FINAL

Report on Carcinogens Background Document for

Trichloroethylene

December 13 - 14, 2000

Meeting of the
NTP Board of Scientific Counselors
Report on Carcinogens Subcommittee

Prepared for the:
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Criteria for Listing Agents, Substances or Mixtures in the Report on Carcinogens

U.S. Department of Health and Human Services
National Toxicology Program

Known to be Human Carcinogens:

There is sufficient evidence of carcinogenicity from studies in humans, which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer.

Reasonably Anticipated to be Human Carcinogens:

There is limited evidence of carcinogenicity from studies in humans which indicates that causal interpretation is credible but that alternative explanations such as chance, bias or confounding factors could not adequately be excluded; or

There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors: (1) in multiple species, or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site or type of tumor or age at onset; or

There is less than sufficient evidence of carcinogenicity in humans or laboratory animals, however; the agent, substance or mixture belongs to a well defined, structurally-related class of substances whose members are listed in a previous Report on Carcinogens as either a *known to be human carcinogen, or reasonably anticipated to be human carcinogen* or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

Summary of NIEHS Report on Carcinogens Review Group (RG1) and NTP Executive Committee Interagency Working Group for the Report on Carcinogens (RG2) actions for the nomination to upgrade trichloroethylene (TCE) to a *known to be human carcinogen* in the 10th RoC.

The RG1 reviewed the available carcinogenicity data for the nomination to upgrade TCE to a *known to be human carcinogen* in the 10th RoC. After applying the criteria for listing substances in the RoC, the RG1 passed a motion, by a vote of 7 in favor to 0 opposed, to recommend that TCE be upgraded in the 10th RoC to a *known to be a human carcinogen* based on the evidence of carcinogenicity from studies in humans. These findings are supported by evidence of malignant tumor formation in experimental animals, and convincing relevant information that TCE acts through mechanisms indicating that it would likely cause cancer in humans. The Summary Statement contained in the TCE draft background document for the December 13–15, 2000 NTP Board RoC Subcommittee meeting summarizes all the relevant information used by the RG1 to support their recommendation to upgrade TCE in the 10th RoC.

The RG2 reviewed the available carcinogenicity data for the nomination to upgrade TCE to a *known to be human carcinogen* in the 10th RoC. After applying the criteria for listing substances in the RoC, a motion recommending TCE be listed in the 10th RoC as a *known to be human carcinogen* was defeated by a vote of 3 in favor to 4 opposed. Reasons given by the RG2 members voting against the motion included the perception that the human studies do not provide sufficient evidence to list as a known human carcinogen mainly because of the lack of adequate exposure assessment information. Therefore, the recommendation going forward from the RG2 is that TCE should remain listed in the RoC as *reasonably anticipated to be a human carcinogen*. The current profile from the 9th RoC, where TCE is listed as *reasonably anticipated to be a human carcinogen*, is attached as appendix C to this background document.

Summary Statement

Trichloroethylene

CASRN 79-01-6

Carcinogenicity

Trichloroethylene (TCE) is *known to be a human carcinogen* based on evidence of carcinogenicity from studies in humans. These findings are supported by evidence of malignant tumor formation in experimental animals, and convincing relevant information that TCE acts through mechanisms indicating that it would likely cause cancer in humans.

A large and generally consistent body of epidemiologic findings provides support for the carcinogenicity of TCE in humans. In cohort studies, where the TCE exposures were best characterized, occupational exposure to TCE was associated with elevated incidence and mortality rates for cancer at several anatomical sites. A meta-analysis found elevated relative risks (RRs) for liver cancer (RR = 1.9, 95% CI 1.0 to 3.4) and kidney cancer (RR = 1.7, 95% CI 1.1 to 2.7), and somewhat less compelling results for non-Hodgkin's lymphoma (RR = 1.5, 95% CI 0.9 to 2.3), prostate cancer (RR = 1.3, 95% CI 1.0 to 1.6), and multiple myeloma (RR = 1.5, 95% CI 0.7 to 3.3) (Wartenberg *et al.* 2000). Although exposure was characterized less accurately in case-control studies, they also showed elevated odds ratios for kidney cancer (Dosemeci *et al*. 1999, Sinks *et al*. 1992, Vamvakas *et al*. 1998) and non-Hodgkin's lymphoma (Hardell *et al*. 1981, Hardell *et al*. 1984, Persson *et al*. 1989), supporting the findings of the cohort studies.

The findings in humans are supported by evidence of carcinogenicity in experimental animals at several of the same tissue sites as found in humans. In mice, TCE increased the incidences of benign and malignant tumors of the liver (NCI 1976; Maltoni *et al*. 1988; NTP 1990), lung (Maltoni *et al*. 1988), and blood (lymphoma) (Henschler *et al*. 1980). In rats, TCE-induced cancers of the kidney (Maltoni *et al*. 1988, NTP 1988, 1990), interstitial-cells of the testis (Maltoni *et al.* 1988, NTP 1988), and possibly leukemias (Maltoni *et al*.1988).

Other Information Relating to Carcinogenesis or Possible Mechanisms of Carcinogenesis

TCE is rapidly absorbed from the gastrointestinal tract and lung. Following absorption, TCE is distributed throughout the body and concentrates in lipophilic tissues (e.g., liver, brain, fat). Oxidation by cytochrome P-450 and conjugation with glutathione are the primary metabolic pathways. TCE metabolism in mice, rats, and humans is qualitatively similar producing the same primary metabolites. Chloral hydrate, dichloroacetic acid, and trichloroacetic acid are the primary toxic metabolites produced by the P-450 pathway and have been associated with liver and lung toxicity in rats and mice. Dichlorovinylcysteine is also a metabolite of the glutathione pathway and has been associated with kidney toxicity.

Renal-cell carcinomas from workers occupationally exposed to high levels of TCE exhibited somatic mutations of the von Hippel-Landau (VHL) tumor suppressor gene, a gene that has been associated with renal-cell carcinomas (Brauch *et al.* 1999). Of renal-cell carcinoma tissues from 44 TCE-exposed persons, 75% had mutations in the VHL gene. Sequencing analysis demonstrated that 39% of these tumors had a C to T transition at nucleotide (nt) 454, resulting in a Pro to Ser amino acid change at codon 81. The nt 454 mutation was found in the adjacent non-neoplastic kidney parenchyma in four patients. Moreover this mutation was both specific to TCE exposure, because it was not found in renal-cell carcinomas from non-exposed patients, and related to disease, because it was not found in germline DNA from either diseased or non-diseased individuals. It is biologically plausible that TCE exposure was related to the kidney tumors observed because (1) the site and histopathological characteristics of the tumors observed in humans and in experimental animals were identical (Vamvakas *et al.* 1993), (2) the molecular mechanism of this type of nephrocarcinogenicity has been elucidated (Dekant *et al.* 1986, cited in Bernauer *et al.* 1996), (3) the metabolites derived from the likely ultimate electrophilic intermediates of the bioactivation of TCE were identical in humans and experimental animals (Birner *et al*. 1993, cited in Clewell *et al*. 1995), and (4) taking the key urinary metabolites (mercapturic acids) as an indicator of the bioactivation of TCE (Birner *et al.* 1993, cited in Clewell *et al.* 1995), humans seem to be more sensitive than rats in developing the primary biochemical lesion leading to the induction of renal cancer.

In general, TCE and most of its major metabolites (chloral hydrate, dichloroacetic acid and trichloroacetic acid) were not potent genotoxins in a broad range of bacterial, lower eukaryotic, and *in vitro* and *in vivo* mammalian cell assays. In mammalian *in vitro* studies, TCE did not induce chromosomal aberrations in Chinese hamster ovary cells, unscheduled DNA synthesis in rat hepatocytes, or gene mutations in human lymphoblastoid cells but it did induce sister chromatid exchange in Chinese hamster ovary cells, gene mutations in mouse lymphoma cells and morphological transformation in rat embryo cells. In rodent *in vivo* studies, TCE did not induce unscheduled DNA synthesis, sister chromatid exchange, dominant lethal mutations or chromosome aberrations. TCE gave mixed results for DNA single-strand breaks or alkali-labile sites in mouse liver and positive results for micronucleus formation in mice. Studies of chromosomal aberrations, aneuploidy, and sister chromatid exchange in peripheral lymphocytes of workers exposed to TCE were considered inconclusive. In contrast to TCE, the dichlorovinylcysteine metabolite appears to be a more potent mutagen. Dichlorovinylcysteine was found to be mutagenic based on *Salmonella* assays and may induce primary DNA damage in mammalian cells *in vitro* and *in vivo*.

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1 Introduction

Trichloroethylene (TCE) is an industrial solvent used for vapor degreasing and cold cleaning of fabricated metal parts. Although no longer used with food, drugs, or cosmetics, TCE was used in the past as a carrier solvent for the active ingredients of insecticides and fungicides; as a solvent for waxes, fats, resins, and oils; as an anesthetic for medical and dental use; and for extraction of spice oleoresins and caffeine from coffee. TCE was listed in the Ninth Report on Carcinogens (RoC) as *reasonably anticipated to be a human carcinogen* based on limited evidence of carcinogenicity from studies in humans, sufficient evidence of malignant tumor formation in experimental animals, and convincing relevant information that TCE acts through mechanisms indicating that it would likely cause cancer in humans (NTP 2000a). TCE was nominated for upgrading to a *known human carcinogen* in the Tenth RoC by the National Institute of Environmental Health Sciences (NIEHS)/National Toxicology Program (NTP) RoC Review Group (RG1) based on recent publications of human studies consistently showing that occupational exposure to TCE results in elevated incidence and mortality rates for liver and kidney cancer in workers (Wartenberg *et al.* 2000).

1.1 Chemical identification

Trichloroethylene (C_2HCl_3, CASRN 79-01-6, mol. wt. = 131.39) also is known by the following names:

ethene, trichloro- (9CI)	Flock Flip	Trichloran
ethylene, trichloro- (8CI)	Fluate	Trichloren
acetylene trichloride	Gemalgene	trichlorethylene
Algylen	Germalgen	trichloroethene
Anamenth	Germalgene	1,1,2-trichloroethene
Benzinol	Lanadin	1,1,2-trichloroethylene
Blacosolv	Lethurin	1,2,2-trichloroethylene
Blancosolv	Narcogen	trichloroethylene (CAN)
Cecolene	Narkogen	Tri-Clene
Chlorilen	Narkosoid	Trielene
1-chloro-2,2-dichloroethylene	Nialk	Trielin
Chlorylea	Perm-A-Chlor	Trieline
Chlorylen	Perm-a-Clor	Triklone

Chorylen	Petzinol	Trilen
Circosolv	Philex	Trilene
Crawhaspol	TCE	Triline
Densinfluat	Threthylen	Trimar
1,1-dichloro-2-chloroethylene	Threthylene	Triol
Dow-Tri	Trethylen	Tri-plus
Dukeron	Trethylene	Vestrol
ethinyl trichloride	Tri	Vitran
ethylene trichloride	Triad	Fleck-Flip
ethylene, 1,1,2-trichloro-	Trial	Westrosol

Trichloroethylene has a UN shipping number of UN1710 and RCRA waste number of U228. The chemical structure of TCE is illustrated in Figure 1-1, and its physical-chemical properties are listed in Table 1-1

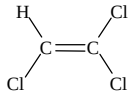

Figure 1-1. Structure of TCE

Table 1-1. Physical-Chemical chemical properties

Property	Information	Reference
Color	colorless, unless dyed blue	HSDB 1997
Physical state	liquid	HSDB 1997
Melting point (°C)	-84.8	Budavari 1996
Boiling point (°C)	86.9	Budavari 1996
Critical pressure (atm)	49.7	HSDB 1997
Critical temperature (°C)	271	HSDB 1997
Specific gravity (liquid) at	1.4642	Budavari 1996

Property	Information	Reference
20 °C or 4 °C		
Odor	ethereal odor, sweet chloroform-like odor	HSDB 1997
Odor threshold:		
Water	10 mg/L	Verschueren 1983, cited in in HSDB 1997
Air	ppm (115 mg/m^3)	Fazzalari 1978; cited in HSDB 1997
Solubility:		
in water at 25 °C	0.11 g/100 g	PPG Industries, Inc. 1997
in organic solvents	Soluble in chloroform, acetone, alcohol, and diethyl ether	HSDB 1997
Vapor density at 87°C and 760 mmHg (g/L)	4.45	PPG Industries, Inc. 1997
Vapor pressure (mm Hg)		
at 0°C	19.9	HSDB 1997
at 20°C	57.8	HSDB 1997

Upon combustion TCE produces irritants and toxic gases, which may include hydrogen chloride. In the presence of moisture and light, TCE decomposes by forming hydrochloric acid (HSDB 1997).

1.2 Packaging and shipping

TCE is generally shipped in 55-gal drums, tank trucks, or single compartment tank cars, with a capacity of 10,000 or 20,000 gal. PPG Industries, Inc., ships from its Louisiana plant and terminals located in New Jersey, Illinois, and California (PPG Industries, Inc. 1997).

2 Human Exposure

2.1 Use

TCE is used mainly as a degreaser for metal parts (CMR 1983, cited in Gist and Burg 1995). Five main industrial groups use TCE in vapor or cold degreasing operations: furniture and fixtures, fabricated metal products, electrical and electronic equipment, transport equipment, and miscellaneous manufacturing industries (IARC 1995e). TCE can be used as an extraction solvent and a chemical intermediate and as a component in adhesives, lubricants, paints, varnishes, paint strippers, pesticides, and cold metal cleaners (ATSDR 1995).

2.2 Production

The International Agency for Research on Cancer (IARC) (1995e) reported that in 1992, two companies in the United States produced a combined annual capacity of 160,000 tons of TCE (145,000 metric tons). The SRI *Directory of Chemical Producers, United States* listed only one producer (SRI 1996).

2.3 Analysis

NIOSH has two methods to determine TCE levels in relatively non-complex atmospheres. NIOSH Method #1022 is meant to measure TCE levels for STEL determinations. It has a working range of 27 to 875 ppm (150 to 4,700 mg/m^3) and is measured using a solid sorbent tube and a gas chromatograph, FID. NIOSH Method #3701 is meant to measure TCE using a tedlar air bag and a portable gas chromatograph with a photoionization detector. This method has a working range of 10 to 1000 ppm (54 to 5400 mg/m^3) (NIOSH 1994).

2.4 Environmental occurrence

Releases of TCE into the environment occur during its manufacture, use, and disposal. Although TCE can be formed by one red microalga and in temperate, subtropical, and tropical algae, nonanthropogenic releases of TCE are negligible (Wu and Schaum 2000).

2.4.1 Air

Most TCE emissions into the atmosphere are from vapor degreasing operations. Releases of TCE to air will also occur at sewage treatment and disposal facilities, water treatment facilities, and landfills. TCE has also been detected in stack emissions from municipal and hazardous waste incinerators (Wu and Schaum 2000).

The Toxic Chemical Release Inventory (TRI) for 1995 (TRI95 1997) contains reports on environmental releases of TCE from 717 U.S. facilities. Of these, 591 reported releases to the atmosphere of more than 2,000 lb (900 kg). Among the 591 facilities, 132 each released 2,000 to 10,000 lb (900 to 4,500 kg), 328 released 10,000 to 50,000 lb (4,500 to 22,700 kg), 114 released 50,000 to 200,000 lb (22,700 to 90,900 kg), and 17 released > 200,000 lb (> 90,900 kg). The total amount of TCE released in 1995 by the 717 facilities was 25,484,235 lb (11,600,000 kg), while the 17 greatest emitters together released 6,100,000 lb (2,800,000 kg). The greatest releases generally were from metalworking facilities, with three sites each reporting under Standard Industrial Classification (SIC) codes 3317 (steel pipe and tubes) and 3714 (motor

vehicle parts and accessories). Other facilities (one each) reported under SICs 3089 (plastics and plastic products, not elsewhere classified), 3671 (electron tubes), and 3721 (aircraft).

2.4.2 Water

Industrial discharges of wastewater streams are the primary releases of TCE into aquatic systems. TCE can also be released to groundwaters via leaching from landfills (Wu and Schaum 2000). TRI95 (1997) included data from 28 facilities that had each released more than 10 lb (4.5 kg) of TCE to water in 1995. Five facilities each released 250 to 280 lb (114 to 127 kg). The total release of TCE to water was 1,477 lb (670 kg). Four of the five facilities were metalworking plants, and one was a plant that produced TCE as a by-product and for onsite use and processing.

2.4.3 Soil

The total releases of TCE to land and underground injection wells in 1995 were 3,577 lb (1,626 kg) and 550 lb (250 kg), respectively (TRI95 1997).

2.5 Environmental fate

2.5.1 Air

TCE in the atmosphere is expected to be present primarily in the vapor phase rather than sorbed to particulates because of its high vapor pressure. Some removal by scavenging during wet precipitation is expected because of the moderate solubility of TCE in water (1.1 g/L). The major degradation process affecting vapor-phase TCE is photooxidation by hydroxyl radicals, with a half-life on the order of one to 11 days (Wu and Schaum 2000).

2.5.2 Soil

The dominant terrestrial fate of TCE is volatilization to air. Because of its moderate water solubility, TCE introduced into soil (e.g., via landfills) has the potential to migrate through the soil into groundwater. Biodegradation in soil is thought to be slow, with a half-life on the order of months to years (Wu and Schaum 2000).

2.5.3 Water

The dominant fate of TCE in water is volatilization with a predicted half-life of minutes to hours. Bioconcentration, biodegradation, and sorption to sediments and suspended solids are not through to be significant (Wu and Schaum 2000).

2.6 Environmental exposure

Because TCE is pervasive in the environment, most people are likely to be exposed to TCE by one or more of the following pathways: ingestion of drinking water, inhalation of ambient air, or ingestion of food. The Third National Health and Nutrition Examination Survey (NHANES III) suggests that about 10% of the population has detectable levels of TCE in their blood. The NHANES III examined TCE concentrations in 677 nonoccupationally exposed individuals from 1988 to 1994. These individuals were selected to represent a ranges of population characteristics such as age, race, gender, and region of residence. TCE levels in whole blood were below the 0.01 μg/L detection limit for about 90% of the people sampled. Assuming that nondetects equal half of the detection limit, the mean concentration was 0.015 μg/L. (Wu and Schaum 2000). The Agency for Toxic Substances and Disease Registry (ATSDR) is developing information on

potential public exposure to TCE and possible long-term health consequences in a subregistry to the National Exposure Registry for hazardous waste sites. The TCE subregistry includes three sites in Michigan, four sites in Indiana, six sites in Illinois, and one site each in Pennsylvania and Arizona. Environmental and tissue data will serve as the basis for estimating exposure (Gist *et al.* 1994).

2.6.1 Air

Air is the primary route of potential environmental exposure to TCE. Mean TCE background levels in air range from 0.03 ppb (0.16 μg/m^3) in rural areas to 0.46 ppb (2.5 μg/m^3) in urban and suburban areas. Areas near emission sources have TCE in the air at concentrations of up to 1.2 ppb (6.4 μg/m^3) (ATSDR 1995).

TCE is one of the volatile organic compounds (VOCs) measured in U.S. Environmental Protection Agency's (EPA's) large-scale Total Exposure Assessment Methodology studies (Wallace *et al.* 1996). In studies in Maryland, New Jersey, and California from 1981 through 1987, determination of TCE exposure via personal air monitors carried by 750 persons for two consecutive 12-hour periods revealed TCE median personal air concentrations of 0.3 to 3.0 μg/m^3. Breath samples taken in the evenings after several hours at home from 50 to 350 persons in two New Jersey cities in 1981 to 1983 and 75 persons in two California towns in 1984 contained TCE at concentrations of 0.1 to 0.9 μg/m^3 (median personal air concentrations of 1.7 to 3.0 μg/m^3). However, TCE was not detected in the breath of 140 persons in Los Angeles, CA (with TCE personal air levels of 0.3 to 1.2 μg/m^3 in 1984 or 1987), nor in the breath of 75 persons in Baltimore, MD (with TCE personal air levels of 1.1 μg/m^3) in 1987.

Ambient air measurements for TCE were obtained from various state and local environmental agencies from 1985 to 1998 by the Aerometric Information Retrieval System (AIRS). These data represent 1,200 measurements from 25 states. The 1998 air levels come from 115 monitors located in 14 states (mean 0.01 to 3.9 μg/m^3, mean = 0.88 μg/m^3). Using this mean and an inhalation rate of 20 m^3 air/day, the estimated inhalation exposure to TCE is 18 μg/day (Wu and Schaum 2000). Table 2-1 summarizes TCE air levels across monitors by year. Table 2-2 summarizes TCE air levels across monitors by land setting and use.

Table 2-1. Mean TCE air levels by year

Year	N	Mean concentration (μg/m^3)	Mean concentration (ppb)
1985	11	1.4	0.26
1986	21	1.39	0.26
1987	53	1.68	0.31
1988	57	4.87	0.91
1989	96	1.69	0.32
1990	59	1.84	0.34
1991	70	2.86	0.53
1992	76	1.37	0.26

Year	N	Mean concentration ($\mu g/m^3$)	Mean concentration (ppb)
1993	84	1.12	0.21
1994	89	0.95	0.18
1995	146	0.78	0.15
1996	150	0.65	0.12
1997	129	0.74	0.14
1998	115	0.88	0.16

Source: Wu and Schaum (2000)

Table 2-2. Mean TCE air levels by land setting and use

Year	N	Mean concentration ($\mu g/m^3$)	Mean concentration (ppb)
Rural	93	0.42	0.08
Suburban	500	1.26	0.24
Urban	558	1.61	0.30
Agricultural	31	1.08	0.20
Commercial	430	1.84	0.34
Forest	17	0.1	0.02
Industrial	186	1.54	0.29
Mobile	39	1.5	0.28
Residential	450	0.89	0.17

Source: Wu and Schaum (2000)

2.6.2 Water

TCE background levels in large bodies of water range from 0.001 to 0.007 ppb (µg/L), while values reported for rainwater and snow are 0.0008 to 0.039 ppb (µg/L) (Gist and Burg 1995). In the U.S. EPA's Contract Laboratory Program Statistical Database, TCE was noted as occurring in approximately 3% of surface-water samples at a geometric mean concentration of 40.2 ppb (individual sample values ranged from 0.0001 to 120 ppb) and in approximately 19% of ground water samples at a geometric mean concentration of 27.3 ppb (individual sample values ranged from < 0.1 to ≤ 27,300 ppb) (U.S. EPA 1989, cited in IARC 1995e). The California survey of large water utilities in 1984 found a median concentration of 3.0 µg/L. Using this median and the average water consumption rate of 2 L/day yields an estimate of 6 µg/day TCE exposure through drinking water (Wu and Schaum 2000). This is consistent with the ATSDR estimated average daily water intake for the general population of 2 to 20 µg/day (ATSDR 1995). Table 2-3 summarizes TCE measurements in rain, surface waters, groundwater, drinking water, and sea water in the United States.

