoate 1566
acetoacetate 1545
alcohol 1365, 1442
lactate 1566-1568, 1574-1575, 1577, 1579, 1581, 1584, 1586, 1588-1592, 1596, 1599, 1601-1604, 1606-1609, 1611-1614, 1616-1619, 1621-1625, 1627, 1628
conversion 1597
molecule 1580
yield 1595, 1599-1600
ethylbenzene 1003, 1391
ethylene
glycol 1112
monomethyl ether 1364
propylene diene rubber 1091
etiology 1376-1377
Eucalyptus timber 1002
European
Environmental Agency 1252
market 1181
Official Medicine Control Laboratory 1181
Pharmacopoeia 1182, 1190, 1195
Union 1287
eutectic
liquid 1532
mixture 1530, 1535, 1537, 1539-1542, 1545-1546, 1548-1550, 1552-1553, 1555-1557
point 1508
solvents 1177
temperature 1532
eutrophication 964
evaporated solvent 942
evaporation 962, 1682
control 910
rate 945, 1004, 1025, 1132
evaporator 1088
excess
free energy 1061
function 1573
molar volume 1574
volume 1574
excipient 1034, 1041, 1180, 1591-1592
exfoliation 1557
exhalation 1370
exhaled air 1155
measurement 1156
sample 1159
volume 1157

exhaust
  air 1654
    purification 1637
    stream 1636, 1667
  fume 1365
  gas 1267, 1640
exothermic
  adsorption mechanism 1638
  decomposition 1126, 1651
  process 1638
  reaction 1510
expander 981
expansion joint filler 913
expeller 984
experimental
  animal 1383, 1426, 1428-1429, 1431
  rat 1433
exposure
  level 1291
  magnitude 1153
  window 1360
extender 1022
extracellular medium 923
extractant 999
extraction 914, 1473, 1513, 1557, 1588
  curve 1623
  efficiency 991, 1584
  method 991
  process 1034
  rate 987, 1623
  solvent 989, 1427, 1514, 1625
  stage 1623
  system 1482
  technique 991
  temperature 986, 1616
  time 1620
  vent 1291
  yield 991
extractive distillation 1014, 1574
extruder 981
extrusion 1079, 1175
eye
  contamination 1335
  irritation 1245

F

fabricated metal product 962
facial cleanser 1592
Fajans' rule 1504
falling melt 1176
  strand devolatilizer 1176
fallopian tube 1359
fat 1176
  accumulation 1432
fatty
  acid
    composition 920
  derivative 1027
    solvent 1708
  change 1431
  degeneration 1382
  liver
    change 1431
    infiltration 1429
  metamorphosis 1426
felting 948-951, 958
Fenton oxidation 1709
fermentation 1593, 1624, 1743, 1760-1762
  primary 1744
  process 1034
  secondary 1744
fermented food 1566
ferrite nanoparticle 1551
fertilization 1359
fertilizer time-controlled release 1177
ferulic acid 1586-1587, 1590
fiber 949, 965, 1017
  polarity 949
  production 1080
Fick's law 1158-1159, 1217, 1684
filament yarn production 1668
filler 1017
film
  diffusion 1640
  dressing 1005
  formation 943, 1023
  forming 1017, 1026
  softness 1025
  -forming capability 1024
filter system 954
filtration pressure 1083
fine aggregate 914
fingerprint 1181, 1275
  project 1181
finishing 1109

Finnish Cancer Registry 1436
fire
  extinguisher 1426
  retardant 1089
first-pass metabolism 1370
flake
  cooking 980
  thickness 986
flaking 980
flame
  ignition 1126
  ionization detector 1127, 1190, 1266
  propagation 1133
  retardant chemical 1427
flammability 1133, 1528
  limits 1132
flammable
  range 1132
  substance 1134
Flannery Decree 1325
flash
  devolatilizer 1176
  point 1136, 1517
    measurement 1133
flashing cement 913-914
flavonoid 1546
flavor compound 1625
flax 965
flexibility 1025
flexible packaging 1665
flexographic printing 1086
flexography 1084
floor covering 1257
Flory-Huggins
  interaction parameter 1173
  theory 1173
flow
  coating 909
  rate 1600, 1685
fluctuation theory 1061
fluid phase partition coefficient 1465
fluidized circulating bed 1493
fluorinated ionic liquid 912
fluorocarbon powder coating 943
fluoropolymer 942-943, 1708
fluorosilane 1107
flushing
  effect 1645
  liquid 1383
  liquid oxygen 1427
foamed adhesive 905
focal necrosis 1428
foetal movement 1360
Food
  and Drug Administration 977, 1591
  industry 965, 1625
  safety 977
  technology 1613
footwear industry 905
forensic laboratory 1181
forestomach 1395
formaldehyde 1411
  determination 1276
  resin 945
foundry binder 1008
fountain solution 1084
fractionation 991
fragrance 945
Franklin definition 1511
free
  energy of solubilization 1054
  fatty acid 979
  halogen 1134
  radical 1223
  surface area 1638
  volume 1533, 1535, 1571
  water content 940
freeze
  drying 1177
  thaw
    stabilizer 1024
  stability 1028
freezing 1706
  point 1025, 1134, 1685
freight-handling equipment 911
fresh water vessel 1092
Freundlich
  adsorption isotherm 1654
  equation 1220, 1234-1235
  isotherm 1638, 1733
frictional pain 1005
Friedel-Crafts
  acylation 1512

alkylation 1512
frontal polymerization 1553
fuel 1674
incomplete combustion 1030
value 944
fueling motor vehicle 1391
fugacity 1589
coefficient 1466-1467
fugitive emission 1012
functional group 938, 1272
fungi 1723
furniture 905, 1257
adhesive 1116
finish 1431
fusion enthalpy 1587

G

galvanic cell 1659
garment 1110
gas
barrier property 1107
chromatogram 1267
chromatograph 1127, 1135, 1162, 1267
chromatographic analysis 1052
chromatography 1052, 1127, 1134, 1138, 1140, 1176, 1264, 1276, 1281, 1283
gas cleaning process 1636
film resistance 1637
phase 1188
stream 1030, 1639
-to-aerosol condensation 1244
gasoline 1030, 1372, 1379, 1391, 1411
gastrointestinal tract 1359, 1370
gastrulation 1359
gate segment 1413
gavage 1383
gelatin 1597
gel-casting forming technology 1008
gene 924
damage 1383
duplicating mutation 1412
mutation 1412, 1419
mutation analysis 1408, 1415
genetic
damage 1396
factor 1371
fingerprint 1408
genotoxic 1381, 1383
carcinogen 1412, 1419
genotoxicity 1408, 1411
geochemical
data 1761
processes 1735
geosmin 1724
German Emission Inventory 1252
gestational
age 1362
period 1363
Gibbs' criteria 1465
glass 1106
article 1107
cloth 1107
transition temperature 906, 1023, 1174, 1506
viscometer 1142
-reinforced plastics 1168
glassware 1106
global
climate system 1240
trend 1566
warming potential 1020, 1706
glomerular
capillary wall 1371
damage 1370, 1373-1374
disease 1371, 1375
lesions 1371
nephritis 1371
glomerulonephritis 1351, 1371-1376, 1451
glomerulopathy 1370
glove liner 1110
glucagon 1429
glucose biosensor 1556
glue 1257, 1431
sniffer 1450
glutathione
conjugation 1421
-S-transferase 1361
glycerol 991
glycol ether 1024, 1364
ester 1028
metabolite 1364
Good Pasture's syndrome 1371-1372, 1451
Gram
-negative bacteria 919, 922, 928-929
-positive bacteria 919-920, 922, 928-929

granular carbon bed 1650
granulation 1040
granulocyte 1401
graphene 1089, 1723, 1725
  oxide 1593
GRAS 1566, 1591, 1624
gravity separator 1646
gravure printing 1086
  ink 1086
grease 998
green
  chemistry 1457
  coffee beans 1622
  process 1110
  reaction medium 1542, 1609
  solvent 1228, 1528, 1579
  strength 903, 904
  tea leaves 1622
greenhouse gas 1241
ground
  level ozone 1310, 1315, 1317
  transportation 995
  water contamination 1031
groundwater 1215-1216, 1383, 1428, 1746, 1749, 1751, 1760, 1774
group
  contribution 1570
    equation of state 1627
    method 1069
  energy interaction parameters 1569
growth
  inhibition 931
  rate 927
  retardation 1042

