Public Health Goal for Trichloroethylene In Drinking Water

Prepared by

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February 1999

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We thank the U.S. EPA (Office of Water; Office of Prevention, Pesticides and Toxic Substances; National Center for Environmental Assessment) and the faculty members of the University of California with whom OEHHA contracted through the UC Office of the President for their peer reviews of the PHG documents, and gratefully acknowledge the comments received from all interested parties. We also thank Dr. Dale Hattis of Clark University for his helpful suggestions.

PREFACE

Drinking Water Public Health Goals

Pesticide and Environmental Toxicology Section

Office of Environmental Health Hazard Assessment

California Environmental Protection Agency

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365) requires the Office of Environmental Health Hazard Assessment (OEHHA) to perform risk assessments and adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires that PHGs be set in accordance with the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which no known or anticipated adverse effects on health will occur, with an adequate margin of safety.
2. PHGs for carcinogens or other substances which can cause chronic disease shall be based solely on health effects without regard to cost impacts and shall be set at levels which OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of insufficient data to determine a level of no anticipated risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.
9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.
10. PHGs adopted by OEHHA shall be reviewed every five years and revised as necessary based on the availability of new scientific data.

PHGs adopted by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs).

Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. Each standard adopted shall be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory in nature and represent only non-mandatory goals. By federal law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists.

PHG documents are used to provide technical assistance to DHS, and they are also informative reference materials for federal, state and local public health officials and the public. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not to be utilized as target levels for the contamination of other environmental media.

Additional information on PHGs can be obtained at the OEHHA web site at www.oehha.ca.gov.

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PUBLIC HEALTH GOAL FOR TRICHLOROETHYLENE IN DRINKING WATER

SUMMARY

A Public Health Goal (PHG) of 0.0008 mg/L (0.8 ppb) was developed for trichloroethylene (TCE) in drinking water. The current California Maximum Contaminant Level (MCL) is 0.005 mg/L (5 ppb) for TCE in drinking water. The PHG was based on the occurrence of hepatocellular carcinomas and adenocarcinomas in mice in two studies, in both sexes, by inhalation and oral routes of administration, and a linear dose-response approach. The carcinogen slope factor (CSF) of 0.013 $(mg/kg\text{-}day)^{-1}$ was based on a geometric mean of four values using the pharmacokinetic dose metric of TCE metabolized dose (AMET). A nonlinear approach yielded a value of 0.005 mg/L (5 ppb). Semi-quantitative estimates of health-protective water concentrations based on the occurrence of kidney cancers in TCE-exposed cardboard workers and limited exposure data were similar, ranging from 0.3 to 1.3 ppb TCE. The PHG was set at a level providing a de minimis theoretical lifetime excess individual cancer risk (10^{-6}) through typical ingestion of tap water. It also includes an allowance for inhalation and dermal exposures to TCE via showering, flushing of toilets, and other typical household uses of tap water that may contain TCE. A health-protective value for noncancer toxicity was also developed. Based on the benchmark dose (BD_{10}) for kidney nephropathy in an oral chronic study in rats, and a 100-fold uncertainty factor, a value of 1.0 mg/L (1 ppm) was derived for TCE.

INTRODUCTION

The purpose of this document is to develop a PHG for trichloroethylene. The document is based on earlier Office of Environmental Health Hazard Assessment (OEHHA) assessments for water (DHS, 1988) and air (DHS, 1990) and particularly a health risk assessment performed by the Lawrence Livermore National Laboratory under contract to OEHHA (Bogen et al., 1988). [Note: prior to the establishment of the California Environmental Protection Agency in 1991 OEHHA was a division of the California Department of Health Services (DHS)].

Trichloroethylene (TCE) is a volatile organic compound (VOC) which has been extensively used as a metal degreaser, a solvent in adhesives, textile manufacturing, paint stripping, and dry cleaning etc. Production in the United States was estimated as about 130,000 metric tons/year (U.S. EPA, 1985; Davidson and Beliles, 1991). There are currently two U.S. manufacturers of TCE with a combined capacity of 145,000 metric tons/year (ATSDR, 1997). Due to widespread use, TCE is a common environmental contaminant. The primary public health concern from chronic low level exposures via contaminated drinking water is the probability of cancer induction.

Rodent cancer bioassays have shown that oral administration of TCE in corn oil leads to an increased incidence of hepatocellular carcinoma in B6C3F1 mice (NCI, 1976; NTP, 1983, 1988, 1990; Maltoni et al., 1986a). In parallel studies, TCE did not induce hepatocellular carcinoma in Osborne-Mendel rats (NCI, 1976), Fischer 344 rats (NTP, 1983), and Sprague-Dawley rats (Maltoni et al., 1988). Fukuda et al. (1983) reported lung tumors in B6C3F1 mice after TCE inhalation exposure. The metabolism of TCE is thought to play a key role in its carcinogenic effects (Buben and O'Flaherty, 1985). Metabolites of TCE, chloral hydrate (CH), trichloroacetic acid (TCA), and dichloroacetic acid (DCA) induced hepatocellular tumors in B6C3F1 mice when

administered in drinking water (Herrn-Freund et al., 1987; Bull et al., 1993; DeAngelo et al., 1991; Daniel et al., 1992; Pereira, 1996). Similar administration of TCA and DCA to rats did not result in liver tumors (Herrn-Freund et al., 1987; Bull et al., 1990; Daniel et al., 1992). Other metabolites such as trichloroethanol (TCOH), its glucuronide (TCOG), and related metabolites may also play a role in the overall mode of action.

CHEMICAL PROFILE

Chemical Identity

Trichloroethylene (TCE) is a volatile, chlorinated hydrocarbon compound that has been widely used as a degreasing solvent. Information on the identity of TCE is provided in Table 1.

Physical and Chemical Properties

Trichloroethylene is a colorless liquid. It is miscible with common organic solvents and is slightly soluble in water. It has a vapor pressure of 50 mm Hg at 20° C and boils at 87° C. Other information on the physical and chemical properties of TCE is provided in Table 2.

Production and Uses

U.S. production of trichloroethylene has decreased in recent years due to restrictions on emissions and substitution by other solvents. In 1982 U.S. production totaled 340 million kg (748 million pounds) (Chemical Marketing Reporter, 1983); in 1985 U.S. production was only 178 million pounds due to industry recycling (Storck, 1987). In 1990 U.S. production was 138 million pounds (IARC, 1995). A minimum purity of 99.85% is required of commercial grades of TCE for use as a chemical reagent (World Health Organization, 1985). Contaminants that have been found in commercial TCE include epichlorohydrin, carbon tetrachloride, 1,2-dichloroethane, trans-1,2-dichloroethylene, cis-1,2-dichloroethylene, pentachloroethane,1,1,1,2- and 1,1,2,2-tetrachloroethane, 1,1,1-trichloroethane, 1,1,2-trichloroethane, 1,1-dichloroethylene, tetrachloroethylene, bromodichloromethane, bromodichloroethylene, chloroform , and benzene (Verschueren, 1983; IARC, 1995). Commercial grades of TCE require stabilizers (up to 2%) in the form of antioxidants or acid-receptors. Natural production of TCE has been reported in temperate, subtropical and tropical algae and in one red microalga (Abrahamson et al., 1995).

