NTP REPORT ON CARCINOGENS BACKGROUND DOCUMENT for TRICHLOROETHYLENE

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NTP Report on Carcinogens Listing For Trichloroethylene

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, 1995e). 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, 1995e). Further, the suggested marginally increased risk for non-Hodgkin's lymphoma in areas with trichloroethylene-contaminated ground water deserves mention (IARC, 1995e). 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, 1976; Maltoni et al., 1988; cited by IARC, 1995e; NTP 243, 1990), increases in tumors of the lung (Maltoni et al., 1988; cited by IARC, 1995e), and lymphomas (Henschler et al., 1980). In rats, TCE induces cancers of the kidney (Maltoni et al., 1988; cited by IARC, 1995e; NTP 273, 1988; NTP 243, 1990), interstitial cell tumors of the testis (Maltoni et al., 1988; cited by IARC, 1995e; NTP 273, 1988), and possibly leukemias (Maltoni et al., 1988; cited by IARC, 1995e).

Other Information Relating 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, 1995e 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, 1995e 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, 1995e 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 trichloroethylene 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, 1995e).

Listing Criteria from the Report on Carcinogens, Eighth Edition

Known To Be A Human Carcinogen:

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 A Human Carcinogen:

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

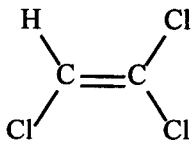
There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors: (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to 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.

1.0 CHEMICAL PROPERTIES

Trichloroethylene
[79-01-6]



1.1 Chemical Identification

Trichloroethylene (C_2HCl_3, mol. wt. = 131.39) is also called:

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	1,12-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
Drawhaspol	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	Vitran
Ethylene, 1,1,2-trichloro-	Trial	Vestrosol
Fleck-Flip	Triasol	

Trichloroethylene (TCE) has a UN shipping number of UN1710 and RCRA waste number of U228.

1.2 Physical-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 20 °C/4 °C	1.4642	Budavari (1996)
Odor	Ethereal odor, sweet chloroform-like odor	HSDB (1997)
Odor Threshold:		
Water	10 mg/L	Verschueren (1983; cited by HSDB, 1997)
Air	21.4 ppm (115 mg/m^3)	Fazzalari (1978; cited by HSDB, 1997)
Solubility:		
Water at 25 °C	0.11 g/100 g	PPG Industries, Inc. (1997)
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 at 0 °C	19.9 mm Hg	HSDB (1997)
Vapor pressure at 20 °C	57.8 mm Hg	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).

1.3 Packaging and Shipping

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

2.0 HUMAN EXPOSURE

2.1 Use

TCE is used mainly as a degreaser for metal parts (CMR, 1983; cited by 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

IARC (1995e) 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, United States* listed only one producer (SRI, 1996).

2.3 Exposure

2.3.1 Environmental Exposure

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 3 sites in Michigan, 4 sites in Indiana, 6 sites in Illinois, and 1 site each in Pennsylvania and Arizona. Environmental and tissue data will serve as the basis for estimating exposure (Gist et al., 1994).

2.3.1.1 Air

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).

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). Among the 591 facilities, 132 released individually 2000 to 10,000 lb (0.9072 to 4.536 Mg); 328 released between 10,000 and 50,000 lb (4.536 to 22.68 Mg); 114 released between 50,000 and 200,000 lb (22.680 to 90.718 Mg); and 17 released greater than 200,000 lb (>90.718 Mg) each. 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).

2.3.1.2 Water

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 (μg/L), while values reported for rainwater and snow are 0.0008 to 0.039 ppb (μg/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 ground water samples at a geometric mean surface water concentration of 40.2 ppb (individual sample values ranged from 0.0001 to 120 ppb) and a geometric mean groundwater concentration of 27.3 ppb (individual sample values ranged from <0.1 to ≤27300 ppb) (U.S. Environmental Protection Agency, 1989; cited by IARC, 1995e).

2.3.1.3 Soil

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).

2.3.1.4 Consumer Products

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 cosmetics and drug products and as a dry cleaning agent have been discontinued (IARC, 1995).

2.3.1.5 Food

TCE has been found in a variety of foods with the highest levels being found in meats, 12-16 ppb (0.09-0.12 μmol/kg), and U.S. margarine, 440-3,600 ppb (3.35-27.4 μmol/kg) (ATSDR, 1995). 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, 1995e).

2.3.2 Occupational Exposure

According to the U.S. National Institute for Occupational Safety and Health (NIOSH, 1990), 401,373 employees in 23,225 plants in the United States during 1980-1983 were potentially exposed to TCE (**Table 2-1**).

Table 2-1. NIOSH National Occupational Exposure Survey (NOES 1980-1983)[a]: By Industry

Industry	Number of Plants	Number of Employees	Number of Female Employees
Agricultural Services	339	1695	1695
General Building Contractors	661	5463	3106
Heavy Construction Contractors	65	5420	5306
Special trade Contractors	834	1879	1287
Food and Kindred Products	190	2062	604
Tobacco Manufactures	43	517	
Textile Mill Products	214	26846	21509
Apparel and Other Textile Products	207	1226	1188
Lumber and Wood Products	505	4932	1189
Furniture and Fixtures	184	1352	
Paper and Allied Products	167	4331	1846
Printing and Publishing	2372	26317	10227
Chemicals and Allied Products	236	10277	3151
Petroleum and Coal Products	256	2020	
Rubber and Misc. Plastic Products	862	15772	2381
Leather and Leather Products	33	65	
Stone, Clay, and Glass Products	275	1494	1341
Primary Metal Industries	379	5047	417
Fabricated Metal Products	2196	49046	30065
Machinery, Except Electrical	1871	22210	2786
Electric and Electronic Equipment	1197	97000	47714
Transportation Equipment	207	9305	559
Instruments and Related Products	984	16293	5032
Miscellaneous Manufacturing Industries	803	6261	2938
Railroad Transportation	22	262	
Trucking and Warehousing	989	5852	5072
Transportation by Air	481	15216	3782
Communication	603	8776	1802
Electric, Gas, and Sanitary Services	117	4336	429
Whole trade- Durable Goods	960	3735	2260
Whole trade - Nondurable Goods	352	704	
Personal Services	277	1044	70
Business Services	716	12973	3475
Auto Repair, Services, and Garages	1295	11197	4861
Miscellaneous Repair Services	406	812	
Health Services	569	11302	9059
Museums, Botanical, Zoological Gardens	82	1643	164
TOTAL	23225	401373	175316

[a] NIOSH (1990)

2.4 Regulations and Criteria

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*).

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).

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	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/operator of any stationary source which 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 trichloroethylene 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.	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 uses, contains, or produces trichloroethylene. 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.	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 trichloroethylene. Specific standards, monitoring, and recordkeeping requirements apply.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	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, trichloroethylene 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 trichloroethylene 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 trichloroethylene 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.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	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 trichloroethylene alone or in a mixture with other HAPs 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 trichloroethylene emissions occurs as defined in 40 CFR 63.2, or at which is located one or more operations that receives 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. Trichloroethylene 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 trichloroethylene as a hazardous substance under section 311(b)(2)(a) of the 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 EPA. Reportable quantity (RQ) for environmental releases of trichloroethylene to water is 100 lb (45.4 kg).