H

Hagen-Poiseuille equation 1469
hair
  dye 945
  spray 945
half-life 936
halogenated
  aliphatic hydrocarbons 1427
  hydrocarbon 1376
  solvents 1134
halorespiration 1741-1742, 1743-1746, 1749, 1751, 1760-1761
  kinetics 1744
halorespirators 1743
Hammett function 1539, 1541
Hansch-Leo fragment method 1062
Hansen
  distance calculation 1707
  solubility parameters 914
hardening process 1258
Harderian gland 1395
hardness 1024
hay fever 1363
hazard
  communication standard 969
  index 1285
hazardous
  air pollutant 973, 1297
  chemical 969
  ingredients 1018
  materials transportation act 1329
  waste 1102, 1328
    definition 1330
  management 1328
headspace
  gas chromatography 1177
  injection 1191
health
  and safety 1289
  hazard 969
  risk 964
heart 1440
heat
  capacity 1502, 1589
  dissipation 1079
  integration 1705
  of combustion 1128
  pump 1705-1706
  pump-assisted distillation 1705
  resistance 1107
  transfer 1518
  -transfer medium 1532
heating
  system 1030
  value 1706, 1709
heavy oil
  feedstock 1707
  upgrading process 1707
Heck reaction 1547

hedonic
effect 1274
odor tone 1274
Helmholtz free energy 1472, 1627
hematological malignancy 1394
hematolymphoproliferative effect 1399
hematopoietic
cancer 1395, 1413
cell 1399
disease 1410-1411
effect 1393
malignancies 1408
neoplasm 1401
system 1426
toxicity 1349, 1351, 1412
hematotoxicity 1395
hematoxicity 1393
hemolymphoreticular neoplasia 1395
Henry's
law 1140, 1173, 1736
constant 1074, 1212-1214, 1576
hepatic
cytochrome P450 1434
necrosis 1423
hepatitis 1428
C virus 1429
hepatocellular
adenoma 1429-1430
carcinoma 1429-1430
hepatocyte
function 1435
necrosis 1432
hepatotoxic 1433-1434
agent 1422, 1430
effect 1426, 1431, 1433, 1436
solvent 1426
hepatotoxicity 1351, 1421-1422, 1425, 1428
mechanism 1423
herbicide 1591
heroin 1181
heterocyclodehydration 1549
heterogeneous
chemical pathway 1244
photocatalysis 1723
reaction 1484
hexane 965, 991, 1619, 1708
extraction method 991
high
pressure phase behavior 1464, 1466, 1468
-solids paint 1281, 1285
Hildebrand solubility parameter 1468
hippocampus 1447
histological damage 1432
histopathological
assessment 1376
change 1428, 1432
examination 1432
injury 1422
Hodgkin's
disease 1399
lymphoma 1393, 1400
Hoffmann’s reflex 1443
hole theory 1535, 1539
hollow-fiber membrane bioreactor 918
homogeneous catalytic reaction 1484-1485
homogenization 1484
hot
air desorption 1650-1651
gas
desorption 1637, 1663
regeneration 1665
melt 901, 1085, 1116
adhesive 904
house renovation 1365
household product 1383, 1431
human 1408
body 1369
carcinogen 1383
effect 1440
health 947, 1257, 1327, 1700
leukemia 1380
lymphocytic tumor 1402
lymphoproliferative disorder 1402
needs 1257
toxicity 911, 1701
humidity 908, 1025, 1217, 1258, 1270
hyaluronic acid 1597
hybrid
process 1674
distillation/pervaporation 1700
separation system 1677
hydratase 1168
hydrate 1033, 1041, 1043, 1179

hydrocarbon 949, 1002, 1369
  exposure 1372, 1374, 1377
  solvent 902, 947, 950, 955, 984, 986-988
  emission 1030
hydrodimerization 1514
hydrodistillation 991
hydrodynamic dispersion 1732
hydrogel 1553
hydrogen
  abstraction reaction 1487
  bond 936, 1043, 1061, 1507
    acceptor 1530, 1532
    donor 1530-1531
      density 1063
    formation 1174, 1612
    interaction 1529, 1607
    network 1534, 1536
    strength 1532, 1567
  bonding 1235, 1467, 1611
  chloride 1659
  peroxide 1546
  production 1745
  sulfide 1666
hydrogenation 1404, 1488
  reaction 1548
hydrogenolysis 1729, 1738, 1741
hydrolase 1544
hydrolase-catalyzed reaction 1544
hydrolysis 939, 1024, 1502
  equilibrium 1595
hydrometallurgical industry 996
hydrometer 1130
hydrophilic 951-952
  membrane 1600
  pervaporation unit 1676
  /lipophilic balance value 1028
hydrophilicity 1602
hydrophobic 951-952
  cosolvent 1060
  fragmental constant 935
  interaction 936
  mechanism 1221
  partitioning 1234
  properties 927
  solvent 923
hydrophobicity 922, 929, 935, 1602
  parameter 935
hydrophylic 959
hydroquinone 1392
  bioactivated 1413, 1419
hydrothermal water 914
hydroxyl
  group 1580, 1587, 1607
  radical 1121, 1224, 1710-1711
hydroxylation 1349
hydroxymethylated resorcinol 1002
hygroscopicity 1043
hypertension 1362
hypertensive kidney 1370
  disease 1375
hyphenated method 1186

I

ideal gas 1212
  solubility 1466
IgA nephropathy 1371, 1375-1376
ignition 1656
  device 1133
  source 1133
illegal medicine 1181
illicit drug 1181
illumination time 1715-1717
image analysis 1020
imidazole 1228
immiscible extractive solvent 1601
immune
  complex 1371
  response 1372
  system 1395
immunosuppression 1370
impact performance 1024
impaired vision 1351
implant 1494
  site 1184
implantable medical device 1005
implantation 1183, 1359
  rate 1362
impregnating solution 1110
impregnation 1016, 1494
impurity 1034, 1036, 1041, 1044, 1047, 1129, 1137, 1178
  concentration 1037, 1041
  profile 1181
inactivation 916, 928

incineration 944, 1011, 1636, 1674, 1676, 1690, 1699-1700, 1708
  facility 1709
incubation time 936
indicating detector tube 1267
indoor
  air 1257
    cleaning system 1722
  application 1176
  pollution 1176
industrial
  application 1362
  boiler 1381, 1430
  coating material 1018
  discharge 1326
  environment 1425
  inhalation 1369
  solvent 1375
  waste incineration network 1709
inert gas 1175
infection-resistant medical device 1005
information processing speed 1292
infrared radiation 943
ingestion 1154, 1369
inhalation 1154, 1158, 1289, 1369, 1383, 1430
  exposure 1335
inhibitor 1413
inhibitory effect 1599
initiator concentration 1022
injection 1183
ink 905, 1110
  solvent-free 1086
  viscosity 1084
inlet zone 1640
inner surface area 1638
inorganic chemical 996
insect repellent 1592
insecticide 1411, 1427, 1431
insolation 1716-1717
insulating fluid 1381
interaction 1174, 1530
  energy 1637
  parameter 1174-1475, 1589
intercellular
  communication 1428
  lipids 1348
interfacial tension 1063-1064
interior coatings application 1025
intermolecular
  force 1061, 1460
  hydrogen bond 1567
internal crystalline structure 1042
internal
  dose 1153
  surface 1639
International Agency for Research on Cancer 1380, 1383, 1393, 1395, 1397, 1401, 1404, 1429-1430
interparticular repulsive force 1024
interspecies hydrogen transfer 1744
interstitial
  inflammation 1370
  kidney disease 1375
  nephritis 1451
interuterine life 1360
intoxication 1183, 1292
intracellular
  concentration 1353
  intraluminal crystal deposition 1372
intralobular protein 1370
intramuscular route 1033
intravascular catheter 1005
iodocyclization 1549
ion
  exchange process 1048
  liquid adsorption 1235
  mobility 1520
  monitoring mode 1190
  pair 1708
ionic
  conductivity 1538
  liquid 912, 1014, 1021, 1228, 1235, 1457, 1500, 1503, 1511, 1528, 1532, 1601, 1708
    adsorbed phase 1237
    adsorption 1234
    alkylsulfate 1502
    binary 1508
    biodegradation 1232-1233, 1236
    chemical degradation 1232
    degradation 1231
    density 1521
      measurement 1522
    environmental
      chemistry 1237

fate 1228
impact 1238
hydrophilic character 1229
impurities 1522
in aquatic organisms 1236
in soil, water, and air 1228
isotropic 1507
mechanism of adsorption 1235
miscibility 1229
movement 1228
Newtonian behavior 1520
phase diagram 1507
room temperature 1500, 1502, 1505, 1510
solubility 1230, 1237
solvent 1511, 1513
ultrasonic irradiation 1232
ultraviolent photodegradation 1232
vapor phase 1237
volatilization 1231, 1236
viscosity 1519
volatility 1501
water
solubility 1229
stability 1501
mobility 1520
radius 1504
salt solution 912
species 996
ionicity 1520
ionization ratio 1539
ionothermal synthesis 1554-1556
iron and steel industry 998
manufacturing process 998
iron sulfide 1748
irradiation 1180
irritation 1274
isoenzyme 1361
isohexane 965
isomeric products 1512
isomerization 921, 1512
isomorphic desolvate 1043, 1045
isopropyl alcohol 1084, 1675, 1677, 1683, 1695, 1701
recovery 1692
isoteniscope 1142
isotherm equation 1638
isothermal measurement 1464
itaconic acid 1553