TCE is widely used as an industrial solvent primarily for the vapor degreasing and cold cleaning of fabricated metal parts. It is also used in textile cleaning and solvent extraction processes. Of the total TCE used in the U.S. in 1982, 66% was used in vapor degreasing, 22% for export, 7% as chemical intermediates, and 5% for miscellaneous uses (Chemical Marketing Reporter, 1983).

Table 1. Chemical Identity of trichloroethylene

Chemical name: Trichloroethylene

Synonyms: TCE, TRI, ethylene trichloride, acetylene trichloride, ethinyl trichloride, 1,1,2-trichloro-ethylene, trichloraethen (German), trichloroaethylene (German), trichloretene (Italian), tricloroetilene (Italian), trielina (Italian), 1-chloro-2,2-dichloroethylene, 1,1-dichloro-2 chloroethylene, 1,1,2-trichloroethylene, 1,1,2-trichloroethene, 1,2,2-trichloroethylene.

Registered trade names: Alglyen, Anamenth, Benzinol, Blacosolv, Cecolene, Chlorilen, Chlorylea, Chlorylen, Circosolv, Crawhaspol, Densinfluat, Dow-Tri, Dukerom, Fleck-Flip, Flock-Flip, Fluate, Gemalgene, Germalgen, Lanadin, Lethurin, NCI-CO4546, Narcogen, Narkigen, Narkosoid, Nialk, Perm-Trial, Perm-a-chlor, Petzinol, Philex, Threthylen, Threthylene, Trethylen, Trethylene, Triad, Trial, Tri-Clene, Tri-Plus, Tri-Plus M,Triasol, Trichloran, Trichloren, Triclene, Trielene, Trielin, Trilen, Trilene, Triline, Trimar, Triol, Vestrol, Vitran, Westrosol.

Chemical formula: C_2HCl_3

Identification numbers:

Chemical Abstracts Service (CAS) Registry number:	79-01-06
NIOSH Registry of Toxic Effects of Chemical Substances (RTECS)® number:	KX4550000
U.S. EPA Hazardous Waste number:	U228
Oil and Hazardous Materials/Technical Assistance Data System (OHM/TADS) number:	7216931
Hazardous Substances Data Bank (HSDB) number:	133
DOT/UN/NA/IMCO shipping:	UN1710
National Cancer Institute (NCI) number:	NCI-C04546

Table 2. Physical and Chemical Properties of Trichloroethylene

Property	Value	References
Molecular weight	131.39 g/mol	IARC (1995)
Color	Clear, colorless	
Physical state	Mobile liquid	
Odor	Chloroform-like	Budavari (1989)
Odor threshold in water	10.0 mg/L	Verschueren (1983)
Boiling point	87° C	Lide (1993)
Melting point	-73° C	Lide (1993)
Solubility		
Water	1.07 g/L (20^0 C)	McNeill (1979)
Organic solvents	Soluble in ethanol, diethyl ether, acetone and chloroform	
Specific Gravity	1.4642 g/cm^3 (20° C)	Lide (1993)
Partition coefficients		
Octanol-water (K_{ow})		
Log K_{ow}	2.42	Leo (1983)
	2.29	Callahan et al. (1979)
	2.61	Hansch et al. (1995)
Vapor pressure	100 mm Hg (31.4 ^{0} C)	Lide (1993)
Henry's law constant	0.020 atm-m^3/mol (20° C)	MacKay & Shiu (1981)
	0.011 atm-m^3/mol (25° C)	Hine & Mookerjee (1975)
Conversion factor: Air at 25°C	1 ppm = 5.37 mg/m^3	IARC (1995)

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Trichloroethylene released to the environment tends to partition to the atmosphere. It has been estimated that 60% to 90% of the annual world production of TCE is released to the environment (WHO, 1985). The environmental degradation of TCE primarily involves atmospheric photooxidation. The key properties of TCE that affect its movement in the environment are its high vapor pressure and relatively low solubility in water.

Air

TCE in the atmosphere is subject to relatively rapid chemical or photochemical degradation. In the troposphere, it is removed by scavenging mechanisms, primarily with hydroxyl free radicals (•OH). Dahlberg (1969) observed the degradation products of atmospheric TCE decay to include phosgene and dichloroacetyl chloride. Gay et al. (1976) also observed formyl chloride when TCE was photooxidized in the presence of nitrogen dioxide. McNeill (1979) lists the decomposition products of TCE, due to autooxidation catalyzed by free radicals, to include hydrochloric acid (HCl), dichloroacetyl chloride, phosgene, carbon monoxide, and hexachlorobutane. The persistence of TCE in the atmosphere is dependent on the concentration of hydroxyl free radicals (•OH) and the extent of vertical and horizontal mixing. A literature review by the U.S. Environmental Protection Agency (U.S. EPA, 1985a) gave 11 days to two weeks as the range of the atmospheric residence time of TCE.

The widespread use and volatile characteristics of TCE, combined with its persistence and transport in the atmosphere, make this chemical a global ambient air contaminant. Highest ambient air concentrations are found in urban environments and near point-sources. Singh et al. (1981) measured mean TCE concentrations of 339 ± 302 parts per trillion by volume (pptv) in Los Angeles, CA, and 188 ± 270 pptv in Oakland, CA, during 1979. Singh et al. (1982) measured ground-level average TCE atmospheric concentrations in seven U.S. cities (in 1980) ranging from 96 ± 93 pptv to 225 ± 298 pptv. They estimated a background TCE concentration of 15 pptv based on global surface level measurements, but primarily represented by a Pacific marine site at Point Arena, CA (40^0N.). The California Air Resources Board (Nystrom, 1986), from preliminary 1985 data, reports average ambient TCE concentrations for several California locations: Los Angeles, 338 ± 223 pptv; San Jose, 730 ± 156 pptv; San Francisco, 348 ± 106 pptv; Stockton, 296 ± 63 pptv; Santa Barbara, 219 ± 123 pptv; and Simi Valley, 116 ± 54 pptv. Industrial releases of TCE into the environment in the U.S. were 53.75 million pounds in 1988, 49.5 million pounds in 1989, 38.9 million pounds in 1990, and 35.1 million pounds in 1991 (U.S.EPA, 1993). Indoor air concentrations of TCE can increase when TCE contaminated water is used domestically. A community water supply with 40 ppm (mg/L) of TCE was estimated to contribute 40 mg/m^3 to bathroom air during showering resulting in a 48 mg inhalation dose/wk (1 hr showering) compared to 42 mg through ingestion (Andelman, 1985).

Soil

TCE in the soil can be lost through volatilization to the atmosphere, downward leaching, or sorption to organic material. The sorption of TCE to soils appears to be correlated to its octanol/water partition coefficient, the organic carbon content of the soil, and the concentration of TCE in the liquid phase. From the soil-water partition coefficient of 0.8 ppm by weight (Urano and Murata, 1985), it follows that TCE is only moderately hydrophobic and thus is

slightly retarded in subsurface movement through soil (NCI, 1983). Bouwer et al. (1981) found, in experiments with trace organics in soil columns, that tetrachloroethylene (PCE) and related halogenated organics, including TCE, have the potential to leach rapidly through the soil.