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	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 is provided. For drinking water the limit is 0.29 g TCE/L and for nondrinking water, the limit is 0.037 g/L.
	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 Recordkeeping. Promulgated: 60 FR 33932, 06/29/95.	EPA has set forth an enforceable drinking water standard to limit trichloroethylene levels at 0.005 ppm to reduce the risk of cancer or other adverse health effects which 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.	MCLG in primary drinking water is zero for trichloroethylene.
	40 CFR 141.60 ff.—Subpart G—National Revised Primary Drinking Water Regulations: Maximum Contaminant Levels. Promulgated: 52 FR 25716, 07/08/87.	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 trichloroethylene is 0.002 mg/L.
	40 CFR 148—PART 148—HAZARDOUS WASTE INJECTION RESTRICTIONS. Promulgated: 53 FR 28154, 06/26/88.	Trichloroethylene is identified as a hazardous waste to be restricted from EPA Class I hazardous waste injection wells.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	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).	Maximum trichloroethylene contaminant level in groundwater for solid waste disposal facilities is 0.005 mg/L. Reportable quantity of trichloroethylene is 100 lb (45.4 kg). Label, packaging, and shipping codes are also 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 MSWLF units and under the CWA, as amended, for MSWLF that are used to dispose of sewage sludge. The criteria ensure the protection of human health and the environment. Maximum contaminant level for trichloroethylene 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 trichloroethylene, the regulatory level is 0.5 mg/L; its hazardous waste number 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 which treat, store, or dispose of hazardous waste; exceptions do exist. Trichloroethylene has a Practical Quantitation Limit (PQL) of 1 µg/L.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	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 are regulated by this subsection to limit release into the environment. Maximum concentration limit for trichloroethylene for residues is 0.005 mg/kg. Maximum Allowable Wastewater Concentration is 6.6 ppm. Maximum Allowable Concentration for trichloroethylene 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.
	40 CFR 302.4—Sec. 302.4 Designation of hazardous substances. Superfund (CERCLA, SARA) reportable quantity (RQ) is 100 lb (45.4 kg).	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 EPA is required if the RQ is released to the environment.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	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, to aid in the development of regulations, guidelines, and standards. As of 1/1/87, trichloroethylene was listed under the specific toxic chemical listings.
	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 which will apply to all regulations issued concerning specific classes and categories of point sources of industrial effluents under parts 402 through 699. Trichloroethylene 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).	Regulates discharge of waste streams from several categories of industrial processes that involve electroplating or electroless plating. The concentration limit of trichloroethylene 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.	EPA gives pretreatment standards for existing sources (PSES) for metals and organics in effluents from several manufacturing categories. Limitations represent the degree of effluent reduction attainable by application of Best Available Technology (BAT).

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 414.91 ff.—Subpart I—Direct Discharge Point Sources That Use End-of-Pipe Biological Treatment.	Effluent limitation for trichloroethylene maximum concentrations for any one day is 54 μg/L, 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	Effluent limitation for trichloroethylene maximum concentrations for any one day is 69 μg/L, for any monthly average is 26 μg/L.
	40 CFR 414.110 ff.—Subpart K—Indirect Discharge Point Sources.	Effluent limitation for trichloroethylene maximum concentrations for any one day is 69 μg/L, 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 trichloroethylene 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.
	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 trichloroethylene while performing any of the following six metal finishing operations on any basis material: Electroplating, Electroless Plating, Anodizing, Coating (chromating, phosphating, and coloring), Chemical Etching and Milling, and Printed Circuit Board Manufacture.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
EPA	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 trichloroethylene to waters of the U.S. or that introduce trichloroethylene into a 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 which discharges or may discharge trichloroethylene to U.S. waters or which introduces or may introduce trichloroethylene 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 or trichloroethylene 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 trichloroethylene resulting from the manufacture of electronic crystals, cathode ray tubes, and luminescent materials.
FDA	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.	Trichloroethylene may be safely used in the color additive Annatto extract, including pigments precipitated therefrom.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
F D A	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 volatile organic chemical (VOC) trichloroethylene in bottled water is 0.005 mg/L.
	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 volatile organic chemical (VOC) trichloroethylene 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 more than 150 ppm trichloroethylene.
	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.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
FDA	21 CFR 173.290—Sec. 173.290 Trichloroethylene.	Tolerances are established for residues of trichloroethylene 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.	Trichloroethylene may be safely used in adhesives intended for use as components of articles intended for use in packaging, transporting, or holding food.
NIOSH	1/78. Special Occupational Hazard review of Trichloroethylene. DHEW Pub. No. (NIOSH) 78-130, NTIS No. PB8-1226987.	NIOSH recommends that trichloroethylene be treated as a potential occupational carcinogen. Summary of NIOSH recommendation: recommended exposure limit—25 ppm TWA; 2 ppm ceiling limit (1 hr) as a waste anesthetic gas.
	3/77. Criteria for a Recommended Standard....Occupational Exposure to Waste Anesthetic Gases and Vapors. Pub. No. 77-140, NTIS No. PB274 238.	
	6/6/75. Current Intelligence Bulletin #2—Trichloroethylene (TCE). In: NIOSH Current Intelligence Bulletin Reprints-Bulletins 1 through 18 (1975-1977). Pub. No. 78-127, NTIS No. PB83-105080.	

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
N I O S H	1973. Criteria for a Recommended Standard....Occupational Exposure to Trichloroethylene. 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-hr TWA. Ceiling 2000 ppm (1090 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-hr TWA.

[a] The regulations in this table have been updated through 62 Federal Register 37448, July 11, 1997.

3.0 HUMAN STUDIES

Case reports, descriptive studies, case-control studies, cohort studies, and environmental drinking-water studies reported through 1995 are reviewed in IARC (1995e, pp. 95-104; see Appendix A). Weiss (1996) reviewed essentially the same literature with the addition of one cohort study that had not been published in the open literature. The case-control studies reviewed included those for liver, malignant lymphoma, Hodgkin's disease, renal-cell carcinoma, cancer of the colon, brain tumors, childhood brain tumors, childhood leukemia, and tumors at multiple sites. Most of these studies did not provide relative risk estimates for exposure to only TCE; rather these studies defined occupational exposure or the occupational exposure of the parent using a broad solvent group of which TCE was one of several solvents, or by job or industry title. The cohort studies were primarily of three occupational groups: TCE production workers including workers who had undergone biological monitoring (the reason for which is unknown), aircraft maintenance workers, and workers employed in miscellaneous manufacturing industries. TCE exposure of these cohorts occurred during its use as a metal degreaser. Most workers studied in these cohorts, generally, had low-level TCE exposure, although a small number of those studied may have had high-level peak exposure to TCE. IARC placed greatest weight on the conclusions of three cohort studies (Spirtas et al., 1991; Axelson et al., 1994; and Anttila et al., 1995; all cited by IARC 1995e). These studies were considered particularly relevant for the epidemiologic evaluation of TCE since they contained the better exposure measures, and each study had a sufficiently long follow-up period. Additionally, IARC combined results from these studies in an attempt to examine consistency of results across studies. Based on these three most informative studies, IARC noted a consistently elevated risk for cancer of the liver and biliary tract, with a statistically significant elevated risk for liver and biliary tract cancer with 23 observed cases and 12.87 expected cases (RR = 1.79; 95% Confidence Interval [CI] 1.13-2.68) (all three studies combined), and a modestly elevated risk for non-Hodgkin's lymphoma with 27 cases observed and 18.9 expected (RR = 1.42; 95% CI 0.94-2.09). IARC, additionally, noted a marginally increased risk for non-Hodgkin's lymphoma and exposure to TCE-contaminated ground water in two studies. In each study, statistically significant risks were not consistently seen across all subgroups. Based on their review, IARC concluded that there was limited evidence for the carcinogenicity of TCE in humans. Weiss (1996), evaluating the same body of literature, considered the evidence for a causal association quite limited owing to the small increases in site-specific cancer risks and to the few observed numbers of site-specific cancers.