J

jet engine fuel 1128
joint
sealant application 1009
strength 911
jointing 911
jojoba 965
991
Jouyban-Acree model 1070, 1074

K

kaolinite 1235
Kapustinskii equation 1503
Karl Fischer method 1144
karyomegaly 1381
karyotype 1411, 1418
karyotypic pattern 1409, 1415
kauri-butanol value 1140
Kelvin
equation 1639
theory 1653
keratin 1348
kerosene 1377
ketal 1039
keto-enol
ratio 1041
tautomer 1086
tautomerism 1041
ketone 902, 1039, 1364
ketoxime 1611
key recovery operation 1674
kidney 1159, 1183, 1369-1371, 1392, 1429
biopsy 1376
cancer 1376-1377, 1379-1383, 1385-1386
death 1380
epidemiology 1386
risk 1378, 1386
carcinogenicity 1370
damage 1376
function 1374, 1375, 1425
injury 1372
stone 1375
kinematic viscosity 1476
kinetic
energy 1638
studies 1596

Knoevenagel condensation 1542-1543
known human carcinogen 1413
Kupffer cell hyperplasia 1434

L

labile organic carbon 1745
lacquer 1126, 1130, 1140, 1426
lactamide 1594
lactate dehydrogenase 1436
lactate ester 1566
lactic acid 1567, 1594, 1602, 1624
laminating adhesive 905
lamination 905, 1168
land disposal 1203
Langmuir isotherm 1638, 1733
laser flash photolysis 1487
latency period 1384-1385
latex 1023
  system 1024
lattice 1043
  energy 1503-1504, 1506, 1508, 1530
laundering 948
laundry workers 1382, 1386
layered gallium phosphate 1555
Le Châtelier's principle 1596
leakage 910, 963
leaking
  tank 1203
  valves 1124
leather dye 1363
leather treatment 1381
lecithin 966, 982
Legendre transform 1465
letterpress 1084
leukemia 1363, 1380, 1393, 1395-1396, 1401, 1403, 1408, 1410
leukemic cell 1409, 1419
leukemogenesis 1408
leukocyte 1416
leukoencephalopathy 1452
Lewis acid 1513
  catalyzed dehydration 1546
life cycle 1101
  analysis 1675
  assessment 1020, 1690, 1701
  inventory 1691
lifetime 1257
ligand 1604
  -free condition 1604
light
  emitting diode 1705
  -induced synthesis 1609
lignin 1547, 1708
limb defect 1364
limestone 913
limonene 916, 923, 1003, 1616-1617
linear isotherm 1733
linen 948-949
lipase 939-940, 1544, 1546, 1599, 1601
  enantioselectivity 940
  stereoselectivity 939
lipid
  extraction 1557
  membrane 1369
  peroxidation 1365
  solubility 1370
lipolytic enzyme 924
lipophilic 959, 1369
  character 1579, 1617
  chemical 1159, 1348, 1361
  layer 1183
  molecule 1365
  properties 927
lipopolysaccharide 922
liposome 920
lipstick 945
liquefied natural gas 1706
liquid
  chromatography 1051-1052, 1593
  dosage formulation 1055
  phase 1188
  behavior 1579
  composition 1578
  -liquid
    equilibrium 1614
    immiscibility 1459
    miscibility 1579-1580
    transition temperature 1581
    -vapor equilibrium 1681
liquidus range 1507, 1510
lithium ion battery 1706
lithography 1084
liver 1183, 1349, 1370, 1392, 1422, 1428
  biopsy 1430

blood flow 1422
body weight 1433
cancer 1426, 1429, 1431, 1436
cirrhosis 1426-1427, 1429
damage 1426, 1430, 1432, 1435
disease 1423
dysfunction 1426, 1435
enzyme 1431-1432, 1434-1435
fat accumulation 1426
function 1434-1435
test 1433
metabolic capacity 1422
necrosis 1422, 1426, 1428
steatosis 1426-1427
toxicant 1426
toxicity 1428
log-linear solubilization model 1074
longitudinal dispersivity 1733
lower
atmosphere 1022
pollution 1120
explosion limit 1654, 1666
flammable limit 1132
lowest achievable emissions rate 1317
lube oil feedstock 1030
lubricant 911, 953, 1383
lubrication 1140
lumber 1000
lung 1156, 1158-1160, 1164, 1167-1168, 1369, 1428, 1440
cancer 1395
function 1245, 1363
lutein 1618
lycopene 1618-1619
lymphatic cancer 1413
lymphoblastic leukaemia 1365
lymphoblastoma 1393
lymphocyte 1395, 1400-1401, 1415
lymphocytic neoplasm 1401
lymphohematopoietic 1391
cancer 1400
risk ratio 1399
malignancy 1394-1395, 1399
system 1395
lymphoid 1399
lymphoma 1391, 1400, 1412
cell 1416
lysozyme 1557

M

Macleod-Sugden correlation 1473
macrophage 1395
macropores 1642
maintenance repainting 909
malformation 1361
malignant
lymphoma 1394, 1401
neoplasm 1353, 1394
mambrane separation performance 1674
mammary gland 1395
mandelic acid 1168
man-made fiber 1079, 1081
production 1080
industry 1121
manufacturer 1181
manufacturing process 962
Marangoni flow 1020
marine 1092
and naval personnel 1385
coating 1098
Corps Base Camp 1385
marrow depression 1351
mascara 945
mass
diffusivity 1476
separating agent 1478
spectrometer 1186, 1464
spectrometry 1162
transfer 1457, 1484
coefficient 1214
zone 1640
material
safety data sheet 1284, 1335
synthesis 1492, 1553
temperature 1259
maternal benzene exposure 1363
matrix effect 1188
maximum
achievable control technology 973, 1321
effective pore diameter 1653
permissible breakthrough concentration 1644
viscosity 1099
meat consumption 1379
mechanical
abrasion 908

dispersion 1732
extraction 1291
mixture 1530
oil extraction 991
mechanism 1412
mechanistic injury 1426
mechanochemical extraction 1557
medical 1086, 1592
device 1004-1005
monitoring 1425
tubing 1005
melamine 1604
crosslinkable alkyd 943
melt adhesive 902
melting
curve 1134
point 1036, 1507-1508, 1530, 1532, 1587
temperature 1589
membrane 1477, 1683, 1685, 1708
bilayer 929
cascade 1708
function 920
hydrophobic part 920
module 1596
permeability 929, 1159, 1371, 1636
photocatalytic reactor 1726
process 1646
separation 1674, 1725
structure 920
thickness 920
unit 1675, 1677
vapor extraction 1707
-assisted distillation 1678
membranous nephropathy 1376
memory loss 1350
mental health dysfunction 1364
mesangial IgA deposits 1370
mesangium 1371
mesityl oxide 1039
mesodermal cell layer 1359
mesomorphic crystalline solid 1507
mesophase range 1507
mesopores 1642
mesoporous silica 1556
metabolic
activity 926
change 1426
detoxification 1183
pathway 1168, 1349, 1741
process 1349
rate 1158
metabolism 1154, 1433
inhibition 1349
metabolite 1154, 1361, 1370, 1381, 1408, 1412
metal
addition 1725
casting 1007
cleaning 962, 1379
process 964
cutting 962
degreaser 1165
degreasing agent 1381, 1430
extraction 1529
fabricating 962, 1122
industry 1122
fabrication 963
industry 1121
finishing 908
industry 1382, 1427
separation 1550-1551
solvent extraction 996
-catalyzed organic reaction 1529, 1546
-cleaning 1364
-degreasing operation 1427
metallic scaffold 1183
methacrylic ester copolymer 945
methanogens 1744
methanol 1121
methodology aspect 1178
methyl ethyl ketone 902, 1005
methylene chloride 1602
micelle 952
formation 1231
Michael addition 1550
Michaelis-Menten
kinetics 1752
parameters 1752
microalgae 1616
biomass 991
oil extraction 991
microalgae processing 991
microautoradiography 1116
microbial
cell 916