Many studies have indicated that TCE is transformed to 1,2-DCE in soils and aquifer systems. Parsons et al. (1984), Wood et al. (1985), Dresen and Hoffman (1986), Boateng et al. (1984), and Cline and Viste (1985) independently studied TCE or PCE spills in Florida, California, Washington, Connecticut, and Wisconsin. 1,2-DCE was found in the plumes from the spills although there was no known source for it. A conclusion drawn from each study was that TCE was degrading to 1,2-DCE. Proof that TCE microbially degrades to 1,2-DCE in soil was given by Kleopfer et al. (1985), who studied anaerobic degradation in soils taken at depths of 1 to 17 feet from a Des Moines TCE spill-site. They used soybean meal to assure anaerobic conditions. All soils spiked with [^{13}C]-1abeled TCE produced [^{13}C]-labeled 1,2-DCE after 6 wk of incubation. None of their set of rigorous controls showed formation except for one that was thought to be incompletely sterilized. The rate of transformation could not be determined because of volatilization. Actual concentrations of TCE measured in soils range from 5.6 to 300 ppb by weight in soi1 samples taken from the vicinity of industrial producers and consumers of TCE (U.S. EPA, 1985a).

Water

In surface waters TCE volatilizes rapidly into the atmosphere. Wind speed, agitation of the water, and water and air temperatures affect evaporation rates. Photodegradation and hydrolysis are slow decay processes and do not appear to be important in the overall removal of TCE (McNeill, 1979). Dilling et al. (1975) observed TCE to have a slow decomposition rate in dilute aqueous solutions. They measured a half-life of 10.7 months at ambient temperatures in the dark. In the presence of sunlight, 75% of the TCE decomposed in 12 months, compared to a 54% loss over the same period in the dark. In contrast, Dilling et al. (1975) showed that the loss of TCE from agitated dilute aqueous solution occurs exponentially with an evaporation half-life of 21 ± 3 min. The U.S.EPA (1985a) summarized several studies of surface waters, including one by Zoeteman et al. (1980) who measured a half-life of TCE in the Rhine River of 1 to 4 days and one by Smith et al. (1980) who estimated half-lives of TCE in surface waters ranging from 3 hr for rapidly moving shallow streams to 10 h or longer for ponds or lakes. TCE concentrations in drinking water supplies from surface waters have been measured in 133 cities through federal surveys (U.S. EPA, 1985a). Thirty-two percent of the treated drinking waters contained TCE concentrations ranging from 0.06 to 3.2 µg/L and averaging 0.47 µg/L. Thirty percent of all systems sampled contained a TCE level below 1 µg/L and the remaining 2% contained TCE concentrations between 1 and 4 µg/L.

In the groundwater TCE has been found to degrade slowly by microbial action. Wood et al. (1985), Parsons et al. (1984, 1985), Dresen and Hoffman (1986), Boateng et al. (1984) and Cline and Viste (1985) independently studied TCE or perchloroethylene (PCE) spills in Florida, California, Washington, Connecticut and Wisconsin. The plumes from the spills showed progressively less of the parent compounds (PCE and/or TCE) and progressively more dichloroethylene (DCE) in the form of *cis*-1,2-DCE and *trans*-l, 2-DCE. Wood et al. (1985) measured the microbial half-lives of the parent compounds and possible degradation products under laboratory conditions and reported the values shown in Table 3. These investigators interpret these data to support the hypothesis that PCE degrades to TCE, which then degrades to the three DCE isomers listed in Table 3. The DCE isomers then degrade to vinyl chloride.

Table 3. Microbial half-lives derived by Wood et al. (1985).

Compound	Half-life (d)
Vinyl chloride	ND[a]
trans-l,2-Dichloroethylene (*trans*-l,2-DCE)	ND
cis-1,2-Dichloroethylene (*cis*-l,2-DCE)	ND
1,l-Dichloroethylene (1,l-DCE)	53
Trichloroethylene (TCE)	43
Tetrachloroethylene (PCE)	34

a ND = No detectable reduction in concentration during observations over periods averaging 30 to 60 d.

The degradation products and relative degradation rates found by Wood et al. are supported by a number of laboratory "microcosm" studies intended to simulate groundwater aquifer conditions (Parsons et al., 1984, 1985; Barrio-Lage et al., 1986; Wilson et al., 1986; Bouwer and McCarty, 1983; Vogel and McCarty, 1985).

Field measurements were made by Roberts et al. (1980) (data reported in Bouwer et al., 1981) on the decrease in concentration of various volatile halogenated organic compounds present (initially at concentrations of 2 to 20 µg/L) in reclaimed tertiary effluent (i.e., treated sewage water) that was injected into an aquifer in Palo Alto, California. Over the 11-month observation period the concentration of TCE decreased with a half-life of approximately 1 to 1.5 yr. This half-life is similar to that calculated from their data for PCE and 1,1,1-trichloroethane, but longer than that of approximately 20 to 30 d observed for 4 trihalomethanes ($CHBr_3$, $CHClBr_2$, $CHCl_2Br$, and $CHC1_3$; the reported concentration of $CHCl_3$ declined only until 140 d after injection stopped, after which it remained constant at approximately 1 µg/L).

Other field measurements of contamination showed that TCE degradation varies with the amount and type of local microorganisms. Cline and Viste (1985) studied the products of organic solvent degradation in the groundwater plumes from solvent-recovery facilities and landfill leachate. Both 1,2-DCE isomers were detected in groundwater near solvent-recovery facilities that had soil organic matter or other carbon sources, but presence of TCE-degradation products was not detected in groundwater that passed beneath an undisclosed industrial site in an organic-poor environment.

Hydrolytic loss of TCE was found to be either nonexistent or much slower in the sterile, control environments used in microcosm experiments than in test environments that were microbiologically active. Parsons et al. (1984, 1985) reported no loss of TCE from sterile control microcosms in either 3- or l6-wk laboratory experiments. Parson and Lage (1985) showed transformation of TCE in the sterilized controls containing TCE, water, and aquifer sediment in 8-wk experiments. They concluded that the hydrolytic processes were much slower than the microbial ones. Dilling et al. (1975) measured the disappearance of TCE from aerated water that was purified by deionization followed by treatment with activated charcoal. They calculated a half-life of 10.7 months for the disappearance of TCE. These investigators ascribed the loss of TCE solely to hydrolysis.

TCE concentrations in groundwater have been measured extensively in California. The data were derived from a survey of large water utilities in California (i.e., utilities with more than 200 service connections). The survey was conducted by the California Department of Health Services (DHS, 1986). From January 1984 through December 1985, wells in 819 water systems were sampled for organic chemical contamination. The water systems use a total of 5550 wells, 2947 of which were sampled. TCE was found state-wide in 187 wells at concentrations up to 440 µg/L, with a median concentration of 3.0 µg/L. Generally, the most contaminated wells and the wells with the highest concentrations were found in the heavily urbanized areas of the state. Los Angeles County registered the greatest number of contaminated wells (i.e., 149).