Table 2-3. TCE levels in water

Water type	Location	Year	Mean	Median	Range (µg/L)	Number of samples	Reference
Industrial effluent	US	1983	--	0.5	--	--	IARC 1995e
Surface waters	US	1983	--	0.1	--	--	IARC 1995e
Rainwater	Portland, OR	1984	0.006	--	0.002-0.02	--	Ligocki *et al.* 1985
Groundwater	MN	1983	--	--	0.2-144	--	Sabel and Clark 1984
	NJ	1976	--	--	<1,530	--	Burmaster 1982
	NY	1980	--	--	<3,800	--	Burmaster 1982
	PA	1980	--	--	<27,300	--	Burmaster 1982
	AZ		--	--	8.9-29	--	IARC 1995e
	MA	1976	--	--	<900	--	Burmaster 1982
Drinking water	US	1976	--	--	0.2-49	--	IARC 1995e
	US	1977	--	--	0-53	--	IARC 1995e
	US	1978	--	--	0.5-210	--	IARC 1995e
	NJ	1984 -85	23.4	--	maximum 67	1,130	Cohn *et al.* 1994
	CA	1984	--	--	8-12	486	U.S. EPA 1987
	CA	1984	66	--	--	486	U.S. EPA 1987
	NC	1984	5	--	--	48	U.S. EPA 1987
	ND	1984	5	--	--	48	U.S. EPA 1987
	MA		--	--	maximum 267	48	U.S. EPA 1987

Source: Wu and Schaum (2000)

2.6.3 Consumer products

TCE is present in typewriter correction fluids, paint removers, strippers, adhesives, spot removers, and rug-cleaning fluids (Gist and Burg 1995). Uses of TCE as an extraction solvent for cosmetics and drug products and as a dry-cleaning agent have been discontinued (IARC 1995e).

2.6.4 Food

TCE has been found in a variety of foods with the highest levels found in meats, at 12 to16 ppb (0.09 to 0.12 μmol/kg), and U.S. margarine, at 440 to 3,600 ppb (3.35 to 27.4 μmol/kg) (ATSDR 1995). TCE had been used as a solvent for extraction of natural fats and oils, spices, hops, and caffeine (from coffee), but the U.S. Food and Drug Administration (FDA) banned these uses in 1977 (IARC 1995e).

2.7 Occupational exposure

According to the U.S. National Institute for Occupational Safety and Health (NIOSH) National Occupational Exposure Survey (NIOSH 1990), 401,373 employees in 23,225 plants in the United States were potentially exposed to TCE from 1980 to 1983 (Table 2-4).

Table 2-4. Numbers of U.S. workers (total and female) potentially exposed to TCE from 1980 to 1983, by industry

Industry	Plants	Total workers	Female workers
Agricultural services	339	1,695	1,695
General building contractors	661	5,463	3,106
Heavy construction contractors	65	5,420	5,306
Special trade contractors	834	1,879	1,287
Food and kindred products	190	2,062	604
Tobacco manufactures	43	517	-
Textile mill products	214	26,846	21,509
Apparel and other textile products	207	1,226	1,188
Lumber and wood products	505	4,932	1,189
Furniture and fixtures	184	1,352	-
Paper and allied products	167	4,331	1,846
Printing and publishing	2,372	26,317	10,227
Chemicals and allied products	236	10,277	3,151
Petroleum and coal products	256	2,020	-
Rubber and miscellaneous plastic products	862	15,772	2,381
Leather and leather products	33	65	-
Stone, clay, and glass products	275	1,494	1,341
Primary metal industries	379	5,047	417
Fabricated metal products	2,196	49,046	30,065
Machinery, except electrical	1,871	22,210	2,786
Electric and electronic equipment	1,197	97,000	47,714
Transportation equipment	207	9,305	559
Instruments and related products	984	16,293	5,032

Industry	Plants	Total workers	Female workers
Miscellaneous manufacturing industries	803	6,261	2,938
Railroad transportation	22	262	-
Trucking and warehousing	989	5,852	5,072
Transportation by air	481	15,216	3,782
Communication	603	8,776	1,802
Electric, gas, and sanitary services	117	4,336	429
Wholesale trade - durable goods	960	3,735	2,260
Wholesale trade - nondurable goods	352	704	-
Personal services	277	1,044	70
Business services	716	12,973	3,475
Auto repair, services, and garages	1,295	11,197	4,861
Miscellaneous repair services	406	812	-
Health services	569	11,302	9,059
Museums, botanical, zoological gardens	82	1,643	164
TOTAL	23,225	401,373	175,316

Source: National Occupational Survey (NIOSH 1990)

2.8 Regulations and criteria

FDA regulations govern the presence of TCE in color additives, in bottled water, in food as extraction solvent residues and as indirect additives as migrants from adhesives and other materials used in food packaging.

The Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) for time-weighted-average (TWA) exposure to TCE in workroom air in a 40-hour work week is 100 ppm (537 mg/m^3), with a ceiling value of 200 ppm (1,070 mg/m^3) (29 CFR 1910.1000 1996 [CHEMLIST 1997]). The NIOSH considers TCE to be a potential occupational carcinogen, recommending that exposure be limited to the lowest feasible concentration. The NIOSH recommended exposure level (REL) is 2 ppm (11 mg/m^3) during use of TCE as an anesthetic and a 10-hour TWA of 25 ppm (130 mg/m^3) during all other exposures (Ludwig 1994). The threshold limit value (TLV) recommended by the American Conference of Governmental Industrial Hygienists (ACGIH) (1992, 1996) is 50 ppm (269 mg/m^3), and the recommended short-term exposure limit or ceiling is 100 ppm (537 mg/m^3). The ACGIH (1996) classified TCE as A5 (*not suspected as a human carcinogen*).

The U.S. EPA regulates TCE as a hazardous air pollutant under the Clean Air Act (CAA) 1990 Amendments and as a VOC subject to emission standards under CAA Section 111 (40 CFR Part 60 1995) (CHEMLIST 1997).

Under the Safe Drinking Water Act (SDWA), the maximum contaminant level (MCL) for community and nontransient, noncommunity water systems is 0.005 mg/L (40 CFR Part 141 1996) (CHEMLIST 1997). The World Health Organization (WHO) recommended a provisional

guideline value for TCE in drinking water of 0.070 mg/L (WHO 1993). Based on a 1985 study by Buben and O'Flaherty, the WHO (1993) calculated a total daily intake of 0.0238 mg/kg body weight (b.w.) by applying an uncertainty factor of 3,000 to the study's lowest observable adverse effect level of 100 mg/kg b.w. per day when mice were exposed five days a week for six weeks. The observed adverse effects were minor effects on relative liver weight. For derivation of the provisional guidance value of 70 µg/L, 10% of the total daily intake was allocated to drinking water.

TCE is regulated under Resource Conservation and Recovery Act (RCRA) as a halogenated organic compound and under the Land Disposal Restrictions. Under the latter regulation, hazardous wastes that contain total concentrations of halogenated organic compounds of at least 1,000 mg/L (liquids) or 1,000 mg/kg (nonliquids) are prohibited from land disposal. Under 40 CFR 268.40 and 268.48, treatment standards are given for wastewater and non-wastewater extract concentrations, or the applicable Technology Code (40 CFR 268.42) is given (CHEMLIST 1997).

TCE is regulated under Sections 110 and 313 of the Superfund Amendment Reauthorization Act (SARA). Priority data needs that were established under Section 110 include exposure levels in humans living near hazardous waste sites and other populations and epidemiological studies on health effects, including carcinogenicity. Under SARA Section 313, the Emergency Planning and Community Right-to-Know Act, and the TRI, 40 CFR Part 372 Subpart D (1992), TCE is one of the 19 substances for which the *de minimus* for reporting was changed from 1.0% to 0.1%. Under the TRI, since 1989, manufacturers of at least 25,000 lb/yr (11,350 kg/yr) and other handlers of at least 10,000 lb/yr (4,540 kg/yr) must report releases of TCE to any environmental medium. Under 40 CFR Part 302 Table 302.4, TCE is on the Comprehensive Environmental Responsibility Compensation and Liability Act (CERCLA) List of Hazardous Substances, with a reportable quantity (RQ) for releases set at 100 lb (45.4 kg) (CHEMLIST 1997).

TCE is regulated under the Clean Water Act (CWA) Sections 301, 307, and 311 (40 CFR Part 423 1996; 40 CFR Parts 116 and 117 1996). TCE is a priority pollutant in final discharges resulting from steam electric power generation. It is designated a hazardous substance if discharged to navigable waters. The RQ for notification is 100 lb (45.4 kg) (CHEMLIST 1997).

Table 2-5 summarizes EPA regulations that affect TCE. Table 2-6 summarizes FDA regulations. Table 2-7 summarizes OSHA regulations.

Table 2-5. U.S. EPA regulations

EPA Regulations	
Regulatory action	**Effect of regulation and other comments**
40 CFR 60—PART 60—STANDARDS OF PERFORMANCE FOR NEW STATIONARY SOURCES. Promulgated: 48 FR 48335, 10/18/83.	The provisions of this part apply to the owner oroperator of any stationary source that contains an affected facility (a stationary source with an apparatus to which a standard is applicable).
40 CFR 60.480 ff.—Subpart B—Standards of Performance for Equipment Leaks of VOC in the Synthetic Organic Chemicals Manufacturing Industry.	Each owner or operator of facilities producing TCE as an intermediate or final product must demonstrate compliance with the provisions of this subpart.
40 CFR 60.660 ff.—Subpart NNN—Standards of Performance for Volatile Organic Compound (VOC) Emissions from Synthetic Organic Chemical Manufacturing Industry (SOCMI) Distillation Operations. Promulgated: 55 FR 26942, 06/29/90.	This subpart affects distillation units not discharging their vent steams into a recovery system, or a combination of two or more distillation units and a common recovery system into which their vent steams are discharged, which use, contain, or produce TCE. Specific standards, monitoring, and recordkeeping requirements apply.
40 CFR 60.700 ff.—Subpart RRR—Standards of Performance for Volatile Organic Compounds Emissions from Synthetic Organic Chemical Manufacturing Industry (SOCMI) Reactor Processes. Promulgated: 58 FR 45962, 08/31/93.	This subpart affects reactor units not discharging their vent steams into a recovery system, or a combination of two or more reactor units and a common recovery system into which their vent steams are discharged, which use, contain or produce TCE. Specific standards, monitoring, and recordkeeping requirements apply.
40 CFR 61—PART 61—NATIONAL EMISSION STANDARDS FOR HAZARDOUS AIR POLLUTANTS. Promulgated: 38 FR 8826, 04/06/73. U.S. Codes: 42 U.S.C. 7401, 7412, 7414, 7416, 7601.	This part lists substances that, pursuant to section 112 of the CAA, have been designated as hazardous air pollutants, and applies to the owner or operator of any stationary source for which a standard is prescribed under this part. As of 50 FR 52422, 12/23/95, TCE was listed because of the serious health effects, including cancer, from ambient air exposure.
40 CFR 63—PART 63—NATIONAL EMISSION STANDARDS FOR HAZARDOUS AIR POLLUTANTS FOR SOURCE CATEGORIES. Promulgated: 57 FR 61992, 12/29/92. U.S. Codes: 42 U.S.C. 7401 et seq.	Standards that regulate specific categories of stationary sources that emit (or have potential to emit) one or more hazardous air pollutants are listed in this part pursuant to section 112(b) of the CAA.
40 CFR 63.100 ff.—Subpart F—National Emission Standards for Organic Hazardous Air Pollutants From the Synthetic Organic Chemical Manufacturing Industry. Promulgated: 59 FR 19454, 04/22/94.	This subpart applies to chemical manufacturing process units that manufacture TCE and are located at a plant site that is a major source as defined in section112(a) of the CAA. Owners and operators of sources subject to this subpart shall comply with the requirements of subparts G and H of this part.
40 CFR 63.110 ff.—Subpart G—National Emission Standards for Organic Hazardous Air Pollutants From the Synthetic Organic Chemical Manufacturing Industry for Process Vents. Promulgated: 59 FR 19468, 4/22/94.	The provisions of this subpart apply to all process vents, storage vessels, transfer racks, and wastewater streams within a source subject to subpart F of this part. Emission standard: Emissions of TCE shall be controlled to the level represented by a given equation (see 40 CFR 63.112[a]). Specific process vent and methods and procedures provisions apply.

EPA Regulations	
Regulatory action	**Effect of regulation and other comments**
40 CFR 63.460 ff.—Subpart T—National Emission Standards for Halogenated Solvent Cleaning. Promulgated: 59 FR 61805, 12/2/94.	Individual batch vapor, in-line vapor, in-line cold, and batch cold solvent cleaning machines that use TCE alone or in a mixture with other hazardous air pollutants listed in a total concentration greater than 5%. Specific batch cold cleaning, vapor, in-line, and alternative standards and monitoring and recordkeeping requirements apply.
40 CFR 63.680 ff.—Subpart DD—Applicability and designation of affected sources. Promulgated: 61 FR 34158, 07/01/96.	The provisions of this subpart apply to plant sites at which a major source of TCE emissions occurs as defined in 40 CFR 63.2, or at which is located one or more operations that receive offsite materials as specified in 40 CFR 63.680(b).
40 CFR 63.800 ff.—Subpart JJ—National Emission Standards for Wood Furniture Manufacturing Operations. Promulgated: 60 FR 62936, 12/7/95.	The provisions of this subpart apply to each facility that is engaged in the manufacture of wood furniture or wood furniture components and that is a major source as defined in 40 CFR 63.2. TCE is excluded from use in cleaning and washoff solvents.
40 CFR 116—PART 116—DESIGNATION OF HAZARDOUS SUBSTANCES. Promulgated: 43 FR 10474, 03/13/1978. U.S. Codes: 33 U.S.C. 1251 et seq.	This regulation designates TCE as a hazardous substance under section 311(b)(2)(a) of the Federal Water Pollution Control Act (FWPCA). The regulation applies to discharge of the substances identified in table 116.4 to surface waters.
40 CFR 117—PART 117—DETERMINATION OF REPORTABLE QUANTITIES FOR HAZARDOUS SUBSTANCES. Promulgated 44 FR 50776, 08/29/79. U.S. Codes: FWPCA 311(b)(2)(A) and 501(a) as amended by the CWA of 1977.	Discharges to water of amounts equal to or greater than the RQ must be reported to the EPA. The RQ for environmental releases of TCE to water is 100 lb (45.4 kg).
40 CFR 132—PART 132—WATER QUALITY GUIDANCE FOR THE GREAT LAKES SYSTEM. Promulgated: 60 FR 15387, 03/23/95. U.S. Codes: 33 U.S.C. 1251 et seq.	Water criteria for protection of human health are provided. The limits for TCE are 0.29 g/L in drinking water and 0.037 g/L in non-drinking water.
40 CFR 141—PART 141—NATIONAL PRIMARY DRINKING WATER REGULATIONS. Promulgated: 40 FR 59570, 12/24/75. U.S. Codes: Public Health Service Act sections 1413-1416, 1445, and 1450 as amended by 1974 SDWA. U.S.C. 300.	To protect a safe drinking water supply, community and non-transient, non-community water systems must monitor for certain compounds listed.
40 CFR 141 ff.—Subpart D—Reporting, Public Notification and Record keeping. Promulgated: 60 FR 33932, 06/29/95.	The EPA has set forth an enforceable drinking water standard to limit TCE levels to 0.005 ppm to reduce the risk of cancer or other adverse health effects that have been observed in laboratories.
40 CFR 141.50 ff.—Subpart F—Maximum Contaminant Level Goals. Promulgated: 50 FR 46901, 11/13/85, and others.	The maximum contaminant level goal for TCEin primary drinking water is zero.
40 CFR 141.60 ff.—Subpart G—National Revised Primary Drinking Water Regulations: Maximum Contaminant Levels. Promulgated: 52 FR 25716, 07/08/87.	The maximum contaminant levels apply to community water systems and non-transient, non-community water systems based on the best available technology treatment techniques. The MCL for TCE is 0.002 mg/L.

EPA Regulations	
Regulatory action	**Effect of regulation and other comments**
40 CFR 148—PART 148—HAZARDOUS WASTE INJECTION RESTRICTIONS. Promulgated: 53 FR 28154, 06/26/88.	TCE is identified as a hazardous waste to be restricted from EPA Class I hazardous waste injection wells.
40 CFR 257—PART 257—CRITERIA FOR CLASSIFICATION OF SOLID WASTE DISPOSAL FACILITIES AND PRACTICES. Promulgated: 56 FR 51016 10/9/91. U.S. Codes: 42 U.S.C. 6907(a)(3) and 6944(a); 33 U.S.C. 1345(d).	The maximum TCE contaminant level in groundwater for solid waste disposal facilities is 0.005 mg/L. The RQ of TCE is 100 lb (45.4 kg). Label, packaging, and shipping codes also are listed in the Hazardous Materials Table.
40 CFR 258—PART 258—CRITERIA FOR MUNICIPAL SOLID WASTE LANDFILLS. Promulgated: 56 FR 51016, 10/09/91. U.S. Codes: 33 U.S.C. 1345(d) and (e); 42 U.S.C. 6907(a)(3), 6912(a), 6944(a) and 6949a(c).	The provisions of this part establish minimum national criteria under RCRA, as amended, for all municipal solid waste landfill (MSWLF) units and under the CWA, as amended, for MSWLF units that are used to dispose of sewage sludge. The criteria ensure the protection of human health and the environment. The maximum contaminant level for TCE is 0.005 mg/L.
40 CFR 261—PART 261—IDENTIFICATION AND LISTING OF HAZARDOUS WASTES. Appendix VIII—Basis for Listing Hazardous Waste. Promulgated: 45 FR 33119, 05/19/80; 53 FR 13388, 04/22/88. U.S. Codes: 42 U.S.C. 6905, 6912(a), 6921, 6922, and 6938.	Appendix VIII is a consolidated list of hazardous constituents identified in this part. Solid wastes containing these constituents are subject to notification requirements of RCRA section 3010 and must be disposed of in RCRA-permitted facilities. For TCE, the regulatory level is 0.5 mg/L; its hazardous waste number is D040.
40 CFR 264—PART 264—STANDARDS FOR OWNERS AND OPERATORS OF HAZARDOUS WASTE TREATMENT, STORAGE, AND DISPOSAL FACILITIES, Appendix IX. List (Phase 1) of Hazardous Constituents for Ground-Water Monitoring. Promulgated: 45 FR 33221, 05/19/80. U.S. Codes: 42 U.S.C. 6905, 6912(a), 6924, and 6925.	The provisions of this part establish minimum national standards which define the acceptable management of hazardous waste, and apply to owners and operators of all facilities that treat, store, or dispose of hazardous waste; exceptions do exist. TCE has a practical quantitation limit of 1 μg/L.
40 CFR 266—PART 266—STANDARDS FOR THE MANAGEMENT OF SPECIFIC HAZARDOUS WASTES AND SPECIFIC TYPES OF HAZARDOUS WASTE MANAGEMENT FACILITIES. Promulgated: 50 FR 666, 1/4/85. U.S. Codes: 42 U.S.C. 6905, 6912(a), 6924, and 6934.	Standards to control emissions are promulgated for generators, transporters, and users of materials used in a manner that constitutes disposal. Affected compounds are listed in 40 CFR 266.40.
40 CFR 266.100 ff.—Subpart H—Hazardous Waste Burned in Boilers and Industrial Furnaces. Promulgated: 56 FR 7208, 02/21/91.	Hazardous waste burned or processed in a boiler or industrial furnaces is regulated by this subsection to limit release into the environment. The maximum concentration limit for TCE in residues is 0.005 mg/kg. The maximum allowable wastewater concentration is 6.6 ppm, and the maximum allowable concentration in solid waste is 0.05 ppm.
40 CFR 302—PART 302—DESIGNATION, REPORTABLE QUANTITIES, AND NOTIFICATION. Promulgated: 50 FR 13474, 04/04/85. U.S. Codes: 42 U.S.C. 9602, 9603, and 9604; 33 U.S.C. 1321 and 1361.	This part designates under section 102(a) of CERCLA 1980 those substances in the statutes referred to in section 101(14) of CERCLA, identifies reportable quantities for these substances, and sets forth the notification requirements for releases of these substances. This part also sets forth reportable quantities for hazardous substances designated under section 311(b)(2)(A) of the CWA.

EPA Regulations	
Regulatory action	**Effect of regulation and other comments**
40 CFR 302.4—Sec. 302.4 Designation of hazardous substances. Superfund (CERCLA, SARA) reportable quantity (RQ) is 100 lb (45.4 kg).	The EPA designated as hazardous those substances that when released into the environment may present substantial danger to the public health or welfare or the environment. Notification of the EPA is required if the RQ is released to the environment.
40 CFR 372—PART 372—TOXIC CHEMICAL RELEASE REPORTING: COMMUNITY RIGHT-TO-KNOW. Promulgated: 53 FR 4525, 02/16/88. U.S. Codes: 42 U.S.C. 11013, 11028.	This part sets forth requirements for the submission of information relating to the release of toxic chemicals under section 313 of Title III of SARA (1986). Information collected under this part is intended to inform the general public and the communities surrounding covered facilities about releases of toxic chemicals, to assist research, and to aid in the development of regulations, guidelines, and standards. TCE is listed under the specific toxic chemical listings, with 1/1/87 as the effective date for reporting.
40 CFR 401—PART 401—GENERAL PROVISIONS. Promulgated: 39 FR 4532, 02/01/74, as amended at 47 FR 24537, 06/04/82. U.S. Codes: 33 U.S.C. 1251 et seq.	The provisions of this part set forth the legal authority and general definitions that will apply to all regulations issued concerning specific classes and categories of point sources of industrial effluents under parts 402 through 699. TCE is listed as a toxic pollutant.
40 CFR 413—PART 413—ELECTROPLATING POINT SOURCE CATEGORY. Promulgated: 46 FR 9467, 01/28/81. U.S. Codes: 33 U.S.C. 1251 et seq., as amended by the CWA of 1977 (Public Law 95-217).	This part regulates discharge of waste streams from several categories of industrial processes that involve electroplating or electroless plating. The concentration limit of TCE is 0.01 mg/L.
40 CFR 414—PART 414—ORGANIC CHEMICALS, PLASTICS, AND SYNTHETIC FIBERS. Promulgated: 52 FR 42568, 11/5/87. U.S. Codes: 33 U.S.C. 1311, 1314, 1316, 1317, and 1361.	The EPA gives pretreatment standards for existing sources for metals and organics in effluents from several manufacturing categories. Limitations represent the degree of effluent reduction attainable by application of best available technology.
40 CFR 414.91 ff.—Subpart I—Direct Discharge Point Sources That Use End-of-Pipe Biological Treatment.	The effluent limitation for TCE maximum concentrations for any one day is 54 μg/L and for any monthly average is 21 μg/L.
40 CFR 414.101 ff.—Subpart J—Direct Discharge Point Sources That Do Not Use End-of-Pipe Biological Treatment	The effluent limitation for TCE maximum concentrations for any one day is 69 μg/L and for any monthly average is 26 μg/L.
40 CFR 414.110 ff.—Subpart K—Indirect Discharge Point Sources.	The effluent limitation for TCE maximum concentrations for any one day is 69 μg/L and for any monthly average is 26 μg/L.
40 CFR 423—PART 423—STEAM ELECTRIC POWER GENERATING POINT SOURCE CATEGORY. Promulgated: 47 FR 52304, 11/19/82. U.S. Codes: 33 U.S.C. 1311; 1314(b), (c), (e), and (g); 1316(b) and (c); 1317 (b) and (c); and 1361.	The provisions of this part apply to TCE discharges resulting from the operation of a generating unit by an establishment generating electricity for distribution and sale, which results from a process utilizing fossil-type or nuclear fuel in conjunction with a thermal cycle that uses the steam water system as the thermodynamic medium.

