Potential Health Effects of Occupational Chlorinated Solvent Exposure

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ABSTRACT: Based on toxicology, metabolism, animal studies, and human studies, occupational exposure to chlorinated aliphatic solvents (methanes, ethanes, and ethenes) has been associated with numerous adverse health effects, including central nervous system, reproductive, liver, and kidney toxicity, and carcinogenicity. However, many of these solvents remain in active, large-volume use. This article reviews the recent occupational epidemiology literature on the most widely used solvents, methylene chloride, chloroform, trichloroethylene, and tetrachloroethylene, and discusses other chlorinated aliphatics. The impact of studies to date has been lessened because of small study size, inability to control for confounding factors, particularly smoking and mixed occupational exposures, and the lack of evidence for a solid pathway from occupational exposure to biological evidence of exposure, to precursors of health effects, and to health effects. International differences in exposure limits may provide a "natural experiment" in the coming years if countries that have lowered exposure limits subsequently experience decreased adverse health effects among exposed workers. Such decreases could provide some evidence that higher levels of adverse health effects were associated with higher levels of solvent exposure. The definitive studies, which should be prospective biomarker studies incorporating body burden of solvents as well as markers of effect, remain to be done.

KEYWORDS: chlorinated solvents; occupational exposure; trichloroethylene; tetrachloroethylene; health effects; cancer

BACKGROUND

Chlorinated methanes, ethanes, and ethenes are among the most widely used and useful chemical compounds. Chlorinated methanes are methyl chloride (CAS 74-87-3), methylene chloride (dichloromethane, CAS 75-09-2), chloroform (trichloromethane, CAS 67-66-3), and carbon tetrachloride (CAS 56-23-5), with 1–4 chlorines, respectively, substituted for hydrogens. The main use of

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methyl chloride is in the manufacture of silicone; the other three compounds have been used as solvents, paint removers, degreasers, cleaning compounds, and chemical intermediates.

There are nine chlorinated ethanes. Most are used primarily to produce other chemicals rather than as solvents. The chief use of ethyl chloride (75-00-3) has been in the production of the gasoline fuel additive tetraethyl lead. As leaded gasoline use has declined, so has the use of ethyl chloride.[1] Ethylidene dichloride (1,1-dichloroethane, CAS 75-34-3) and ethylene dichloride (1,2-dichloroethane, CAS 107-06-2) are chemical intermediates in the production of chlorinated ethenes. Methyl chloroform (1,1,1-trichloroethane, CAS 71-55-6) was widely used as a solvent but is being phased out, except for use in closed systems.[2] The other trichloroethane, vinyl trichloride (1,1,2-trichloroethane, CAS 79-00-5), and the four higher chlorinated compounds (1,1,1,2-tetrachloroethane, CAS 630-20-6; 1,1,2,2-tetrachloroethane, CAS 79-34-5; pentachloroethane, CAS 76-01-7; and hexachloroethane, CAS 67-72-1) are all used mainly as chemical intermediates.

The five chlorinated ethenes include vinyl chloride (CAS 75-01-4) and vinylidene chloride (1,1-dichloroethylene, CAS 75-35-4), used primarily as precursors for polyvinyl chloride and polyvinylidene chloride (plastic wrap) respectively, and three solvents/degreasers: 1,2-dichloroethylene (CAS 540-59-0), trichloroethylene (TCE, CAS 79-01-6), and tetrachloroethylene (perchloroethylene, PCE, CAS 127-18-4). The latter two are widely used, especially for metal degreasing and clothes cleaning. Vinyl chloride has been classified as a human liver carcinogen, and occupational exposure has been limited by regulatory bodies in many countries. Exposure regulations for the other chlorinated ethenes are less restrictive.

Based on toxicology, metabolism, animal studies, and human studies, occupational exposure to chlorinated aliphatic solvents (methanes, ethanes, and ethenes) has been associated with a number of adverse health effects including central nervous system, reproductive, liver, and kidney toxicity, and carcinogenicity. However, many of these solvents remain in active and even in large-volume use. There has been much discussion in the literature as to whether toxicity and carcinogenicity of these solvents has been established, disproved, or is still in doubt.[3–10]

The intent of this article is to present the most recent field and clinical studies on solvent-exposed workers and to suggest what studies are needed to resolve ambiguities regarding the toxicity and carcinogenicity of these solvents.