Food

The average concentrations of TCE in food in the U.S. were: 0.9 (0-2.7) ppb in grain-based foods; 1.8 (0-12) ppb in 'table-ready' foods; 73.6 (1.6-980) ppb in butter and margarine; 3.8 (0-9.5) ppb in cheese products; 0.5 (0-1.7) ppb in peanut butter; 3.0 (0-9.2) ppb in ready-to-eat cereal products; and 1.3 (0-4) ppb in highly processed foods (Heikes & Hopper, 1986; Heikes, 1987). Process waters in 3/15 food processing plants were found to contain 3-7.8 ppb TCE but no TCE was found in the food products (Uhler & Diachenko, 1987). Daft (1989) detected TCE in 5/372 fatty and non-fatty food samples at concentrations of 2-94 ppb (mean, 49 ppb). The concentrations of TCE in food in the U.K. were: 0.3-10 ppb in dairy products, 12-22 ppb in meat, non-detect (ND)-19 ppb in oils and fats, ND-60 ppb in beverages, ND-7 ppb in fruits and vegetables and 7 ppb in cereals.

METABOLISM AND PHARMACOKINETICS

Trichloroethylene is rapidly absorbed across the surface of the lungs and gastrointestinal tract. Although some TCE can be absorbed through the skin, the rate and extent of dermal absorption are limited in contrast with more lipophilic xenobiotic compounds.

There is very little information on the distribution of TCE in humans; however, data from animal studies indicate that TCE distributes to all tissues. The concentration of TCE in a given tissue depends on the route of exposure, partition coefficients of TCE in each tissue, and on the rates of metabolism and elimination. Once in the blood, TCE is metabolized via cytochrome P450 enzymes initially to chloral (trichloroacetaldehyde). Chloral, following hydration to chloral hydrate (CH) undergoes additional metabolism and ultimately forms metabolites including trichloroethanol (TCOH), trichloroethanol glucuronide (TCOG), trichloroacetic acid (TCA), and dichloroacetic acid (DCA).

Absorption

Ingestion

TCE is readily absorbed across the gastrointestinal (GI) tract of animals. Data on GI absorption of TCE in humans is limited; however, case reports of poisoning after ingestion of TCE indicate that GI absorption in humans is also extensive.

Animal Studies

Animal mass-balance studies with radiolabeled TCE have typically recovered most of the dose in excretion products as unchanged TCE or one of its metabolites. In its review of GI absorption of TCE by animals, the EPA (U.S. EPA, 1985a) equated percent recovery of radiolabel with percent of TCE absorbed. This approach assumes that the radioactivity recovered in the urine, feces, carcass, and cage air has been absorbed through the gut prior to its distribution and/or elimination by a given route. However, it should be pointed out that this assumption may not be entirely correct. For example, the TCE measured in cage air (which presumably came from exhalation) may include TCE retained in material that passed through the digestive tract without systemic absorption. In addition, mass-balance studies generally recover 2.0 to 4.0% of the radioactivity in the carcass. These reports have not provided data on the specific disposition of radioactivity within the carcass (i.e., whether or not radioactivity remained in the gut), and it is possible that some of the carcass radioactivity is due to unabsorbed material.

Mass-balance studies using radiolabeled TCE demonstrate that mice can metabolize 38 to 100% and rats can metabolize 15 to 100% of an oral dose of TCE administered in a corn-oil vehicle (Parchman and Magee 1982; Dekant et al., 1984; Prout et al., 1985; Mitoma et al., 1985; Buben and O'Flaherty, 1985; Rouisse and Chakrabarti, 1986). For both species, the lower values were obtained after treatment with large doses (>1000 mg/kg). In general, these data indicate that absorption of TCE through the GI tract is considerable, and at very low concentrations, nearly complete.

Withey et al. (1983) examined the effect of different vehicles on the rate and extent of absorption of TCE in rats as measured by serial blood samples collected over a five-hr period. Gastrointestinal absorption of TCE was slowed significantly by the use of corn oil as a vehicle, compared with an aqueous solution. After an 18 mg/kg IG dose of TCE in water, TCE reached a peak concentration in blood within 5.6 min. When the same dose was given in corn oil, the blood concentration profile exhibited two distinct peaks, one within 5 to 10 min and a second peak at approximately 100 min after dosing. Furthermore, the maximum concentration of TCE in blood was almost 15 times greater when TCE was administered in water (14.7 μg/mL) compared to oil (<1.0 μg/mL). Likewise, the observed area under the blood concentration-time curve (AUC) was estimated to be 218 times greater with TCE administered in water (241.5 μg-min/mL) rather than in oil (1.11 μg-min/mL). Thus, a very significant decrease was observed in the rate and extent of GI uptake for TCE administered as an oil solution as compared with an aqueous solution. When TCE is administered in corn oil, it appears that its high solubility in this vehicle slows its diffusion from the GI tract. In any event, the results of the mass-balance studies referred to above demonstrate clearly that TCE administered orally in a vehicle is readily, albeit not necessarily rapidly, absorbed systemically.

D'Souza et al. (1985) determined that the extent of absorption of TCE across the GI tract was dependent on whether test animals (male Sprague-Dawley rats) were fasted or non-fasted. Following an oral dose of 10 mg/kg TCE as a 50% aqueous suspension in a polyethylene glycol-based dispersant (Pegosperse 400-MS), TCE was rapidly and extensively absorbed from the GI tract of fasted rats. Arterial blood had measurable levels of TCE within 30 sec of treatment, and blood concentrations of TCE peaked within 6 to 10 min. Although specific data were not given for non-fasted animals, the authors reported that the blood levels of TCE in fasted animals were two to three times greater than in non-fasted animals.

Hobara et al. (1987) studied the intestinal absorption and subsequent metabolism of TCE in 60 adult male and female mongrel dogs (8 to 12 kg body weight) with a surgically implanted intestinal circulation system. Solutions containing 0.1, 0.25, or 0.5% TCE (weight/volume) were perfused through the jejunum, ileum, and colon of dogs anesthetized with 25 to 30 mg/kg sodium pentobarbital and placed on respirators. Each TCE solution comprised 500 mL of an aqueous solution of TCE dissolved in Tween 80 (1:1 by volume). The absorption of TCE was observed to be 50 to 70% of the administered TCE dose after 2 hr. There were no significant differences in the absorption rates of TCE and water among the 3 intestinal regions studied and the absorption rate for TCE was observed to be constant over time.

Human Studies

No experimental studies have been conducted on humans to evaluate the extent of absorption following ingestion of TCE. Defalque (1961) cited a number of cases of accidental poisoning from ingestion of TCE. The U.S. EPA (1985a) listed several additional instances of poisoning, and observed that these reports suggest that absorption of TCE across the GI tract of humans is extensive.