One retrospective cohort study reviewed prior to publication by IARC (1995e) has been the focus of continued discussion within the scientific community. Henschler et al. (1995a) compared the incidence of renal cancer among 169 male workers (of 183 identified workers) in a German cardboard factory exposed for at least one year (between 1956 and 1975) to TCE, with that for a comparison group of 190 unexposed male workers in the same factory. The follow-up period averaged 34 years and the incidence of cancer among workers was compared to the expected cancer rates using two registries (Denmark and the former German Democratic Republic [GDR]). TCE was the primary organic solvent used for cleaning and degreasing, while other agents that were occasionally used were of negligible quantity. Direct exposure measurements were unavailable [although Brüning et al. (1996) were able to give some qualitative classifications]; workers were classified as exposed or not exposed based on working in three locations. Potentially high levels of TCE exposure may have been encountered by

workers. In the cardboard-machine area, TCE was kept in open barrels and used biweekly to soak rags for cleaning machinery. Workers reported leaving often for fresh air and experiencing drowsiness, headaches, and a sweet taste in the mouth. In two other areas, the locksmith's area and the electrical workshop, TCE was also kept in open barrels, and metal parts were dipped into open baths of TCE for degreasing. No protective measures were used; workers manually dipped the metal parts without using gloves, then set them out to dry in the work area, and then returned the used TCE to the open barrel. In addition, they used TCE to clean floors, work clothes, and their hands.

By the study's closing date of December 31, 1992, five exposed workers and no control workers had been diagnosed with kidney cancer, primarily renal cell carcinoma. Four of the renal cell tumors originated in the tubule epithelia. Additionally, by mid-1993, two more exposed workers were diagnosed with kidney cancer. Three of the seven workers who developed cancer had worked in the cardboard-machine area, one in the locksmith's area, and three in the electrical workshop. The SIR (standardized incidence ratio) was 7.97 (95% CI = 2.59-18.59) based on the Danish rates and 9.66 (CI = 3.14-22.55) based on the GDR rates. By the end of 1992, 50 exposed workers had died, as had 52 control workers. Of the 50 exposed workers who died (SMR = 0.79), 15 died from malignant neoplasms (SMR = 1.01); two of these died from renal cancer (SMR = 3.28, 95% CI, 0.40-12). Of the 52 control workers who died (SMR = 1.03), 15 died from malignant neoplasms (SMR = 1.16), none of which was renal cancer. Time between exposure and diagnosis of renal cancer was 18 years or more. There was no significant difference between the groups in body mass index, blood pressure, diuretic intake, smoking habits, and drinking habits. These factors were not used directly in the analysis to confirm the lack of confounding.

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).

The study has been criticized on a number of grounds. IARC (1995e) noted that the study may have been initiated after the observation of a cluster. Swaen (1995) and Bloemen and Tomenson (1995) also noted the study was a cluster study, high exposures were speculative, physician and hospital records should not be compared with general population mortality rates, and a general inventory of cancer incidence was not performed. Weiss (1996) was also concerned about the possibility of increased disease surveillance because of a suspected cluster.

Henschler et al. (1995b) responded by stating that cluster studies have commonly been a mechanism for identifying human occupational carcinogens, and that epidemiological studies not initiated by a cluster have only occasionally identified human carcinogens successfully. They further replied that although exposure data were not obtainable, the factory's consumption of TCE was well documented and its operational processes were well described. Furthermore, they noted that the best morbidity records available were used and that the absence of increased kidney cancer in the other studies may have been related to the much lower TCE exposures experienced by these other cohorts.

In summary, the concerns raised about the Henschler et al. (1995a) study have generally limited its usefulness for assessing the causal evidence for the human carcinogenicity of TCE; however, the utility of this study may be to promote further research regarding the possible association between renal cell carcinoma incidence and TCE exposure.

A recent population based case-control study in Montreal (Fritschi and Siemiatycki, 1996) found a significantly increased risk of melanoma from occupational exposure to trichloroethylene (see **Table 3-1**). However, the association was based on a relatively small number of exposed subjects and there did not appear to be a difference in the exposure categories. The trichloroethylene analysis was part of a larger study that examined melanoma occurrence in relation to 85 individual substances in 13 occupations and 20 industries. The odds ratio (OR) estimate of the relative risk of melanoma, based on four exposure cases, was 3.4 (95% CI = 1.0-12.3) for the category of potentially substantial exposure to trichloroethylene. A similar OR of 3.4 (exposure cases = 4; 95% CI = 1.0-12.3) was found for the substantial exposure category.

Table 3-1 Post IARC (1995) Human Studies of Trichloroethylene

Design	Population Group	Exposure	Effects	Potential Confounders	Comments	Reference
case-control	**Cases:** 103 men resident in Montreal, Canada, with histologically confirmed cutaneous melanoma, aged 35-70; response rate = 83% **Controls:** Two groups - 1) 533 cancer patients, excluding lung cancer 2) 533 population controls from electoral lists or random digit dialing; response rate = 71%	**Evaluation:** semistructured probing interview for detailed information about all jobs of each subject throughout working life; chemists and industrial hygienists evaluated exposure to 294 substances, including trichloroethylene, by consideration of occurrence, exposure frequency, concentration of substance; assigned exposure categories **Categories:** unexposed, insubstantial exposure, substantial exposure	**Estimation:** analyzed exposures with four or more cases of melanoma; used unconditional logistic regression model, including three confounders (age, years of schooling, ethnicity), to derive odds ratios (OR) for melanoma risk for three exposure groups; pooled data from two control groups after confirmation of similar results from independent analyses **OR** (95% CI; no. cases) for melanoma risk: 3.8 (1.1-13.6; 4) for insubstantial exposure to trichloroethylene 3.4 (1.0-12.3; 4) for substantial exposure to trichloroethylene 3.6 (1.5-9.1; 8) for any exposure to trichloroethylene	age, ethnic origin, origin of parents, birthplace, residence for first 15 years, height, weight, years of schooling, annual income, recent hobbies; information from structured questionnaire no information obtained on adult exposure to sun	weakened by small number of cases	Fritschi and Siemiatycki (1996)

Abbreviations: OR = odds ratio; CI = confidence interval

4.0 EXPERIMENTAL CARCINOGENESIS

Experimental carcinogenicity studies conducted by NTP are reported in NTP (1988; 1990, pp. 34-51; see Appendix B). These and other studies conducted prior to 1995 are reviewed in IARC (1995e, pp. 105-109; see Appendix A). More recent experimental carcinogenicity studies were not located. Based on the studies conducted, IARC (1995e) concluded that there was sufficient evidence in experimental animals for the carcinogenicity of TCE.

NTP (1988) conducted a two-year carcinogenicity study to evaluate for strain differences among rats (ACI, August, Marshall, Osborne-Mendel) in their sensitivity to TCE administered by gavage. NTP concluded that these studies were inadequate because of chemically induced toxicity, reduced survival, and deficiencies in study conduct. Despite these limitations, a significant increase in the incidence of renal tubule-cell adenoma occurred in male Osborne-Mendel rats and interstitial cell neoplasms of the testis were observed in Marshall rats.