EPA Regulations	
Regulatory action	**Effect of regulation and other comments**
40 CFR 433—PART 433— METAL FINISHING POINT SOURCE CATEGORY. Promulgated: 48 FR 32485, 07/15/83. U.S. Codes: 33 U.S.C. 1311, 1314(b)(c), (e), and (g), 1316(b) and (c), 1317(b) and (c), 1318, and 1361.	The provisions of this subpart apply to plants which discharge TCE while performing any of the following six metal finishing operations on any base material: electroplating, electroless plating, anodizing, coating (chromating, phosphating, and coloring), chemical etching and milling, and printed circuit board manufacture.
40 CFR 464—PART 464—METAL MOLDING AND CASTING POINT SOURCE CATEGORY. Promulgated: 50 FR 45247, 10/30/85. U.S. Codes: 33 U.S.C. 1311, 1314(b), (c), (e), and (g), 1316(b) and (c), 1317(b) and (c), 1318, and 1361.	The provisions of subparts A through D apply to metal molding and casting facilities that discharge or may discharge TCE to waters of the United States or that introduce TCE into a publicly owned treatment works (POTW).
40 CFR 467—PART 467—ALUMINUM FORMING POINT SOURCE CATEGORY. Promulgated: 48 FR 49149, 10/24/83. U.S. Codes: 33 U.S.C. 1311, 1314(b), (c), (e), and (g), 1316(b) and (c), 1317(b) and (c), 1318, and 1361.	This part applies to any aluminum forming facility that discharges or may discharge TCE to U.S. waters or that introduces or may introduce TCE into a POTW.
40 CFR 468— PART 468—COPPER FORMING POINT SOURCE CATEGORY. Promulgated: 48 FR 36957,08/15/83. U.S. Codes: 33 U.S.C. 1311, 1314(b), (c), (e), and (g), 1316(b) and (c), 1317(b) and (c), and 1361.	The provisions of this part apply to discharges of TCE resulting from the manufacture of formed copper and copper alloy products.
40 CFR 469—PART 469—ELECTRICAL AND ELECTRONIC COMPONENTS POINT SOURCE CATEGORY. Promulgated: 48 FR 15394, 04/08/83. U.S. Codes: 33 U.S.C. 1311, 1314, 1316, 1317, 1318, and 1361.	The provisions of subparts B through D are applicable to discharges of TCE resulting from the manufacture of electronic crystals, cathode ray tubes, and luminescent materials.

Source: The regulations in this table have been updated through 62 Federal Register 37448, 11 July 1997.

Table 2-6. FDA regulations

FDA regulations	
Regulatory action	**Effect of regulation and other comments**
21 CFR 73—PART 73—LISTING OF COLOR ADDITIVES EXEMPT FROM CERTIFICATION. Promulgated: 42 FR 15643 03/22/77. S. Code: 21 U.S.C. 321, 341, 342, 343, 348, 351, 352, 355, 361, 362, 371, 379e	This part lists color additives that are exempt from certification in foods, drugs, cosmetics, and medical devices.
21 CFR 73.30—Sec. 73.30 Annatto extract.	TCE may be safely used in the color additive Annatto extract, including pigments precipitated therefrom.
21 CFR 103—PART 103—QUALITY STANDARDS FOR FOODS WITH NO IDENTITY STANDARDS. Promulgated: 42 FR 14325 03/15/77. U.S. Code: 21 U.S.C. 321, 341, 343, 348, 349, 371, 379e.	The label of a food is required to state its quality based on, but not limited to, levels of microorganisms and such physical characteristics as turbidity, color, flavor, and odor.
21 CFR 103.35—Sec. 103.35 Bottled Water. Promulgated: 60 FR 57123 11/13/95 [Sec. 103.35 was removed 6/13/96.] U.S. Code: 21 U.S.C. 321, 341, 343, 3348, 349, 371, 379e.	The allowable level for VOC TCE in bottled water is 0.005 mg/L.

FDA regulations	
Regulatory action	**Effect of regulation and other comments**
21 CFR 165.110 ff—Subpart B—Requirements for Specific Standardized Beverages—Bottled water. Promulgated: 60 FR 57124 11/13/95. U.S. Code: 21 U.S.C. 321, 341, 343, 343A, 348, 349, 371, 379e.	The regulations in subparts A and B govern the labeling and effective chemical substance limits for specific standardized beverages. The allowable level for VOC TCE in bottled water is 0.005 mg/L.
21 CFR 172—PART 172—FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION. Promulgated: 42 FR 14491 03/15/77. U.S. Code: 21 U.S.C. 321, 341, 342, 348, 371, 379e.	The regulations in subparts A through I govern the amount of food additives allowed for human consumption.
21 CFR 172.560—Sec. 172.560 Modified hop extract.	The residues of the modified hop extract, manufactured from hops by initial extraction and fractionation, may not contain TCE at more than 150 ppm.
21 CFR 173—PART 173—SECONDARY DIRECT FOOD ADDITIVES PERMITTED IN FOOD FOR HUMAN CONSUMPTION. Promulgated: 42 FR 14526 03/15/77. U.S. Code: 21 U.S.C. 321, 342, 348.	The subparts A through D govern which polymer substances, polymer adjuvants for food treatments, enzyme preparations, microorganisms, solvents, lubricants, release agents, and related substances may be used in food for human consumption.
21 CFR 173.290—Sec. 173.290 TCE.	Tolerances are established for residues of TCE resulting from its use as a solvent in the manufacture of foods: 25 ppm in decaffeinated ground coffee, 10 ppm in decaffeinated soluble (instant) coffee extract, and 30 ppm in spice oleoresins.
21 CFR 175— PART 175—INDIRECT FOOD ADDITIVES: ADHESIVES AND COMPONENTS OF COATINGS. Promulgated: 42 FR 14534 03/15/77. U.S. Code: 21 U.S.C. 321, 342, 348, 379e.	The subparts A through C deal with components of adhesives and of coatings that may migrate into food from packaging.
21 CFR 175.105— Sec. 175.105 Adhesives.	TCE may be safely used in adhesives intended for use as components of articles intended for use in packaging, transporting, or holding food.

Source: The regulations in this table have been updated through 62 Federal Register 37448, 11 July 1997.

Table 2-7. OSHA regulations

OSHA regulations	
Regulatory action	**Effect of regulation and other comments**
1/78. Special Occupational Hazard review of TCE. DHEW Pub. No. (NIOSH) 78-130, NTIS No. PB8-1226987. 3/77. Criteria for a Recommended Standard….Occupational Exposure to Waste Anesthetic Gases and Vapors. Pub. No. 77-140, NTIS No. PB274 238.	TheNIOSH recommends that TCE be treated as a potential occupational carcinogen. Summary of the NIOSH recommendation: recommended exposure limit, 25 ppm TWA; 2 ppm ceiling limit (1 h) as a waste anesthetic gas.
6/6/75. Current Intelligence Bulletin #2—TCE (TCE). In: NIOSH Current Intelligence Bulletin Reprints-Bulletins 1 through 18 (1975-1977). Pub. No. 78-127, NTIS No. PB83-105080.	

OSHA regulations	
Regulatory action	**Effect of regulation and other comments**
1973. Criteria for a Recommended Standard….Occupational Exposure to TCE. DHEW (NIOSH) Pub. No. 73-11025, NTIS No. PB 222 222.	
29 CFR 1910—PART 1910—OCCUPATIONAL SAFETY AND HEALTH STANDARDS. Promulgated: 39 FR 23502, 06/27/74. U.S. Code: 29 U.S.C. 653, 655, and 657.	
29 CFR 1910—Subpart Z—Toxic and Hazardous Substances.	
29 CFR 1910.1000—Sec. 1910.1000 Air contaminants. Promulgated: 58 FR 40191, 07/27/93. U.S. Code: also includes 5 U.S.C. 553.	PEL $\leq$100 ppm (546 mg/m^3) 8-h TWA. Ceiling 2,000 ppm (1,090 mg/m^3)
20 CFR 1926—PART 1926—SAFETY AND HEALTH REGULATIONS FOR CONSTRUCTION. Promulgated: 44 FE 8577, 02/09/79; 44 FR 20940, 04/06/79. U.S. Code: 29 U.S.C. 653, 655, and 657.	
29 CFR 1926—Subpart D—Occupational Health and Environmental Controls.	
29 CFR 1926.55—Sec. 1926.55 Gases, vapors, fumes, dusts and mists. Promulgated: 61 FR 9249, 9250 03/07/96. U.S. Code: 40 U.S.C. 333; 29 U.S.C. 653, 655, and 657.	PEL $\leq$100 ppm (546 mg/m^3) 8-h TWA.

Source: The regulations in this table have been updated through 62 Federal Register 37448, 11 July 1997.

3 Human Cancer Studies

Trichloroethylene is classified by the IARC (1995e) as *probably carcinogenic to humans* (Group 2A) based on sufficient evidence of carcinogenicity in experimental animal and limited evidence of carcinogenicity in humans. A number of TCE studies have been published since the IARC review. These include three major cohort studies (Boice *et al*. 1999, Morgan *et al*. 1998, Ritz 1999), one cohort study update (Blair *et al.* 1998), two kidney cancer case control studies (Dosemeci *et al*. 1999, Vamvakas *et al.* 1998), one melanoma case control study (Fritschi and Siemiatycki 1996), and one case-control study examining cancer at many anatomical sites (Greenland *et al.* 1994). These studies, along with new reviews (Weiss 1996, McLaughlin and Blot 1997, Wartenberg *et al.* 2000) and commentaries (Henschler *et al.* 1995, Bloemen and Tomenson 1995, Swaen 1995, Green and Lash 1999, Vamvakas *et al.* 2000), add greatly to the richness of the data available for evaluation of the carcinogenicity of TCE to humans. Although they are limited by a paucity of directly measured exposures and the generally small numbers of site-specific cancers within studies, these studies overall represent a large and generally consistent body of evidence indicating that TCE is a human carcinogen.

Below is a brief review of the IARC (1995e) findings followed by more detailed evaluations of the most recent studies.

3.1 IARC evaluation

The IARC (1995e) considered case reports, descriptive studies, cohort studies, case-control studies, and drinking-water studies in its comprehensive assessment and review of the possible carcinogenicity of TCE to humans. The case reports and descriptive studies discuss individuals exposed to TCE and other solvents who subsequently developed cancer. Given the number and quality of cohort and case-control studies, the case reports and descriptive studies did not play an important role in the IARC evaluation.

To conduct its assessment, the IARC divided the cohort studies into three occupational groups: (1) dry cleaners, (2) workers who had undergone biological monitoring for exposure to TCE, and (3) workers employed in miscellaneous manufacturing industries.

The cohort studies of dry cleaners were considered least important. These workers likely had only limited exposure to TCE because it was used mainly for spot removal. They also had exposure to other solvents, particularly tetrachloroethylene (also known as perchloroethylene, or PERC), another suspected carcinogen, making chemical-specific inferences difficult.

Two cohort studies evaluated TCE exposure by biological monitoring of urine samples. Axelson *et al.* (1994) followed Swedish workers in a TCE production facility for 32 years. Overall cancer incidence and mortality were not unusual (standardized incidence and mortality ratios [SIRS and SMRs] both were1.0). However, for men only, there was a statistically significant excess of skin cancer (SIR = 2.4, 95% CI 1.0 to 4.7; n = 8) and non-significant excesses of non-Hodgkin's lymphoma (SIR = 1.6, 95% CI 0.5 to 3.6; n = 5) and liver and biliary cancer (SIR = 1.4, 95% CI 0.4 to 3.6;n = 4). In addition, an exposure-response relationship was seen for all cancers combined. The other biomonitoring study (Anttila *et al.* 1995) measured Finnish workers' exposure to three halogenated hydrocarbons (TCE, PERC, and 1,1,1 trichloroethane) and had a

26-year follow-up period. Among those exposed to TCE, there was a slight overall excess incidence of cancer (SIR = 1.1, 95% CI 0.9 to1.2; n = 208); a significant excess of cervical cancer (SIR = 2.4, 95% CI 1.1 to 4.8; n = 8), particularly among those more highly exposed (SIR = 4.4, 95% CI 1.4 to10.0; n = 5); a non-significant excess of liver cancer (SIR = 2.3, 95% CI 0.7 to 5.3; n = 5), particularly among those more highly exposed (SIR = 2.7, 95% CI 0.3 to 9.9; n = 2); and a non-significant excess of non-Hodgkin's lymphoma (SIR = 1.8, 95% CI 0.8 to 3.6; n = 8).

Among the manufacturing studies reviewed by the IARC, one large study looked at aircraft manufacturing (Garabrant *et al.* 1988), another at aircraft maintenance workers (Spirtas *et al.* 1991), and another at cardboard manufacturing plant workers (Henschler *et al.* 1995a). In all of these studies, exposure to TCE was principally from its use as a degreasing agent. In Garabrant *et al.* (1988), only one-third of the jobs involved TCE exposure and individual workers could not be classified as exposed or not. The overall mortality rate was less than expected (SMR = 0.8, 95% CI 0.7 to 0.8; n = 1,804), as was the cancer mortality rate (SMR = 0.8, 95% CI 0.8 to 0.9; n = 453). None of the SMRs for the individual cancer sites were significantly elevated. In Spirtas *et al.* (1991) the highest excess cancer mortalities were observed for liver and biliary, bone, and cervical cancer and non-Hodgkin's lymphoma. The results of this study were updated with longer follow-up by Blair *et al.* (1998, see Section 3.2). Henschler *et al.* (1995), in a relatively small study, identified exposed (n = 169) and unexposed (n = 190) workers from a single factory and developed 34 years of follow-up data. Exposure of the workers was believed to be particularly high as TCE was kept in open barrels and used biweekly to soak rags for cleaning machinery. There were anecdotal reports of acute TCE toxicity among workers. Henschler *et al.* (1995) reported four incident cases of renal-cell carcinoma and one of renal pelvic cancer among the exposed (SIR = 8.0, 95% CI 2.6 to18.6; n = 5). No renal-cell or renal pelvic cancer was observed among the unexposed. Concerns were raised about this study because it was conducted in response to an apparent cancer cluster and because cases identified by abdominal sonography of the entire workforce were compared with registry cases identified by more traditional diagnostic procedures (IARC 1995e, Swaen 1995, Bloemen and Tomenson 1995, Henschler *et al.* 1995). Other manufacturing studies were considered less important.

The IARC reviewed case-control studies of liver cancer, lymphoma, Hodgkin's disease, renal-cell carcinoma, colon cancer, brain tumors, childhood leukemia, and childhood brain tumors, as well as one multisite study. These studies were limited because they generally did not provide TCE-specific risk estimates. Nonetheless, most of these studies showed excess cancer at the same anatomical sites as the cohort studies.

Several cross-sectional studies of TCE-contaminated drinking water also were considered. In each of these, however, exposure was not well quantified, was to several contaminants simultaneously, and was at the community level rather than that of the individual. Two studies showed a weak association between contamination and the incidence of leukemia, and two showed a marginal increase in non-Hodgkin's lymphoma associated with contamination.

In its summary, the IARC pooled data from the cohort studies of Axelson *et al.* (1994), Anttila *et al.* (1995) and Spirtas *et al.* (1991) and reported excess liver and biliary cancer (23 observed, 12.87 expected) and non-Hodgkin's lymphoma (27 observed, 18.9 expected). It also reported a doubled incidence of cervical cancer based on two of these studies.

3.2 Recent cohort studies

Blair *et al.* (1998) extended the follow-up of the Spirtas *et al.* (1991) study of 14,457 aircraft maintenance workers to include an additional eight years (1982 to 1990). The main solvent used was TCE, but several other solvents also were used. TCE was used in bench-top work until 1968 and for vapor degreasing until 1978. Mortality patterns were largely unchanged with the additional follow-up, showing excesses for liver, kidney, bone, breast, cervical, colon, and esophageal cancer and non-Hodgkin's lymphoma and multiple myeloma. There were differences among males and females, and no clear exposure-response patterns were identified. Incidence data were reported for four exposure levels, rather than summarized overall. At the highest exposure level, excess mortality was observed for liver cancer, colon cancer, kidney cancer, and multiple myeloma in men and for kidney cancer in women. Workers with exposure to solvents other than TCE often had relative risks as high as those reported for TCE-exposed workers, particularly for non-Hodgkin's lymphoma, multiple myeloma, and female breast cancer, complicating interpretation. Information on lifestyle factors (e.g., tobacco and alcohol use and diet) and nonoccupational exposures was not available. However, smoking was unlikely to have been a confounder, because it is not known to be associated with most of the cancers found in excess, and two of the three cancers typically associated with smoking (lung and bladder) were not found in excess. Alcohol use and diet were possible but unlikely confounders for the effects reported.

Morgan *et al.* (1998) updated the work of Wong and Morgan (1990) on the mortality experience of 20,508 workers at a Hughes Aircraft manufacturing facility. TCE was used in vapor degreasing units. To categorize exposure, workers employed for at least 30 years were asked to rank the TCE exposure in each job classification. These rankings were combined by industrial hygienists into a four-category exposure scale. The highest exposure category was thought to correspond to a TCE level of about 50 ppm. In the TCE-exposed subcohort, small excesses in mortality were reported for kidney, bladder, ovary, and prostate cancers. The SMRs for these sites in the total cohort were lower. In an analysis by low or high cumulative TCE exposure using a Cox proportional hazards model, the relative risk for each of these four cancers increased with higher exposure. This study was limited by small numbers of cases and lack of direct exposure measurements, information on other occupational or nonoccupational exposures, or lifestyle factors.

Boice *et al.* (1999) studied another cohort of aircraft manufacturing workers, 77,965 employees of Lockheed Martin working at six separate facilities. Exposures included TCE, chromate, PERC, and other solvents. Subjects were enrolled in the study if they were working in 1960. TCE was replaced by PERC in 1966. Exposure assessment was conducted through the development of a job exposure matrix based on "walk throughs" of comparable facilities, interviews with longtime employees, industrial hygiene files, and job descriptions. Exposures were classified as not likely, intermittent, or routine for each of TCE, PERC, chromate, and mixed solvents. Duration of employment also was assessed. Elevated mortality rates were reported for non-Hodgkin's lymphoma, Hodgkin's disease, and cancers of connective tissue, stomach, rectum, and breast. No sites investigated for exposure-response patterns showed significantly positive effects. Results for workers exposed to TCE (but not PERC), PERC (but not TCE), both, or neither (but to other solvents) were not reported, but were said to show the same patterns as the results reported. This common response to all solvents makes it more difficult to infer exposure-specific causation from this study.

Ritz (1999) conducted a study of 3,814 uranium processing workers employed at the Fernald Feed Materials Production Center, using the Comprehensive Epidemiology Data Resource, a public-access database maintained by the U.S. Department of Energy. Exposure was assessed through the development of a job exposure matrix based on ratings provided by a panel of plant experts who had been employed for at least 20 years. Workers were classified into one of four exposure levels. Mortality was evaluated from these data and data on duration of employment. For internal comparisons only, adjustments were made for ionizing radiation dose. External comparisons were made with national, rather than regional, mortality data. Data available for a small subset of workers (those hired after 1967) showed that cigarette smoking rates among workers were less than those for the U.S. population and were not associated with chemical exposures. Thus, smoking was unlikely to have been a confounder. Salary status (hourly vs. salaried) was available as a crude measure of socioeconomic status. Many workers had joint low-level exposures to the three agents assessed (TCE, cutting fluids, and kerosene). Workers also were exposed to respiratory irritants. Moderate cutting fluid exposure always occurred with moderate TCE exposure. No workers had high TCE exposure. At sites for which TCE exposure effects were assessed, mortality rates were elevated for hematopoietic and lymphopoietic, liver, and brain cancer at both low and moderate exposure levels. No brain cancer excess was seen when the data were adjusted for cutting-fluid exposure. Liver cancer showed a strong exposure-response relationship and increased with exposure duration. Mortality rates for esophagus, stomach, liver, pancreas, prostate, brain, and lymphopoietic cancer and Hodgkin's disease were elevated for all workers, compared with U.S. rates.

3.3 Recent case-control studies

Vamvakas *et al.* (1998) conducted a hospital-based case-control study of renal-cell carcinoma. They selected 58 patients with renal-cell carcinoma diagnosed from December 1987 to May 1992 (79% of those identified) and 84 accident patients treated in 1993 from three hospitals within 20 miles of the hospital from which the cancer cases were drawn (75% of those identified). There was no matching, and the cancer patients were older, heavier, and more hypertensive than the controls. Fewer cancer patients smoked, and more took diuretics and did so for longer periods. This disparity in subject selection may have led to control selection bias, although it is not clear whether the differences were related to TCE exposure. The primary exposure to TCE was through metal degreasing. Exposure assessment was through an unblinded interview with a single physician (occasionally assisted). Specific exposure to any of a variety of chemicals was documented with a specially designed questionnaire. Each subject was assigned to one of three exposure classes based on a cumulative exposure calculation.