contamination 933
membrane 919
production 916
structure 929
microbiological quality 1048
microcontaminant removal 1726
microcoulometry 1138
microencapsulation 1040, 1493
microextraction 1557
microfiltration 1083
micronized solid particles 1002
micronuclear change 1408, 1415
microorganism 916, 1110
adaptation 926
mechanism 929
solvent
toxicity 927
-resistant 926, 930
-tolerant 928
micropore volume 1642, 1653
micro-proteinuria 1374
microstructure 1005, 1551
microwave
heating 1556
-assisted drying 1177
mill scale 998
milling 947
Millington equation 1217
mineral
impurity 1044
matter 914
spirits, toluene 902
minimum film forming temperature 1023
mirrors 1723
miscella 981
concentration 987
extraction 987
flow rate 988
percolation rate 980
miscibility 1130, 1458, 1579
mitochondria 927
mitochondrial
defense ability 1431
dysfunction 1431
respiratory chain 1431
mitotic event 1359
mixed
organic solvents 1435
solvents 1061
mixing 910, 1518
mixing
bench 1291
rules 1466, 1471, 1475, 1569
mobile phase 1036
model
assumption 1638
paint 1020
molar
density 1471
volume 939, 1570
mold-making process 1007
molecular
photocatalyst 1723
sieve zeolite 1641, 1643
sieves 1642, 1664
toxicity 917, 919
weight 912, 1022
distribution 1491
molecule hydrophobicity 1235
molten salt system 1500
Monod half-saturation constant 1744
monolayer adsorption 1638
monomer 1044, 1079
conversion 912
ratio 1079
solvent mixture 906
montmorillonite 1235
Montreal Protocol 905, 1103
morphology 1551, 1553, 1567
mortality study 1380
morula 1359
mosquito 1592
mother's bloodstream 1360
motor
fuel 1030
vehicle assembly 1009, 1124
industry 1010, 1121-1122
moving bed reactor 1600
muconic acid 1392
mucosa membrane 1350
mucosal tissue 1005
mucous membrane 1184
multifactorial system 1425

multilayer adsorption 1638
multimer 1567
multi-node condenser 1686
multiple
  chemical sensitivity syndrome 1356
  headspace extraction 1188
  myeloma 1394, 1400
multipoint sampler 1270
multiwalled carbon nanotube 1556
municipal solid waste 1328
muscle 1359
muscular atrophy 1351
mutagenic 1381
  agent 1409
  effect 1383
mutagenicity 1182
mutation 1412
  frequency 1383, 1412, 1418
mutual
  immiscibility 1459
  solubility 1502, 1579
myelodysplastic syndrome 1393, 1394, 1401
myeloid 1395, 1399
myelotoxic effect 1351

N

N,N-dimethylformamide 1436
nail polish 945, 1352
  remover 945
nanocomposite 1107
nanofibril 1557
nanomaterials 1555
nanoparticle 1723
nanotechnology 1054
nanowire 1551, 1556
naphthalene 1461
narcotic 1181
National
  Institute for Occupational Safety and Health 1334, 1391, 1394, 1397, 1403
  Toxicology Program 1383, 1394, 1401, 1431
natural
  attenuation 1730-1731, 1747, 1765, 1767, 1773
    mechanism 1763
    model 1768
  rubber 902
near infrared emitter 943
necrosis 1184, 1382
neonatal deformity 1361
neopentyl glycol diglycidyl ether 1108
nephrocarcinogenicity 1384
nephron 1370
nephrotoxic drugs 1375
nephrotoxicity 1351, 1370
nephrotoxins 1371
nerve conduction 1450
nervous toxicity 1184
neural membrane 1350
neurobehavioral
  effect 1292, 1440
  symptom 1292
neurodevelopmental
  disability 1363
  outcome 1362
neurological damage 1292
neuromuscular problem 1365
neuropsychiatric disability 1452
neurosurgery 1442
neurotoxic 1363
neurotoxicity 1182, 1196, 1292, 1351, 1364
neurotransmitter 1350
  pathway 1364
neutral complex 996
newspaper web pressmen 1380
nitrile rubber 902
nitrocellulose 902, 945
  lacquer 1114
nitrogen
  doping 1724
  oxides 1315
N-methyl pyrrolidone 1592
NMR 1469
  chemical shift 1050
  spectroscopy 1050-1051
non-Hodgkin's lymphoma 1400, 1402, 1409, 1416, 1429
non-immunological effect 1351
non-lymphocytic leukemia 1415
non-methane volatile organic compounds 1252
non-polar extraction solvent 1361, 1707
nose 1183
nucleation 1036, 1042, 1482
  process 1042
nucleophile 1738

nucleophilicity 1612
numerical
  aberration 1413
  model 1772
  simulation 1707

O

obesity 1378
obligate proton reducer 1744
occupational
  association 1378
  epidemiology 1396
  exposure 1351, 1376, 1384, 1425
  history 1408
  medicine 1391
  safety and health act 1334
  Safety and Health Administration 1334
  solvent exposure 1290
  solvents 1423
  trichloroethylene exposure 1386
octanol/water partition coefficient 1062, 1064, 1221, 1236
ocular toxicity 1351
odds ratio 1362
odor 1022, 1025, 1086, 1136, 1140, 1179, 1284
  compound 1724
  definition 1272
  determination 1276
  elimination 906
  intensity 1273
  measurement 1275
  perception 1275
  potential 1276
  sample 1274-1275
  threshold 1272, 1277
odorant 1272
  concentration 1272-1273, 1276-1278
    coated surface 1276
  mixture 1274
  threshold 1277
odorous
  impression 1272
  substance 1272
off-site incineration 1675
off-taste 1140
oil
  industry 1580
  refinery workers 1380
  refining 1379
oilseed 991
  extraction process 978-979
  processing 984
    industry 965
  solvent loss factor 973
old paint removal 1112
olfactometer 1275-1276
olfactometric investigation 1274
olfactometry 1277
olfactory receptor 1272
oligomer 1044
oligomerization 1595
operating
  altitude 908
  cost 1014, 1636, 1643, 1686
optical
  product 1175
  purity 938
optimization 1701
oral 1183
  cavity 1395
  route 1033
  solution 1179
organ damage 1291
organic
  carbon partition coefficient 1221, 1234
  chemical 1121
organic chemical industry 1012
    reactions 1611
  media 933
  phase 923
  reaction 1548-1549
  solvent 1178
    cleaner 1093
    vapor 1369
    waste 1102
    exposure 1380
  synthesis 1033, 1602, 1609, 1625
  vapor 1635
organocatalysis 1549
organogel 1593
organogenesis 1360
organometallic compound 1484
organonitrate 1243
organosoluble silver nanoparticles 1556
OSHA 1394, 1397, 1404

Ostwald coefficient 1140
Othmer equation 1536
outer membrane 921-922
outlet zone 1640
overflow pipe 954
oxidase 1349
oxidation 1749
  capacity 1395
  process 1044, 1723
  reaction 1485, 1488
  technology 1710
oxidative 1553
  microcoulometry 1138
  polymerization 1553
  stress 1364
oxidizing chamber 943
oxygen
  cleaning 911
  site 1725
  vacancy 1725
oxygenated solvent 1376
oxygeneted solvents 1002
ozonation 1708
ozone 1020, 1215, 1252, 1310
  classification area 1316
  depleter 1122, 1241
  depleting 1092, 1223, 1243, 1591, 1602
  destruction 1243
  formation 1092, 1248-1249
    potential 1020, 1247
  ground level 1298
  isopleth diagram 1246-1247
  layer 1022
  precursor 1241
  production capability 1020
  -depleting solvent replacement 1311

P

Paal-Knorr reaction 1543
packaging 1592, 1594
  material 1086
  printing 1666
    industry 1662
packing efficiency 1043
paint 1015, 1126-1127, 1140, 1177, 1257-1258, 1280, 1374
  and surface cleaning 1121
  common solvents 1280
  film 1020
  finish 1291
  fume 1365
  gun 912
  industry 1020-1021, 1136, 1143
  layer 1020
  overspray 910
  pigment 1710
  removal 1113
  remover 1381, 1383, 1430
  solvent stream 1720
  solvent vapor 1711
  sprayer 1374
  stripper 911, 1383
  stripping 909
  thickness 1020
  thinner 1433
  thinning 1288, 1428
painters 1378-1379
painting 910, 995, 1112-1113, 1718
palladium catalyst 1604
pancytopenia 1410, 1416
panel beater 1288
p-anisidine 1602
paper 943
  coating 1381, 1430
  deacidification 1089
parabolic trough reflector 1714
parenchyma 1359
partial
  miscibility 1581
  molar volume 1463
  pressure 1212, 1370, 1645
particle
  abrasion 1660
  morphology 1724
  nucleation 1478
  size 986, 1179
  synthesis 1492
particulate
  matter 1224, 1243-1244, 1315, 1701
  soil 959
partition coefficient 918, 920, 927, 929, 938, 1157, 1158, 1219, 1236, 1584, 1615
patch liquid 913
patching 913