Subsequently, NTP (1990) evaluated the carcinogenicity of epichlorohydrin-free TCE administered by gavage to $B6C3F_1$ mice and F344/N rats. TCE was carcinogenic in $B6C3F_1$ mice, inducing a significant increase in the incidence of hepatocellular carcinomas in males and females and hepatocellular adenomas in females. Although the experiment in male F344/N rats was considered inadequate for evaluating the carcinogenic activity of TCE, a significant increase in the incidence of renal tubule-cell neoplasms occurred in males. TCE was not carcinogenic in female rats.

IARC (1995e) noted that TCE, when tested by inhalation, induced in mice an increased incidence of lymphomas in NMRI mice, liver tumors in ICP mice, and lung tumors in ICR, Swiss, and $B6C_3F_1$ mice. Maltoni et al. (1988; cited by IARC, 1995e) observed an increased incidence of interstitial-cell testicular tumors in Sprague-Dawley rats and noted that TCE possibly induces leukemias in rats.

Rodents exposed to TCE typically exhibit dose-related cytomegaly of the kidney, 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.

5.0 GENOTOXICITY

5.1 Summary of IARC (1995) Genotoxicity Studies

Genotoxicity studies reported prior to 1995 are reviewed in IARC (1995e, pp. 122-133; see Appendix A). In general, TCE was negative for genetic activity in a broad range of bacterial, lower eukaryote, and *in vitro* and *in vivo* mammalian cell assays. It has been suggested that the positive response could be confounded by the use of impure TCE and/or the presence of potentially mutagenic stabilizers (Goeptar et al., 1995). The following is summarized from IARC (1995e).

In prokaryotes, pure TCE did not usually induce gene mutations or DNA damage, while preparations containing epoxide stabilizers were mutagenic. In lower eukaryotes, TCE was negative for the induction of gene conversion and reverse mutations in *Saccharomyces cerevisiae* (with and without metabolic activation), forward mutations in *Schizosaccharomyces pombe* (with and without metabolic activation), mitotic crossing over in *Aspergillus nidulans* (without metabolic activation), and sex-linked recessive lethal mutations in *Drosophila melanogaster* dosed via injection. TCE was positive for the induction of forward mutations in *A. nidulans*

(without metabolic activation) and equivocal for sex-linked recessive lethal mutations in *D. melanogaster* dosed via feed.

In *in vitro* studies using mammalian cells, TCE was negative for the induction of unscheduled DNA synthesis (UDS) in primary rat hepatocytes, gene mutations in human lymphoblastoid cells (with and without metabolic activation), chromosomal aberrations in Chinese hamster ovary (CHO) (with and without metabolic activation), and inhibition of intercellular communication in rat hepatocytes. In contrast, TCE was positive *in vitro* for covalent DNA binding to calf thymus and salmon sperm DNA (with metabolic activation only) and to the DNA of primary mouse and rat hepatocytes, sister chromatid exchanges (SCE) in CHO cells (with and 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 was equivocal for covalent binding to the DNA of mouse and rat liver and negative for DNA of mouse spleen, pancreas, lung, testis, kidney, and brain. When administered orally and/or by inhalation, TCE was negative for the induction of UDS in mouse hepatocytes, SCE in mouse splenocytes and rat lymphocytes, dominant lethal mutations in mice, and chromosomal aberrations in mouse splenocytes and rat lymphocytes. TCE was negative for the induction of micronuclei in mouse bone marrow (when administered i.p.) or in mouse splenocytes, mouse spermatocytes, and rat lymphocytes (when administered by inhalation). It was negative and positive for DNA single-strand breaks/alkali labile sites in mouse liver (administered i.p. or orally) and positive for micronucleated polychromatic erythrocytes in mice treated orally and in rats treated by inhalation.

Several studies were conducted to evaluate for genotoxic effects in occupationally exposed humans. The frequency of sperm head abnormalities was not increased. In two studies evaluating the frequency of SCE in mitogen-stimulated lymphocytes, one reported no increase while a second study reported an increase among TCE-exposed smokers but not among nonsmokers. In two studies, a significant increase in chromosomal damage in mitogen-stimulated lymphocytes was detected.

5.2 Genotoxicity Studies Published Post IARC (1995)

In addition to these *in vitro* and *in vivo* studies reviewed by IARC (1995e), TCE was reported as negative for mitotic recombination (as measured by the eye mosaic test) in *D. melanogaster* exposed to TCE via inhalation (Vogel and Nivard, 1993), negative for the induction of chromosomal aberrations in Chinese hamster lung cells (with and without metabolic activation) (Matsuoka et al., 1996), and negative for the induction of UDS in hepatocytes of $B6C3F_1$ mice (Miyagawa et al., 1995) treated orally. These studies are summarized in greater detail in **Table 5-1**.

TABLE 5-1. SUMMARY OF RECENT TRICHLOROETHYLENE GENOTOXICITY STUDIES

System	Biological Endpoint	Exogenous Metabolic Activation	Form and Purity	Dose Used	Endpoint Response or Activation	Comments	Reference
Lower Eukaryotes							
Drosophila melanogaster strain C-1	mitotic recombination (eye mosaic assay)	n.a.	NG	280 to 4000 ppm via inhalation for 17 h	negative	Genetic principle involves loss of heterozygosity for the wild type, 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 or S9 condition.	Matsuoka et al. (1996)
Mammalian Systems *in vivo*							
B6C3F$_1$ mouse hepatocytes	unscheduled DNA synthesis (UDS)	n.a.	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)