The authors suggested that exposure was higher than in most previous studies. An elevated odds ratio was reported for any exposure to TCE, adjusted for age, gender, smoking, body mass index, blood pressure, and intake of diuretics. In an analysis stratified by age, the odds ratio also was elevated in each 10-year age stratum, and the age-specific odds ratios were homogeneous ($P = 0.7$). There was a marginally significant exposure-response relationship. Green and Lash (1999) criticized the Vamvakas *et al.* (1998) study, citing possible selection bias and suggesting that the controls had less opportunity for high TCE exposure because they were younger and were selected later. They further argued that the study was suspect because the risk was so large (and greater than in previous studies). Vamvakas *et al.* (2000) countered that selection bias was unlikely, noting that exposure was higher than in many other studies, and cited supporting experimental data showing an association between TCE exposure and renal-cell carcinoma.

Dosemeci *et al.* (1999) evaluated the risk of renal-cell carcinoma among men and women exposed to organic solvents in a population-based case-control study in Minnesota (Chow *et al.* 1994). Cases were excluded if they failed to complete an interview or died (to avoid use of next-of-kin interviews); as a result, only 55% of originally identified cases were included in the analysis. In contrast, 97% of controls were included, raising concerns about possible selection bias. Exposure assessment was conducted through the use of a job exposure matrix developed through extensive work at the National Cancer Institute (Dosemeci *et al.* 1994, Gomez *et al.* 1994). An elevated odds ratio was found for all subjects together; it was statistically significant for women but not men. As noted by Dosemeci *et al.* (1999), this gender difference was seen in several previous studies. Results were adjusted for age, smoking, hypertension status, use of diuretics and anti-hypertension drugs, and body mass index; however, concerns about other occupational and nonoccupational exposures and lifestyle differences remain.

As part of a large case-control study of cancer at 19 anatomical sites (Siemiatycki 1991), Fritschi and Siemiatycki (1996) evaluated the risk of melanoma by comparing 103 newly diagnosed men in Montreal, Canada, aged 35 to 70 (83% response rate) with two control groups, one population-based (randomly selected from electoral lists and random-digit dialing, n = 533) and one of other cancer patients from their larger study (n = 533). Data collected by questionnaire included age, ethnicity, residence for the first 15 years of life, height, weight, education, income, and recent hobbies. A semistructured, probing interview was used to elicit detailed job history information, which a team of chemists and industrial hygienists later transformed into potential exposures to specific substances. Melanoma patients were younger, had higher incomes, and were better educated than controls. They participated in more outdoor sports and did more gardening. Adjustment for age, ethnicity, and years of education controlled for all of the measured confounders. Significantly elevated odds ratios were reported for insubstantial, substantial, and any exposure to TCE, based on comparison with a pooled control group of 1,066 subjects. Although the authors had information on many confounding variables, these data were highly correlated and thus difficult to assess individually for the small number of cases observed. Notably missing was information on exposure to the sun, complexion, and number of nevi observed.

Greenland *et al.* (1994) studied a cohort of white male workers at a General Electric transformer assembly plant in Massachusetts. A series of nested case-control analyses were conducted comparing 512 cancer deaths (from disease at a variety of anatomical sites) and 1,202 noncancer deaths. Workers were included if they were employed before 1985, died between 1969 and 1984, had their death reported to and recorded by the company pension office, and had a useable job history record. Information from 18 long-term, knowledgeable employees and industrial hygienists was used to select seven substances for job exposure ratings. A job exposure matrix was developed and combined with data on job title, department, and building to assign each worker to one of four exposure categories. For TCE, these were later reduced to two categories, exposed or unexposed. No statistically significant odds ratios were reported, but odds ratios were elevated for pancreatic cancer (OR = 1.6, 95% CI 0.8 to 3.3; n = 33) and oral, pharyngeal, and laryngeal cancer (OR = 1.3, 95% CI 0.5 to 3.1; n = 21). Odds ratios for esophageal, stomach, colon, rectum, liver and biliary, lung, prostate, bladder, kidney, and brain cancer, lymphoma, and leukemia all were < 1.2. Limitations of the study included selection bias, exposure misclassification, loss to follow-up, and uncontrolled confounding.

3.4 Reviews

As noted above, the IARC (1995e) reviewed the carcinogenicity of TCE. Its summary focused on three cohort studies (Axelson *et al.* 1994, Anttila *et al.* 1995, Spirtas *et al.* 1991), noting limitations of the exposure assessments and the likelihood of uncontrolled confounding. Nonetheless, the findings were summarized as showing 23 cases of liver and biliary cancer where 12.87 were expected, 27 cases of non-Hodgkin's lymphoma where 18.9 were expected, and a doubled risk of cervical cancer. The risk of kidney cancer was not elevated except in the study of Henschler *et al*. (1995), but this result was considered less relevant, because the study was initiated in response to observation of a cancer cluster. The risk for bladder cancer was not increased in the two Scandinavian cohort studies, but was elevated in the two U.S. cohort studies. Generally, case-control studies did not add substantially to this assessment, but were consistent with the findings of the cohort studies. A weak association was reported between TCE in groundwater and leukemia incidence, as well as a marginal increase in the incidence of non-Hodgkin's lymphoma. The two most important findings were considered to be elevated risks of liver and biliary cancer and of non-Hodgkin's lymphoma.

Weiss (1996), in assessing the carcinogenicity of TCE, reviewed the three cohort studies emphasized by the IARC (1995), along with an unpublished study of Hughes Aircraft workers (Wong and Morgan 1990) and several case-control studies. Liver cancer showed a small excess in all four cohort studies (16 cases where 9.5 were expected). Although biliary cancer was reported in only two of the four studies, they showed a doubling of risk (12 cases where 6.2 were expected). The risk of Hodgkin's disease was not elevated, but the risk of non-Hodgkin's lymphoma showed an exposure-response relationship, and the elevated risk was supported by a case-control study (Hardell *et al.* 1981). Weiss reported that the cohort studies did not show excess bladder or kidney cancer, overall. He noted the excess of these cancers reported by Henschler *et al.* (1995), but questioned its relevance because this study appeared to have been initiated in response to a cluster report. He reported no excess of oral, esophageal, colon, rectal, or pancreatic cancer, but one case-control study showed an association of TCE exposure with colon cancer (Fredriksson *et al.* 1989). No evidence of excess lung or brain cancer was found, although the incidence of prostate cancer was slightly elevated. Weiss concluded that the only plausible excesses suggested by the data were for liver cancer, biliary tract and kidney cancer, and non-Hodgkin's lymphoma. He argued that the absence of excess lung cancer in these studies, in contrast to the animal studies, was attributable to biological differences. Overall, he viewed the data as weak, because of the rarity of disease, the relatively small relative risks, and the lack of clear exposure-response patterns.

McLaughlin and Blot (1997) reviewed the possible association between TCE or PERC exposure and renal-cell cancer. They noted that known risk factors included cigarette smoking, high body weight, analgesic and diuretic use, high blood pressure, and, perhaps, a high-protein diet. They reviewed the same five cohort studies emphasized by the IARC (1995e) and Weiss (1996), plus studies by Garabrant *et al.* (1988) and Shindell and Ulrich (1985). In the latter study, McLaughlin and Blot (1997) inferred the absence of excess kidney cancer, even though it was not reported specifically, because both observed total cancer and observed nonrespiratory cancer were much lower than expected. They were critical of the Henschler study because it appeared to have been initiated in response to a cluster observation and because of methodological concerns, including the use of different diagnostic procedures with exposed and unexposed individuals. In summarizing this set of cohort studies, they noted that only Henschler *et al.* (1995) showed an

association between TCE and kidney cancer risk. They noted that Spirtas *et al.* (1991) was the most informative study, because of good exposure assessment and statistical power and long-term follow-up, and that it showed virtually no excess in cancer mortality.

McLaughlin and Blot (1997) also reviewed six case-control studies of kidney cancer (Asal *et al.* 1988, Harrington *et al.* 1989, Sharpe *et al.* 1989, Partanen *et al.* 1991, Siemiatycki 1991, Greenland *et al.* 1994). They reported that although these studies addressed solvent exposures, exposure to TCE was unlikely in some of the studies. Two studies showed elevated odds ratios, but McLaughlin and Blot (1997) argued that these studies provided little support for a causal association. They concluded that there was "no credible evidence of an association between risk of renal-cell cancer and TCE". An important limitation of this review was that the authors failed to distinguish between males and females or incidence and mortality in their evaluations.

A review by Wartenberg *et al.* (2000) added to previous reviews by including updates of two of the major cohorts (Blair *et al.* 1998, Morgan *et al.* 1998), two new cohort studies (Boice *et al.* 1999, Ritz 1999), and several new case-control studies. Several of these showed positive results for some anatomical sites. Wartenberg *et al.* (2000) divided the cohort studies into three tiers: Tier I, in which TCE exposure was inferred for individual study subjects and was best characterized; Tier II, in which there was putative TCE exposure, but it was less well characterized; and Tier III, studies of dry cleaners and laundry workers. Cohort results for both incidence and mortality were tabulated for each cancer site reported and were summarized as an average relative risk. Some of the averages were calculated on sets of studies that were heterogeneous as assessed by the Q statistic (e.g., kidney cancer, $P < 0.01$), but it was beyond the scope of the review to address possible explanations for that heterogeneity. Case-control studies were tabulated for kidney cancer, liver cancer, and lymphoma (both Hodgkin's disease and non-Hodgkin's lymphoma). Community-based (groundwater) studies also were reviewed.

The Tier I studies (10 articles representing seven cohorts) showed elevated average relative risks (RR > 1.2) for incidence of the following cancers:

- cervical cancer (RR = 2.4, 95% CI 1.2 to 4.8; n = 8)
- skin cancer (RR = 2.4, 95% CI 1.2 to 4.7; n = 8)
- liver cancer (RR = 1.9, 95% CI 1.0 to 3.4; n = 12)
- kidney cancer (RR = 1.7, 95% CI 1.1 to 2.7; n = 21)
- rectal cancer (RR = 1.7, 95% CI 1.0 to 3.0; n = 12)
- non-Hodgkin's lymphoma (RR = 1.5, 95% CI 0.9 to 2.3; n = 22)
- Hodgkin's disease (RR = 1.5, 95% CI 0.6 to 3.7; n = 4)
- multiple myeloma (RR = 1.5, 95% CI 0.7 to 3.3; n = 10)
- lymphohematopoietic cancer (RR = 1.4, 95% CI 1.0 to 2.0; n = 40)
- larynx cancer (RR = 1.4, 95% CI 0.4 to 5.0; n = 2)
- prostate cancer (RR = 1.3, 95% CI 1.0 to 1.6; n = 95)

The Tier I studies showed elevated average relative risks for mortality for the following cancers:

- Hodgkin's disease (RR = 2.0, 95% CI 1.1 to 3.4; n = 16)

- multiple myeloma (RR = 1.9, 95% CI 1.0 to 3.7; n = 18)
- cervical cancer (RR = 1.8, 95% CI 0.5 to 6.5; n = 5)
- liver cancer (RR = 1.7, 95% CI 0.2 = 16.2; n = 4)

In addition, the relative risk of kidney cancer mortality was slightly elevated (RR = 1.2).

Although incidence data for Tier II studies were relatively sparse, one study (Sinks *et al.* 1992), initiated in response to a cluster report, showed a large excess of kidney cancer (RR = 3.7, 95% CI 1.7 to 8.1; n = 6). Among the Tier II studies, the only average relative risks for mortality > 1.2 were for liver cancer (RR = 2.0, 95% CI 1.3 to 3.3; n = 15) and kidney cancer (RR = 1.3, 95% CI 0.9 to 1.7; n = 41). The liver cancer mortality studies were heterogeneous, but the kidney cancer mortality studies were not. Tier III studies were more difficult to interpret, as exposure to TCE was not well characterized. The case-control studies were plagued by poor exposure characterization. Nonetheless, several showed results supporting the cohort studies (kidney, Dosemeci *et al.* 1999, Sinks *et al.* 1992, Vamvakas *et al.* 1998; non-Hodgkin's lymphoma, Hardell *et al.* 1981, 1984, Persson *et al.* 1989). The community-based studies also were difficult to interpret, because the exposure was not specific to the individual and generally was to several solvents and contaminants simultaneously. Nonetheless, elevated risks were reported for leukemia, non-Hodgkin's lymphoma, multiple myeloma, and bladder cancer.

Wartenberg *et al.* (2000) summarized their view as consistent with that of the IARC (1995e) and Weiss (1996), but they argued that the evidence more strongly suggested an association of TCE exposure with liver and kidney cancer and provided some support for associations with non-Hodgkin's lymphoma and Hodgkin's disease. Further, they argued that there was some evidence for association of TCE exposure with cervical cancer and possibly with multiple myeloma and prostate, laryngeal, and colon cancer.

3.5 Discussion

There is a large body of evidence assessing the possible carcinogenicity of TCE in humans. These studies were conducted in a variety of countries and in many different types of workplaces. Overall, the cohort studies showed some consistency in the reporting of elevated rates of both incidence and mortality, particularly for liver cancer, kidney cancer, non-Hodgkin's lymphoma, multiple myeloma, and prostate cancer. Sparser data showed elevated risks for esophageal, cervical, pancreatic, laryngeal, and colon cancer and Hodgkin's disease.

A strength of the cohort studies, in general, was their size and long follow-up periods. The seven best-characterized cohort studies included over 120,000 workers and followed them for an average of over 30 years. However, a limitation of these studies was the small number of site-specific cancers observed. For example, for the sites of greatest concern—liver and biliary cancer, kidney cancer, non-Hodgkin's lymphoma, Hodgkin's disease, and cervical cancer—the reported incidences were 12, 21, 22, 4, and 8, respectively, and the reported deaths were 33, 37, 56, 16, and 5. (The deficit in cases relative to deaths existed because most studies reported mortality only.) An additional strength of the cohort studies was that two of the four most recent studies used state death certificates as the comparison population, rather than national death certificates, removing some of the concern about regional variation in mortality rates.

Another strength of the cohort studies was the extensive work done to characterize exposures. Two studies measured exposures, although not on a repeated basis. In other studies, exposures were inferred from interviews with longtime employees, industrial hygiene assessments, and occasional area monitors. The use of job exposure matrices, particularly when supplemented with facility-specific information, has been shown to provide moderately good exposure classification relative to classification by exposure measured with passive dosimeters (Tielemans *et al*. 1999). However, this approach makes comparison across studies difficult. More comprehensive exposure measurement schemes could be designed, but they would be expensive to implement. Because most analyses condensed the exposure classifications into two groups, exposure misclassification would most likely bias results towards the null. In addition, some of the studies reported results for entire cohorts even though only a portion of the cohort was exposed to TCE, which likely resulted in underestimation of the actual risks of disease.

A related issue is that most exposures, despite being occupational, were relatively low, limiting the sensitivity of the studies. In addition, TCE use was phased out of many of the workplaces between 1960 and 1980. For such workplaces, cumulative exposure would depend on jobs held, date of first employment, and duration of employment. In studies with later start dates (e.g., Boice *et al.* 1999 started enrollment nearly 10 years later than the other recent cohort studies), workers likely had lower cumulative exposures; however, this cannot be assessed from the published information.

A complication in interpreting the results based on external comparison populations is that there was a moderate “healthy worker” effect in most of these studies. That is, total SMRs and total cancer SMRs tended to be < 1.0, often around 0.8. Use of these levels as baselines for comparisons would result in null to slightly elevated SMRs for specific cancer sites among exposed workers in studies where risk actually was elevated over that for similar non-exposed working populations. However, the latter comparison typically was not made. Internal comparisons would provide better exposure-specific evaluations.

Finally, confounding is a concern for all epidemiologic studies. The absence of data on personal characteristics (such as hypertension and high body weight), lifestyle factors (such as tobacco use, alcohol consumption, and diet), and nonoccupational exposures (such as residential exposures and hobbies) makes confounding difficult to assess. However, for confounding to be a major concern, the factors would have had to be associated with both exposure and disease. Such associations are unlikely but cannot be ruled out, because no data were presented to allow direct evaluation of confounding.

The case-control studies are of limited use, as most did not report TCE-specific risks. However, those that did generally supported the findings of the cohort studies. A concern about the studies discussed in detail above is the possibility of control selection bias, as there were documented differences between the cases and controls; however, the studies did not directly assess the likelihood of bias. The community-based studies were even more difficult to interpret, because they lacked quantitative chemical-specific exposure information for individuals.

3.6 Summary

The number and sophistication of studies assessing the possible carcinogenicity of TCE is impressive. Although the studies are not perfectly consistent, strong patterns emerge. In

particular, associations with TCE exposure generally were observed for kidney cancer, liver cancer, non-Hodgkin's lymphoma, multiple myeloma, and prostate cancer. Particular aspects of design or implementation may limit the usefulness or interpretation of individual studies, but, by and large, these studies were well designed and executed. Viewed from the perspective of Hill's aspects of causation (Hill 1965), several of the criteria are fulfilled. Moderately strong associations were observed for some outcomes, with limited positive biological gradient (exposure-response) data. TCE was not specific as evidenced by the multiple cancers observed. However, the results did show temporality (at least in the cohort studies), coherence, and were supported by animal studies. Based on Hill's aspects, there are strong data supporting a causal relationship between TCE exposure and human cancer.

Table 3-1. Recent cohort studies (including all SMRs or RRs > 1.2 and based on more than one death)

Reference	Study design	Population	Exposure	Effects	Potential confounders
Blair *et al.* 1998 U.S.	historical cohort	14,457 aircraft maintenance workers employed ≥ 1 yr between 1952 and 1956 and followed through 1990. Comparison population was unexposed workers for incidence analyses and Utah death certificates for mortality analyses.	Exposure was assessed with a job exposure matrix based on industrial hygiene walk throughs, interviews, historical records, monitoring data, job descriptions, and two surveys of vapor degreasers (Stewart *et al.* 1991). Each job was scored on exposure intensity, frequency, and duration. Exposures were to multiple solvents, although TCE was the main solvent used historically, through 1978.	Workers exposed to TCE showed nonsignificant mortality excesses for esophageal cancer (RR = 5.6, 95% CI 0.7–44.5; n = 10), bone cancer (RR = 2.1, 95% CI 0.2–18.8; n = 5), non-Hodgkin's lymphoma (RR = 2.0, 95% CI 0.9–4.6; n = 28), cervical cancer (RR = 1.8, 95% CI 0.5–6.5; n = 5), breast cancer (RR = 1.8, 95% CI 0.9–3.3; n = 20), kidney cancer (RR = 1.6, 95% CI 0.5–5.1; n = 15), buccal cavity or pharyngeal cancer (RR = 1.4, 95% CI 0.4–5.2; n = 9), colon cancer (RR = 1.4, 95% CI 0.8–2.4; n = 54), Hodgkin's disease (RR = 1.4, 95% CI 0.2–12.0; n = 5), liver and biliary cancer (RR = 1.3, 95% CI = 0.5–3.4; n = 15), multiple myeloma (RR = 1.3, 95% CI 0.5–3.4; n = 14), pancreatic cancer (RR = 1.2, 95% CI 0.6–2.3; n = 33), and bladder cancer (RR = 1.2, 95% CI 0.5–2.9; n = 17). Dose-response assessments were inconclusive.	Exposures to solvents were not mutually exclusive, making attribution to a single agent difficult. Information on lifestyle factors and non-occupational exposures was not available.

Reference	Study design	Population	Exposure	Effects	Potential confounders
Morgan *et al.* 1998 U.S.	historical cohort	20,508 aircraft manufacturing employees employed ≥ 6 mo between 1950 and 1985 and followed through 1993, of whom 4,733 were TCE-exposed. For internal cohort analyses, the comparison population was the unexposed workers. For overall SMRs, comparison population was the U.S.	Exposure was assessed with a job exposure matrix based on exposure ranking provided by workers employed for 30 or more years	Elevated mortality rates among those exposed to TCE were found for cancer of the bladder (SMR = 1.4, 95% CI 0.6–2.7; n = 8), kidney (SMR = 1.3, 95% CI 0.6–2.6; n = 8), ovary (SMR = 1.2, 95% CI 0.5–2.4; n = 8), and prostate (SMR = 1.2, 95% CI 0.7–1.8; n = 21).	There was no discussion of other occupational exposure, including exposure to other solvents. Information on lifestyle factors and non occupational exposure was not available.
Boice *et al.* 1999 U.S.	historical cohort	77,965 aircraft manufacturing employees employed ≥ 1 yr in or after 1960 and followed through 1996. Comparison population was the California population.	Exposure was assessed with a job exposure matrix based on walk throughs of comparable facilities, interviews of longtime employees, industrial hygiene files, and job descriptions. TCE was used through 1966.	Elevated mortality rates were reported for Hodgkin's disease (SMR = 2.8, 95% CI 0.8–7.1; n = 4); cancer of the connective tissue (SMR = 1.9, 95% CI 0.4–5.7; n = 3), stomach (SMR = 1.3, 95% CI 0.8–2.1; n = 17), breast (SMR = 1.3, 95% CI 0.5–2.7; n = 7), and rectum (SMR = 1.3, 95% CI 0.6–2.5; n = 9); and non-Hodgkin's lymphoma (SMR = 1.2, 95% CI 0.7–2.0; n = 14)	Exposures to solvents were not mutually exclusive, making attribution to a single agent difficult. Information on lifestyle factors and other occupational and non-occupational exposure was not available.

Reference	Study design	Population	Exposure	Effects	Potential confounders
Ritz (1999) U.S.	historical cohort	3,814 uranium processing workers employed ≥ 3 mo between 1951 and 1972 and followed through 1991. For internal cohort analyses, comparison population was the unexposed workers. For overall SMRs, comparison population was the U.S.	Exposure was assessed with a job exposure matrix based on ratings provided by a panel of plant experts who had been employed at least 20 yr.	For exposure duration > 5 yr and an exposure lag of 15 yr, elevated mortality rates were reported for brain cancer (RR = 5.4, 95% CI 0.9–33.9; n = 3), liver cancer (RR = 2.9, 95% CI 0.5–17.3; n = 3), and hematopoietic and lymphopoietic cancer (RR = 1.8, 95% CI 0.8–4.1; n = 12).	Limited data were available to assess the effects of smoking. Salary status (hourly vs. salaried) could be used as a crude measure of socioeconomic status. For internal comparisons, adjustments were made for ionizing radiation dose. Many TCE exposures were confounded by exposure to cutting fluid, kerosene, and respiratory irritants.