Dermal Absorption

Animal Studies

Tsurata (1978) applied 0.5 mL of pure TCE liquid to the (clipped) abdominal skin of mice for periods of 5 to 15 minutes; the TCE was contained on the skin by a small impermeable chamber glued to the skin patch studied. The estimated percutaneous absorption rate ranged from 7.82 to 12.1 μg/min-cm^2. The corresponding dermal absorption rate measured during in vitro experiments (using excised mouse abdominal skin) was 1.125 μg/min-cm^2.

Jakobson et al. (1982) monitored the concentration of TCE in the blood following administration of pure TCE liquid to the backs of guinea pigs; the TCE was contained on the skin by a small impermeable chamber glued to the skin patch studied. TCE was absorbed rapidly and reached a peak concentration in the plasma (0.79 μg/mL) within 30 min. Despite continued exposure, plasma levels of TCE decreased gradually after this time.

Bogen et al. (1992) studied the dermal absorption of dilute aqueous TCE in hairless guinea pigs. The animals were exposed to 10-100 ppb solutions for 70 min. The mean permeability constant k_p (mL/cm^2-hr) was 0.23 ± 0.04 with 10 min (initial) concentrations ranging from 19 to 110 ppb and radiolabel loss rates of 12-17%/hr over the 70 min observation period.

McCormick and Abdel-Rahman (1991) observed a role for testosterone in dermal penetration of [^{14}C]TCE in rats. TCE penetration was greater in female and castrated male rats than in untreated male Sprague-Dawley rats. Female rats administered testosterone showed decreased penetration of TCE.

Human Studies

Stewart and Dodd (1964) estimated the rate of dermal absorption of TCE in humans by measuring the alveolar concentration of TCE in three subjects who immersed their thumbs in

liquid TCE (98% pure) for 30 minutes. The mean peak concentration of TCE in alveolar air (0.5 ppmv) occurred within 30 minutes of exposure. The relatively small amount of TCE present in exhaled breath indicates that absorption of TCE through the skin is limited. Stewart and Dodd (1964) noted that there was considerable individual variation in the rate of absorption and concluded that the dermal absorption of TCE depended on the thickness and area of skin exposed.

Sato and Nakajima (1978) also studied the characteristics of dermal absorption of liquid TCE in humans. The extent of absorption was evaluated by measuring the concentration of TCE in blood and exhaled air of individuals who had immersed one hand in neat liquid TCE for 30 minutes. Measurements were made at the end of exposure, as well as intermittently over a 10-hr follow-up period. The highest levels of TCE were found immediately after the end of exposure (203.11 μg/mL in blood, 28.66 μg/mL in breath) and decreased thereafter. Sato and Nakajima (1978) noted that the conditions of this experiment did not represent a typical occupational exposure and that under average work conditions dermal contact with TCE would probably not result in the absorption of toxic quantities.

Weisel and Jo (1996) investigated the multi-route exposure of 11 subjects to TCE in tap water. The TCE concentrations in exhaled breath were elevated in each subject after both inhalation and dermal exposures during showering. Breath concentrations were also elevated after dermal exposure via bathing. In contrast to ingestion, after inhalation and dermal exposure, the exhaled breath had elevated levels for extended time periods, indicating that TCE was distributed via the bloodstream prior to metabolism. The concentrations of TCE in water were 20-40 μg/L. The amount of TCE expired per μg/L of water after dermal exposure was 0.03 ± 0.011 μg and after inhalation exposure was 0.074 ± 0.08 μg. The calculated internal dose from inhalation exposure ranged from 60 to 250 μg TCE. The amount of TCE expired after inhalation and dermal shower exposures were similar, suggesting nearly equivalent internal doses for these two exposure routes. Ingestion of 2 L of tap water containing the concentrations used in the study, assuming 100% GI tract absorption, yields maximum internal dose estimates for TCE of 30-300 μg. Thus for typical showering and drinking activities, each exposure route contributes similar internal doses, and the total internal dose from a 10-min shower or a 30-min bath is greater than that from ingesting 2 L of water. It should be noted that this study addresses only showering and bathing exposures. Other household activities such as flushing toilets, washing clothes etc. would be expected to add to these exposures particularly via the inhalation route..

Pulmonary Uptake

The human blood/air partition coefficient of TCE has been estimated to be between 9.2 and 15, and TCE readily diffuses across the lungs into the capillaries of the alveoli (Eger and Larson, 1964; Sato et al., 1977; Monster, 1979). For a given concentration of TCE, pulmonary uptake depends on the solubility of TCE in blood and tissue, the volume and rate of perfusion of tissues, the rate of elimination; and on the rate of alveolar ventilation, i.e., that fraction of respiratory ventilation from which volatile organic compounds may be cleared by absorption into alveolar capillary blood (Fernandez et al., 1977; Astrand, 1975).

Under non-steady-state conditions, the amount of TCE that initially enters arterial blood depends primarily on the concentration difference of TCE between alveolar and venous blood (Fernandez et al., 1977; Monster, 1979). Several studies have found that the uptake of TCE from the lungs is rapid during the first 30 to 60 minutes of exposure, but that the rate of uptake decreases

as TCE concentration in body tissues approaches steady state (Monster, 1979; Fernandez et al., 1977).

Under steady-state conditions, the net uptake (the difference between the ambient and alveolar air concentrations, multiplied by alveolar ventilation rate) is theoretically equal to the amount of TCE removed from the body by metabolism. But experimental human studies of pulmonary uptake of TCE have generally not approximated steady-state conditions. Because, prior to the attainment of a steady-state condition, net uptake (i.e., retention) varies as a function of time, generalizations that can be made from reported values of percent uptake are necessarily restricted to the specific exposure regime used.

Animal Studies

Andersen et al. (1980) exposed rats to TCE for 3 hr at concentrations that ranged from 30 to 6000 ppmv. The rate of pulmonary uptake in rats was concentration dependent; at the lowest exposure concentration (30 ppmv) the uptake of TCE was linear. Uptake deviated from linearity at concentrations of TCE > 100 ppmv.

Stott et al. (1982) evaluated the metabolism of TCE in rats and mice exposed to 10 or 600 ppmv ^{14}C-labeled TCE for 6 hr. Radiolabel was recovered in expired air (as CO_2 and unchanged TCE), as well as in the urine, feces, and carcass. Pulmonary absorption of TCE was evident in both rats and mice, because radiolabeled CO_2 and urinary metabolites were generated as a result of exposure. However, the net uptake of TCE appeared to differ between species at the higher TCE concentration of 600 ppmv because the amount of unchanged TCE exhaled after exposure to this concentration, as a percent of total body burden of measured TCE, was (at 21.1%) 10 times greater than the corresponding percent (2.1%) observed after exposure to 10 ppmv TCE. A similar change was not observed in mice, which exhaled unchanged from 1% to 2% of the measured TCE body burden at both concentrations.