Abbreviations: n.a. = not applicable; NG = not given

6.0 OTHER RELEVANT DATA

6.1 Absorption, Distribution, Metabolism, and Excretion

6.1.1 Absorption and Distribution

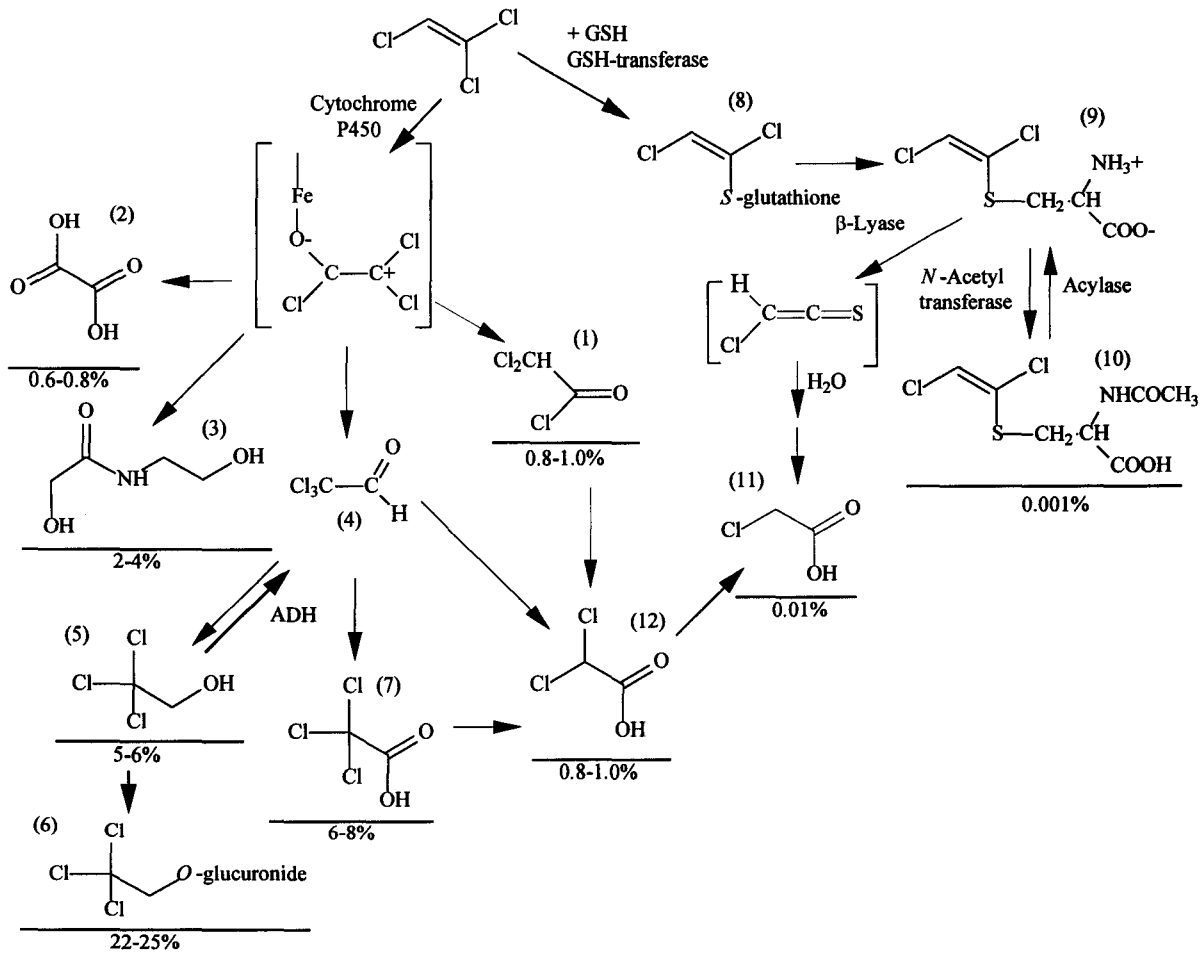
Studies in rats and mice have found rapid absorption of TCE through the lungs and from the gastrointestinal tract but negligible absorption through skin (IARC, 1995e). After 4 hours of exposure to 529 ppm (2840 mg/m^3, 21.6 mmol/m^3), male Fischer 344 rats had blood TCE concentrations of 35.5 μg/mL (0.27 μmol/mL), while females exposed to 600 ppm (3220 mg/m^3, 24.5 mmol/m^3) had blood TCE concentrations of 25.8 μg/mL (0.196 μmol/mL) (Fisher et al., 1991; cited by IARC, 1995e). Male and female B6C3F$_1$ mice were exposed for four hours to 110-748 ppm (591-4020 mg/m^3, 4.50-30.6 mmol/m^3) and 42-889 ppm (226-4780 mg/m^3, 1.72-36.4 mmol/m^3), respectively. The highest mean blood concentration seen for males was 7.3 μg/mL (0.056 μmol/mL) after exposure to 748 ppm (4020 mg/m^3, 30.6 mmol/m^3) while females reached a high of 6.3 μg/mL (0.048 μmol/mL) after exposure to 368 ppm (1980 mg/m^3, 15.1 mmol/m^3) (Fisher et al., 1991; cited by IARC, 1995e).

Mice given 280 mg/kg (2.13 mmol/kg) radiolabeled TCE in a 10-minute inhalation exposure were studied by whole body autoradiography (Bergman, 1983; cited by IARC, 1995e). TCE was found throughout the body in well-perfused organs; redistribution to adipose tissue occurred after 30 minutes. TCE is concentrated in lipophilic organs such as liver or brain due to an oil:water partition coefficient of 900:1 (Müller et al., 1975; Kilburn and Warshaw, 1993; both cited by Gist and Burg, 1995). Ovaries (Manson et al., 1984; cited by Gist and Burg, 1995) and spermatocytes (Land et al., 1979; cited by Gist and Burg, 1995) are other tissues in which TCE concentrates.

6.1.2 Metabolism and Excretion

Rats and mice metabolize TCE via two different methods—oxidation by cytochrome P450 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 by Bernauer et al., 1996) (see **Figure 6-1**).

Figure 6-1. Proposed Metabolism of TCE in Rats. Underlined compounds are identified urinary metabolites (IARC, 1995e). (Figure modified from Dekant et al., 1984; Dekant, 1986; both cited by 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. Percentages were determined after an oral dose of 200 mg/kg.



More than 99% of urinary TCE metabolites stem from cytochrome P450-catalyzed reactions (Dekant et al., 1984; cited by IARC, 1995e). 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 by Vamvakas, 1993), or by rearrangement of a non-epoxide intermediate (Miller and Guengerich, 1982; cited by Vamvakas, 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 trichloroacetic acid (TCA) (Butler, 1949; Daniel, 1963; Kimmerle and Eben, 1973; all cited by IARC, 1995e). TCA glucuronide has been found in the urine of non-human primates treated with TCE by intramuscular injection (Müller et al., 1982; cited by IARC, 1995e). Dichloroacetic acid (DCA) may be formed by a rearrangement of the putative epoxide intermediate 1,1,2-trichlorooxirane and subsequent hydrolysis (Hathway, 1980; cited by IARC, 1995e) or by biotransformation of choral hydrate or TCA (Larson and Bull, 1992b; cited by IARC, 1995e). Oxalic acid may be formed by oxidation of DCA (Larson and Bull, 1992b; cited by IARC, 1995e) 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; cited by IARC, 1995e). *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; cited by IARC, 1995e). 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).

Most TCE metabolites found in experimental animals have also been found in humans (see **Table 6-1**) and there is no evidence that the metabolism of TCE in animals differs from human metabolism (IARC, 1995e). Based on *in vitro* metabolism studies with 23 human hepatic microsomal samples, Lipscomb et al. (1997) concluded that CYP2E1 was predominantly responsible for the microsomal-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 (GI) 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) TCE in a 5% aqueous Alkamuls emulsion, the liver eliminated 10-fold more drug than 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 for three hours to TCE at concentrations up to 315 ppm (1690 mg/m^3, 12.9 mmol/m^3), metabolism was not saturated (Ikeda, 1977; Nomiyama and Nomiyama, 1977; both cited by Lee et al., 1996). This finding led the authors to hypothesize

that a single pass through the liver is sufficient to completely remove TCE from the blood. Based on these data, Lee et al. (1996) concluded that since 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 by Templin et al. (1993; cited by Stenner et al., 1997). Stenner et al.(1997) performed a study to determine if enterohepatic recirculation of trichloroethanol and TCA could explain the TCA concentrations seen in blood following administration of TCE. Male F344 rats with and without intact enterohepatic recirculation were given intravenous doses of 100 mg/kg (0.669 mmol/kg) trichloroethanol. The results demonstrated that roughly 36% of the trichloroethanol and 76% of the TCA in systemic blood was due to enterohepatic recirculation. Urinary excretion of TCA was decreased by 80% in rats lacking enterohepatic recirculation following intravenous administration of trichloroethanol (Stenner et al., 1997). Using these as well as previous findings, the authors concluded that enterohepatic recirculation can account for the delay seen prior to the appearance of TCA in the blood after administration of oral doses of TCE.