Additional information on these compounds can be found in a supplementary table available from the author or at http://www.cdc.gov/niosh/ext-suppmat/Chlorinated-Solvents/. TABLE 1 lists all the compounds and their toxicity ratings by the International Agency for Research on Cancer (IARC) and other organizations; TABLE 2 gives volumes of use and numbers of workers potentially exposed for the same compounds.

TABLE 1. Chlorinated solvents and related compounds: toxicity assessments

Common/ generic names	Composition	CAS number	IARC group[a]	IARC–human	IARC–animal	NTP'11[b]	WHO[c]	EPA IRIS[d]	U.S. NIOSH REL[e]
Chlorinated methanes									
Methyl chloride, chloromethane	CH_3Cl	74-87-3	3	I	I	N/A	Possible central nervous system (CNS) and reproductive toxin (ICSC 419)	D	Lowest feasible[f]
Methylene chloride, dichloromethane	CH_2Cl_2	75-09-2	2B	I	S	R	Possible CNS and liver toxin, carcinogen (ICSC 58)	B2	Lowest feasible[f]
Chloroform, trichloromethane	$CHCl_3$	67-66-3	2B	I	S	R	Possible CNS, liver, kidney toxin, carcinogen (ICSC 27, CICAD 58)	B2	2 ppm; lowest feasible[f]
Carbon tetrachloride	CCl_4	56-23-5	2B	I	S	R	Possible CNS, liver, kidney toxin, carcinogen (ICSC 24)	B2	2 ppm; lowest feasible[f]
Chlorinated ethanes									
Ethyl chloride, 1-chloroethane	C_2H_5Cl	75-00-3	3	NC	L	Nominated	Possible CNS toxin (ICSC 132)	N/A	Caution[g]
Ethylidene dichloride, 1,1-dichloroethane	$C_2H_4Cl_2$	75-34-3	N/A	—	—	N/A	Possible CNS, liver, kidney toxin (ICSC 249)	C	100 ppm; caution[g]
Ethylene dichloride, 1,2-dichloroethane	$C_2H_4Cl_2$	107-06-2	2B	I	S	R	Possible CNS, liver, kidney toxin, probable carcinogen (ICSC 250, CICAD 1)	B2	1 ppm; lowest feasible[f]; caution[g]

Continued.

TABLE 1. ***Continued.***

Common/ generic names	Composition	CAS number	IARC group[a]	IARC–human	IARC–animal	NTP_11[b]	WHO[c]	EPA IRIS[d]	U.S. NIOSH REL[e]
Methyl chloroform, 1,1,1-trichloroethane	$C_2H_3Cl_3$	71-55-6	3	I	I	Nominated	Possible cardiac, CNS, liver, kidney toxin (ICSC 79)	D	350 ppm; caution[g]
Vinyl trichloride, 1,1,2-trichloroethane	$C_2H_3Cl_3$	79-00-5	3	ND	L	N/A	Possible CNS, liver, kidney toxin (ICSC 80)	C	10 ppm; lowest feasible[f]; caution[g]
1,1,1,2-tetrachloroethane	$C_2H_2Cl_4$	630-20-6	3	ND	L	Nominated	Possible CNS toxin (ICSD 1486)	C	Caution[g]
1,1,2,2-tetrachloroethane	$C_2H_2Cl_4$	79-34-5	3	I	L	Nominated	Possible CNS, liver, kidney toxin (ISCS 332, CICAD 3)	C	1 ppm; lowest feasible[f]; caution[g]
Pentachloroethane	C_2HCl_5	76-01-7	3	ND	L	Nominated	Possible CNS toxin (ICSD 1394)	N/A	Caution[g]
Hexachloroethane	C_2Cl_6	67-72-1	2B	I	S	Nominated	Possible CNS, liver, kidney toxin (ICSC 51)	C	1 ppm; lowest feasible[f]; caution[g]
Chlorinated ethenes									
Vinyl chloride, chloroethylene	C_2H_3Cl	75-01-4	1	S	S	K	Possible circulatory system, liver, spleen toxin, known carcinogen (ICSC 82)	A	Lowest feasible[f]
1,1-dichloroethylene, vinylidene chloride	$C_2H_2Cl_2$	75-35-4	3	I	L	Nominated	Possible liver, kidney toxin (ICSC 83, CICAD 51)	C	Lowest feasible[f]

Continued.