Human Studies

Fernandez et al. (1977) simulated the uptake, distribution and elimination of TCE after inhalation exposure. Their model separated the body into a pulmonary compartment, a compartment responsible for metabolism (the liver), and three tissue types, the muscle group, fat group, and vessel-rich group. Fernandez et al. (1977) calculated the partial pressure of TCE in different tissues during an 8 hr exposure to 100 ppmv TCE. In the well perfused vessel-rich and muscle groups, the concentration of TCE increased rapidly over the first two hours of exposure. As the partial pressure of TCE equilibrated between tissues and inspired air, the rate of uptake diminished, and became relatively constant by the end of the 8 hr exposure period. The concentration of TCE in the poorly perfused (fat) compartment increased much more slowly, and continued to increase for approximately one hour after the end of exposure.

Various studies have reported the "percent retention" (i.e., net uptake as a percent of alveolarly ventilated amount) of TCE for experimental inhalation exposures. These studies estimated percent uptake by measuring the TCE concentration in inhaled and alveolar-exhaled air, subtracting the ratio of the latter to the former from one, and multiplying by 100%. As noted previously, under non-steady-state conditions these values will vary with the duration of exposure. This variation is apparent in the broad range of values that have been reported for the percent of TCE retained. For example, Soucek and Vlachova (1960) found that the percent of TCE retained varied from 58 to 70% in individuals exposed to 93 to 158 ppmv TCE for 5 hr.

Bartonicek (1962) reported 58% retention of TCE after a 5-hr exposure to 194 ppmv. Nomiyama and Nomiyama (1971, 1974) found that approximately 35% of a dose of TCE was retained in individuals exposed to 252 to 380 ppmv TCE for 2.7 hr. Monster et al. (1976) measured the pulmonary uptake of TCE in six subjects exposed to 70 or 140 ppmv TCE for 4 hr. Uptake was found to be rapid during the first 30 minutes of exposure, but after this time uptake became relatively constant and remained so for the duration of the experiment. Subjects exposed to 70 and 140 ppmv TCE retained 5.6 ± 1.1 and 5.4 ± 0.28 mg TCE/ppmv TCE in air. Thus, percent retention of TCE was not affected significantly by exposure concentration in this study. Monster et al. (1979) calculated the pulmonary uptake in five individuals exposed to 70 ppmv TCE, 4 hr/d for 5 days. The average quantity of TCE retained during this exposure scenario was 450 ± 51 mg/d, which was approximately 44% ± 5.5% of the estimated total alveolarly respired dose.

The amount of TCE taken up by the body is affected by differences in alveolar ventilation rate. During exercise or work, the alveolar ventilation rate increases and exposure to TCE under these conditions results in a greater uptake of TCE. When volunteers were exposed to 70 or 140 ppmv TCE while under a work load (2.5 hr x 100 watts) the uptake of TCE increased to approximately 2.5 times what it was at rest (Monster et al., 1976). Astrand and Ovram (1976) also reported that the uptake of TCE doubled in subjects under a 50- to 150-watt workload exposed to 100 or 200 ppmv TCE in air compared to resting subjects who were similarly exposed.

Wallace et al. (1997) studied the uptake of nine VOCs including TCE at environmentally relevant concentrations in five human subjects. TCE concentrations in three experiments ranged from 800 to 1300 $\mu g/m^3$. Uptake over 10 hr and elimination over an additional 24 hours were measured to within 5% precision in exhaled breath. A four-compartment model was fitted to the data. The mean residence times (τ) for TCE in the four compartments were: 0.15; 0.68; 4.8; and 29 hr, respectively. The mean distributions in the body (*a*) for TCE in the four compartments were 21, 24, 19, and 31%, respectively.

Pleil & Lindstrom (1997) evaluated the elimination of a number of VOCs including TCE with a "single breath canister" technique for sample collection and GC-MS analysis. Seventeen subjects were studied following controlled four-hr chamber exposure to TCE at 550 mg/m^3. The maximum blood concentrations ranged from 729 to 1749 $\mu g/L$. The elimination data was fit to a three compartment model (blood, highly perfused, moderately perfused) with half-lives ranging from 0.5-4.1 min for blood, 15-62 min for the highly perfused compartment and 262-1146 min for the moderately perfused compartment. In a subsequent chamber study six subjects were exposed to 100 ppm TCE for four hr followed by purified air for 20 hr (Pleil et al., 1998). Matched breath and blood samples were collected periodically. The concentration data were modeled with respect to time course and the blood/breath relationship. At equilibrium conditions at the end of the exposure, blood levels could be predicted using breath elimination curve calculations and a literature based partition coefficient with a mean calculated:measured ratio of 0.98 ± 0.12 SE across all subjects. Blood/breath comparisons at equilibrium gave in vivo partition coefficients with a mean of 10.8 ± 0.60 SE. The authors found that about 78% of TCE entering the body during inhalation exposure is metabolized, stored, or excreted through routes other than exhalation.

Distribution

TCE diffuses readily through blood and into body tissues. Studies with experimental animals have measured TCE or its metabolites in most organs and tissues. A combination of experimental and theoretical data indicate that TCE becomes widely distributed within the human body.

Animal Studies

Barrett et al. (1939) exposed dogs and rabbits to water vapor saturated with TCE (1.2 g/L) for 25 to 28 minutes. TCE and its metabolites were found in the blood, skeletal muscle, fat, liver, kidney, lungs, and heart of both species. The highest concentrations were measured in the adipose tissue of these animals (44 to 48 mg/100 g). In both rabbits and dogs, the lowest quantities of TCE occurred in the muscle (4 to 7 mg/l00 g). TCE was detected in the cerebrum, cerebellum, blood, liver, lungs, and perirenal fat of rats 24 hr after the end of exposure (200 ppmv TCE, 6 hr/d for 4 d). The greatest amounts of TCE were measured in perirenal fat (55.9 to 75.4 nmol/g) and the lowest amounts in liver (2.4 to 5.5 nmol/g) (Savolainen et al., 1977).

Parchman and Magee (1982) found that some of the radioactivity from a dose of ^{14}C-labeled TCE (10 to 1000 mg/kg) was covalently bound to liver protein of rats and mice. Low levels of radioactivity were also associated with the DNA fraction from both species. However, Parchman and Magee (1982) were unable to distinguish whether it was TCE or a metabolite that was bound to DNA or whether the radioactivity in the DNA fraction was due to contamination with protein.

Male rats given 10, 100, or 1000 mg/kg of TCE orally 5 d/wk for 6 wk had measurable levels of TCE, TCA, and trichloroethanol in the blood, heart, testes, vas deferens, seminal vesicles, prostate, epididymis, adrenals, fat, liver, kidneys, muscle, lungs, and brain (Zenick et al., 1984). In general, blood and tissue levels increased in a dose-dependent manner, indicating that TCE and its two major metabolites accumulate in tissue. For example, animals that received 1000 mg/kg of TCE had 30 to 50% more TCA in their reproductive organs than the 100 mg/kg group. The concentration of trichloroethanol in the epididymis and vas deferens did not change substantially with dose. However, the concentration of trichloroethanol was three to seven times higher in the testes, prostate, and seminal vesicles of high-dose animals than in animals that received 100 mg/kg TCE.