Table 3-2. Recent case-control studies

Reference	Study design	Population	Exposure	Effects	Potential confounders
Vamvakas *et al.* 1998. Germany	case-control	58 cases of renal-cell carcinoma diagnosed in a hospital between 12/1/87 and 5/31/92 and 84 accident patients from three nearby hospitals.	Exposure assessment was by unblinded interview using a questionnaire.	OR for renal-cell carcinoma was elevated (OR = 10.8, 95% CI 3.4–34.8; n = 19). The effect increased with exposure intensity.	There are concerns about selection bias, other occupational and non-occupational exposure, and lifestyle factors (other than smoking).
Dosemeci *et al.* 1999 U.S.	case-control	438 cases of renal-cell carcinoma identified through the Minnesota Cancer Surveillance System and 687 age- and gender-stratified controls identified through random-digit dialing (ages 20–64) or the Health Care Financing Administration (ages 65 and over).	Exposure assessment was based on an extensive job exposure matrix developed previously at the NCI and on reported work histories.	OR for renal-cell carcinoma was elevated for all subjects (OR = 1.3, 95% CI 0.9–1.9; n = 55) and was statistically significant for women (OR = 2.0, 95% CI 1.0–4.0; n = 22), but not for men.	Possible selection bias (55% of originally identified cases and 97% of controls were included). Data on other occupational and nonoccupational exposure and lifestyle factors (except smoking) were not available.
Fritschi and Siemiatycki (1996) Canada	case-control	103 newly diagnosed cases of melanoma among men aged 35–70 and two sets of controls: 533 population-based randomly selected controls and 533 cancer controls.	A structured questionnaire was used for general demographic and risk-factor information, followed by a semistructured, probing interview for detailed information about all jobs. These data were translated into a list of potential exposures to several substances.	OR for melanoma was significantly elevated for any exposure to TCE (OR = 3.6, 95% CI 1.5–9.1; n = 8).	This study had extensive confounder information but no data on exposure to the sun, complexion, or number of nevi.

Reference	Study design	Population	Exposure	Effects	Potential confounders
Greenland *et al.* 1994 U.S.	nested case-control	512 cancer deaths as cases (at a variety of anatomical sites) and 1,202 noncancer deaths as controls, all white males employed at a transformer production facility before 1985 and deceased between 1969 and 1984.	Exposure was assessed with a job exposure matrix based on job title, department, and building. Based on information from 18 longtime, knowledgeable employees and industrial hygienists, exposure to seven substances was characterized.	No elevated ORs were statistically significant, but elevated ORs were reported for pancreatic cancer (OR = 1.6, 95% CI 0.8–3.3, n = 33) and oral, pharyngeal, and laryngeal cancer (OR = 1.3, 95% CI 0.5–3.1; n = 21).	Exposures to substances other than TCE were not mutually exclusive, making attribution to a single agent difficult. Information on lifestyle factors and other occupational and nonoccupational exposure was not available.

4 Studies of Cancer in Experimental Animals

4.1 Experimental carcinogenesis

The carcinogenicity of TCE was investigated by the National Cancer Institute (NCI 1976) and the NTP (1988, 1990). These and a few other studies conducted before 1995 were reviewed by the IARC (1995e, pp. 105-109; see Appendix A). More recent experimental carcinogenicity studies were not located. The principal findings of the carcinogenicity studies are summarized below. Based on the studies reviewed, the IARC (1995e) concluded that there was sufficient evidence of carcinogenesis in experimental animals for TCE.

4.1.1 Gavage studies

The NCI (1976) tested industrial grade (> 99% pure; containing 0.19% epoxybutane and 0.09% epichlorohydrin) TCE in Osborne-Mendel rats and B6C3F_1 mice. Groups of 50 animals of each species and sex were tested at the maximum tolerated dose (MTD) and one half the MTD. Twenty animals of each species and sex were used as controls. Carbon tetrachloride was used as a positive control. Rats were exposed to time-weighted average doses of 549 and 1,097 mg/kg, male mice were exposed to 1,169 and 2,339 mg/kg, and female mice were exposed to 869 and 1,739 mg/kg. All animals were exposed by oral gavage five days/week for 78 weeks. Animals were observed until terminal sacrifice at 110 weeks for rats and 90 weeks for mice.

Mortality in treated and control rats was high with only 3/20, 8/50, and 3/50 male rats and 8/20, 13/48, 13/50 female rats surviving in the control, low-dose, and high-dose group, respectively. No significant differences in tumor incidence were observed in rats. However, there was a highly significant, dose-related increase in hepatocellular carcinomas in both male and female mice (Table 4-1).

Table 4-1. Summary of tumors and their incidences in B6C3F$_1$ mice administered TCE by gavage for two years

Mouse sex/tumor type	TCE gavage doses			
	Colony controls	Vehicle control	869 mg/kg (female) 1,169 mg/kg (male)	1,739 mg/kg (female) 2,339 mg/kg (male)
	Survival adjusted tumor incidence/Number examined			
Males				
Liver				
Hepatocellular carcinoma	5/77	1/20	26/50**	31/48**
Forestomach papilloma	0/77	0/20	0/50	1/48
Females				
Liver				
Hepatocellular carcinoma	1/80	0/20	4/50	11/47**

Source: NCI 1976.

**P ≤ 0.01, statistically different from vehicle controls based on the survival-adjusted Cox and Tarone test.

The NTP (1988) conducted a two-year carcinogenicity study to compare the differences in sensitivity to TCE administered by gavage among four strains of rats (ACI, August, Marshall, and Osborne-Mendel). TCE, stabilized with diisopropylamine (8 ppm) and containing no epichlorohydrin, was administered in corn oil five days per week at concentrations of 500 or 1,000 mg/kg for 103 weeks. Both sexes of all four rat strains were observed to be susceptible to the nephrotoxic effects of TCE. Tubular cell cytomegaly and toxic nephropathy occurred in 82% to 100% and 17% to 80% of the treated animals, respectively. These effects were not observed in controls. However, the NTP concluded that this study was inadequate because of chemically induced toxicity, reduced survival, and incomplete data documentation. Despite these limitations, the incidence of renal tubular-cell adenoma was significantly increased in male Osborne-Mendel rats, and interstitial-cell neoplasms of the testis were observed in Marshall rats. No statistically significant increases in tumors of any type were observed in ACI or August rats; however, interstitial cell tumors of the testis occurred with a positive trend in ACI rats. The tumor data for male and female Osborne-Mendel and Marshall rats are summarized in Table 4-2.

Table 4-2. Tumor incidences in Osborne-Mendel and Marshall rats administered TCE by gavage for two years

Rat strain/tumor type	TCE gavage doses			
	Untreated controls	Vehicle control	500 mg/kg	1,000 mg/kg
	Tumor response/Number examined			
Osborne-Mendel				
Kidney tubular cell adenoma				
Males	0/50	0/50	6/50**	1/50
Females	1/50	0/50	0/50	1/49
Marshall				
Kidney tubular cell adenoma				
Males	2/49	0/49	1/50	0/47
Females	1/49	1/50	1/48	0/44
Testicular tumors				
Interstitial cell tumor	16/46	17/46	21/48	31/48**
Interstitial cell tumor or malignant interstitial cell tumor	16/46	17/46	21/48	32/48**

Source: NTP 1988.

**P ≤ 0.01, statistically different from vehicle controls based on the survival adjusted incidental tumor test

Subsequently, the NTP (1990) evaluated the carcinogenicity of epichlorohydrin-free TCE administered by gavage to F344/N rats and B6C3F_1 mice (Appendix B). Survival of treated male rats and male mice was significantly reduced compared to vehicle controls in these experiments. Male F344/N rats exposed to TCE had an increased incidence of renal tubular-cell neoplasms at the high dose and mesotheliomas at the low dose (Table 4-3); however, these results were considered inadequate for evaluating the presence or absence of a carcinogenic response because of poor survival. TCE was not carcinogenic in female rats. TCE was carcinogenic in B6C3F_1 mice, inducing a significant increase in the incidence of hepatocellular carcinomas and adenomas in both sexes; and malignant lymphoma, lymphoma or leukemia, and alveolar or bronchiolar adenoma in females. However, the increased incidence of malignant lymphoma, lymphoma or leukemia, and alveolar or bronchiolar adenoma were not considered to be related to TCE exposure for several reasons. The incidence of malignant lymphoma and leukemia were within the historical control ranges and the combined incidence of alveolar or bronchiolar adenoma and carcinoma was not significant. Primary tumor data for mice are summarized in Table 4-4.

Table 4-3. Primary tumor incidences in male F344/N rats administered TCE by gavage for two years

Tumor type	TCE gavage doses			
	Untreated controls	Vehicle control	500 mg/kg	1,000 mg/kg
	Tumor response/Number examined			
Males				
Kidney				
Tubular cell adenocarcinoma	0/49	0/48	0/49	3/49*
Tubular cell adenoma or carcinoma	0/49	0/48	2/49	3/49*
Peritoneum				
Malignant mesothelioma	1/50	1/50	5/50**	0/49
All mesothelioma	1/50	1/50	5/50**	1/49

Source: NTP 1990

*P ≤ 0.05, statistically different from vehicle controls by the incidental tumor test.

**P ≤ 0.05, statistically different from vehicle controls by life table analysis (not significant by incidental tumor test).

Table 4-4. Primary tumor incidences in B6C3F$_1$ mice administered TCE by gavage for two years

Tumor type	TCE gavage doses	
	Vehicle control	1,000 mg/kg/day
	Tumor response/Number examined	
Males		
Liver		
Adenoma	7/48	14/50**
Carcinoma	8/48	31/50**
Adenoma or carcinoma	14/48	39/50**
Females		
Lungs		
Alveolar or bronchiolar adenoma	0/48	4/48*[a]
Adenoma or carcinoma	1/48	4/48
Hemapoietic system		
All malignant lymphoma	7/48	13/49* [a]
Lymphoma or leukemia	7/48	14/49* [a]
Liver		
Adenoma	4/48	16/49**
Carcinoma	2/48	13/49**
Adenoma or carcinoma	6/48	22/49**

Source: NTP 1990

*P ≤ 0.05, statistically different from vehicle controls by life table analysis.

**P ≤ 0.01, statistically different from vehicle controls by life table analysis.

[a] Results were not significant based on the incidental tumor test.

The IARC (1995e) reviewed two other studies where TCE was administered by gavage. Van Duuren *et al.* (1979) administered 0.5 mg TCE once per week for 74 weeks to 30 male and female ICR:Ha Swiss mice. Forestomach tumors were not increased compared to vehicle controls. Tumor data for other sites were not reported. Maltoni *et al.* (1986) administered 50 or 250 mg/kg TCE four to five days per week for 52 weeks to groups of 30 male and female Sprague-Dawley rats. A nonsignificant increase in leukemias was observed in the male rats.

4.1.2 Inhalation studies

The IARC (1995e) reviewed several inhalation studies and noted that TCE induced an increased incidence of lymphomas in female NMRI mice (Henschler *et al.* 1980), liver tumors in male Swiss mice (Maltoni *et al.* 1986, 1988), and lung tumors in female ICR, male Swiss, and female $B6C3F_1$ mice (Fukuda *et al.* 1983, Maltoni *et al.* 1986, 1988). Henschler *et al.* (1980) did not find an increase in tumors in groups of 30 male and female Wistar rats or Syrian hamsters exposed 6 hours/day, five days/week for 18 months to air containing TCE at 100 or 500 ppm. Sprague-Dawley rats exposed to air containing TCE at concentrations of 50 to 450 ppm did not show an increased incidence of tumors (Fukuda *et al.* 1983). Inhalation exposure to TCE was carcinogenic to Sprague-Dawley rats, inducing dose-related Leydig cell tumors of the testis (23.8% at 3,240 mg/m^3), renal tubular adenocarcinoma (3.1% at 3,240 mg/m^3) and cytokaryomegaly (77.7% at 3,240 mg/m^3) in male rats (Maltoni *et al.* 1986, 1988).

4.2 Summary

Exposure to TCE resulted in tumors at multiple sites (liver, kidney, lung, testis, and hematopoietic system) in experimental animals depending of the species, strain, sex, and route of administration. TCE administerd by gavage produced liver tumors in both sexes of mice ($B6C3F_1$) but not in rats and kidney tumors in male rats (Osborne-Mendal and F344/N) but not in mice. Other tumors produced by gavage administration included testicular tumors in Marshall rats and mesotheliomas (low dose) in male F344/N rats. Inhalation exposure to TCE induced lung tumors in male Swiss and female ICR and $B6C3F_1$ mice but not in rats or hamsters. Other tumors observed from inhalation of TCE included lymphomas in female NMRI mice, liver tumors in male Swiss mice, and testicular and kidney tumors in Sprague-Dawley rats.

5 Genotoxicity

5.1 Genotoxicity studies reviewed in IARC (1995e)

Genotoxicity studies reported before 1995 were reviewed by the IARC (1995e, pp. 122-133; see Appendix A). In general, TCE was not genotoxic in a broad range of bacterial, lower eukaryotic, and *in vitro* and *in vivo* mammalian cell assays. It has been suggested that the few positive responses observed could have been due to impurities in TCE and/or the presence of potentially mutagenic stabilizers (Goeptar *et al.* 1995). The following is summarized from IARC (1995e).

In prokaryotic systems, pure TCE usually did not induce gene mutations or DNA damage, whereas TCE preparations containing epoxide stabilizers were mutagenic. In lower eukaryotic systems, TCE did not induce gene conversion or reverse mutations in *Saccharomyces cerevisiae* (with or without metabolic activation), forward mutations in *Schizosaccharomyces pombe* (with or without metabolic activation), mitotic crossing over in *Aspergillus nidulans* (without metabolic activation), or sex-linked recessive lethal mutations in *Drosophila melanogaster* exposed via injection. TCE induced forward mutations in *A. nidulans* (without metabolic activation) and gave equivocal results for sex-linked recessive lethal mutations in *D. melanogaster* exposed via feed.

In *in vitro* studies with mammalian cells, TCE did not induce unscheduled DNA synthesis (UDS) in primary rat hepatocytes, gene mutations in human lymphoblastoid cells (with or without metabolic activation), chromosomal aberrations in Chinese hamster ovary (CHO) cells (with or without metabolic activation), or inhibition of intercellular communication in rat hepatocytes. In contrast, TCE gave positive results *in vitro* for covalent binding to calf thymus and salmon sperm DNA (with metabolic activation only) and primary mouse and rat hepatocyte DNA, sister chromatid exchanges (SCE) in CHO cells (with or without metabolic activation), gene mutations in mouse lymphoma cells (with metabolic activation only), inhibition of intercellular communication in primary mouse hepatocytes, and morphological transformation in rat embryo cells.

In vivo, TCE administered orally or by intraperitoneal (i.p.) injection gave equivocal results for covalent binding to mouse and rat liver DNA and negative results for binding to mouse spleen, pancreas, lung, testis, kidney, or brain DNA. When administered orally or by inhalation, TCE did not induce UDS in mouse hepatocytes, SCE in mouse splenocytes or rat lymphocytes, dominant lethal mutations in mice, or chromosomal aberrations in mouse splenocytes or rat lymphocytes. TCE did not induce micronuclei in mouse bone marrow when administered i.p. or in mouse splenocytes, mouse spermatocytes, or rat lymphocytes when administered by inhalation. TCE gave both negative and positive results for DNA single-strand breaks or alkali-labile sites in mouse liver (administered i.p. or orally) and positive results for micronucleated polychromatic erythrocytes in mice exposed orally and in rats exposed by inhalation.

Genotoxic effects in occupationally exposed humans were evaluated in several studies. TCE exposure did not increase the frequency of sperm-head abnormalities. One study evaluating the frequency of SCE in mitogen-stimulated lymphocytes reported no

increase, whereas a second study reported an increase among TCE-exposed smokers but not among nonsmokers. Two studies detected a significant increase in chromosomal damage in mitogen-stimulated lymphocytes.

5.2 Genotoxicity studies published after the IARC (1995e) review

The mutagenicity of TCE and its metabolites chloral hydrate (CH), dichloroacetic acid (DCA), trichloroacetic acid (TCA) trichloroethanol, S-(1,2-dichlorovinyl)-1-cysteine (DCVC), and S-(1,2-dichlorovinyl) glutathione (DCVG) was recently reviewed by Moore and Harrington-Brock (2000). These researchers concluded that TCE and its metabolites CH, DCA, and TCA are unlikely to induce tumors in humans because very high doses are required for genotoxicity. There was not enough information to assess the mutagenicity of trichloroethanol and the two TCE conjugates, DCVC and DCVG; although, there was some evidence that DCVC is a more potent mutagen than CH, DCA, or TCA (see Section 5.4 for discussion of genotoxicity studies of TCE metabolites).

TCE did not induce mitotic recombination (as measured by the eye mosaic test) in *D. melanogaster* exposed via inhalation (Vogel and Nivard 1993), chromosomal aberrations in Chinese hamster lung cells (with or without metabolic activation) (Matsuoka *et al.* 1996), or UDS in hepatocytes of $B6C3F_1$ mice exposed orally (Miyagawa *et al.* 1995).

The ability of TCE to modulate DNA methylation and the expression of immediate-early protooncogenes was evaluated by Tao *et al.* (1999). Female $B6C3F_1$ mice were administered TCE by gavage (1000 mg/kg TCE) five days per week. The mice were sacrificed after 5, 12, or 33 days of administration. TCE decreased methylation both of the total DNA and the promoters for c-*jun* and c-*myc* genes and increased the expression of their mRNA.

TCE's ability to induce gene mutations and small deletions was tested in *lac*Z transgenic mice. Male and female mice were exposed by inhalation to 0; 203; 1,153; and 3,141 ppm TCE, six hours per day for 12 days. Animals were sacrificed 14 and 60 days following last exposure and the mutation frequency in bone marrow, spleen, kidney, liver, lung, and testicular germ cells determined. The researchers observed that TCE did not induce base-change or small-deletion mutations in any of the tissues examined (Douglas *et al.* 1999).

These studies are summarized in greater detail in Table 5-1.

Table 5-1. Genotoxic effect of TCE in recent studies[a]

System	Effect	Metabolic Activation	Form and purity	Exposure level	Response (+/-) activation	Comments	Reference
Lower eukaryotes							
Drosophila melanogaster strain C-1	mitotic recombination (eye mosaic assay)	NA	NG	280 to 4000 ppm via inhalation for 17 h	negative	genetic principle involves loss of heterozygosity for the wild type and white-eye color gene resulting from mitotic recombination between two X chromosomes	Vogel and Nivard 1993
Mammalian systems *in vitro*							
Chinese hamster lung cell line CHL/Ius	chromosomal aberrations	-/+	NG	0.33, 0.66, and 1.31 mg/mL for 6, 24, and 48 h -S9 and 6 h +S9	negative/ negative	no increase in chromosomal aberrations at any exposure period with or without S9	Matsuoka *et al.* 1996
Mammalian systems *in vivo*							
$B6C3F_1$ mouse hepatocytes	UDS	NA	NG	600 and 1200 mg/kg (single gavage treatment)	negative	hepatocytes were collected 24, 39, and 48 h after treatment and exposed to [^{3}H]thymidine for 4 h	Miyagawa *et al.* 1995
*Lac*Z transgenic mice (male and female)	base-change and small-deletion mutation	NA	NG	0, 203, 1153, 3141 mg/kg (inhalation)	negative	mutation frequency in bone marrow, kidney spleen, liver, lung, and testicular germ cells determined	Douglas *et al.* 1999
$B6C3F_1$ mice (female)	DNA modulation and expression of immediate-early protooncogenes	NA	NG	1000 mg/kg by gavage five days/week	positive	TCE decreased methylation of DNA and the promoters for *c-jun* and *c-myc* genes and increased the expression of their mRNA	Tao *et al.* 1999

[a] NA = not applicable; NG = not given; UDS = unscheduled DNA synthesis

5.3 Genotoxicity studies of structural analogues

A knowledge-based structure-activity approach (MULTICASE) was used to examine the structural basis for, among other things, the induction of aneuploidy in *A. nidulans* by chlorinated alkanes and alkenes (Rosenkranz and Klopman 1996). Data on induction of aneuploidy by 35 chlorinated alkanes or alkenes came from Crebelli *et al.* (1992, cited in Rosenkranz and Klopman 1996). Compared with inactive compounds, compounds inducing aneuploidy had significantly higher water solubilities (1.157 vs. 0.764, $P = 0.02$) and significantly lower octanol-water partition coefficient values (log P = 1.988 vs. 2.424, $P = 0.009$). Nine structural fragments were found to correlate with the ability to induce aneuploidy in 11 of 12 chemicals. One of these fragments, Cl-CH=C-Cl, is found in TCE.

5.3.1 Vinyl chloride

Green (1990) observed that vinyl chloride's wide range of effects in many species was characteristic of a genotoxic carcinogen. As reviewed in IARC (1979), vinyl chloride induced UDS in primary rat hepatocytes, gene mutation in cultured Chinese hamster lung cells, gene conversion in yeast, and DNA damage and mutation in bacteria. It also induced sex-linked recessive lethal mutation in *D. melanogaster* and was mutagenic in plants and *S. pombe* (but not other fungi). In mice and rats exposed *in vivo*, vinyl chloride induced chromosomal aberrations, SCE, and micronuclei in bone marrow cells and alkylated DNA in various tissues. Workers exposed to vinyl chloride vapor showed induction of chromosomal aberrations in peripheral blood lymphocytes. Two additional studies of exposed workers indicated negative results for SCE, while one study indicated a weakly positive response. Green (1990) suggested that vinyl chloride's carcinogenic activity resulted from its metabolism by microsomal mixed-function oxidases to chloro-oxirane (chloroethylene oxide) and chloroacetaldehyde, two mutagenic metabolites, and concluded that vinyl chloride was a classical genotoxin causing cancer by somatic mutation.

5.3.2 Vinylidene chloride

As reviewed in the IARC (1987b), vinylidene chloride was mutagenic in plant cells and bacteria and induced mutation and gene conversion in yeast. Although it was not mutagenic or clastogenic in cultured Chinese hamster lung cells, it did induce UDS in primary rat hepatocytes. *In vivo*, vinylidene chloride did not induce dominant lethal mutations in mice or rats or chromosomal aberrations in bone marrow cells of rats, but did induce UDS in mice.

5.3.3 Tetrachloroethylene

Tetrachloroethylene has generally given negative results in most genetic toxicology assays (IARC 1995c). Tetrachloroethylene was not active in the SOS chromotest with *Escherichia coli* and was not mutagenic in bacteria in the absence of metabolic activation. Purified tetrachloroethylene was not mutagenic in *Salmonella typhimurium* or *E. coli* in the presence of rat liver S9. However, purified tetrachloroethylene was mutagenic in *S. typhimurium* TA100 in the presence of rat liver glutathione *S*-transferase, glutathione, and rat kidney microsomes (Vamvakas *et al.* 1989). In stationary-phase

yeast, it did not induce gene conversion, mitotic recombination, or reverse mutation, but conflicting data were obtained for cells in logarithmic growth.