patent 1458
  fraud 1181
paternal occupational exposure 1364
pathogen 1005
  destruction 1726
pathogenesis 1371
pathogenic bacteria 1723
pathological change 1428, 1431
pavement sample 1141
payback period 1698
peel strength 904, 906
penetrable septa 1005
penetration enhancing agent 1592
Pensky-Martens closed cup 1133
pentachlorophenol 1002
perception threshold 1272
perchloroethylene 914, 959, 1364, 1381-1382, 1385, 1430-1431, 1729
percutaneous absorption 1347-1348
perfect gas law 1140
perfluorinated solvents 1528-1529
perfusion 1157-1158, 1167, 1494
perillic acid 923
peripheral
  blood lymphocyte 1412
  nervous system 1292
  neuropathy 1011, 1351
  neurotoxic effect 1349
periportal fat accumulation 1434
Perkin reaction 1541
permanganate time test 1136
permeability 1108, 1180
permeate
  flux 1683
  pressure 1677
  stream 1686
permeation 1682
  process 1684
permissible exposure limit 967, 1153, 1310, 1334
permit program 1324
permitted daily exposure 1196
perovskite photocatalyst 1723
peroxide 1041, 1044
  radical 1724
peroxisome proliferation 1428
peroxyl radical 1215
Perturbed Hard Chain Theory 1466
pervaporation 1596, 1624, 1674, 1677-1678, 1690, 1695
  membrane 1597, 1686
  reactor 1599
  unit 1675
  -assisted
    esterification 1597
    membrane reactor 1597
pesticide 1383, 1591, 1723
petrochemical
  exposure 1379
  industry 1377
  plant 1670
petrol tanker driver 1411
petroleum
  fraction 1374
  industry 1032, 1124
  products 1378-1379, 1408
  recovery 1058
  refining 1377, 1440
    industry 1030
  worker 1376
  -derived feedstock 1566
pH 1137
phantom phenomenon 1073
pharmaceutical 1086, 1381, 1383, 1427, 1430, 1458, 1492, 1592, 1723
  activity 1052
  agent 1592
  application 938
  applications 1054, 1592
  excipient 1183
  field 1034
  formulation 1040, 1175
  formulator 1054
  industry 1033, 1177, 1512, 1614, 1669, 1674
  ingredient 1557
  plant 1676, 1699
  preparation 1179
  process 1677
  product 1034, 1037, 1055, 1181
  science 1054
  specification 1195
  substance 1178
pharmacokinetics 1164
  model 1167, 1169

pharmacology 1625
pharmacopoeia 1048, 1050, 1178
pharmacopoeial monograph 1040
phase
  analyzer 1462
  behavior 1460, 1462-1463, 1574, 1577
  boundaries 1456
  diagram 1460, 1506-1507, 1509, 1579, 1581
  equilibrium 1458, 1570, 1674
    behavior 1576
    measurement 1462, 1578
  toxicity 917, 919
  transition 1456, 1580
phenol-formaldehyde resin 902
phenolic acid 1590
phenylglyoxylic acid 1168
Philadelphia chromosome 1412, 1419
pH-metric titration 1125
phosgene 1713
phosphatides 982
phosphine oxide 999
phospholipid 929, 981
  biosynthesis 1352
  headgroup 921
  layer 1724
  synthesis 922
photionization 1190
photoacoustic gas monitor 1270
photoactive
  perovskite oxynitride 1724
  zone 1724
photoactivity 1724-1725
photocatalyst 1723, 1725
photocatalytic
  oxidation 1708, 1722
  treatment 1723
  water treatment 1723
photochemical
  activation 1487
  ozone creation 964, 1020
  process 1121
  reaction 1298, 1317
  reactivity 1143
  replacement 1487
  smog 1241, 1245
photocopier toner 1433
photo-corrosion 1724
photodegradation 1163
photoefficiency 1710
photoinitiator 906
photolysis 1243
photon correlation spectroscopy 1469
photothermal
  destruction 1719
  reactor 1719
physical
  exertion 1158-1159
  hazard 969
  instability 1045
  interaction 1179
  workload 1154
physico-chemical
  instability 1043, 1045
  properties 939
physisorption 1637
phytochemical industry 1588
phytoremediation 1708
phytosanitary 1625
  industry 1591
phytosterols 966
picture frame 905
piezometric method 1522
pigment
  loading 942
  removal 951
pipeline coating 913
piston pump 954
placenta 1359, 1363
  tissue 1361
planet 916
plasma transaminase 1436
plasticization 1026
plasticizer 914, 1044
plastisol 901-902
pleural potential stem cell toxicant 1395
plug flow 1731
plume
  classification scheme 1761
  databases 1765
  length 1733, 1765-1767
  thickness 1765
  width 1765
pluripotent toxin 1399
pluropotent stem cell 1413

plywood 1114
pneumonia 1395
polar 951
  material 952
  metabolites 1361
  solvent 929, 935, 1005, 1042, 1107, 1348, 1508, 1567
  system 1035
  washing solvent 1107
polarity 927, 935, 1258, 1567, 1570, 1580, 1592, 1602, 1620, 1625
  index 1062, 1708
pollutant 1057
  adsorbent combination 1639
  concentration 1648
  discharge rate 1326
  formation 1241
  management practice 1330
pollution prevention act 1330
poly(acrylic acid) 1556
poly(ethylene terephthalate) 1080
poly(vinyl fluoride) 912
polyacrylic resin 1015
polyacrylonitrile 1597
polyaddition 901, 1015
  adhesive 901
polyamide 902, 949, 1015
polyaniline 1174, 1553
polybenzimidazole 911
polybutylene 903
polycaprolactone 1593
polycarbonate 1008, 1175-1176
polychlorinated biphenyl 1709
polychloroprene 902-903
  adhesive 904
polycondensation 901, 1015, 1556, 1594
  adhesive 902
polycyclic aromatic hydrocarbon 1557
polydimethylsiloxane membrane 1707
polydispersity 1594
polyester 902, 945, 949, 1017, 1282
  coating 943
  coil coating 942
  saturated 1015
polyethylene 1175
  high-density 1079
  linear low-density 1079, 1176
  low-density 1079
polyethylene glycol 1044
polyimide 902, 906
  adhesive 906
polyisobutene 1511
polyisobutylene 902
polymer 1086, 1121
  and fiber 1122
  dispersion 1022
  fusion 1025
  manufacture industry 1079
  manufacturing industry 1080
  recovery 1079
  solution 1131
  surface area 1024
  synthesis 1491
  -solvent interaction 1173
  -solvent phase behavior 1460
polymeric
  adsorbents 1641
  device 1005
  network 913
  particle 1024
polymerization 901, 1023, 1079, 1091
  adhesive 901
  cost 1079
  reaction 1490, 1553
polymethylmethacrylate 1475
polymorph 1042
polymorphic
  change 1042
  form 1045
  transformation 1033, 1043, 1067
polymorphism 1041, 1070, 1361, 1507
polyneuropathy 1450
polypropylene 1079
polypyrrole film 1552
polystyrene 1079, 1174, 1459
polysulfide 903, 909
polyurethane 902-903, 905-906, 911, 914, 1004, 1015, 1017, 1110, 1114, 1282, 1625
  dispersion 1116
  hot-melt adhesive 906
  industry 1592
polyvinylchloride 903, 1009, 1015, 1180
  chlorinated 906
  pipe 906

pore
  diameter 1637
  diffusion 1638
  size 1643
    distribution 1653-1654
  structure 1637
  system 1642
porous
  bed 1482
  stone 1107
post-mortem examination 1376
potential association 1382
potlife 1116
pottery 1106
powder
  coating 942, 1011, 1282, 1284
  coating booth 1282
  flowability 1179
  metallurgy complex shape 1008
  paint 1281
  varnish 1258
Poynting correction 1466
Prandtl number 1476
precipitate formation 1044
precipitation 1045, 1592
precision
  aerospace cleaning 911
  part 1592
precombustion 1007
preconstruction permitting 1316
predictive capability 1475
prefrontal lobotomy 1442
pregerm layer stage 1359
pregnancy 1361-1362
  solvent exposure 1359
premanufacture notification 1333
pre-narcotic symptoms 1350
prenatal exposure 1363
preparation 909
preparative chromatography 1036
prescription medication 1430
preservative 1002
press operator 1374
pressure
  correction 1472
  swing distillation 1674
  -sensitive adhesive 902, 905
primary precursor 1241
primer 902, 905, 911, 914, 943, 1002
  bath 1009
  coating 1094
priming 913, 1009
print industry 1085
printed wiring board 906
printing 1109-1110, 1379
  factory worker 1434
  industry 1084, 1086, 1121, 1409
    solvent release 1084
  ink 1176, 1381, 1433
  plate 1084
  solvent 1176
probable human carcinogen 1122
process
  configuration 1677
  safety management 969
processability 1041
processing technology 965
prochiral
  center 938
  ketone 1545
product
  formulation 1289
  odor 1026
production
  activity 1268
  cycle 917
  rate 905
  scale 913
  scheduling 910
  stage 1259
professional indoor use 1021
programmed temperature vaporisation 1187
progressive damage 1376
prokaryotic organism 1540
proliferative glomerulonephritis 1371
propellant 945
  solvent 1005
protease 924, 940
protective
  component 1242
  equipment 1153
  purposes 1022
protein 992, 1557
  binding 1422

malnutrition 1422
proteinuria 1351
protic
ionic liquid 1507
solvent 1008
proton
leakage 920
transfer reaction mass spectrometry 1177
protonation 1512
protozoa 1724
Pseudomonas oleovorans 917
pseudopolymorph 1043
pseudopolymorphic transformation 1043
pseudopolymorphism 1041
pseudo-steady state 1681, 1701
public welfare 1327
publications 1457
pulmonary 1369
blood 1158
vessel 1156
capillaries 1371
clearance 1158
infection 1245
perfusion 1348
ventilation 1158
pulp
and paper 1121
industry 1088
pulping 1489
pumping 1518
purification 1602
processes 1178
step 1637
purity 1034, 1136, 1674
pycnometer 1130
method 1130
pyrite 1551