TABLE 1. ***Continued.***

Common/ generic names	Composition	CAS number	IARC group[a]	IARC–human	IARC–animal	NTP_11[b]	WHO[c]	EPA IRIS[d]	U.S. NIOSH REL[e]
1,2-dichloroethylene, dichloroethene	$C_2H_2Cl_2$	(mix) 540–59–0 (cis) 156–59–2 (trans) 156–60–5	N/A	—	—	N/A	Possible liver toxin (ICSC 436)	N/A	200 ppm
TCE, 1,1,2-trichloroethylene	C_2HCl_3	79-01-6	2A	L	S	R	Possible CNS, liver, kidney toxin, probable carcinogen (ICSC 81)	N/A	Lowest feasible[f]
Perchloroethylene, tetrachloroethylene	C_2Cl_4	127-18-4	2A	L	S	R	Possible CNS, liver, kidney toxin, probable carcinogen (ICSC 76)	N/A	Lowest feasible[f]

NOTE: N/A (not assessed).

[a]IARC = International Agency for Research on Cancer; Groups: 1 (human carcinogen), 2A (probable human carcinogen), 2B (possible human carcinogen), 3 (not classifiable as to human carcinogenicity). Evidence for carcinogenicity: S (sufficient), L (limited), I (inadequate), ND (no data as to carcinogenicity).

[b]NTP 11 = National Toxicology Program Report on Carcinogens, 11th edition; K = known to be a human carcinogen; R = reasonably anticipated to be a human carcinogen.

[c]WHO = World Health Organization; CICAD = Concise International Chemical Assessment Document; ICSC = International Chemical Safety Card.

[d]EPA IRIS = Integrated Risk Information System; weight of evidence characterization: A = human carcinogen; B2 = probable human carcinogen based on sufficient evidence of carcinogenicity in animals; C = possible human carcinogen; D = not classifiable as to human carcinogenicity.

[e]NIOSH Recommended Exposure Limits.[65]

[f]Potential occupational carcinogen, NIOSH Pocket Guide Appendix A.[66]

[g]All chloroethanes are given a "caution" rating because of their structural similarity to the four chloroethanes shown to be carcinogenic in animals. NIOSH Pocket Guide Appendix C.[67]

TABLE 2. Chlorinated solvents and related compounds: volume of use and regulations

Common/ generic names	CAS number	Uses	Volume of use in the United States[a] (year)	Estimated no. of U.S. workers potentially exposed[b]	Volume of use in Europe[a] (year)	Estimated no. of European workers potentially exposed[c]	U.S. OSHA PELs[d]	Other PELs[e]
Chlorinated methanes								
Methyl chloride, chloromethane	74-87-3	Manufacture of silicone	347 (1998)[C]	10,000	417 (1998)[C]	—	100 ppm	50 ppm (Germany, Spain, United Kingdom)
Methylene chloride, dichloromethane	75-09-2	Solvent, paint remover, degreaser	231 (1998)[C]	1,400,000	346 (1998)[C]	285,000	25 ppm	50 ppm (Spain); 3A (Germany)
Chloroform, trichloromethane	67-66-3	Solvent, chemical intermediate	204 (1998)[C]	96,000	273 (1998)[C]	—	50 ppm	0.5 ppm (Germany); 2 ppm (Spain, United Kingdom)
Carbon tetrachloride	56-23-5	Degreaser, chemical intermediate	50 (1998)[C]	104,000	26 (1998)[C]	77,000	10 ppm	0.5 ppm (Germany); 2 ppm (United Kingdom); 5 ppm (Spain)
Chlorinated ethanes								
Ethyl chloride, 1-chloroethane	75-00-3	Largest use production of tetraethyl lead, refrigerant, solvent	49 (1986)[B]	50,000	—	—	1000 ppm	3B (Germany); 100 ppm (Spain); 1000 ppm (United Kingdom)
Ethylidene dichloride, 1,1-dichloroethane	75-34-3	Solvent, chemical intermediate	11,922 (1998)[G]	2,000	9,495 (1998)[G]	—	100 ppm	100 ppm (Germany, Spain, United Kingdom)
Ethylene dichloride, 1,2-dichloroethane	107-06-2	Primarily used to produce vinyl chloride	8,468 (1992)[A]	83,000	—	—	50 ppm	C2 Germany; C2, 5 ppm (Spain)
Methyl chloroform, 1,1,1-trichloroethane	71-55-6	Industrial cleaner/degreaser	91 (1997)[D]	2,500,000	30 (1997)[D]	—	350 ppm	100 ppm (Spain); 200 ppm (Germany)
Vinyl trichloride, 1,1,2-trichloroethane	79-00-5	Chemical intermediate in production of vinylidene chloride	186 (1980s)[E]	1,000	—	—	10 ppm	10 ppm (Germany, Spain)
1,1,1,2-tetrachloroethane	630-20-6	Solvent, chemical intermediate	—	—	—	—	—	—