Tetrachloroethylene did not induce sex-linked recessive lethal mutation in *D. melanogaster*, UDS in rat primary hepatocytes, chromosomal aberrations or SCE in cultured Chinese hamster lung cells (with or without metabolic activation), or mutation in mouse lymphoma cells (with or without metabolic activation). However, DNA binding of radioactively labeled tetrachloroethylene to calf thymus DNA *in vitro* in the presence of metabolic activation and to DNA and proteins of mouse and rat liver, kidney, and stomach *in vivo* were reported. Tetrachloroethylene also induced cell transformation in Fischer rat embryo cells but not in mouse BALB/c-3T3 cells. In *in vivo* studies, the frequencies of gene conversion and reverse mutation were not increased in a host-mediated assay using yeast recovered from the liver, lungs, and kidneys of mice treated with tetrachloroethylene. Exposure to tetrachloroethylene significantly increased DNA damage (strand breaks or alkali-labile sites) in mouse liver and kidney, but not lung.

The IARC (1995c) noted that two studies of workers occupationally exposed to tetrachloroethylene reported small increases in peripheral lymphocytes showing numerical chromosome abnormalities (Ikeda *et al.* 1980) and SCE frequency in subjects who smoked (Seiji *et al*. 1990). Neither study controlled for the possible confounding effects of smoking.

5.4 Genotoxicity studies of metabolites

5.4.1 Chloral hydrate

Chloral hydrate has been extensively evaluated for its ability to induce aneuploidy in various test systems (IARC 1995a). It induced aneuploidy in the absence of metabolic activation in fungi, human lymphocytes *in vitro*, secondary spermatocytes of mice exposed *in vivo* (in three of four studies), and bone marrow cells of mice exposed *in vivo*. Chloral hydrate significantly increased the frequency of micronuclei in Chinese hamster cell lines and human lymphocytes *in vitro* and in bone marrow erythrocytes (in two of four studies) and spermatids (in two of three studies) of mice exposed *in vivo*. Where evaluated, the micronuclei most frequently were induced by numerical rather than structural chromosomal damage.

The IARC (1995a) noted conflicting results for DNA damage by chloral hydrate. It was mutagenic, with or without metabolic activation, in *S. typhimurium* TA100 (two of four studies) and in TA104 (one study) but not in TA1535, TA1538, or TA98. It gave negative results for mitotic crossing over in *A. nidulans* in the absence of metabolic activation, but weakly positive results for meiotic recombination and gene conversion (but not reverse mutation) in *S. cerevisiae* in the presence and absence of metabolic activation, respectively. It induced somatic mutation in *D. melanogaster*, but not DNA-protein cross-links in rat liver nuclei or DNA single-strand breaks or alkali-labile sites in primary rat hepatocytes. Chloral hydrate was a weak inducer of SCE in cultured human lymphocytes. *In vivo*, it induced mitotic gene conversion in a host-mediated assay with *S. cerevisiae* recovered from mouse lungs. One laboratory reported a significant increase in strand breaks in liver DNA of exposed rats and mice, whereas another laboratory reported

negative results. Chloral hydrate did not induce chromosomal aberrations in mouse bone marrow cells, spermatogonia, spermatocytes, or oocytes. However, one study reported a significant increase in chromosomal aberrations in mouse secondary spermatocytes. CH induced mutations at the Tk locus in a mouse lymphoma assay (Harrington-Brock *et al.* 1998, cited in Moore and Harrington-Brock 2000). The predominantly small colony Tk mutants indicated that most CH-induced mutants resulted from chromosomal mutations rather than point mutations.

5.4.2 Dichloroacetic acid

The results for genetic toxicity of DCA in prokaryotic and animal cells are inconsistent (IARC 1995b). In *S. typhimurium*, DCA did not induce differential toxicity in DNA-repair-deficient strains but was mutagenic. DCA did not induce λ prophage in *E. coli*, nor did it induce DNA strand breaks in cultured human CCRF-CEM cells (without metabolic activation) or in mouse or rat hepatic cells. *In vivo*, acute administration of DCA induced DNA strand breaks in liver cells of rats and mice in one laboratory, but another laboratory using higher doses reported no DNA strand breakage in rat or mouse hepatic cells after single or repeated administrations, or in epithelial cells from mouse spleen, stomach, and duodenum after a single administration.

5.4.3 Trichloroacetic acid

As reviewed in IARC (1995d), TCA was not mutagenic to *S. typhimurium*, nor did it induce λ prophage in *E. coli*, with or without metabolic activation. TCA, neutralized to avoid the effects of low pH, was not clastogenic in cultured human lymphocytes. TCA did not induce DNA strand breaks in cultured or human CCRF-CEM cells (without metabolic activation) or in mouse or rat hepatic cells. *In vivo*, TCA administered acutely induced DNA strand breaks in liver cells of rats and mice in one laboratory, but another laboratory using higher doses reported no increase in DNA strand breaks in rat or mouse hepatic cells or in mouse epithelial cells from the stomach or duodenum. TCA injected into Swiss mice induced abnormal sperm morphology and micronuclei and chromosomal aberrations in bone marrow cells, but in C57BL/JfBL/Alpk mice, TCA did not induce micronuclei at a 10-fold higher dose.

5.4.4 Trichloroethanol

Trichloroethanol was found to be negative in the *Salmonella* assays (DeMarini *et al.* 1994, cited in Moore and Harrington-Brock 2000). It has not been evaluated by other assays.

5.4.5 Trichloroethylene conjugates (DCVC and DCVG)

Both DCVC and DCVG are capable of inducing point mutations as evidenced by their mutagenicity in bacteria (Vamvakas *et al.* 1988 and DeMarini *et al.* 1994, cited in Moore and Harrington-Brock 2000). DCVC and DCVG were found to be mutagenic based on *Salmonella* assays. There is some indication that DCVC can induce primary DNA damage in mammalian cells *in vitro* and *in vivo* (Jaffe *et al.* 1985 and Vamvakas *et al.* 1989, cited in Moore and Harrington-Brock 2000). DNA damage in kidney tubules was induced *in vivo* and *in vitro* by DCVC, and double-strand breaks were found in LLC-PK_1

cells (Jaffe *et al.* 1985, Vamvakas *et al.* 1992, both cited in Vamvakas *et al.* 1993). Addition of radiolabeled cysteine conjugates to bacterial and renal cells resulted in covalent binding to DNA (Bhattacharya and Schultze, 1972, 1973a,b, Vamvakas *et al.* 1988, both cited in Vamvakas *et al.* 1993). Pyridine nucleotide oxidation was induced by DCVC incubated with kidney mitochondria (Meadows *et al.* 1988, Vamvakas *et al.* 1992, both cited in Vamvakas *et al.* 1993). Vamvakas and Koster (1993, cited in Moore and Harrington-Brock 2000) observed that DCVC can induce the expression of two protooncogenes, c-*fos* and c-*myc*, but their involvement in tumor induction is unknown.

5.5 Summary

The available data indicate that TCE and its metabolites are not potent genotoxic chemicals. Most studies, in a broad range of test systems, were negative or equivocal. In general, high doses were required to induce a positive response. TCE did not induce gene mutations in human cells and studies of chromosomal aberrations, aneuploidy, and SCE in peripheral lymphocytes of workers exposed to TCE were considered inconclusive. Limited data for DCVC and DCVG indicate that these metabolites can induce point mutations and that DCVC may induce DNA damage in mammalian cells; however, the relevance to human tumors is uncertain.

6 Other Relevant Data

6.1 Absorption, distribution, metabolism, and excretion

Sex-, species-, and strain-dependent differences in absorption, distribution, metabolism, and excretion of TCE are important for understanding differences in susceptibility and in determining which metabolites are associated with toxicity. TCE in vapor or liquid form is readily absorbed through the lungs and gastrointestinal tract and distributed throughout the body via the circulatory system. Because the blood/gas partition coefficient is about 1.5 to 2.5 times lower in humans than in rats and mice, absorption and distribution of inhaled TCE is not as efficient in humans as in rodents. Dermal absorption of the vapor is negligible; however, significant dermal absorption may occur following direct skin contact with the liquid or with aqueous solutions of TCE (Lash *et al.* 2000a). Several studies in rats and mice reviewed by the IARC (1995e) showed rapid absorption of TCE through the lungs and from the gastrointestinal tract (IARC 1995e). Mean blood TCE concentrations after four hours of exposure to TCE in air were 35.5 µg/mL (0.27 µmol/mL) in male Fischer 344 rats exposed at a concentration of 529 ppm (2,840 mg/m^3, 21.6 mmol/m^3) and 25.8 µg/mL (0.196 µmol/mL) in females exposed at 600 ppm (3,220 mg/m^3, 24.5 mmol/m^3) (Fisher *et al.* 1991). Male and female B6C3F$_1$ mice were exposed for four hours to TCE at concentrations of 110 to 748 ppm (591 to 4,020 mg/m^3, 4.50 to 30.6 mmol/m^3) and 42 to 889 ppm (226 to 4,780 mg/m^3, 1.72 to 36.4 mmol/m^3), respectively. The highest mean blood concentration in males was 7.3 µg/mL (0.056 µmol/mL) after exposure at 748 ppm (4,020 mg/m^3, 30.6 mmol/m^3) and in females was 6.3 µg/mL (0.048 µmol/mL) after exposure at 368 ppm (1,980 mg/m^3, 15.1 mmol/m^3) (Fisher *et al.* 1991).

Following absorption, TCE is distributed to three major compartmental tissue groups: richly perfused tissues (e.g., liver, kidneys, lungs), poorly perfused tissues (e.g., muscle, skin), and adipose tissue (Lash *et al.* 2000a). Mice given 280 mg/kg b.w. (2.13 mmol/kg) of radiolabeled TCE in a 10-minute inhalation exposure were studied by whole body autoradiography (Bergman 1983). TCE was found throughout the body in well-perfused organs; redistribution to adipose tissue occurred after 30 minutes. With an oil-water partition coefficient of 900:1, TCE is concentrated in lipophilic organs such as liver or brain (Müller *et al.* 1975, Kilburn and Warshaw 1993, both cited in Gist and Burg 1995). Other tissues in which TCE concentrates are ovaries (Manson *et al.* 1984, cited in Gist and Burg 1995) and spermatocytes (Land *et al.* 1979, cited in Gist and Burg 1995).

The amount of TCE available for conversion to toxic metabolites is determined largely by blood flow and metabolic rate. TCE is metabolized via two major pathways: oxidation by cytochrome P-450 and conjugation with glutathione (Byington and Leibman 1965, Leibman 1965, Dekant *et al.* 1986, 1990, Commandeur and Vermeulen 1990, Goeptar *et al.* 1995, all cited in Bernauer *et al.* 1996; Lash *et al.* 2000a) (see Figure 6-1). Chloral hydrate, dichloroacetic acid (DCA), and trichloroacetic acid (TCA) are the metabolites most often associated with liver and lung damage whereas 1,2-dichlorovinylcysteine (DCVC), a metabolite produced through a glutathione pathway has been associated with kidney toxicity (Clewell *et al.* 2000, Lash *et al.* 2000a). The data indicate that mice

metabolize and eliminate TCE faster than rats. This is consistent with the observation that mice are more susceptible than rats to liver injury and carcinogenesis (Lash *et al.* 2000a).

More than 99% of urinary TCE metabolites stem from reactions catalyzed by cytochrome P-450 (Dekant *et al.* 1984,). One such reaction is the oxidation of TCE to chloral, which may proceed through rearrangement of the putative epoxide intermediate 1,1,2-trichlorooxirane (Powell 1945, Bonse *et al.* 1975, both cited in Vamvakas *et al.* 1993), or by rearrangement of a non-epoxide intermediate (Miller and Guengerich, 1982, cited in Vamvakas *et al.* 1993). Upon contact with aqueous solutions, chloral is rapidly converted to its hydrate (IARC, 1995a). Reduction of chloral hydrate yields trichloroethanol and trichloroethanol glucuronide while oxidation results in TCA (Butler 1949, Daniel 1963, Kimmerle and Eben 1973). TCA glucuronide has been found in the urine of non-human primates administered TCE by intramuscular injection (Müller *et al.* 1982).

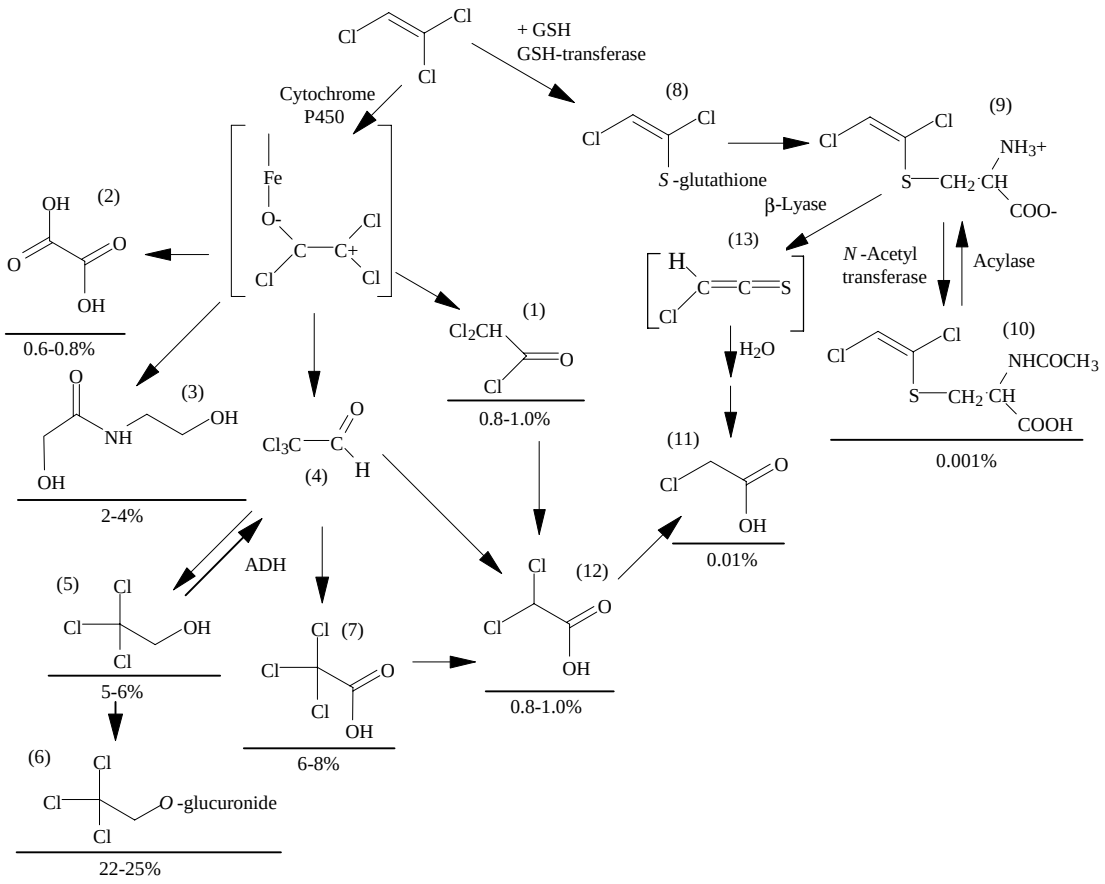

Figure 6-1. Proposed metabolism of TCE in rats

Source: IARC 1995e.

Underlined compounds are identified urinary metabolites (IARC 1995e). (1) dichloroacetyl chloride, (2) oxalic acid, (3) *N*-(hydroxyacetyl)aminoethanol, (4) chloral, (5) trichloroethanol, (6) trichloroethanol glucuronide, (7) trichloroacetic acid, (8) dichlorovinylglutathione, (9) *S*-1,2-dichlorovinylcysteine, (10) *S*-1,2-dichlorovinyl-*N*-acetylcysteine, (11) monochloroacetic acid, (12) dichloroacetic acid, (13) chlorothiketene. Percentages were determined after an oral dose of 200 mg/kg. Compounds shown in brackets are postulated intermediates.

DCA may be formed by a rearrangement of the putative epoxide intermediate 1,1,2-trichlorooxirane and subsequent hydrolysis (Hathway 1980) or by biotransformation of choral hydrate or TCA (Larson and Bull 1992). Oxalic acid may be formed by oxidation of DCA (Larson and Bull 1992) or by cleavage, either enzymatic or non-enzymatic, of 1,1,2-trichlorooxirane followed by spontaneous elimination of two equivalents of hydrochloric acid, reaction with water, and oxidation (Dekant *et al.* 1984). *N*-Hydroxyaminoacetylethanol is thought to be formed by the reaction of TCE oxidized intermediates with aminoethanol or phosphatidylethanol with subsequent hydrolysis of the acylated lipid (Dekant *et al.* 1984). There are significant quantitative differences between rats and mice in the metabolism of TCE to TCA and DCA (Green 1990). TCE

metabolism in the mouse is linear over a wide range of dose levels, while metabolism becomes saturated in the rat at relatively low dose levels.

In the less common of the two metabolic pathways, TCE is conjugated to glutathione. The result is dichlorovinylglutathione (DCVG), which can be converted to *S*-1,2-dichlorovinylcysteine (DCVC). DCVC can then follow one of two paths, forming either monochloroacetic acid or *N*-acetyldichlorovinylcysteine, which has been found to be excreted in a dose-dependent manner after experimental exposure of rats and human volunteers to TCE (Bernauer *et al.* 1996).

TCE metabolism in humans and laboratory animals is qualitatively similar. Most TCE metabolites found in experimental animals also have been found in humans (see Table 6-1); however, rodents have a much higher capacity to metabolize TCE than humans (IARC 1995e, Fisher 2000, Lash *et al.* 2000a). Based on *in vitro* metabolism studies with 23 human hepatic microsomal samples, Lipscomb *et al.* (1997) concluded that the CYP2E1 form of cytochrome P-450 was predominantly responsible for the microsome-mediated metabolism of TCE. Furthermore, the lack of uniformity among these samples in their capacity to metabolize TCE suggested to these investigators that subpopulations of individuals may exist with increased susceptibility to TCE.

After TCE is absorbed from the gastrointestinal tract, first-pass elimination by the liver and lungs play a major role in clearing TCE. When male Sprague-Dawley rats were injected with 0.17 mg/kg (1.3 μmol/kg) of TCE in a 5% aqueous Alkamuls emulsion, the liver eliminated 10 times more chemical as did the lungs on the first pass (Lee *et al.* 1996). As the dose increased beyond 1 to 2 mg/kg (8 to 15 μmol/kg), hepatic first-pass elimination diminished. In human subjects exposed by inhalation to TCE at concentrations up to 315 ppm (1,690 mg/m^3; 12.9 mmol/m^3) for three hours, metabolism was not saturated (Ikeda 1977, Nomiyama and Nomiyama 1977, both cited in Lee *et al.* 1996). This finding led the authors to hypothesize that a single pass through the liver was sufficient to remove TCE from the blood completely. Based on these data, Lee *et al.* (1996) concluded that because metabolism should not be saturated by the daily doses of TCE to which humans are exposed, first-pass elimination should remove a substantial portion of the TCE from the blood before it reaches extra-hepatic organs.

A substantial delay between elimination of TCE from blood and appearance of the metabolite TCA in blood was reported in Templin *et al.* (1993, cited in Stenner *et al.* 1997). Stenner *et al.* (1997) performed a study to determine whether enterohepatic recirculation of trichloroethanol and TCA could explain the TCA concentrations seen in blood following administration of TCE. Male Fischer F344 rats with and without intact enterohepatic recirculation were given trichloroethanol at an intravenous (i.v.) dose of 100 mg/kg (0.669 mmol/kg). The results demonstrated that roughly 36% of the trichloroethanol and 76% of the TCA in systemic blood were due to enterohepatic recirculation. Urinary excretion of TCA following i.v. administration of trichloroethanol was decreased by 80% in rats lacking enterohepatic recirculation (Stenner *et al.* 1997). Using these and previous findings, the authors concluded that enterohepatic recirculation could account for the delayed appearance of TCA in the blood after oral administration of TCE.

Table 6-1. Metabolites of TCE by species

Metabolite[a]	References
Rats	
N-acetyl-*S*-(1,2-dichlorovinyl)-*L*-cysteine (10)	Dekant *et al.* 1986, 1990, Commandeur and Vermeulen 1990)
N-acetyl-*S*-(2,2-dichlorovinyl)-*L*-cysteine (isomer of 10)	Dekant *et al.* 1986, 1990, Commandeur and Vermeulen 1990)
chloroacetic acid (11)	Green and Prout 1985
dichloroacetic acid (12)	IARC 1995e
N-(hydroxyacetyl)aminoethanol (3)	IARC 1995e
oxalic acid (2)	IARC 1995e
trichloroacetic acid (7)	Kimmerle and Eben 1973
trichloroethanol (5)	Kimmerle and Eben 1973
trichloroethanol glucuronide (6)	IARC 1995e
Chimpanzees, baboons, and rhesus monkeys	
trichloroacetic acid glucuronide (formed from 7)	Müller *et al.* 1982
Humans	
N-acetyl-*S*-(1,2-dichlorovinyl)-*L*-cysteine (10)	Birner *et al.* 1993, Bernauer *et al.* (1996)
N-acetyl-*S*-(2,2-dichlorovinyl)-*L*-cysteine (isomer of 10)	Birner *et al.* 1993, Bernauer *et al.* (1996)
chloral hydrate (formed from 4)	Cole *et al.* 1975
N-(hydroxyacetyl)aminoethanol (3)	Dekant *et al.* 1984
oxalic acid (2)	Dekant *et al.* 1984
trichloroacetic acid (7)	Cole *et al.* 1975
trichloroethanol (5)	Cole *et al.* 1975
trichloroethanol glucuronide (6)	Cole *et al.* 1975

[a]Numbers in parentheses correspond to the numbers in Figure 6-1.

TCE metabolites are excreted primarily in the urine; however, up to 30% can be eliminated by excretion in the bile (Gist and Burg 1995). The major metabolites found in human urine are trichloroethanol, trichloroethanol glucuronide, and TCA (Cole *et al.* 1975, Clewell *et al.* 2000). However, Nomiyama and Nomiyama (1971, cited in Clewell *et al.* 2000) demonstrated that the relative amounts of TCA and trichloroethanol excreted by men and women differed; women excreted more TCA and less trichloroethanol than men.