Q

quantitative monitoring 1289
quartz crystal microanalysis 1552
quasi-optimal design 1675, 1677, 1683, 1701

R

rabbit 1395, 1410
racemic mixture 938, 1549
radiation
cured material 905
curing 942
technology 943
radical 1224
process 1122
scavenging 1623
radiolysis 1180
rail car 1112
rancidity 982
random effects model 1386
Raoult's law 1060
activity coefficient 938-939
rat 1410
rate
constant 1474
of air flow 1258
raw material 1674
rayon 949, 1079-1080, 1666
production 1121
reactant 1079
reaction
medium 1036, 1489, 1529, 1532, 1548, 1555, 1610
mixture 1079
rate 1484-1485, 1513, 1548
vessel 1404
reactive
distillation 1484, 1599
unit 1600
hot melt 904-905
intermediate 1183
oxygen species 1724
polyurethane 913
resin 1017
separation process 1600
solvent 1108
thinner 1258
reactor
configuration 1723
design 1710
recalcitrance 1758, 1759
recharge 1735
reciprocal translocation 1412
reclaimed asphalt 914
recleaning 955
recombination 1724
recovered solvent value 1636
recovering system 954

recovery 1584, 1700
  system 1674
recrystallization 1602
  process 1179
rectification 1646, 1678
rectifier performance 1680
recycling 1102, 1281
red blood cell 1156
Redlich-Kister polynomial equation 1573
redox
  behavior 1551
  potential 1551
reduced fertility 1362
reductive
  dechlorination 1746, 1758-1760
    rate 1741
reductive dehalogenation 1745
refinery 1030
  process 1030
refining 982
refinishing 1287
reflux 1680
  ratio 1674, 1677, 1682
refraction index 1132, 1139, 1567-1568
refractive dispersion 1139
refrigerant 1383, 1426-1427
refrigeration cycle 1685
refrigerator recycling 1669
refurbished panel 1287
regenerated
  adsorber 1667
  cellulose 1080
regeneration
  basic principles 1650-1651
  conditions 1640
  energy 1706
  mechanism 1726
  zone 1650
regenerative epithelium 1370
regioselectivity 938, 1513, 1544, 1601
regulations in North America 1297
regulatory
  aspect 1178
  constraints 1709
  standards 1709
reinforcing material 1017
Rekusolv process 1669-1670
relative
  humidity 1179, 1657, 1713, 1716-1717
  permittivity 939, 1062, 1064, 1567
  risk 1386
relaxation process 1043
remediation technology 1708
removal rate 1175
renal
  cancer 1385
  cell
    cancer 1382, 1384
  carcinoma 1382-1383
  damage 1371
  failure 1371
  impairment 1374
  tubular cell carcinoma 1382
  -toxic effect 1349
renewable
  hydrocarbon source 1456
  monomer 1553
repairing system 922
reproducibility 1036
reproductive
  process 1362
  toxicity 1349, 1351
repulsive force 1024, 1466
residence time 989
residual
  adsorption capacity 1650
  Helmholtz energy 1569
  humidity 1180
  load 1645
  moisture 1174
  risk 1323
  solvent 1034, 1039, 1042, 1176-1178, 1180-1181, 1186, 1195, 1276-1277
  solvents 1178
  water 1079
resin production 1079
resorcinol 1110
resource availability 1700
Resource Conservation and Recovery Act 975, 1328
respirator 1348, 1403
  mask 1163
respiratory
  irritant 1242

protection 1289
system 1121
tract 1359
restenosis 1184
retardation
coefficient 1733
factor 1735
retention time 1036
return rate 1698
reversible absorption 1557
Reynolds number 1477, 1685
rheological properties 1079
rheology 1035
rhinitis 1291, 1352
ring structure 1567
risk
assessment 1396, 1425
factor 1379
road marking paint 1020, 1252
roadwork sector 914
rolling 909, 980, 1017
Romberg stance 1443
roof
cement 913
coating 914
roofing application 914
room
load 1258
temperature 1258
rosin 945, 1114
rotary letterpress ink 1086
rotogravure
printing 1661
worker 1434
rotor
adsorber 1650
design 1650
rubber 1017, 1443
adhesion 1110
and plastics industry 1090, 1121-1122
industry 914
-modified adhesives 901
rust 998

S

Safe drinking water act 1326
safety 1034
reasons 1656
salt melting point 1503
salting 1188
sample
collection 1163
recognition 1274
sampling organic vapor 1161
saturation degree 922
Saybolt viscometer 1142-1143
scaffold 1086, 1593, 1608
schizophrenia 1364
Schmitt number 1476
scouring 1109
screen printing 1553
screw press 984
scrub resistance 1025, 1028
sealant 901, 903
smell 903
world market 903
sealing 910, 913
seamen 1394, 1401
seaweed 965
secondary
emission 1012
reactions 1512
seed 991
seepage velocity 1731, 1769
selectivity 940
self-propelled vessel 1113
semiconductor 1551, 1705
industrial waste 1705
industry 1364, 1705
sensitive indicator 1428, 1432
sensitivity 1375
separation
factor 1473, 1574, 1583, 1615
medium 1532
process 1588
selectivity 1708
sequential quadratic programming 1705
serum
alanine aminotransferase 1433
serum
bile acid 1435
content 1435
creatinine 1374
enzyme 1432
setting lotion 945

sewage sludge 1328
shape-controlled synthesis 1555
shear thinning behavior 1520
shelf stability 1098
ship 1101
  repair 1092, 1102
shipbuilding 1092, 1102
shipyards 1092
shoe 1380
  industry 902, 904, 1362
  manufacture 1363
  manufacturing 1380
  plant 1450
shoes 1380
shrinkage 945, 948-951, 958
sick building syndrome 1356
side
  effect 1182, 1592
  product 1037, 1041
  reaction 933, 1038, 1041
silica gel 1642
silicone 902-903
  sealant 903
silk 948-949
  fiber 1557
simulation technique 1155
single drop microextraction 1189
sister
  chromatid 1409
  exchange 1408-1409, 1412, 1415
sizing agent 1107
skin 1392, 1395, 1592
  absorption 1335, 1369, 1391
  dosimetry 1392
  condition 1352
  permeability 1348
  protective
    device 1403
    measure 1285
skull formation 1365
sludge inoculum 1127
smectite 1235
smell 1272
smog 1022, 1317
  formation 1223
smoking 1257, 1378
  history 1379
Snyder's polarity 906
soap 951
sodium salts 1505
softener 1258
soil 1383, 1432
  air porosity 1217
  diffusion
    characteristic 1217
  coefficient 1218
  evaporation half-live 1220
  matrix pathway 1217
  washing treatment 1592
soiling 951
solar
  cell 1086, 1107
  insolation 1719
  photocatalytic oxidation 1710
  photoreactor 1712, 1715, 1720
  radiation 1215
  -UV intensity 1716
sol-gel drying methods 1495
solid
  dosage form 1041
    manufacture 1045
  phase microextraction 1189
  waste 1328
    definition 1329
solidification point 1134
solid-liquid interface 1216
solubility 1045, 1096, 1140, 1213, 1461, 1578, 1586
  active ingredient 1002
  calculation 1589
  parameter 1020, 1062, 1064, 1570
solubilization
  curve 1066
  profile 1070
solute
  degradation 1014
  hydrophobicity 1062
  movement 1222
solution adhesive 901, 902
solvate 1033-1034, 1041, 1043, 1045, 1179
  structure 1043
solvated form 1045
solvating
  ability 1591

extractant 997
solvatochromic dye 1537
solvency 1457
solvent
abuse 1361
abuser 1363
additive 1051
adsorption 1216
by soil or sediment 1220
isotherm 1655
allergen 1352
allergic symptom 1352
allergy 1352
alternative 911
alveolar concentration 1347
analysis 1125
anesthetics 1350
antimicrobial effect 926
application 1635
atmospheric
half-life 1224
photodegradation 1223
residence time 1224
biodegradation 1215
first-order kinetic model 1223
half-life 1223
probability 1223
biological origin 916
blood concentration 1348
bonding 1005
bound 1179
carcinogenic potency 1353
chemical
inertness 1036
stability 1036
chlorinated 1729
class 1 1193
classification 1298
cleaning 998, 1007, 1009, 1092
coalescing 1022
color 1129
compatibilizing 1116
concentration 1206, 1208, 1278, 1347, 1350, 1656, 1654
concentration gradient 1348
condensation 1664
consumption 1528
content 943
critical properties 1456
data 1088
deasphalting process 1707
degradation in soil and sediment 1222
degradation in water 1215
density 1521, 1533
depressant effect 1350
dermal uptake 1348
desorption 1644
diffusion
coefficient 1217
rate 1217
direct exposure 1242
dissolving power 1457
distillation 955
dry deposition 1224
duration of exposure 1347
emission 902, 942, 944, 1002, 1012, 1080, 1099, 1255, 1297
emulsion 962
environmental
chemistry 1203
effect 1298
exposure 1440
impact 1014, 1203
environmentally-friendly 1546
evaporation 1004, 1017
rate 1020, 1177
exchange 1496
exposure 1153, 1288-1289, 1353, 1380
limit 1298
risk assessment 1356
extraction 965, 1131, 1141
extraction recovery 999
fate mechanism 1225
filtration 955
flooding 1058
gel 1108
green 1457
growth-inhibiting effect 926
half-life 1214, 1219
hazardous 1018
hydrolysis reaction 1224
hydrophilic 1221
hydrophobic 1220
immunological effects 1352