Continued.

TABLE 2. ***Continued***.

Common/ generic names	CAS number	Uses	Volume of use in the United States[a] (year)	Estimated no. of U.S. workers potentially exposed[b]	Volume of use in Europe[a] (year)	Estimated no. of European workers potentially exposed[c]	U.S. OSHA[d]	Other PELs[e]
1,1,2,2-tetrachloroethane	79-34-5	Solvent, chemical intermediate	—	4,000	—	—	5 ppm	1 ppm (Germany)
Pentachloroethane	76-01-7	Solvent, chemical intermediate	—	200	—	—	—	5 ppm (Germany)
Hexachloroethane	67-72-1	Moth repellent, lubricating oil ingredient	—	8,500	—	—	1 ppm	1 ppm (Germany, Spain); 5 ppm (United Kingdom)
Chlorinated ethenes								
Vinyl chloride, chloroethylene	75-01-4	Primarily used to produce polyvinyl chloride	6741 (1997)[F]	81,000	8751 (1997)[F]	41,300	1 ppm	C1 (Germany); 3 ppm (Spain)
1,1-dichloroethylene, vinylidene chloride	75-35-4	Primarily used to produce poly (vinylidene chloride) copolymers	79 (1992)[A]	3,000	—	—	—	3B, 2 ppm (Germany); 5 ppm (Spain)
1,2-dichloroethylene, dichloroethene	(mix) 540-59-0 (cis) 156-59-2 (trans) 156-60-5	Degreaser	—	200	—	—	200 ppm	200 ppm (Germany, Spain, United Kingdom)
TCE, 1,1,2-trichloroethylene	79-01-6	Degreaser	89 (1997)[F]	401,000	108 (1997)[F]	284,000	100 ppm	C1 (Germany); 80 mg/L TCA in urine end of work week (Spain)
Perchloroethylene, tetrachloroethylene	127-18-4	Dry-cleaning solvent, degreaser	136 (1997)[F]	688,000	127 (1997)[F]	870,000	100 ppm	3B (Germany) 25 ppm (Spain); 50 ppm (United Kingdom)

NOTE: [110]Use data from A—Reed 1993[106], B—Miller 1993[1], C—Chemical Economics Handbook 1999[107], D—Leder *et al*, 1999[108], E—IARC 1999[109], F—Cowfer and Gorensek 1997[110], G—Jebens 1999.[111]

[a] in thousands of metric tons.

[b] from NIOSH 1990.[112]

[c] From CAREX statistics for 19 European Union countries.[113]

[d] U.S. Occupational Safety and Health Administration: permissible Exposure Limit (time-weighted average) for an 8-h day. From U.S. ICSC.[114]

[e] Permissible Exposure Limit (time-weighted average) for an 8-h day. From EC ICSC and country-specific regulations[114–118]. German categories: C1 (human carcinogen), C2 (animal carcinogen), 3A (probably category 4 or 5 but insufficient data for occupational exposure limit [Maximale Arbeitsplatz Konzentrationen, MAK] value), 3B (insufficient evidence for classification, MAK possible if not genotoxic). MAKs are not assigned to C1 and C2 chemicals.

METHODS

We focus on the most widely used of these solvents (methylene chloride, chloroform, TCE, PCE) and discuss other chlorinated aliphatic solvents and related compounds, such as vinyl chloride. A PubMed search in July 2005 on solvents, health effects, and occupational exposure found 3193 citations. Within this group, the epidemiology literature published since 1990 on health effects of occupational exposure was reviewed and summarized (TABLE 3; available from author or at http://www.cdc.gov/niosh/ext-supp-mat/Chlorinated-Solvents/). When two or more updates were published on the same study population, the most recent is cited. Case reports and the literature on environmental exposure were excluded. Meta-analyses and reviews are not included in the tables of studies. Because abstracts do not provide enough information to assess a study, only papers that could be obtained were included.