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 urine in humans are trichloroethanol, trichloroethanol glucuronide, and TCA (Cole et al., 1975; cited by IARC, 1995e).

Table 6-1. Metabolites of TCE by Species

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

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

6.2 Pharmacokinetics

The maximum metabolic rate (V_{max}) for TCE in rats is 100.6 µg/min (0.77 µmol/min) with a Michaelis constant (k_m) of 5.05 µg/mL (0.038 µmol/mL). Absorption by organs occurs with the following organ-to-blood partition coefficients: GI 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/hr (1.636 mmol/hr) based on the V_{max} found in rats using the allometric relationship (Human V_{max}) = (Rat V_{max}) [70/(Rat wt., kg)]$^{0.7}$ (Gargas et al., 1986; cited by Rappaport, 1993). Of the absorbed dose of TCE, 0.75 is the fraction metabolized (F_M) as obtained from estimated human clearance rates (Sato and Nakajima, 1987; cited by Rappaport, 1993). Using these two values, Rappaport (1993) calculated that 178.3 mg/m^3 (1,357 mmol/m^3) is the highest mean TCE concentration to which a person can 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 humans exposed to varying levels of TCE was examined for the presence of TCE metabolites (Bernauer et al., 1996). After inhalation of 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 in addition to a slow rate of elimination compared to the oxidatively formed metabolites. When five male volunteers were exposed to 70 ppm (380 mg/m^3, 2.9 mmol/m^3) TCE for 4 hours per day over a 5-day period, trichloroethanol concentrationsin urine rose rapidly, then stabilized, and remained high for the duration of the 5 days (Monster et al., 1979; cited by IARC, 1995e). 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 slowly eliminated 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; cited by IARC, 1995e). The difference is even more marked in rats; high levels of TCA are present in the blood for up to 30 hours in contrast to trichloroethanol and chloral hydrate, which are cleared from the blood with a half-life of 1to 2 hours (Kimmerle and Eben, 1973; cited by IARC, 1995e).

6.3 Structure-Activity Relationships

6.3.1 Chlorinated Alkanes and Alkenes

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

6.3.2 Structural Analogues

Structural analogues of TCE include vinyl chloride (chloroethylene), vinylidene chloride (1,1-dichloroethylene), and 1,1,2,2-tetrachloroethylene (perchloroethylene).

6.3.2.1 Vinyl Chloride

Based on human epidemiological studies and case reports, and rodent carcinogenicity data, IARC (1979) concluded that there was sufficient evidence for the carcinogenicity of vinyl chloride to humans and experimental animals, respectively. IARC (1987a) reaffirmed vinyl chloride's evaluation as a human carcinogen, citing several additional epidemiological studies and case reports. Occupational exposure to vinyl chloride is associated with increased risks for 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, 1987). 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 excessive fetal mortality among wives of workers exposed to vinyl chloride, and several others 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's gland tumors in rats and hamsters, nephroblastomas in rats, forestomach papillomas and melanomas 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).

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 unscheduled DNA synthesis (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 lethals in *D. melanogaster* and was mutagenic in plants and *S. pombe* (but not other fungi). In rodents exposed *in vivo*, vinyl chloride induced chromosomal aberrations, SCE, and micronuclei in bone marrow cells, and alkylated DNA in tissues of mice and rats. 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 sister chromatid exchanges (SCE), while one study indicated a weakly positive response. Green (1990) suggested that vinyl chloride's carcinogenic activity results from its metabolism by microsomal mixed-function oxidases to choro-oxirane (chloroethylene oxide) and chloroacetaldehyde, two mutagenic metabolites, and concludes that vinyl chloride is a classical genotoxin causing cancer by somatic mutation.

6.3.2.2 Vinylidene Chloride

IARC (1987b) concluded that vinylidene chloride was not classifiable as a human carcinogen because of inadequate evidence and also considered the evidence for its carcinogenicity to animals to be limited. There were no data available on its genetic and related effects in humans. Green (1990) stated that the question of vinylidene chloride's carcinogenicity

has never been resolved, although as the closest analogue of the well established carcinogen vinyl chloride, it might be expected to be carcinogenic.

Experimental carcinogenicity 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 treatment-related neoplasms in rats and hamsters; in mice, however, males showed a treatment-related increase in the incidence of kidney adenocarcinomas, females showed an increase in the incidence of mammary carcinomas, and both males and females showed an increase in pulmonary adenomas. Mice given several subcutaneous administrations showed no tumors at injection sites. Maltoni et al. (1984a,b; cited by Green, 1990) found severe nephrotoxicity in Swiss mice exposed to high doses, and tumors in only 2 of 18 surviving mice. Male Swiss mice were more susceptible to nephrotoxic effects than were other mouse strains, rats, and hamsters. Green (1990) suggests that kidney damage in Swiss mice may facilitate expression of the weak genotoxic potential of vinylidene chloride's metabolites.

As reviewed by 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 treated mice.

6.3.2.3 Tetrachloroethylene

IARC (1995c) has evaluated tetrachloroethylene as probably carcinogenic to humans, 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 carcinomas (IARC, 1995c). Mice exposed to high doses by inhalation showed exposure-related increases in hepatocellular adenomas and carcinomas (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 tubule-cell adenomas and adenocarcinomas in male rats (NTP, 1986). In a study by Anna et al. (1994; cited by IARC [1995e]), 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 to liver tumors from concurrent and historical control animals.

Tetrachloroethylene is generally negative in most genetic toxicology assays (IARC, 1995c). Tetrachloroethylene was not active in the SOS chromotest with *Escherichia coli* and was not mutagenic to bacteria in the absence of metabolic activation. Purified tetrachloroethylene was not mutagenic in *S. 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 kidney microsomes (Vamvakas et al, 1989; cited by IARC, 1995c). In stationary-phase yeast, it did not induce gene conversion, mitotic recombination, or reverse mutations, while conflicting data were obtained for cells in logarithmic growth. Tetrachloroethylene was negative for the induction of sex-linked recessive lethal mutations in *D. melanogaster*, unscheduled DNA synthesis in rat primary hepatocytes,

chromosomal aberrations or SCE in cultured Chinese hamster lung cells (with and without metabolic activation), and for mutations in mouse lymphoma cells (with and 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* have been reported. It was also reported positive for cell transformation in Fischer rat embryo cells but not in mouse BALB/c-3T3 cells. In *in vivo* studies, the frequency of gene conversion and reverse mutations was not increased in a host-mediated assay using yeast recovered from the liver, lungs, and kidneys of mice treated with tetrachloroethylene. A significant increase in DNA damage (strand breaks/alkali-labile sites) in mouse liver and kidney, but not lung, was detected after treatment.

IARC (1995c) noted two studies of workers occupationally exposed to tetrachloroethylene in which small increases of peripheral lymphocytes showing numerical chromosome abnormalities (Ikeda et al., 1980; cited by IARC, 1995c), and SCE frequency in subjects who smoked (Seiji et al, 1990; cited by IARC, 1995c). In both studies, the possible confounding effects of smoking were not controlled.

6.3.3 Metabolites

6.3.3.1 Dichloroacetic Acid and Trichloroacetic Acid

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

The genetic toxicity of DCA in prokaryotic or animal cells is 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*, DCA administered acutely induced DNA strand breaks in liver cells of rats and mice in one laboratory, while another laboratory using higher doses reported the absence of DNA strand breakage in rat and mouse hepatic cells after single or repeated dosing, or in epithelial cells from mouse spleen, stomach, and duodenum after a single dose.