impurities 1037, 1052
in air 1223
  degradation 1223
incineration 942, 1102, 1674
inhalation 1363
inhaled 1425
inherent toxicity 917, 1196
intake 1361
intestinal uptake 1347
level 1287
life cycle 1675
lifetime 1241-1242
liver toxicity 1425
mass transfer 1707
metabolite 1349
migration 1086
milling 958
mixture 1085, 1175, 1277, 1362, 1434
nanofiltration 1708
  membrane technology 1014
narcotic effect 1350
odor 906
parameter 934
partitioning 1140, 1220, 1348, 1623
percutaneous uptake 1348
photochemical reaction 1237
photodegradation 1215, 1710
physicochemical properties 1215
plasticization 1023
plume 1730
polarity 1537
power 1592
priority pollutant 1325
production 1690
pulmonal absorption 1347
purity 1035, 1041, 1052, 1134, 1137
quality 1041
recovery 1021, 1635, 1638-1639, 1641-1642, 1644, 1646-1647, 1655, 1660, 1665, 1669, 1674, 1701, 1705, 1707
  continuous operation 1707
  improvement 1707
  plant 1636, 1665
  process 1666
  rate 1662
  system 1644, 1647, 1661
recycling 963, 1708
  process 942
relative reactivity 1250
release 962, 1030, 1115, 1118, 1203
removal 1173-1175
replacement 906
residual 1173, 1174-1175, 1195, 1196
selection 901, 1004, 1051, 1079, 1132
  guide 1020
selective extraction 1083
selectivity 1477
solubility 1211
solution 952
stabilizers 1038
standard specification 1141
storage tank 953-954
stream 1719
strength 1469
stripping 1174-1175, 1663
supercritical 1455
phase behavior 1458
supplier 1048
surface tension 1096
thermal stability 1036
tolerance 921-922, 929
toxic effect 1015
toxicity 922, 1349, 1363
toxicodynamics 1347
 toxicokinetics 1347
toxicology 1347
transfer 1118
transformation 921
typical chromatogram 1191
usage 1116
utilization 906, 1298
vapor 1374, 1638
  convective movement 1217
  phase 1224
  pressure 1217, 1219
  uptake 1158
viscosity 1142, 1518
volatilization 1214
from soil 1217
waste 910, 1102
water
  content 1664
  solubility 1217, 1221
wet deposition 1224-1225

-based adhesive 902, 904
-boil defect 943
-template reactant system 1553
-tolerant
bacteria 918, 923-924
Pseudomonas putida 923
strain 922
sonication 991
Sonogashira coupling 1547
soot 1381
sorption 1729, 1732
coefficient 1140-1141
theory 1475
sound speed 1572
Sovová mass transfer model 1623
Soxhlet
apparatus 1129
extraction 987, 1131
soybean oil 1708
specific
gravity 1130
heat capacity 1127
metabolism 1349
resistance 1131
surface area 1555
use 1036
specificity 938, 1513
spectroscopy 1050
sperm
count 1351
production 1361
spermatogenesis 1364
spillage 1203, 1411
spina bifida 1362, 1364
spinal cord 1359
spinneret 1079
spinning 954, 1079
spleen morphology 1395
splenic cell proliferation 1395
spontaneous abortion 1361-1364
sport shoe manufacturer 904
spot remover 1383
spotting 947, 955-956
agent 956
procedure 957
table 956
spray
booth 963, 1291
car painting 1435
coating 1020
gun 956
painters 1443
painting 1287-1288, 1292, 1431
primer 1288
work 1288
sprayability 1099
spraying 909, 1017, 1092
stability 1041
stabilizer 1038
stain
removal 956
resistance 1025, 1028
standard method 1125
state effect 1469
static headspace
injection 1189
injector 1188
stationary source 1316
statistical association fluid theory 1468
steam
consumption 1653, 1661
desorption 1644, 1646, 1651, 1659, 1662
1667
principle 1645
pipe 953
steatosis 1426
steel cutting 1092
stem cell 1399
differentiation 1395
level 1401
stent 1005, 1183-1184
restenosis 1183
stereoselective synthesis 1611
stereoselectivity 1546
steric separation effect 1643
sterols 983
Stille reaction 1547
Stoddard
compound 1377
solvent 947, 1433
stoichiometric relationship 1043
Stokes-Einstein product 1516
stone 1106

storage 910
  time 1277
storm water 1325
stratosphere 1092, 1223-1224, 1242
stratospheric
  cloud 1244
  ozone 1241, 1243, 1310
    depletion 1242, 1314
    layer 1324
    protection 1324
stratum corneum 1348
stress
  distribution 911
  forces 1132
stripping 995
  column 981
  evaporation 1014
  solvent 1174-1175
structural
  adhesive 903
  chromosomal aberration 1413
  information 1050
structure
  elucidation 1050
  marking 1020
Sturm Test 1232
styrene 1003, 1164-1165, 1168
  divinylbenzene resin 1643
  resin 1017
  -butadiene
    copolymer 902
    -styrene copolymer 903
subacute proliferative glomerulonephritis 1372
subcritical water extraction 1617
subcutaneous tissue 1359
submicropores 1642
substrate activation 1607
subtilisin 938
sugar coating 1040
suicidal exposure 1422
sulfate reducing bacteria 1749
sulfonated polystyrene nanofibers 1725
sulfur dioxide 908, 1315
sunlight 1715, 1720
  fluctuation 1719
supercapacitor 1517
supercritical
  carbon dioxide 1110, 1485, 1490
  chromatography 1482
  conditions 1456, 1484
  extraction 1460, 1477
    process 1577
  fluid 1005, 1175, 1457-1458, 1460, 1469, 1493, 1528-1529
    chromatograph 1463-1464
    concentration 1460
    diffusion 1475
    extraction 1616, 1622
      application 1481
    fractionation applications 1481
    leaching applications 1479
    polymerization reactions 1491
    processing 1475
    sorption applications 1482
    system 1472
    technology 1577
    transport properties 1469
  fractionation 1478, 1480
  leaching 1479
  liquid carbon dioxide 1706
  phase 1484
  pressure 1461
  process 1579
  solution 1492
  solvent 1461
    as reaction medium 1483
    catalytic reactions 1486
    heterogeneous reaction 1488
    non-catalytic reaction 1487
    reaction rate 1474
    reactions 1489
    regeneration 1479
    sorption behavior 1475
    swelling 1475
  step 1478
  technology 1455
  water 1484-1485, 1489
  xenon 1487
surface
  activity 951
  cleaning 909, 1090, 1112
  crystallinity 1180
  energy 1024

film 1015
fissures 1131
lubricity 1005
preparation 902, 908, 1093
profiling 1094
reaction 1660
tension 1024, 1062, 1472-1473, 1502, 1536, 1579, 1592, 1624
variation 1020
treatment 1016, 1280
water 1223
surfactant 951-953, 964, 1023, 1055
aggregation 952
efficacy 1472
mechanism of action 952
system 1024
sustainable applications 1458
sustained release tablet 1035
Suzuki
coupling 1547
-Miyaura
cross-coupling reaction 1625
reaction 1604
swelling 949, 1382, 1477, 1599
switchable
miscibility 1708
solvent 1708
mechanism 1708
synergistic
hepatotoxicity 1436
liver toxicant 1434
toxic effect 1434, 1436
synergy 1457
syngas production 1557
synthetic
fuel processing 1489
rubber product 1091