In cohort mortality studies, the common metrics are the standardized mortality ratio (SMR), comparing mortality in a cohort with mortality in the general population, adjusted for age, sex, gender, and calendar period, and the rate ratio (RR, also known as relative risk), comparing mortality in one subcohort with that in another. Similarly, cancer incidence studies use the standardized incidence ratio (SIR) and or the RRs. Because cancer is the only chronic disease group for which mandatory reporting and state registries are widespread, SIR studies for cardiovascular, respiratory, and other chronic diseases are rarely feasible.

Case–control and exposed-referent cross-sectional studies compare exposure among individuals with and without disease or physiological changes among exposed and unexposed individuals, using unadjusted and adjusted odds ratios (OR).

RESULTS

Reviews of the levels of occupational exposure to chlorinated solvents over time have documented generally decreasing exposures from the 1940s for TCE, PCE, and other solvents.[11–14] Epidemiological studies of solvent-exposed cohorts generally have found higher risks of adverse health effects among those exposed before 1970. However, studies of recently exposed workers have continued to document adverse health effects. These include neurological effects, kidney and liver damage, reproductive effects, cardiovascular effects, and cancer. These studies are cited below in system/disease groupings and then by solvent.

The short-term narcotic effects of chlorinated solvents have been known since the mid-19th century. Several chlorinated solvents, especially chloroform and TCE, were used for anesthesia until fairly recently.[15,16] The literature on long-term neurological effects of solvent exposure has focused on tests of

sensory abilities, such as failure in blue-yellow color discrimination or pattern recognition.[17–21]

Exposure to chlorinated solvents has been associated with kidney and liver damage in case reports for 80 years and has been studied more systematically for about 20 years.[22,23] Case–control and cross-sectional exposed-referent studies have examined somatic cell mutations and kidney proteins in the urine of individuals exposed and unexposed to chlorinated solvents; however, differences between solvent-exposed and -unexposed individuals in levels of various proteins in the urine have not been related to clinical signs of kidney damage.[24–40]

Although inhalation is the main route of occupational exposure to chlorinated solvents, there is very little literature on short- or long-term effects on the respiratory system. Elevated SMRs for respiratory disease mortality not associated with duration of employment have been seen in cohort studies,[41–43] but lung cancer has not been associated with solvent exposure.

Cardiac arrhythmias often occur when TCE was used as an anesthetic.[44] Arrhythmia and other transient adverse cardiac effects have been associated with occupational exposure to methylene chloride, chloroform, and TCE.[43,45–49] The "healthy worker" effect, which typically leads to a reduction in observed numbers of cardiovascular deaths in occupational cohorts, could mask a low-to-moderate increase in cardiovascular mortality.[50]

Reproductive effects, including both gamete damage and developmental damage to the embryo and fetus, have been reported in a number of studies of solvent-exposed workers.[51–59] Spontaneous abortions or delays in becoming pregnant among solvent-exposed women show consistency for PCE but not TCE.[60–63]

There have been a few studies of immunological effects, including the occurrence of autoimmune diseases, in solvent-exposed workers, some reporting increased risk, others reporting lack of risk.[64–69]

Based on animal studies and human case reports of damage to the liver, biliary tract, and urinary organs from chlorinated solvent exposure, these organs have become a focus of epidemiology investigations. Many case–control cancer studies have targeted the liver, biliary tract, and urinary organs[70–73]; others have investigated breast and nervous system cancer.[74–76] In the Scandinavian countries, groups of workers monitored for acute or long-term solvent exposure or known from census records to have worked in certain industries have been linked to cancer registries.[48,77–80]