6.2 Pharmacokinetics

The maximum metabolic rate (V_{max}) for TCE in rats is 6.04 mg/h (0.046 mmol/h) with a Michaelis constant of 5.05 µg/mL (0.038 µmol/mL). Absorption by organs occurs with the following organ-to-blood partition coefficients: gastrointestinal tract, 1.35; liver, 2.17; spleen 0.63 (Varkonyi *et al.* 1995).

Another study calculated the V_{max} in humans to be 215.0 mg/h (1.636 mmol/h) based on the V_{max} found in rats using the allometric relationship (human V_{max}) = (Rat V_{max}) $[70/(\text{rat wt., kg})]^{0.7}$ (Gargas *et al.* 1986, cited in Rappaport 1993). Of the absorbed dose of TCE, 0.75 is the fraction metabolized based on estimated human clearance rates (Sato and Nakajima, 1987, cited in Rappaport 1993). Using these two values, Rappaport (1993) calculated that 178.3 mg/m^3 (1,357 mmol/m^3) was the highest mean TCE concentration to which a person could be exposed while maintaining linear kinetics. This is slightly lower than the occupational threshold limit value of 269.0 mg/m^3 (50 ppm; 2.047 mmol/m^3) (ACGIH 1996).

The urine of three male volunteers exposed to TCE by inhalation at a concentration of 40, 80, or 160 ppm (217 to 869 mg/m3) for six hours was examined for the presence of TCE metabolites (Bernauer *et al.* 1996). After inhalation of TCE at 160 ppm, excretion of the mercapturate metabolites, *N*-acetyl-*S*-(1,2-dichlorovinyl)-*L*-cysteine and *N*-acetyl-*S*-(2,2-dichlorovinyl)-*L*-cysteine, seemed to become saturated, while excretion of oxidatively formed metabolites increased linearly. Elimination of mercapturates in humans exhibited a biphasic nature and was slower than elimination of the oxidatively formed metabolites. When five male volunteers were exposed to TCE at 70 ppm (380 mg/m^3, 2.9 mmol/m^3) four hours per day for five days, trichloroethanol concentrations in urine rose rapidly, then stabilized and remained high for the duration of the five days of exposure (Monster *et al.* 1979). Urinary excretion of TCA continued to rise until the end of exposure. The major metabolites of TCE are cleared from humans at very different rates. TCA is eliminated slowly in urine with a half-life of about 52 hours, but trichloroethanol and trichloroethanol glucuronide are eliminated rapidly with half-lives of about 10 hours (Müller *et al.* 1972, 1974). The difference is even more marked in rats; TCA is present in the blood at high levels for up to 30 hours in contrast to trichloroethanol and chloral hydrate, which are cleared from the blood with a half-life of 1 to 2 hours (Kimmerle and Eben 1973).

6.3 Metabolites

DCA, TCA, and chloral hydrate have been evaluated for carcinogenicity by the IARC; however, DCVC has not been classified. The IARC findings and other relevant data are briefly discussed below. Genotoxicity data for these metabolites were discussed in Section 5.

6.3.1 Dichloroacetic Acid and Trichloroacetic Acid

The IARC (1995b) concluded that the evidence for the carcinogenicity of DCA was inadequate in humans and limited in experimental animals (Group 3). In four studies, oral administration of pH-neutralized DCA to male B6C3F_1 mice resulted in an increased incidence of hepatocellular adenoma and carcinoma. In hepatic carcinomas sampled from DCA-exposed mice, expression of c-*myc* and c-H-*ras* was increased approximately 3-fold and 4-fold, respectively. Although the frequency of mutations at codon 61 of H-*ras* was not significantly different between liver tumors in exposed and control mice, the spectra of the mutations in DCA-exposed mice showed a significant increase in CTA and a corresponding decrease in AAA.

The IARC (1995d) concluded that there was inadequate evidence in humans and limited evidence in experimental animals for the carcinogenicity of TCA (Group 3). TCA significantly increased the incidence of hepatocellular adenoma and carcinoma in two drinking-water studies with B6C3F_1 male mice (IARC 1995d). In hepatic carcinomas sampled from TCA-exposed mice, expression of c-*myc* and c-H-*ras* was increased approximately 6-fold and 4-fold, respectively.

6.3.2 Chloral hydrate

IARC evaluated chloral and chloral hydrate as not classifiable as to their carcinogenicity in humans (Group 3), citing inadequate evidence in humans and limited evidence in animals (IARC 1995a). In an experimental carcinogenicity study that the IARC deemed adequate, male mice given chloral hydrate by gavage showed a significantly increased incidence of hepatic adenomas and carcinomas.

The NTP has issued a draft report on the toxicology and carcinogenicity of chloral hydrate (NTP 2000b). Groups of female B6C3F_1 mice received chloral hydrate in distilled water by gavage at concentrations of 0, 10, 25, 50, or 100 mg/kg. Some mice were exposed to a single dose and held for 105 weeks while others were exposed 5 days/week. Male mice were only exposed to a single dose of chloral hydrate at 10, 25, or 50 mg/kg. There was equivocal evidence of carcinogenic activity in female mice treated continuously based on increased incidences of pituitary gland pars distalis adenoma. No tumors were increased in female or male mice receiving a single dose of chloral hydrate.

6.3.3 Dichlorovinylcysteine

The IARC has not yet determined a classification for DCVC. DCVC was mutagenic in the Ames test (see Section 5) and highly nephrotoxic (Vamvakas *et al.* 1993, Clewell *et al.* 1995). At concentrations producing small or undetected decreases in cell growth, DCVC induced Ca^{2+}-dependent DNA damage. Following this DNA fragmentation, an increase was seen in adenosine diphosphate ribosylation of nuclear proteins (Vamvakas

et al. 1992, cited in Vamvakas *et al.* 1993), which, if moderate, was shown in mouse fibroblasts to be associated with increased cell proliferation (Muehlematter *et al.* 1988, cited in Vamvakas *et al.* 1993). Before collapse of the mitochondrial membrane potential, cytosolic Ca^{2+} concentrations were increased by DCVC in renal cells (Vamvakas *et al.* 1990, cited in Vamvakas *et al.* 1993). Tumor promoters that induce oxidative stress commonly produce such an effect (Vamvakas *et al.* 1993).

6.4 Immune suppression

Sprague-Dawley rats and $B6C3F_1$ mice given TCE by i.p. injection showed inhibition of immune system activity, as demonstrated by decreases in splenocyte viability, inhibition of lipopolysaccharide-stimulated mitogenesis, inhibition of hepatic natural killer cells, and inhibition of natural cytotoxic cell activities in all groups of effector cells (IARC 1995e).

6.5 Molecular changes in human tumors

Brüning *et al.* (1997) examined tissues from 23 patients with renal-cell carcinoma and high occupational exposure to TCE. All 23 patients had aberrations of the von Hippel-Lindau (VHL) tumor suppressor gene compared to mutation frequencies of 33% to 55% in patients with renal-cell carcinoma but without known occupational exposure to TCE. In a similar study, Brauch *et al.* (1999) reported evidence for a linkage between TCE exposure and somatic mutation of the von Hippel-Lindau (VHL) tumor suppressor gene, a known molecular-genetic cause for renal-cell carcinoma (Gnarra *et al.* 1994). The cases were 44 renal-cell carcinoma patients who were registered as former employees of metal-processing factories in Germany with histories of high cumulative TCE exposure. TCE exposure was ranked as one of three levels (high, medium, or low) by a defined scoring system that integrated total exposure time as well as frequency and duration of acute adverse effects. For evaluation of the effects of TCE exposure, 107 controls were recruited who had renal-cell carcinoma but were not registered as having been exposed to TCE. Of these controls, 34 were from the same geographic location as the TCE-exposed patients, and 73 were from other regions in Germany. DNA was isolated from tumor tissue of both the TCE-exposed and control patients by microdissection. DNA also was isolated from the adjacent non-neoplastic kidney parenchyma of the 44 TCE-exposed renal-cell carcinoma cases.

Controls for the analysis of germline VHL gene status included the lymphocyte DNA from the 44 TCE-exposed renal-cell carcinoma patients and 97 nondiseased individuals, 47 of whom had been exposed to TCE and 50 of whom were population controls without any history of TCE exposure. DNA was isolated from lymphocytes of these individuals.

Exons 1, 2, and 3 of the VHL gene from the tumor DNA of the 44 TCE-exposed renal-cell carcinoma patients were amplified by polymerase chain reaction (PCR) and analyzed by single-strand conformation polymorphism and sequencing. *VHL* mutations were identified in 33 (75%) of the samples, and 14 (42%) had multiple mutations. Most of the mutations were located in exon 1 (52%), with 20% occurring in exon 2 and 28% in exon 3. The majority of the mutations (54%) were missense mutations, of which 89% involved a cytosine change; 19 samples had a C to T change, and 5 had a C to G change. Of the 33 samples with *VHL* mutations, 13 (39%) had a C to T change at nucleotide (nt) 454 (in

exon 1), which codes for a Pro to Ser change at codon 81. This nt 454 mutation occurred at a greater frequency (41%) in those patients classified as having a high severity of exposure than those with either a medium (25%) or low (0%) severity of exposure.

DNA from tumors of the 107 renal-cell carcinoma controls and lymphocyte DNA from the germline *VHL* status controls were screened for the nt 454 mutation with a PCR–restriction fragment length polymorphism assay. None of these samples had the nt 454 mutation, suggesting that this mutation was both specific for TCE exposure (as evident from the non-TCE-exposed renal-cell carcinoma controls) and disease-related (as evident from the germline controls). The nt 454 mutation was found in the adjacent non-neoplastic kidney parenchyma in four TCE-exposed renal-cell carcinoma patients.

In contrast, Schraml *et al.* (1999) analyzed DNA from normal and renal-cell carcinoma tissues from 12 patients with occupational exposure to varying levels of TCE and other solvents. Comparison of these results with data obtained from sporadic renal-cell carcinoma failed to suggest a unique mutation pattern in the VHL gene of renal tumors associated with exposure to TCE. However, TCE exposure was not as severe as in the study reported by Brauch *et al.* (1999). Subjects in this study were exposed to varying doses of TCE; whereas, the Brauch *et al.* (1999) study included subjects with prenarcotic symptoms (e.g., dizziness, nausea, equilibrium disorders).

6.6 Mechanisms of carcinogenesis

6.6.1 Liver cancer

Hepatocellular carcinomas have been reported in some strains of mice but not in rats exposed to TCE (see Section 4), and species and strain differences in metabolism of TCE to TCA and DCA are thought to account for this difference (Goeptar *et al.* 1995, Maronpot *et al.* 1995, Clewell *et al.* 1995). Channel *et al.* (1998) demonstrated that TCE given in drinking water to $B6C3F_1$ mice induced lipid peroxidation, peroxisome proliferation, and mitogenesis without an increase in apoptosis. This initial cellular response may be characteristic of the mouse liver and may provide further explanation of the species and strain differences. TCA is a peroxisome proliferator at doses that induce liver cancer in mice; however, the actual mechanisms of carcinogenesis may be only loosely associated with peroxisome proliferation.

Data suggest that the level of expression of the peroxisome proliferator activated receptor alpha ($PPAR_\alpha$) may be involved in carcinogenesis. Mice with a targeted disruption of the $PPAR_\alpha$ gene did not develop tumors when exposed to a potent peroxisome proliferator while mice of the same strain with an intact gene did develop tumors (Bull 2000). TCE-induced peroxisome proliferation has not been demonstrated in rats (Elcombe 1985). Goeptar *et al.* (1995) concluded that the species difference in TCE-induced peroxisome proliferation was most likely due to saturation of the oxidative metabolism of TCE in the rat, thereby limiting the maximal levels of TCE to below those required to induce this effect.

The relevance of peroxisome proliferation to carcinogenesis in humans is controversial. Human cells and mouse cells respond differently to peroxisome proliferators (Bull 2000).

Exposure to peroxisome proliferators induces a much weaker response in humans compared to mice. This may be explained by the relatively low levels of $PPAR_\alpha$ expressed in human liver (Maloney and Waxman 1999, Bull 2000). Maloney and Waxman (1999) conducted cell transfection studies to investigate the interactions of peroxisome proliferators with cloned human and mouse $PPAR_\alpha$ and $PPAR_\gamma$, an isoform of $PPAR_\alpha$. $PPAR_\gamma$ is highly expressed in many human tissues, including colon, heart, liver, testis, spleen, hematopoietic cells, and fat. Their data showed that human $PPAR_\alpha$ was less sensitive than mouse $PPAR_\alpha$ to some but not all peroxisome proliferators. Human and mouse $PPAR_\alpha$ showed similar sensitivity to TCA and DCA. $PPAR_\gamma$ was not activated by TCA or DCA.

Both TCA and DCA induced hepatocellular adenomas and carcinomas in mice (see Section 6.3.3.1), possibly mediated through the induction of peroxisome proliferation, cytotoxicity, and reparative hyperplasia (Maronpot *et al.* 1995). However, Barton *et al.* (1999) questioned the role of DCA in TCE-induced liver cancer. Their data suggested that the low concentrations of DCA present in the liver would be insufficient to contribute significantly to TCE-induced liver cancer. The involvement of TCA and DCA in TCE-induced hepatocellular carcinoma in mice is supported by studies in which strain differences in the incidence of liver tumors correlated with differences in the oxidative metabolism of TCE. For example, TCE induced liver tumors in Swiss and $B6C3F_1$ mice (NTP 1986; Maltoni *et al.* 1986, cited in Goeptar *et al.* 1995) but not NMRI mice (Henschler *et al.* 1980, cited in Goeptar *et al.* 1995). In Swiss and $B6C3F_1$ mice, TCA and DCA accounted for 7% to 12% and 2% of the administered TCE, respectively (Green and Prout 1985, cited in Goeptar *et al.* 1995), but in the NMRI mice, TCA and DCA each accounted for only 0.1% of the TCE dose (Dekant *et al.* 1984, cited in Goeptar *et al.* 1995). By this line of reasoning, the ability of TCE to induce liver tumors in humans would depend on the rate of formation of TCA and DCA and on the induction of peroxisome proliferation in liver cells. Although humans appear more similar to mice than to rats in their ability to oxidatively metabolize TCE, they metabolize approximately 60 times less TCE on a body-weight basis than mice at similar exposure levels, and TCA does not appear to induce peroxisome proliferation in human hepatocytes (Goeptar *et al.* 1995).

Bull (2000) reviewed four possible modes of action for TCE-induced liver cancer: somatic mutation, modification of cell signal pathways, cell death and reparative hyperplasia, and hepatomegaly and cytomegaly. He concluded that there is no evidence that clearly associates a genotoxic effect of TCE or its metabolites with liver cancer. The data suggested that TCE induced liver tumors by modifying cell-signaling systems involved in cell division and death and indicated that DCA and TCA induce tumors by separate mechanisms. DCA differentially inhibits normal cell replication at low doses but stimulates marked cell replication within liver tumors at high doses resulting in a nonlinear dose-response relationship. Only the differential inhibition of normal cell replication was observed with TCA. TCA appears to induce tumors with a higher rate of replication than those induced by DCA. At high doses, DCA increases the growth rate of tumors with a less malignant phenotype.

6.6.2 Lung cancer

TCE administered by inhalation significantly increased the incidence of lung tumors (adenoma and carcinoma) in female (but not male) B6C3F_1 mice and male (but not female) Swiss mice. TCE is not carcinogenic in the rat lung. Mechanistic studies on mouse lung tumor formation suggest that chloral formation in Clara cells may explain the sex and species differences (Goeptar *et al.* 1995, Green *et al.* 1997). High cytochrome P-450 activity and impaired metabolism of chloral in Clara cells are believed to be responsible for the toxic and carcinogenic effects observed in the mouse lung (Green 2000). TCE metabolism in the human lung was reported to be about 600 times less than in the mouse lung (Green 2000).

Mouse Clara cells studied *in vitro* were found to have relatively high cytochrome P-450 activity and relatively low activities of alcohol dehydrogenase, the enzyme that converts chloral to trichloroethanol, and uridine diphosphate glucuronosyl transferase, the enzyme responsible for the glucuronidation of trichloroethanol (Odum *et al.* 1992, cited in Clewell *et al.* 1995). Thus, chloral would be anticipated to accumulate in mouse Clara cells, which may explain the formation of lung tumors in mice. Consistent with this hypothesis, exposure of mice to chloral resulted in lesions in lung Clara cells similar to those caused by a 10-fold higher concentration of TCE (Odum *et al.* 1992, cited in Clewell *et al.* 1995). Goeptar *et al.* (1995) hypothesized that the absence of smooth endoplasmic reticulum in human lung Clara cells (Smith *et al.* 1979, cited in Goeptar *et al.* 1995) implied a lack of cytochrome P-450 activity and a corresponding lack of risk for chloral accumulation.

6.6.3 Kidney cancer

In contrast to tumors of the lung and liver, kidney tumors were found in rats but not in mice, and at doses associated with a high incidence of nephrotoxicity (Goeptar *et al.* 1995, Clewell *et al.* 1995). Goldsworthy *et al.* (1988) did not find evidence that TCE induced kidney cancer in male rats by $\alpha_{2\mu}$-globulin protein droplet accumulation; however, experiments with tetrachloroethylene indicated that protein droplet accumulation did occur with this chemical. With TCE, nephrotoxicity has most often been associated with toxic metabolites; however, the relative importance of various metabolic pathways and species differences in toxic responses is controversial.

In a minor mercapturic metabolic pathway, TCE is conjugated to glutathione in the liver. The conjugated TCE is further metabolized in the kidney to the cysteine conjugate DCVC and then to a reactive intermediate (Birner *et al.* 1993, cited in Clewell *et al.* 1995). The mutagenic and nephrotoxic properties of the *S*-1,2 isomer of DCVC are described in Sections 5.4.5 and 6.3.3, respectively. The question is not whether or not DCVC is nephrotoxic but whether or not sufficient amounts of TCE or DCVG reach the kidneys to produce enough reactive metabolites to cause toxicity (Lash *et al.* 2000b). The data are mixed on this question. Lash *et al.* (2000b) reported that oxidative or glutathione-derived metabolites from TCE can form within the kidneys at appreciable rates. On the other hand, Green *et al.* (1997b) questioned the role of glutathione conjugation and DCVC in renal toxicity and carcinogenicity. They conducted studies with male Fischer 344 rats and male B6C3F_1 mice given TCE (1, 10, or 42 days) or

DCVC (1 or 10 days) by gavage. In this study, the glutathione conjugation pathway accounted for less than 0.01% of the dose and was higher in the mouse than the rat. DCVC was 5 to 10 times more nephrotoxic to mice compared to rats and the nephrotoxic dose in rats was three orders of magnitude higher than the level of DCVC formed from TCE *in vivo*. They also noted the lack of correlation between metabolism of TCE to DCVC and renal cancer in both rats and mice.

Dow and Green (2000) suggested that increased excretion of formic acid may play a role in TCE kidney cancer. Male Fischer 344 rats exposed to metabolites of TCE (TCA and trichloroethanol) excreted higher amounts of formic acid in their urine. Rats receiving chloral or DCVC did not excrete higher amounts of formic acid. Formic acid is not a product of TCE metabolism; however, metabolites of TCE may interact with vitamin B12 and produce a folate deficiency. Folate deficiency affects formate metabolism resulting in increased formic acid excretion. Sustained excretion of high levels of formic acid may result in renal toxicity.

Lash *et al.* (2000b) reviewed evidence for four possible modes of action of TCE-induced kidney cancer: (1) peroxisome proliferation, (2) accumulation of the male rat-specific protein α_{2u}-globulin, (3) direct genotoxicity, and (4) acute and chronic toxicity. These authors concluded that there was little evidence that the first two mechanisms are important for TCE-induced kidney cancer; however, the data do suggest that different modes or combinations of several modes of action may be important. These researchers also questioned the role of formic acid excretion proposed by Dow and Green (2000) because there is no evidence that formic acid produces renal tumors. Renal effects mediated through the glutathione conjugation pathway include cytotoxicity, induction of DNA repair, and proliferative responses. High doses of DCVC may produce oxidative stress, protein and DNA alkylation, and mitochondrial dysfunction followed by inhibition of active transport, ATP depletion, cytotoxicity, and acute tubular necrosis. At lower doses, less severe effects on mitochondrial function, oxidative stress, and selective alkylation of protein and DNA may lead to altered gene expression and cell growth.

Goeptar *et al.* (1995) concluded that it seemed improbable that the oxidative pathway would become saturated in humans at likely exposure levels of TCE. However, urinary excretion of *N*-acetylated DCVC (a detoxification product of DCVC) has been detected in humans occupationally exposed to TCE (Birner *et al.* 1993, cited in Clewell *et al.* 1995).

Furthermore, one human study strongly suggested that kidney damage was associated with exposure to TCE. Brüning *et al.* (1996) compared the urinary protein patterns of 17 patients diagnosed with renal-cell cancer after many years of high-level occupational exposure to TCE with those of 35 renal-cell cancer patients not exposed to TCE. Exposure to TCE was associated with degreasing, production of rubber boxes, and cleaning of cardboard-making machines. These exposures were without protection from hoods, ventilating systems, or the use of gloves. The average year of initial exposure was 1959, mean exposure duration was 15.2 years, mean time of diagnosis for renal-cell carcinoma was 1990, and mean latency period was 30.4 years. Symptoms of exposure

included dizziness, headache, a sense of drunkenness, and drowsiness. The postoperative period for the unexposed patients was similar to that for the TCE-exposed patients.

In all 17 exposed patients, protein excretion patterns indicated tubule damage in their remaining kidney. Among the 35 non-exposed patients, 12 had tubule damage, 4 had glomerular and tubule damage, and 1 had glomerular damage. Brüning *et al.* (1996) concluded that although their data were limited, the findings supported the likelihood that chronic tubule damage contributed to the induction of renal-cell cancer by TCE. This finding is consistent with the involvement of the mercapturic metabolic pathway in the metabolism of TCE in humans (Brüning *et al.* 1996).

It is biologically plausible that the observed kidney tumors were related to TCE exposure, for four reasons: (1) the site and histopathological characteristics of the tumors observed in patients and experimental animals were identical (Vamvakas *et al.* 1993), (2) the molecular mechanism of this type of nephrocarcinogenicity has been elucidated (Dekant *et al.* 1986, cited in IARC 1995e), (3) the metabolites derived from the likely ultimate electrophilic intermediates of the bioactivation of TCE were identical in humans and in experimental animals (Birner *et al.* 1993, cited in Clewell *et al.* 1995), and (4) taking the key urinary metabolites (mercapturic acids) as an indicator of the bioactivation of TCE (Birner *et al.* 1993, cited in Clewell *et al.* 1995), humans seem to be more sensitive than rats in developing the primary biochemical lesion leading to the induction of renal cancer.