T

tablet
coating 1179
storage 1180
tag
closed tester 1133
open cup 1133
tangent pinch point 1674-1675
tank
farms 1670
venting gas 1670
tanker 1038
target organ 1153
taste 1179
Taylor diffusion coefficient 1470
tear strength 905
temperature 908, 928, 1217
templating agent 1556
teratogen 1360-1361
teratogenic 1363
influence 1360
teratogenicity 1182, 1196
terpenes 916
test chamber 1277
testicular germ cell tumor 1363
tetrachloroethane 959
tetrachloroethene 1381
tetrachloroethylene 947, 950, 1164-1165, 1381
tetrafluoroborate 1235
tetrahydrofuran 906, 1674
adsorption isotherm 1657
tetrahydroisoquinolines 1549
textile 964, 1086, 1723
cleaning 1110
fiber water content 950
finishing 947, 958
industry 1109, 1165, 1383, 1427
processing 1364
theoretical tray 1674
therapeutic
agent 1005
efficacy 1045
thermal
conductivity 1471, 1472, 1488, 1502
detection 1190
diffusivity 1476
efficiency 1128
inactivation 937
oxidation 1636
thermodynamic
behavior 1570
equilibrium 933, 1188
model 938, 1570
parameters 1573
study 1576
thermodynamics 1456
thermogravimetric analysis 1186

thermoplastic laminating film 905
thiazolidinone derivatives 1603
thickening agent 945
thickness 1555
thin
  solar cell 1551
  -film transistor 1705
  -layer chromatography 1052
  -wall hollow part 1008
thinner 1099
thinning
  agent 1258
  effect 1259
  solvent 1099
thiol 1607
thiophene 1549
three-dimensional printing 1028
threshold limit value 1153-1154, 1165, 1178, 1310, 1347, 1369
throat 1183
thrombocytopenia 1393
thyme
  essential oil 1616
  leave 1617
thymol 1587-1588, 1617, 1625
timber 1002
tire cord 1109
tissue
  development 1365
  engineering 1593
  membrane 1158-1159
  necrosis 1184
  repair mechanism 1349
titanium dioxide 1712
  catalyst 1710
titrant 1052
titration 1126
tobacco smoke 1357
tocopherol 966, 981-983, 1615
toluene 922, 924, 1003, 1289, 1349, 1363, 1365, 1374, 1391, 1410, 1434, 1592
  adsorption 1658
  penetration 923
  toxicity 1434
topcoat 942, 1288
topoisomerase 1412-1413, 1419
topology 1567
total
  carbon concentration 1266, 1269
  evaporation method 1264
Toth isoterm 1475
toxic
  chemical release inventory 1203
  compound 922
  effect 1361, 1370
  metabolite 1426
  nephritis 1371
  nephropathy 1381
  pigment 1102
  Substances Control Act 976,t 1332
toxicity 919, 1045, 1412, 1434, 1540
toxicodynamics 1347
toxicokinetic
  data 1429
  process 1350
toxicokinetics 1347
  modeling 1350
toxicological
  aspect 1034
  effect 1393
toxicology 1350, 1441
trace impurity 1181
tracheitis 1352
transamination 1607
transdermal 1183
transesterification 938-939, 1039, 1502, 1544, 1593, 1595
transfer data 1030
transformation 1401
transition-state theory 1474
transport
  phenomena 1456
  properties 1464
  segment 1413
transportation 1699
  equipment cleaning 1112
tray assembly 905
trichloroacetic acid 1364, 1428
trichloroethane 914, 947
trichloroethene 1729
trichloroethylene 1376, 1381-1387
trichloromethyl free radical 1426
trimethylbenzene 1289
trimethylolpropane trimethacrylate 1108

triple point 1589
trophoblast 1359
tropopause 1242
troposphere 1223-1224, 1242, 1244, 1252, 1265
tropospheric
  air pollution 1240
  ozone 1020, 1240, 1241, 1244-1245, 1314
    formation 1240, 1243
  photochemistry 1243
truck 1112
  maintenance 995
Tsuji-Trost reaction 1548
tube morphology 1725
tuberculosis 1395
tubing system 1005
tubular
  degeneration 1370
  epithelium 1382
  filter 1083
  injury 1371
  lumen 1372
tumor
  antigen 1371
  formation 1353
  production 1428
tunable
  physico-chemical properties 1457
  reaction rate 1485
  solvent 1567
tung 965
turbidity 1131, 1140
turbulent diffusion 1241
turpentine 947
two-component paints 1281
typewriter correction fluid 1383

U

ultrasonic cleaning system 911
ultrasonication 1556
ultrasound-assisted extraction 1014
ultraviolet 1723
umpolung carboligation 1546
unconsciousness 1292
unfolding 936
UNIFAC
  group contribution 1589-1590
  interaction parameters 1630
  model 1591
  modeling 1628
uniform mixing 1079
unit cell volume 1043
universal primer 906
unloading 955
untreated polyolefin film 1086
urban pollution 1249, 1314
urinary
  bladder 1359
  concentration 1364
  phenol excretion 1403
  urobilinogen 1432
urine 1434
  excretion 1370
urogenital
  structure 1360
  system 1359
urothelial cancer 1378
uterine fluid 1359
uteroplacental circulation 1359
uterus 1359-1360
UV
  intensity 1717
  radiation 908
  -protecting composition 1116

V

vacuum regeneration 1671
valve
  monitoring 1081
  replacement 1081
van der Waals
  equation 1458
    of state 1458
  forces 1637, 1653
  interaction 936
van't Hoff's
  plot 1074
  regression 1073
vanillic acid 1587, 1590
vapor
  degreasing 911, 1128, 1427
  exposure 1392
  flow rate 1678, 1692
  mixture 1132
  permeation 1624
  permeation unit 1677

pressure 1142, 1213, 1219, 1569, 1592
recovery 1671
-liquid
equilibrium 1575, 1579, 1685
phase behavior 1459
-phase movement 1217
vaporization heat 1569-1570, 1684
variable volume system 1463
varnish 1126, 1258, 1280, 1383, 1426
application 1259
varnished furniture 1276
surface 1276
varnishing plant emission 1268
vascular 1359
lesion 1592
vegetable
oil 965, 1708
extracting facility 972
vehicle
collision repair 1287
industry 1292
refinishing 1287
product 1280
veneer 1114
venous blood 1158, 1169
concentration 1169
ventilation 1270, 1288
vertical dispersivity 1733
vessel wall degradation 1183
vibrating-tube densitometer 1522
vinyl
acetate 939
butyrate 939
chloride 1385
fluoride 912
liner 1364
resin 1017
viral antigen hepatitis B 1371
virgin
olive oil 991
solvent production 1699
virus 1723-1724
viscose
fiber 1666
filament
yarn 1666
plant 1668
film 1666
industry 1666
production 1669
rayon industry 1443
viscosity 902, 914, 1004, 1079, 1096, 1099, 1116, 1143, 1521, 1534-1535, 1552, 1579
reduction 1259
visible
light 1610
activated catalyst 1722-1723
activation 1725
activity 1724
irradiation 1609
utilization 1723
spectrum 1724
vitamin
D 1557
E 966, 1615
VOC 1143, 1240, 1255-1256, 1280-1281, 1297, 1310
concentration 1264, 1713, 1719
calculation 1264
emission 943, 1298
measurement 1270
-free composition 906
Vogel-Tamman-Fulcher equation 1520
volatile
impurities 1047, 1050, 1181-1182
product 1188
substance 1257
volatility 1258, 1361, 1576
volatilization 962, 1219, 1729, 1736
rate 1219
volume resistance 1131

W

Wacker 948
Walden rule 1520
waste
classification system 1709
gas cleaning process 1635
management 1330
solvent
incineration 1674
plant 1690
recovery 1705
technology 1674
stream 1674

treatment plant 1127
wastewater 1281
discharge 1326
treatment 931, 1088, 1232
plant 1236
water 1002, 1432
activity 934, 935
contamination 1422
content 1658
cooling 954
ion dissociation constant 1486
isotherm 1658
maximum contaminant level 1327
miscibility 1025
photolysis 1215
pollutant 1723
separator 953-954
stream 1722
supercritical 1457
transportation 1113
treatment 1725
-based paint 1281
waterborne paint 1020
waterproofing 913, 947, 1009
agent 958
liquid-applied membrane 913
wavelength 1050
weather conditions 1099
weatherability 1025
weathering 1132
performance 943
weight 1379
wet
coating process 1017
deposition 1237
spinning 1079
wettability 1043, 1108
white
blood cell 1395
matter hyperintensity 1453
spirit 943, 947
whitened layer 1028
whitening 1028
Wilkinson catalyst 1548
Wilson model 1061
wind 1241
conditions 1219
wine 1566
wood
coating 943
finishing 1116
furniture industry 1114
humidity exposure 1000
preservation 1000
preservative 1002
stain 1003, 1116
wool 948, 949
woolen
fabric 950
knitwear 958
work task 1288
worker exposure 1291
working
capacity 1645, 1650, 1653, 1657
time 1640
workplace 1347
conditions 1289
environment 1643
exposure 1386
regulations 967
wound dressing 1004
woven glass cloth 1107
Wright respirometer 1163

X

xanthophyll 1618
xenobiotic metabolism 1361
xerogel 1495, 1553
x-ray diffraction pattern 1045
xylene 902, 914, 1289, 1374, 1433-1434, 1592
isomer 1434
treatment 1434

Y

yeast cell 918
yellowing 945
yellowness index 1129

Z

zero shear viscosity 906
Ziegler-Natta polymerization 1512
zinc
diphosphonate 1555
oxide 1724
zygote 1359
zymbal gland 1395