Occupational cohort studies have been concentrated in a few industries: cellulose triacetate or cellulose fiber production[81–86]; aircraft manufacturing or maintenance[43,87,88]; dry cleaning[41,42]; and various industries (mainly metalworking, electronics, painting, printing, and dry cleaning) using TCE.[89–91] In general, findings in the cohort studies have not been consistent, even within the same industries. For example, in the aerospace industry, Blair *et al*.[43] found increasing risk for colon and liver cancer and for multiple myeloma

with increasing TCE exposure, whereas Boice *et al*.[87] and Morgan *et al*.[88] saw no increases for those sites. However, both Blair *et al*.[41] and Ruder *et al*.[42] found elevated SMRs for bladder, cervical, and esophageal cancer, and both found increased respiratory disease mortality among PCE-exposed dry-cleaning workers. There are several possible explanations for inconsistent results among cohorts in the same industry. The cohorts may actually have had different combinations of exposures. A carcinogen might be associated with cancer at more than one site, and by chance one site might have been in excess in one cohort, another site in a second cohort. Individuals exposed to several carcinogens might develop a cancer associated with any one of them, and the distribution of cancers could vary by chance from cohort to cohort.

Methylene Chloride

Six case–control studies in populations with multiple chemical exposures have evaluated associations with methylene chloride exposure for biliary and liver cancer or renal cell carcinoma (RCC) and no increase was found.[70,71] For breast, brain, and rectal cancers, associations were found between level of exposure and cancer OR.[74,75,92,93] A case–control study of spontaneous abortion in exposed women found no association.[62] Mortality studies conducted in cellulose triacetate manufacturing cohorts exposed to acetone and methanol as well as methylene chloride show divergent findings of excess prostate and cervical cancer,[81] brain cancer and Hodgkin lymphoma,[82] biliary and liver cancer,[83] colon cancer,[85,86] and ischemic heart disease.[84] Within an aircraft manufacturing cohort exposed to many chemicals, any methylene chloride exposure was associated with increased risk of non-Hodgkin's lymphoma (NHL), multiple myeloma, and breast cancer.[43] One exposure assessment, also in triacetate production, found a correlation between the level of methylene chloride and level of carboxyhemoglobin.[49]

Chloroform

Three case–control studies evaluated risks of biliary and liver cancer, RCC, and astrocytomas and chloroform exposure and found some evidence of an effect on RCC risk.[70,71,75] Two cross-sectional exposed-referent studies looked at pregnancy outcomes among women who worked during their pregnancies. Dentists who used chloroform-based root canal sealers, among other chemicals, had longer time to pregnancy leading to live birth than did nonexposed women.[52] Chloroform-exposed lab workers were more likely than the unexposed to experience spontaneous abortions.[94] A greater percentage of exposed than unexposed workers had low serum prealbumin and transferrin, lower

scores for attention, memory, and perception, and higher scores for fatigue, depression, and anger.[95]

Carbon Tetrachloride

Five case–control studies found no association between carbon tetrachloride exposure and biliary and liver cancer or RCC[70,71]; some evidence for breast cancer, but not increasing risk with increasing exposure[74]; some effect for colon and rectal cancer[96]; and a dose–response relationship for brain cancer.[75] Exposure was associated with increased OR of scleroderma in men but not women.[97] Exposures to women working in their second or third trimester appeared to increase the risk of a small-for-gestational-age liveborn baby.[51] A study of hepatic proteins in the urine found significant differences between carbon tetrachloride-exposed men and the unexposed and also between the unexposed and "normal ranges."[32] Within an aircraft manufacturing cohort exposed to many chemicals, any carbon tetrachloride exposure was associated with increased risk of NHL and myeloma (especially in women), and breast cancer.[43]

Tetrachloroethylene

Since 1990, there have been seven case–control, two cross-sectional, twelve cross-sectional exposed-referent, three linkage, and four cohort studies of PCE published; all but five of these focused on workers in the dry-cleaning industry with few or no other chemical exposures. Within the cohorts or study populations with multiple exposures, three studies found some increased risk of scleroderma and of biliary and liver or brain cancer[64,70,75]; others found no increased risk for RCC[71] or for any cancer.[87]

Neurological studies found exposure-correlated differences between groups (any versus none or high versus low) for pattern memory and recognition and blue-yellow color confusion.[17,19,20] Higher rates of reproductive failure among PCE-exposed women and of eccentric sperm morphology and motility among PCE-exposed men; suggestions of longer times to pregnancy among PCE-exposed women and the partners of PCE-exposed men have been reported.[54,55,58,63] Three studies of spontaneous abortion in exposed women have shown increased risks, especially for dry-cleaning machine operators.[60–62]