6.6.4 Structural analogues

Structural analogs of TCE include vinyl chloride (chloroethylene), vinylidene chloride (1,1-dichloroethylene), and tetrachloroethylene. Tetrachloroethylene appears to be the most similar to TCE in the sites of tumor formation. The genotoxic effects of these structural analogues were discussed in Section 5.

6.6.4.1 Vinyl chloride

Based on human epidemiological studies and case reports and rodent carcinogenicity data, the IARC (1979) concluded that there was sufficient evidence for the carcinogenicity of vinyl chloride in humans and experimental animals. The IARC (1987a) reaffirmed vinyl chloride's evaluation as a human carcinogen (Group 1), citing several additional epidemiological studies and case reports. Occupational exposure to vinyl chloride was associated with increased risks of angiosarcoma of the liver, hepatocellular carcinoma, brain and lung tumors, and malignancy of the hematopoietic and lymphatic system. Some studies indicated a possibility of increased risk of gastric and gastrointestinal cancer (other than liver) (IARC 1987a). Green (1990) noted that workers in vinyl chloride manufacturing also experienced increases in tumors of the skin and thyroid, although a causal relationship was not established. One study indicated excess fetal mortality among wives of workers exposed to vinyl chloride, and several other studies reported increased rates of birth defects in children whose parents lived in communities with vinyl chloride–poly(vinyl chloride) or other chemical processing facilities (IARC 1979).

Vinyl chloride has been extensively tested in rats, hamsters, and mice via inhalation exposure and oral, subcutaneous, and i.p. administration. Oral administration or inhalation of vinyl chloride induced Zymbal gland tumors in rats and hamsters, nephroblastoma in rats, forestomach papilloma and melanoma in hamsters, and pulmonary and mammary gland tumors in mice (IARC 1979, 1987a). In all three species, exposure to vinyl chloride induced hemangiosarcoma of the liver (IARC 1979, 1987a, Green 1990). Vinyl chloride was carcinogenic in rats exposed prenatally (IARC 1979).

6.6.4.2 Vinylidene chloride

The IARC (1999) concluded that vinylidene chloride was not classifiable as to its carcinogenicity in humans because of inadequate evidence (Group 3) and considered the evidence for its carcinogenicity in animals to be limited. No data were available on its genetic and related effects in humans. Green (1990) stated that the question of vinylidene chloride's carcinogenicity had never been resolved, although, as the closest analog of the well-established carcinogen vinyl chloride, it might be expected to be carcinogenic.

Carcinogenicity of vinylidene chloride has been tested via inhalation and oral administration in mice and rats, via topical application and subcutaneous administration to mice, and via inhalation in hamsters (IARC 1987b). Oral administration produced negative results in mice and rats. Inhalation produced no exposure-related neoplasms in rats and hamsters; in mice, however, males showed an exposure-related increase in the incidence of kidney adenocarcinoma, females showed an increase in the incidence of mammary carcinoma, and both males and females showed an increase in pulmonary adenoma. Mice given several subcutaneous administrations showed no tumors at injection sites. In Swiss mice exposed to vinylidene chloride at high doses, Maltoni *et al.* (1984a,b, cited in Green 1990) found severe nephrotoxicity, and tumors in only 2 of 18 surviving mice. Male Swiss mice were more susceptible to nephrotoxic effects than were other mouse strains, rats, or hamsters. Green (1990) suggested that kidney damage in Swiss mice may have facilitated expression of the weak genotoxic potential of vinylidene chloride's metabolites.

6.6.4.3 Tetrachloroethylene

The IARC (1995c) evaluated tetrachloroethylene as probably carcinogenic to humans (Group 2A), based on limited evidence in humans and sufficient evidence in experimental animals. In epidemiological studies, occupational exposure to tetrachloroethylene presented increased risk for esophageal cancer, non-Hodgkin's lymphoma, and cervical cancer. In experimental carcinogenicity studies, mice given tetrachloroethylene by gavage showed an increased incidence of hepatocellular carcinoma (IARC 1995c). Mice exposed to high doses by inhalation showed exposure-related increases in hepatocellular adenoma and carcinoma (NTP 1986). Rats exposed to high doses by inhalation showed a dose-related increase of mononuclear-cell leukemia; also observed but not statistically significant was an increase in the incidence of renal tubular-cell adenoma and adenocarcinoma in male rats (NTP 1986). In a study by Anna *et al.* (1994), the liver tumors induced in mice treated chronically with tetrachloroethylene for up to 76 weeks exhibited a decreased frequency of H-*ras*

mutations and an increased frequency of K-*ras* mutations, compared with liver tumors from concurrent and historical control animals.

6.7 Summary

TCE is rapidly absorbed from the gastrointestinal tract and lungs. The liquid can be absorbed through the skin; however, dermal absorption of the vapor is negligible. Following absorption, TCE is distributed throughout the body and concentrates in lipophilic tissues (e.g., liver, brain, fat). Oxidation by cytochrome P-450 and conjugation with glutathione are the primary metabolic pathways. Chloral hydrate, DCA, and TCA are the primary toxic metabolites produced by the P-450 pathway and have been associated with liver and lung toxicity. DCVC is a metabolite of the glutathione pathway and has been associated with kidney toxicity. Although TCE metabolism in mice, rats, and humans are qualitatively similar, there are significant quantitative species and sex differences. Mice metabolize TCE faster than rats and rats metabolize TCE faster than humans. Human studies have shown that women excrete more TCA and less trichloroethanol than men.

Several structural analogues (vinyl chloride, vinylidene chloride, and tetrachloroethylene) and metabolites (chloral hydrate, DCA, and TCA) of TCE have been tested for carcinogenicity. Most of these chemicals have induced liver tumors in mice.

TCE induces liver cancer in mice but not in rats. Species and strain differences in metabolism of TCE to TCA and DCA may provide an explanation for these susceptibility differences. These metabolites may induce liver cancer through peroxisome proliferation, cytotoxicity, and mitogenesis. Strain differences in oxidative metabolism show some correlation with liver tumor incidence. Humans metabolize about 60 times less TCE on a body-weight basis than mice at similar exposure levels and TCA does not appear to induce peroxisome proliferation in human hepatocytes.

Lung cancer has been induced in female $B6C3F_1$ mice and male Swiss mice but not in rats following inhalation exposure to TCE. High cytochrome P-450 activity and impaired metabolism of chloral in Clara cells are believed to be responsible for the carcinogenic effects. Chloral formation in Clara cells may explain the sex and species differences.

Unlike liver and lung tumors, kidney tumors are induced in rats but not in mice exposed to TCE. Glutathione conjugation of TCE in the liver and further metabolism to DCVC in the kidney may be related to kidney carcinogenicity; however, there are data that question this. It is likely, that several different modes of action are involved and include cytotoxic, repair, and proliferative responses.

Mechanistically, renal-cell carcinomas from workers occupationally exposed to high levels of TCE exhibited somatic mutations of the VHL tumor suppressor gene, a gene that has been associated with renal cell carcinomas (Brauch *et al.* 1999). Moreover, this mutation was found to be both disease-related and specific for TCE exposure. It is biologically plausible that kidney tumors observed in humans may be related to TCE exposure. The site and histopathological characteristics of the tumors observed in patients and the metabolites derived from the likely ultimate electrophilic intermediates of the

bioactivation of TCE were identical in humans and in experimental animals. Furthermore, humans seem to be more sensitive than rats in developing the primary biochemical lesion leading to the induction of renal cancer.

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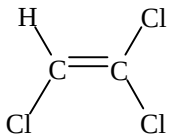
Appendix A: Excerpts from the IARC Monograph on the Evaluation of the Carcinogenic Risk of Chemicals to Humans Volume 63 (Dry Cleaning, Some Chlorinated Solvents and Other Industrial Chemicals) Trichloroethylene pp. 75-158 (1995). A-1 - A-84.

Appendix B: Excerpts from the 1990 National Toxicology Program (NTP) Technical Report Toxicology and Carcinogenesis Studies of Trichloroethylene (Without Epichlorohydrin) [CAS No. 79-01-6] in F344/N Rats and B6C3F1 Mice (Gavage Studies) (TR-243) pp. 16-60

Appendix C: Report on Carcinogens (RoC), 9th Edition Profile for Trichloroethylene. C-1 – C-5

TRICHLOROETHYLENE
CAS No. 79-01-6
First listed in the *Ninth Report on Carcinogens*



CARCINOGENICITY

Trichloroethylene (TCE) is *reasonably anticipated to be a human carcinogen* based on limited evidence of carcinogenicity from studies in humans, sufficient evidence of malignant tumor formation in experimental animals, and convincing relevant information that trichloroethylene acts through mechanisms indicating it would likely cause cancer in humans.

Epidemiological data are limited for evaluating the carcinogenicity of trichloroethylene in humans. Studies have suggested that occupational exposure to TCE causes cancer of the liver and biliary tract, and also non-Hodgkin's lymphoma (IARC V.63, 1995). Another study has indicated that occupational exposure to TCE has been associated with cancer of the kidneys (Henschler et al., 1995a,b; Brüning et al., 1997). Results of three cohort studies consistently indicate an excess relative risk for cancer of the liver and biliary tract, with a total of 23 observed cases, whereas 12.87 were expected (RR = 1.8), and a moderately elevated risk for non-Hodgkin's lymphoma (IARC V.63, 1995). Further, the suggested marginally increased risk for non-Hodgkin's lymphoma in areas with trichloroethylene-contaminated ground water deserves mention (IARC V.63, 1995). For a cohort of cardboard workers exposed almost exclusively to high levels of TCE, the standardized incidence ratio for kidney cancer was 7.97 (95% CI = 2.59-18.59) (Henschler et al., 1995a).

The findings in humans are predated and supported by evidence in experimental animals. Target site concordance for TCE-induced tumors is consistent between humans and rodents. In mice, TCE causes increases in benign and malignant tumors of the liver (NCI 2, 1976; Maltoni et al., 1988; cited by IARC V.63, 1995; NTP 243, 1990), increases in tumors of the lung (Maltoni et al., 1988; cited by IARC V.63, 1995), and lymphomas (Henschler et al., 1980). In rats, TCE induces cancers of the kidney (Maltoni et al., 1988; cited by IARC V.63, 1995; NTP 243, 1990; NTP 273, 1988), interstitial cell tumors of the testis (Maltoni et al., 1988; cited by IARC V.63, 1995; NTP 273, 1988), and possibly leukemias (Maltoni et al., 1988; cited by IARC V.63, 1995).

ADDITIONAL INFORMATION RELEVANT TO CARCINOGENESIS OR POSSIBLE MECHANISMS OF CARCINOGENESIS

Mechanistically, renal cell carcinomas (RCCs) from workers occupationally exposed to high levels of TCE exhibited somatic mutations of the von Hippel-Landau (VHL) tumor suppressor gene, a gene that has been associated with renal cell carcinomas (Brüning et al., 1997). RCC tissues from all 23 TCE-exposed persons [mainly from Henschler et al. (1995a) cohort] analyzed thus far showed aberrations of the VHL gene, with 30% having aberrations in exon 1, 44% in exon 2, and 26% in exon 3. By comparison to TCE-unexposed RCC patients, VHL mutation frequencies of 33-55% were found in different cohorts, with about 24% affecting exon 2.

There is biological plausibility of the kidney tumors observed and TCE exposures because (1) site and histopathological characteristics of the tumors observed in patients and in experimental animals are identical (Vamvakas et al., 1993); (2) the molecular mechanism of this type of nephrocarcinogenicity has been elucidated (Dekant et al., 1986; cited by IARC V.63, 1995 and Bernauer et al., 1996); (3) the metabolites derived from the likely ultimate electrophilic intermediates of the bioactivation of TCE are identical in humans and in experimental animals (Birner et al., 1993; cited by IARC V.63, 1995 and Clewell et al., 1995); and (4) taking the key urinary metabolites (mercapturic acids) as an indicator of the bioactivation of TCE (Birner et al., 1993; cited by IARC V.63, 1995 and Clewell et al., 1995), humans seem to be more sensitive than rats in developing the primary biochemical lesion leading to the induction of renal cancer.

Rodents exposed to TCE typically exhibit dose-related cytomegaly of the kidneys, the lesion often being more severe in males, with none or few being found in male or female vehicle-control mice or rats. Toxic nephropathy commonly occurs in the solvent-exposed rodents, likewise being more frequent and more severe than seen in controls. In humans, substantially more cases of tubule cell damage were found among renal cell carcinoma patients who had been exposed to high levels of TCE over many years than among RCC patients who had not been exposed to TCE (Henschler et al., 1995a).

Studies of chromosomal aberrations, aneuploidy, and sister chromatid exchanges in peripheral lymphocytes of workers exposed to TCE were considered inconclusive. In rodents, TCE did not induce chromosomal aberrations, dominant lethal mutations, sister chromatid exchange, or unscheduled DNA synthesis, whereas an increase in micronuclei and DNA single-strand breaks/alkaline labile sites was observed. TCE did not induce gene mutations in human cells. In mammalian cells *in vitro*, TCE induced cell transformation, sister chromatid exchange, and gene mutations, but not chromosome aberrations (IARC V.63, 1995).

PROPERTIES

TCE is a colorless liquid with a sweet, chloroform-like odor. Upon combustion TCE produces irritants and toxic gases, which may include hydrogen chloride. In the presence of moisture and light, it decomposes by forming hydrochloric acid (HSDB, 1997).

USE

TCE is used mainly as a degreaser for metal parts. Five main industrial groups use TCE in vapor or cold degreasing operations: furniture and fixtures, fabricated metal products, electrical and electronic equipment, transport equipment, and miscellaneous manufacturing industries (IARC V.63, 1995). TCE can be used as an extraction solvent and a chemical intermediate and as a component in adhesives, lubricants, paints, varnishes, paint strippers, pesticides, and cold metal cleaners (ATSDR, 1995-H008).

PRODUCTION

IARC (V.63, 1995) reported that two companies in the United States produced TCE ca. 1992 with a combined annual capacity of 160,000 tons (145,000 metric tons or Mg). The SRI *Directory of Chemical Producers in the United States* listed only one producer (SRIa, 1996).

EXPOSURE

Air is the primary route of potential environmental exposure to TCE. Most of the TCE emissions into the atmosphere are from vapor degreasing operations. Mean TCE background levels in air range from 0.03 parts per billion (ppb) (0.16 $\mu g/m^3$) in rural areas to 0.46 ppb (2.5 $\mu g/m^3$) for urban and suburban areas. Areas near emission sources have up to 1.2 ppb (6.4 $\mu g/m^3$) TCE in the air (ASTDR, 1995-H008).

The Toxic Chemical Release Inventory for 1995 (TRI95, 1997) contains reports on environmental releases of TCE from 717 U.S. facilities. Of these, 591 reported releases to the atmosphere of more than 2000 lb (0.9072 Mg), with releases ranging from 2000 to > 200,000 lb. The total amount of TCE released in 1995 by the 717 facilities was 25,484,235 lb (11,559 Mg), while the 17 greatest emitters together released 6.1 million lb (2770.4 Mg). The greatest releases were generally from metalworking facilities, with 3 sites each reporting under Standard Industrial Classification (SIC) codes 3317 (steel pipe and tubes) and 3714 (motor vehicle parts and accessories). Other facilities (1 each) reported under SICs 3089 (plastics and plastic products, not elsewhere classified), 3671 (electron tubes), and 3721 (aircraft).

TCE is one of the volatile organic compounds (VOCs) measured in the U.S. EPA's large-scale Total Exposure Assessment Methodology (TEAM) studies (Wallace et al., 1996). In studies in the United States (Maryland, New Jersey, and California) in the 1980s (1981-1987), determination of TCE exposure via personal air monitors carried by 750 persons for two consecutive 12-hour periods revealed TCE median personal air concentrations of 0.3 to 3.0 $\mu g/m^3$. Breath samples taken in the evenings after several hours at home from 50 to 350 persons in two New Jersey cities in 1981-1983 and 75 persons in two California towns in 1984 had 0.1 to 0.9 μg TCE/m^3 (median personal air concentrations of 1.7-3.0 $\mu g/m^3$). However, in 1984 and 1987, TCE was not detected in the breath of 140 persons in Los Angeles, CA (personal air levels were 0.3-1.2 $\mu g/m^3$), nor in 1987 in 75 persons in Baltimore, MD (personal air levels were 1.1 μg TCE/m^3).

Industrial discharges of wastewater streams are the primary release of TCE into aquatic systems. TRI95 (1997) includes data from 28 facilities that had each released more than 10 lb (4.5 kg) TCE to water in 1995. Five facilities each released 250 to 280 lb (114 to 127 kg). The total release of TCE to water was 1477 lb (0.670 Mg). Four of the five facilities were metalworking plants; one was a plant that produced TCE as a by-product and for onsite use and processing. TCE background levels in large bodies of water range from 0.001 to 0.007 ppb ($\mu g/L$), while values reported for rainwater and snow are 0.0008 to 0.039 ppb ($\mu g/L$) TCE (Gist and Burg, 1995). In the U.S. EPA's Contract Laboratory Program Statistical Database, TCE was found in approximately 3% of surface water samples and 19% of groundwater samples at geometric mean surface water concentration of 40.2 ppb (individual sample values ranged from 0.0001 to 120 ppb) and geometric mean ground water concentration of 27.3 ppb (individual sample values ranged from <0.1 to ≤27300 ppb) (USEPA, 1989; cited by IARC V.63, 1995). The total releases of TCE to land and underground injection wells in 1995 were 3577 lb (1.622 Mg) and 550 lb (0.249 Mg), respectively (TRI95, 1997).

TCE is present in typewriter correction fluids, paint removers, strippers, adhesives, spot removers, and rug-cleaning fluids (Gist and Burg, 1995). Former uses of TCE as an extraction solvent for cosmetic and drug products and as a dry cleaning agent have been discontinued (IARC V.63, 1995).

TCE has been found in a variety of foods with the highest levels being found in meats, 12-16 ppb (0.09-0.12 $\mu mol/kg$), and U.S. margarine, 440-3,600 ppb (3.35-27.4 $\mu mol/kg$)

(ATSDR, 1995-H008). TCE had been used as an extraction solvent for natural fats and oils, spices, hops, and caffeine (from coffee), but FDA banned these uses in 1977 (IARC V.63, 1995).

According to the National Institute for Occupational Safety and Health (NIOSH, 1990), 401,373 employees in 23,225 plants in the United States National Occupational Exposure Survey (1981-1983) were potentially exposed to TCE.

REGULATIONS

EPA regulates TCE as a Hazardous Air Pollutant under the Clean Air Act (CAA) 1990 Amendments and as a Volatile Organic Compound (VOC) subject to emission standards under the CAA Section 111 (40 CFR Part 60, 1995) (CHEMLIST, 1997).

Under the Safe Drinking Water Act, the Maximum Contaminant Level (MCL) for community and nontransient, noncommunity water systems is set at 0.005 mg/L (40 CFR Part 141, 1996) (CHEMLIST, 1997). The World Health Organization (WHO, 1993) recommended a provisional guideline value for TCE in drinking water of 0.070 mg/L. Based on a 1985 study by Buben and O'Flaherty, WHO (1993) calculated a total daily intake (TDI) of 0.0238 mg/kg bw by applying an uncertainty factor of 3000 to the study's LOAEL (lowest observable adverse effect level) of 100 mg/kg bw/day when mice were exposed for 5 days/week for 6 weeks. The observed adverse effects were minor effects in relative liver weight. Ten percent of the TDI was allocated to drinking water to derive the provisional guideline value of 70 µg/L.

TCE is regulated under RCRA as a Halogenated Organic Compound (HOC) and under the Land Disposal Restrictions. Under the latter, hazardous wastes that contain total concentrations of HOCs of at least 1000 mg/L (liquids) or 1000 mg/kg (nonliquids) are prohibited from land disposal. Under 40 CFR 268.40 and 268.48, treatment standards are given for wastewater and nonwastewater extract concentrations, or the applicable Technology Code (40 CFR 268.42) is given (CHEMLIST, 1997).

TCE is regulated under Sections 110 and 313 of the Superfund Amendment Reauthorization Act (SARA). Priority data needs established under Section 110 include exposure levels in humans living near hazardous waste sites and other populations and epidemiological studies on health effects, including carcinogenicity. Under EPCRA Section 313 (Community Right-to-Know and the Toxic Chemical Release Inventory [TRI], 40 CFR Part 372 Subpart D, 1992), TCE is one of the 19 substances for which the de minimus for reporting changes from 1.0 percent to 0.1 percent. Under TRI, since 1989, manufacturers of at least 25,000 lb/yr (11,350 kg/yr) and other handlers of at least 10,000 lb/yr (4,540 kg/lb) must report releases of TCE to any environmental medium. Under 40 CFR Part 302 Table 302.4, TCE is on the CERCLA List of Hazardous Substances with an RQ for reporting releases of 100 lb (45.4 kg) or more (CHEMLIST, 1997).

TCE is regulated under the Clean Water Act (CWA) Sections 301, 307, and 311 (40 CFR Part 423, 1996; 40 CFR Parts 116 and 117, 1996). TCE is a priority pollutant in final discharges resulting from steam electric power generation. It is designated a hazardous substance if discharged to navigable waters. The Reportable Quantity (RQ) for notification is 100 lb (45.4 kg) (CHEMLIST, 1997).

FDA regulations govern the presence of TCE in color additives, bottled water, food as extraction solvent residues, and as indirect additives as migrants from adhesives, etc., used in food packaging.

The OSHA Permissible Exposure Limit (PEL) for time-weighted average (TWA) exposure in a 40-hour work week to TCE in workroom air is 100 ppm (537 mg/m^3) with a ceiling value of 200 ppm (1070 mg/m^3) (29 CFR 1910.1000, 1996 [CHEMLIST, 1997]). NIOSH considers TCE to be a potential occupational carcinogen, recommending that exposure be limited to the lowest feasible concentration. NIOSH recommends a REL (Recommended Exposure Level) of 2 ppm (11 mg/m^3) during use of TCE as an anesthetic and a 10-hour TWA of 25 ppm (130 mg/m^3) during all other exposures (Ludwig, 1994). The Threshold Limit Value (TLV®) recommended by ACGIH is 50 ppm (269 mg/m^3); the Short-Term Exposure Limit or Ceiling recommended is 100 ppm (537 mg/m^3). ACGIH (1996) classified TCE as A5 (*Not Suspected as a Human Carcinogen*). Regulations are summarized in Volume II, Table B-117.