Pfaffenberger et al. (1980) dosed male rats by gavage with 1 to 10 mg/d of TCE for 25 d. TCE levels were measured in fat and blood at nine separate times during the treatment period. TCE was detected at very low levels (<1.0 μg/L) in serum, while the amount of TCE present in adipose tissue depended on dose. Animals given 1.0 mg/d had an average concentration of 280.0 ng/g TCE in their fat, while those that received 10.0 mg/d had an average of 20,000 ng/g. Measurements were also made three and six days after dosing was discontinued. Animals from both treatment groups had an average of 1.0 ng/g of TCE in adipose tissue. Serum concentrations of TCE were <1.0 μg/L (1.0 mg/d TCE) and 6.0 μg/L (10.0 mg/d TCE). The values reported by Pfaffenberger et al. (1980) are mean values and are based on measurements from 12 animals taken over the course of the experiment. The authors noted that there was considerable fluctuation in individual values, and that no steady increase in the 1evels of TCE

in blood or fat was observed. However, the relatively large amounts of TCE measured in fat over the 25 days of treatment indicate that some accumulation of TCE occurs with continued exposure.

Human Studies

TCE distribution depends on the partition coefficient, volume of distribution, and tissue-specific perfusion rate, as well as on the volume of venous blood in equilibrium with a given tissue type. After accounting for these variables the model of Fernandez et al. (1977) (discussed above in the subsection on Pulmonary Uptake) predicted that the body burden of TCE in the muscle and vessel-rich (well-perfused) tissue groups would increase only slightly with repeated inhalation exposure (100 ppmv, 6 hr/d, 5 d/wk). Because of TCE's high fat solubility and the limited perfusion of adipose tissue, TCE is eliminated slowly from fat, and repeated exposure is expected to cause a progressive accumulation of TCE in this tissue. Under these conditions (100 ppmv, 6 hr/d, 5 d/wk), TCE concentration is predicted by the Fernandez et al. model to reach equilibrium in adipose tissue in 5 to 7 d. Once adipose tissue becomes saturated, this model predicts that the concentration of TCE in fat will remain relatively constant as long as exposure concentration remains constant.

Bartonicek (1962) exposed eight volunteers to 194 ppmv TCE for 5 hr and measured the excretion of TCE and its metabolites TCA and trichloroethanol (TCOH) in feces, sweat, and saliva (on day 3 post-exposure) and in blood and urine (on days 2 to 22 post-exposure). The measured metabolites were found in feces, sweat, and saliva on the third day after exposure at average concentrations of approximately 18, 4.2, and 0.27 mg TCA+TCOH/100 mL, respectively. The metabolites excreted in feces represented about 8.4% of all measured metabolites excreted in feces and urine on day 3 after exposure. Metabolites in blood and urine decreased exponentially by a factor of about 10 from day 2 to day 22 after exposure. Intervening consumption of alcohol by the subjects appeared to influence the measurements of urinary metabolites by transiently increasing their concentration after consumption, particularly for TCOH.

De Baere et al. (1997) evaluated tissue distribution of TCE and metabolites in one subject following a fatal ingestion of TCE mixed with beer. The TCE concentrations found were: stomach contents, 95.7 mg/mL; blood, 210 μg/L; liver, 747 μg/g; kidney, 78.8 μg/g; and lung, 9.25 μg/g. TCA concentrations in liver and kidney were 21.0 and 27.5 μg/g, respectively. TCOH concentrations were: liver, 15.7 μg/g; kidney, 78.7 μg/g; lung, 4.0 μg/g. The blood TCE concentration was high compared to the reported average fatal value of 27 μg/mL (range, 3 to 110 μg/mL). The liver TCE concentration of 747 μg/g is the highest ever reported (range of other values, 5 to 250 μg/g).

Metabolism

TCE is initially transformed by the cytochrome P450 dependent mixed function oxygenases (MFO) to an intermediate electrophilic epoxide, trichloroethylene oxide (TCE-oxide) (Byington and Leibman, 1965; Henschler, 1977; Bonse et al., 1975). There is considerable speculation regarding this epoxide; it is not clear whether it is an obligate intermediate or if it exists in free form (available to bind cellular macromolecules) (Henschler, 1977; Henschler et al., 1979; Miller and Guengerich, 1982, 1983).

TCE-oxide is subsequently metabolized by one of four paths. The predominant pathway is one in which TCE-oxide rearranges spontaneously to chloral. Chloral is then rapidly hydrated to form chloral hydrate. Chloral hydrate undergoes oxidation to trichloroacetic acid (TCA), and some of the TCA contributes to the formation of dichloroacetic acid (DCA) and carbon dioxide (CO_2). Recent studies cast doubt on the importance of DCA as a TCE metabolite. Toxipeus and Frazier (1998) used an isolated perfused rat liver and found that the DCA concentration in the perfusion medium decreased rapidly over the two-hour exposure period. There was no DCA detectable in the liver following exposure to initial concentrations of 25 and 250 μM DCA. Only 5-10% of the initial DCA was found in the perfusion fluid and 0.2% in bile following exposure. Merdink et al. (1998) dosed male B6C3F1 mice i.v. with TCE, CH, TCOH, or TCA and orally with TCE only. DCA was not detectable above the 1.9 μM detection limit in whole blood. The authors conclude that DCA is likely formed as a short-lived intermediate metabolite. Its rapid elimination relative to its formation from TCA prevents the accumulation of measurable concentrations in blood. Moghaddam et al. (1997) observed that the intestinal microflora of mice played little or no role in the metabolism of TCE or CH to DCA.

Conjugates of TCA (TCA-glucuronide and TCA-CoA) have also been identified. Alternatively, chloral hydrate can be reduced to trichloroethanol (TCOH). Most of the TCOH reacts with glucuronyl transferase to form trichloroethanol glucuronide (urochloralic acid, TCOG) (Barrett et al., 1939; Powell, 1945,1947; Butler, 1948; Byington and Leibman, 1965; Nomiyama and Nomiyama, 1971; Muller et al., 1972; Kimmerle and Eben, 1973a; Cole et al., 1975; Ikeda et al., 1980a; Hathaway, 1980; Miller and Guengerich, 1982, 1983; Parchman and Magee, 1982; Stott et al., 1982; Costa and Ivanetich, 1984; Green and Prout, 1985; Dekant et al., 1984; Prout et al., 1985). The metabolism of TCE has been reviewed by IARC (1979), WHO (1985), and the U.S. EPA (1985a).

Although TCA, TCOH, and trichloroethanol glucuronide (TCOG) are the principal metabolites formed, the isolation of a number of minor metabolites can only be explained by the presence of other metabolic paths. Under certain conditions, TCE-oxide forms dichloroacetyl chloride; this rearranges to dichloroacetic acid (DCA) (Kline and Van Duuren, 1977; Hathaway, 1980; Dekant et al., 1984). TCE-oxide can also undergo oxidation and hydrolysis to formic acid, glyoxylic acid, oxalic acid, CO_2, and carbon monoxide (CO). Monochloroacetic acid has been occasionally recovered, but little is known about its formation (Bonse et al., 1975; Hathaway, 1980; Miller and Guengerich, 1982, 1983; Dekant et al., 1984; Fetz et al., 1978; Traylor et al., 1977; Soucek and Vlachova, 1960; Bartonicek, 1962; Ogata and Saeki, 1974; Green and Prout, 1985). Recent isolation of *N*-(hydroxyacetyl)-aminoethanol (HAAE) indicates the presence of a fourth (and separate) biotransformation of TCE-oxide. No details of HAAE formation have been characterized (Dekant et al., 1984).