IARC (1995d) concluded that there is inadequate evidence in humans and limited evidence in experimental animals for the carcinogenicity of TCA. TCA induced a significant increase in the incidence of hepatocellular adenomas and carcinomas in two B6C3F_1 male mouse drinking water studies (IARC, 1995d). Expression of c-*myc* and c-H-*ras* was increased by approximately 6-fold and 4-fold, respectively, in hepatic carcinomas sampled from TCA-treated mice.

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, while another laboratory using higher doses reported no increase in DNA strand breaks in rat and mouse hepatic cells, or in mouse epithelial cells from stomach and duodenum. TCA was reported as positive for the induction of micronuclei and chromosomal aberrations in bone marrow cells and abnormal sperm morphology after injection into Swiss mice, but negative for micronuclei induction at a 10-fold higher dose injected in C57BL/JfBL/Alpk mice.

6.3.3.2 Chloral Hydrate

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

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 treated *in vivo* (in three of four studies), and in bone marrow cells of mice treated *in vivo*. Chloral hydrate induced a significant increase in 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 treated *in vivo*. Where evaluated, the micronuclei were most frequently induced by numerical rather than structural chromosomal damage.

IARC (1995a) noted conflicting results for DNA damage caused by chloral hydrate. It was mutagenic, with and without metabolic activation, in *S. typhimurium* TA100 (two of four studies) and in TA104 (single study) but not in TA1535, TA1538, or TA98. It was negative for mitotic crossing over in *A. nidulans* in the absence of metabolic activation, but weakly positive for meiotic recombination and gene conversion (but not reverse mutations) in *S. cerevisiae* in the presence and absence of metabolic activation, respectively. It induced somatic mutations in *D. melanogaster*, but was negative for DNA protein cross-links in rat liver nuclei and for DNA single strand breaks/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. cerevisae* recovered from mouse lungs. One laboratory reported a significant increase in DNA strand breaks in liver DNA of treated rats and mice, while another laboratory reported a negative study. Chloral hydrate did not induce chromosomal aberrations in mouse bone marrow cells, spermatogonia, spermatocytes, or oocytes. However, a significant increase in chromosomal aberrations in mouse secondary spermatocytes was reported for one study.

6.3.3.3 Dichlorovinylcysteine

Dichlorovinylcysteine is mutagenic in the Ames test and highly nephrotoxic (Vamvakas et al., 1993; Clewell et al., 1995). DNA damage in kidney tubules was found to be induced *in vivo* and *in vitro* by *S*-(1,2-dichlorovinyl)-*L*-cysteine, and in LLC-PK_1 cells, double-strand breaks were found (Jaffe et al., 1985; Vamvakas et al., 1992; both cited by Vamvakas et al., 1993). Radiolabeled cysteine conjugates added to bacterial and renal cells resulted in covalent binding to DNA (Bhattacharya and Schultze, 1972, 1973a,b; Vamvakas et al., 1988; cited by

Vamvakas et al., 1993). Pyridine nucleotide oxidation is induced by *S*-(1,2-dichlorovinyl)-*L*-cysteine incubated with kidney mitochondria (Meadows et al., 1988; Vamvakas et al., 1992; both cited by Vamvakas et al., 1993). At concentrations producing small or undetected decreases in cell growth, the cysteine metabolite induces Ca^{2+}-dependent DNA damage. Following this DNA fragmentation, an increase is seen in ADP-ribosylation of nuclear proteins (Vamvakas et al., 1992; cited by Vamvakas et al., 1993), which, if moderate, has been shown in mouse fibroblasts to be associated with increased cell proliferation (Muehlematter et al., 1988; cited by Vamvakas et al., 1993).

Prior to the collapse of the mitochondrial membrane potential, cytosolic Ca^{2+} concentrations are increased by *S*-(1,2-dichlorovinyl)-*L*-cysteine in renal cells (Vamvakas et al., 1990; cited by Vamvakas et al., 1993). Tumor promoters that induce oxidative stress commonly produce such an effect (Vamvakas et al., 1993). IARC has not yet determined a classification for dichlorovinylcysteine.

6.4 Immune Suppression

Sprague-Dawley rats and B6C3F1 mice given i.p. doses of TCE 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) reported on a study that concluded that a linkage existed between a known molecular genetic cause for renal cell carcinoma [i.e., somatic mutations of the von Hippel-Lindau (*VHL*) tumor suppressor gene] and exposure to TCE. Somatic *VHL* mutations are a known causative molecular event in renal cell carcinoma (Gnarra et al., 1994). Tumor tissues from 23 patients with renal cell cancer and a history of occupational exposure to high levels of TCE were evaluated. The patients all had worked with TCE in small, poorly ventilated areas and frequently experienced room temperatures between 30° and 50 °C (85° - 124 °F). They reported dizziness, headache, nausea, and drowsiness, a pronounced smell of TCE in the work area, and a need for frequent breaks to get fresh air outside the work area. The average long-term exposure to TCE was 21.8 years. The cases did not come from a single source, but rather from two case-control studies and pending legal compensation cases.

DNA was isolated from microdissected tumor cells, amplified by polymerase chain reaction (PCR), and analyzed using single-strand conformation polymorphism (SSCP) and sequencing. Renal cell carcinoma tissue from all 23 TCE-exposed patients had an abnormal SSCP pattern in at least one of the *VHL* exons (30% of the of the aberrations were in exon 1, 44% of the band shifts occurred in exon 2, and 26% were in exon 3). Although sequencing analyses were not yet completed, four SSCP band shifts were confirmed as *VHL* mutations. Based on the much lower reported frequency of *VHL* mutations (33-55%) in renal cell carcinomas from non-exposed patients (Gnarra et al., 1994; Shuin et al., 1994; Foster et al., 1994; Whaley et al., 1994) and the lower frequency of exon 2 mutations (24%) in cases where a *VHL* mutation was present (Gnarra et al., 1994), Brüning et al. (1997) concluded that these data provided further proof for human renal carcinogenicity induced by high occupational exposure to TCE. This analysis provides interesting new data suggesting a possible direct molecular

association between exposure and a potentially important somatic alteration in renal cell carcinoma. These preliminary findings should be regarded with caution. Not all VHL gene mutations had been confirmed by sequencing. Exposure was not precisely determined for each individual, cases were not selected systematically from a well-defined study base, and comparison subjects from the same base were not used.

7.0 MECHANISMS OF CARCINOGENESIS

7.1 Liver Cancer

Hepatocellular carcinomas have been reported in some strains of mice but not in rats treated with TCE (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). Both TCA and DCA induce hepatocellular adenomas and carcinomas in mice (section 6.3.3.1), possibly mediated through the induction of peroxisome proliferation, cytotoxicity, and reparative hyperplasia (Maronpot et al., 1995). TCE-induced peroxisome proliferation has not been demonstrated in the rat (Elcombe, 1985). Goeptar et al. (1995) concluded that the species difference in TCE-induced peroxisome proliferation was most likely due to the 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 involvement of TCA and DCA in TCE-induced hepatocellular carcinomas in the mouse is further supported by studies in which strain differences in the incidence of liver tumors correlate with differences in the oxidative metabolism of TCE. For example, TCE induces liver tumors in Swiss and B6C3F_1 mice (NTP, 1986; Maltoni et al., 1986, cited by Goeptar et al., 1995) but not NMRI mice (Henschler et al., 1980; cited by Goeptar et al., 1995). In the former strains, TCA and DCA account for 7-12 and 2% of the TCE administered, respectively (Green and Prout, 1985; cited by Goeptar et al., 1995), while in the latter strain, TCA and DCA each accounts for only 0.1% of the TCE dose (Dekant et al., 1984; cited by Goeptar et al., 1995). Based on this line of reasoning, the ability of TCE to induce liver tumors in humans depends 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).