Four studies of kidney proteins in urine have been done in dry-cleaner populations; there is no consistency between studies, not even for the referent ranges.[36–39] Studies of hepatic or immunological changes found differences between dry cleaners and referents but could not correlate those changes with clinical effects.[33,35,68,69]

Three studies linked census records for those working as "dry cleaner or laundry worker" or a database of those being monitored for PCE exposure to cancer registries, finding statistically significant increased risks for liver and pancreatic cancer, Hodgkin's disease, and leukemia.[78,79,98] As noted above, updates of two cohorts of dry-cleaning workers found elevated SMRs for bladder, cervical, and esophageal cancer, and both found increased respiratory disease mortality.[41,42]

Trichloroethylene

Since 1990, there have been sixteen case–case or case–control, three cross-sectional, five cross-sectional exposed-referent, two linkage, and seven cohort studies published. Many of these studies did not report contemporaneous exposure to other chemicals, but it is likely that such exposures occurred.

A total of 40% of 263 TCE-exposed workers developed severe generalized dermatitis within 3 months of their first exposure; unaffected co-workers with longer durations of exposure differed significantly only in their tumor necrosis factor-α (TNF-α) genotypes which could not independently differentiate cases from controls.[65] TCE-exposed and -unexposed co-workers in a printing factory differed in serum levels of cytokines but not in clinical signs or symptoms[67]; another study of printers found no differences in nerve function between TCE exposed and unexposed[21]; and a study of semen parameters and endocrine profiles in a TCE-exposed factory (no referents) saw deviations from the World Health Organization normal parameters for semen and a correlation between dehydroepiandrosterone sulphate and years of TCE exposure.[56,99] Time to pregnancy was delayed for women with high exposures.[63] Two studies of spontaneous abortion in exposed women had conflicting results of no increased risk[61] and a threefold increased risk.[62] Case–control studies of scleroderma (systemic sclerosis) and oral cleft defects in babies of women who worked in their first trimester found increased risk for TCE exposure.[57,64,66,100]

Studies of liver and kidney proteins in urine or somatic mutations have been done in RCC case–case, RCC case–control, and cross-sectional exposed-referent populations. Statistically significant findings of "urinary protein patterns indicative of kidney damage" or of somatic mutations could not be related causally to TCE exposure in cases or to clinical effects among TCE-exposed workers.[24,26–29,31,40] A weak relationship was seen between levels of urinary *N*-acetyl-β-gluoosaminidase and concurrent hours per week exposed to TCE.[101] Bolt *et al*.[24] recently studied excretion of α_1-microglobulin among RCC cases and controls, with some cases and some controls having been exposed to TCE. Among the RCC cases but not among the controls there was a significant difference in α_1-microglobulin levels in the urine.[24] Excess RCC among those exposed to TCE has been reported in a number of studies.[30,71–73,91]

Other studies of cancer among those exposed to TCE have reported increased risks for cancer overall, for liver and brain cancer in several studies, and for esophageal, stomach, biliary, pancreatic, colon, cervical, and prostate cancer, NHL, and multiple myeloma.[43,75,78,80,89,90] Other studies have reported no increased cancer risk among the TCE exposed.[48,87,88]

Other Chlorinated Solvents

Dosemeci *et al*.[71] examined RCC risk among those exposed to methyl chloride, 1,2-dichloroethane, 1,1,1-trichloroethane, or 1,1,2-trichloroethane and found an increase risk for dichloroethane-exposed women. A follow-up years later on seamen previously poisoned in a methyl chloride accident found a greater risk of cardiovascular death than among referent seamen not exposed to methyl chloride.[77]

Two 1,1,1-trichlorethane case–control studies looked at scleroderma risk, one finding an elevation associated with self-reported exposure, but no elevation associated with exposure reevaluated by an expert[64]; the other study showed elevated risk for men but not women.[97] An innovative study linked a register of workers monitored for serum 1,1,1-trichloroethane levels with subsequent cancer registry records. Several SIRs were elevated, especially those for cancer of the central nervous system, NHL, and myeloma.[78] A retrospective cohort study of aircraft maintenance workers with numerous chemical exposures found elevated RRs for NHL in men and myeloma and breast cancer in women.[43] A case–control study found nonlinear increases in astrocytoma risk with increasing cumulative exposure.[75] Among women reporting 1,1,1-trichloroethane exposure before and during pregnancy, two studies found increased odds of spontaneous abortion[61,62]; while in another study time to pregnancy was not delayed.[63]

DISCUSSION

The impact of studies to date has been limited by small study size and/or inability to control for confounding factors, particularly smoking and mixed occupational exposures, the lack of evidence linking occupational exposure to biological evidence of exposure, to precursors of health effects, to health effects, and varying, inconsistent outcomes. However, a number of studies consistently have reported increases in bladder and cervical cancer among those exposed to PCE[41,42,78] and of kidney, liver, and brain cancer among those exposed to TCE.[30,43,71–73,75,80,91,98] Among PCE-exposed men and women, there have also been consistent reports of spontaneous abortion or other fertility problems[54,55,60–63] and neurological problems.[17,19,20]

Carcinogenic metabolites may be formed via pathways that exhibit a high degree of genetic polymorphisms. For example, trichloroacetic acid (TCA) forms

from PCE and TCE via CYP2E1-mediated metabolism, whereas mutagenic metabolites S-(l,2-dichlorovinyl)-L-cysteine and S-(l,2,2-trichlorovinyl)-L-cysteine form via the glutathione pathway and are deactivated via the *N*-acetyltransferase pathway.[102,103] All three pathways are highly polymorphic, and risk does depend on genotypes as well as on exposure.[104] Most of the biomarker studies have not evaluated variation in susceptibility by genotype.

For some of these solvents (methyl chloride, ethyl chloride, 1,1-dichloroethane, tetra-, penta-, and hexachloroethane, and dichloroethylene) there is little or no literature on human health effects. Large cohorts of workers exposed to solvents mainly used as chemical intermediates in closed systems might be difficult to assemble, but the number of study participants needed for cross-sectional biomarker studies is much smaller.

The biomarker studies to date, although showing some significant differences between exposed and referent groups, or between an exposed group and laboratory reference values, have for the most part not demonstrated any link between these changes in immunological parameters or levels of kidney and liver proteins in the urine and health effects. This is at least partially due to the retrospective nature of many studies. High or low levels of urinary proteins in tests conducted after an exposure has occurred may have been out of range before the exposure began; high or low levels of urinary proteins in tests conducted after a diagnosis has been made may not have been out of range before the diagnosis. In addition, the connections between, for example, unusual levels of urinary proteins and kidney damage have not been explored in prospective studies.

The cohort studies lack information on nonoccupational exposures or exposures in other jobs. In most industries, solvent-exposed workers are exposed to a number of solvents as well as to other substances (e.g., heavy metals) that have been associated with the development of cancer and other chronic diseases.

For some solvents, TCE in particular, the literature reexamining and reappraising field studies and clinical studies is as extensive or more extensive than the primary literature. Although these studies can be quite useful, particularly in calling attention to overlooked research or in meta-analysis of studies that can be combined, they cannot replace the primary studies. Some of the effort going into these reviews and meta-analyses could be redirected to filling in the gaps in the investigative studies.

In the future, international differences in exposure limits may provide a "natural experiment" if countries such as Germany and Spain, which have limited exposure, subsequently experience decreased adverse health effects among exposed workers. Such decreases could provide some evidence that higher levels of health effects (previously in those countries or concurrently in countries such as the United States with higher exposure limits) were associated with higher levels of solvent exposure.

CONCLUSION

The definitive studies will be those whose results and conclusions are accepted universally, whether or not those results show an association of solvent exposure with a health effect. To achieve consensus, those studies should incorporate body burden, not merely ambient levels, of solvents as well as biological markers of effect. Ideally the studies would be prospective, to establish preexposure base lines for physiological outcomes and background levels for solvent body burden, would genotype participants for variations in genes coding for enzymes in relevant metabolic pathways, and would find methods to clarify the association between subclinical physiological changes and health effects. If possible, exposed individuals studied would be exposed predominantly to a single solvent. This last condition could be met for PCE with the participation of dry-cleaning workers (NIOSH [National Institute for Occupational Safety and Health] has conducted a pilot study fulfilling most of the conditions listed above).[105] There may not be a working population exposed only to TCE or only to one of the other chlorinated solvents. For all of the chlorinated aliphatic solvents, the definitive studies remain to be done.

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SUPPLEMENTAL TABLES

Supplemental tables are available from author or at http://www.edc.gov/niosh/ext-supp-mat/Chlorinated-Solvents/.

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