7.2 Lung Cancer

TCE, when administered by inhalation, induces a significant increase in the incidence of lung tumors (adenomas and carcinomas) in female (but not male) B6C3F_1 mice and male (but not female) Swiss mice. 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). Mouse Clara cells studied *in vitro* were found to have relatively high cytochrome P450 activity and relatively low activity for alcohol dehydrogenase (ADH), the enzyme that converts chloral to trichloroethanol, and for uridine diphosphate (UDP) glucuronosyl transferase, the enzyme responsible for the glucuronidation of trichloroethanol (Odum et al., 1992; cited by 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 by 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 by Goeptar et al., 1995) implies a lack of cytochrome P450 activity and a corresponding lack of risk for chloral accumulation.

7.3 Kidney Cancer

In contrast to tumors of the lung and liver, kidney tumors are 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). In a minor mercapturic metabolic pathway, TCE is conjugated to glutathione in the liver. The conjugated TCE is further metabolized in the kidney to cysteine conjugate dichlorovinylcysteine (DCVC) and then to a reactive intermediate (Birner et al., 1993; cited by Clewell et al., 1995). The mutagenic and nephrotoxic properties of the *S*-1,2 isomer of DCVC are described in section 6.3.3.3.

Goeptar et al. (1995) concluded that it seemed improbable that the oxidative pathway would become saturated in humans at the levels of TCE to which they are likely to be exposed. 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 by Clewell et al., 1995).

Furthermore, one human study strongly suggests that kidney damage is 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 that for 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 of the unexposed patients was similar to that of the TCE-exposed patients.

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

There is excellent 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, 1995e); (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 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 Clewel et al.,

1995), humans seem to be more sensitive than rats in developing the primary biochemical lesion leading to the induction of renal cancer.

7.4 Structural Analogues

As discussed in 6.3.2, the structural analogues of TCE include vinyl chloride (chloroethylene), vinylidene chloride (1,1-dichloroethylene), and 1,1,2,2-tetrachloroethylene. Of the three analogues, TCE appears to be most similar in tumor sites to vinylidene chloride and tetrachloroethylene.

Vinyl chloride is carcinogenic in humans and experimental animals. Occupational exposure to vinyl chloride is associated with increased risks for angiosarcoma of the liver, hepatocellular carcinoma, brain and lung tumors, and malignancy of the hematopoietic and lymphatic system. In experimental animal studies, oral administration or inhalation of vinyl chloride induced Zymbal's gland tumors in rats and hamsters, nephroblastomas in rats, forestomach papillomas and melanomas in hamsters, and pulmonary and mammary gland tumors in mice, and hemangiosarcoma of the liver in all three species. Vinyl chloride is considered a genotoxic carcinogen.

In contrast, vinylidene chloride was not classifiable as a human carcinogen because of inadequate evidence and also the evidence for its carcinogenicity to animals is considered to be limited. In experimental carcinogenicity studies, vinylidene chloride induces kidney adenocarcinomas in males and mammary carcinomas in females; both males and females showed an increase in pulmonary adenomas. Vinylidene chloride was genotoxic in some assays, inducing mutations in bacteria and yeast, UDS in primary rat hepatocytes, and UDS in treated mice.

Tetrachloroethylene is classified as probably carcinogenic to humans, 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 carcinomas. Mice exposed to high doses by inhalation showed exposure-related increases in hepatocellular adenomas and carcinomas. 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 tubule cell adenomas and adenocarcinomas in male rats. Tetrachloroethylene is generally negative in most genetic toxicology assays.

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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)

APPENDIX B

Excerpts from the 1990 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)
pp. 7-8, 34-39, 46-51

APPENDIX C

DESCRIPTION OF ONLINE SEARCHES FOR TRICHLOROETHYLENE

DESCRIPTION OF ONLINE SEARCHES FOR TRICHLOROETHYLENE

Searches were limited to 1989 [the year before the NTP bioassay (NTP, 1990) which has an extensive literature review] through September 1997.

Online searches for trichloroethylene [CASRN 79-01-6] were performed in databases on the systems of the National Library of Medicine, STN International, DIALOG, and the Chemical Information System from 1989 to date. Toxicology information was sought in EMIC, EMICBACK, RTECS, and TOXLINE. Occupational safety and health information was obtained from NIOSHTIC. Environmental information was obtained from TRI95 (Toxic Chemical Release Inventory for 1995, online availability 1997) and the Chemical Abstracts file, which was searched by appropriate section codes (59, air pollution and industrial hygiene; 60, waste treatment and disposal; and 61, water). The Chemical Abstracts Service Registry file and SANSS provided chemical identification information.

Market information was sought in The Chemical Economics Handbook.

Regulatory information was obtained from the online database CHEMLIST and the in-house FESA CD-ROM containing the latest *Code of Federal Regulations* and the *Federal Register* pertaining to CFR titles 21 (FDA), 29 (OSHA), and 40 (EPA).

Also, the review of 1200 life sciences journals for current awareness was accomplished using Current Contents on Diskette® (and cumulative issues on CD-ROM).

APPENDIX D

REPORT ON CARCINOGENS (ROC), 9TH EDITION
REVIEW SUMMARY

Report on Carcinogens (RoC), 9th Edition
Review Summary

Trichloroethylene

NOMINATION
Review based on results of an NTP Bioassay of Trichloroethylene (1990), reporting clear evidence of carcinogenicity in experimental animals.

DISCUSSION
Trichloroethylene is used as an industrial solvent for vapor degreasing and cold cleaning of fabricated metal parts. It has also been used as a carrier solvent for the active ingredients of insecticides and fungicides, as a solvent for waxes and oils, as an anesthetic for medical and dental use, and as an extractant for spice oleoresins and for caffeine from coffee. There is clear evidence that trichloroethylene causes malignant tumor formation in multiple species of experimental animals. Epidemiological data are limited for evaluating the carcinogenicity of trichloroethylene in humans although studies have suggested that occupational exposure to trichloroethylene causes cancer of the liver and biliary tract, and also non-Hodgkin's lymphoma. A recently published epidemiology study has indicated that occupational exposure to trichloroethylene has also been associated with renal cancer in workers. The recommendations from the three NTP reviews of this nomination are as follows:

Review Committee	Recommendation	Vote
NIEHS (RG1)	list as a reasonably anticipated human carcinogen	6 yes/2 no*
NTP EC Working Group (RG2)	list as a reasonably anticipated human carcinogen	7 yes/ 1 no*
NTP Board RoC Subcommittee	list as a reasonably anticipated human carcinogen	7 yes/0 no

* No votes cast by reviewers because they felt relevant data supported listing as a *known to be human carcinogen*

Public Comments Received
A total of 3 public comments were received:

- 1 against listing in the RoC in any category
- 2 recommended deferring action until the US EPA had completed its review of the carcinogenic potential of this compound