The formation of glutathione (GSH) conjugates is catalyzed by cytosolic and microsomal GSH *S*-transferases. Substantial nonenzymatic GSH S-conjugate formation may occur with highly electrophilic substrates. S-(1,2-dichlorovinyl)glutathione (DCVG) is formed and goes through further metabolism to yield various metabolites, largely the mercapturic acids (Goeptar et al., 1995). *N*-Acetyl-*S*-(1,2-dichlorovinyl)-L-cysteine (Nac-DCVC) has been identified as a urinary metabolite in rats given an oral dose of 400 mg/kg of TCE. The Nac-DCVC in urine accounted for only 0.1% of the administered dose (Dekant et al., 1986). TCE is also metabolized in vivo to two isomeric mercapturic acids: 1,2-DCVC-Nac, and 2,2-DCVC-Nac. Birner et al. (1993) have detected 1,2-DCVC- and 2,2-DCVC-Nac in the urine of humans occupationally exposed to TCE. Alkaline decomposition of TCE may also produce dichloroacetylene that can yield both 1,2-DCVG and 1,2-DCVC. So the role of GSH-conjugation in forming these metabolites is

inconclusive (Goeptar et al.,1995). The fact that both 1,2-DCVG and 1,2-DCVC have been shown to produce nephrotoxicity in vivo in rats as well as the identification of DCVC-Nac isomers as urinary metabolites of TCE in rats, mice, and humans suggests that these compounds play a role in the toxicity and carcinogenicity of TCE (Dekant et al., 1986, 1990; Commandeur & Vermeulen, 1990; Birner et al., 1993, 1997).

Steel-Goodwin et al. (1996) detected a linear increase of free radicals with increasing TCE concentration in cut liver slices using an EPR/SPIN trapping method with α-phenyl t-butyl nitrone. The TCE concentrations used were very high (2500 to 10,000 ppm). Using immunochemical methods Halmes et al. (1996,1997) detected two TCE protein adducts at 50 and 100 kDa in liver microsomal fractions from male $B6C3F_1$ mice treated with TCE. The amounts of TCE adducts were both dose and time dependent. The data also suggest that one of the protein targets is cytochrome P450 2E1.

Lipscomb et al. (1997) reported differences in cytochrome P450-dependent metabolism of TCE in human microsomal samples. They found TCE metabolism was dependent on CYP 2E1 with minimal involvement of other forms (1A1, 1A2, 3A4). Of 23 human hepatic microsomal samples, three groups could be identified based on the apparent Km values: low (12-20 μM); mid (26-37 μM); and high (> 46 μM). The indicated variation in the capacity to metabolize TCE was less than 10-fold. Channel and Pravecek (1998) studied the metabolism of TCE in B6C3F1 mouse and human liver slices. Both explants tolerated TCE concentrations up to 750 μM without evidence of cytotoxicity. For the mouse apparent Vmax and Km values were 6.14 ng TCA generated/mg protein/min and 215 μM TCE, respectively. The human explant showed only 0.47 ng TCA/mg/min and 30.6 μM TCE, respectively, indicating a higher affinity but lower capacity than the mouse.

Griffen et al. (1998) observed covalent binding of TCE metabolites to proteins in human and rat hepatocytes. One of the targets is likely CYP 2E1 since the 50 kDa adduct in rat hepatocytes was found to comigrate in SDS-PAGE with a protein recognized by an antibody raised against cytochrome P450 2E1. In the human hepatocyte the major TCE adduct migrated to a different position than CYP 2E1.

Excretion

Absorbed TCE is eliminated both by pulmonary release of unchanged TCE and by metabolic transformation into other products which are primarily excreted in urine. There is a large amount of data on the kinetics of TCE metabolism and excretion in animals and humans, perhaps more for TCE than for any other volatile chlorinated organic compound. These data are reviewed extensively in the U.S. EPA (l985a) health-risk assessment document for TCE.

Animals

Early experiments on rats exposed to TCE by inhalation established that TCA is a major metabolite which is excreted in urine and that unmetabolized TCE is excreted by exhalation through the lungs (Forssmann and Holmquest, 1953). Kimmerle and Eben (1973a) studied excretion kinetics of TCE in SPF-Wistar-II rats to TCE by acute and subchronic inhalation. After rats were exposed to 49, 175 and 330 ppmv TCE for 4 hr, they showed an exponential decrease in TCE concentration in expired breath over an 8-hr observation period, as well as in amounts of TCA and trichloroethanol excreted in urine over a 4-d collection period. During

subchronic exposure to 55 ppmv TCE for 8 hr/d, 5 d/wk over a 14-wk period, urinary excretion of TCE metabolites averaged approximately 1.5 mg/kg-day. The metabolites TCOH and chloral hydrate were found at fairly constant levels in blood, and TCE could not be detected in blood. In Wistar rats given 3 to 15 mg/kg TCE by intravenous injection, Withey and Collins (1980) observed TCE concentrations to decrease in blood and perirenal fat with half-life ($t_{1/2}$) values of about 4 min and 3.6 hr, respectively.

TCE elimination from blood in mice and rats given a single oral dose of 1000 mg/kg TCE in corn oil was compared by Prout et al. (1985). Peak blood concentrations of TCE occurred at 1 hr and 3 hr for mice and rats, respectively, with corresponding decay ($t_{1/2}$) values of about 1 hr and 3 hr, respectively. While removal of TCE from mouse blood occurred more rapidly than from rat blood, blood concentrations of the TCE metabolite, TCA, were about 10 times greater in mice than in rats studied over a 48-hr post-exposure observation period. Particularly given the cytotoxicity and possible carcinogenicity of TCA itself (Elcombe, 1985), the differential ability of mice and rats to convert TCE to TCA has been proposed to explain the differential hepatotoxicity and hepatocarcinogenicity of TCE observed in these species (Stott et al., 1982; Buben and O'Flaherty, 1985; Prout et al., 1985).

The pharmacokinetics of inhaled TCE was investigated in Wistar rats (Filser and Bolt, 1979) and Fischer 344 rats (Andersen et al., 1980), using depletion of TCE at various original concentrations in a closed chamber to measure uptake and metabolism. TCE metabolism in Wistar rats was found to saturate above 65 ppmv, where the maximum rate (Vmax) of metabolic elimination was observed to be 28 mg/kg-h. In F344 rats, TCE metabolism was also found to be dose-dependent, saturating above 500 to 1000 ppmv where a Vmax of 24.3 mg/kg-h was observed, yielding a close agreement in estimates of Vmax, but not saturation concentrations, for Wistar and F344 rats.

Mass-balance studies using radiolabeled TCE have been used to study the nature and extent of TCE metabolism in rodents and primates. Daniel (1963) dosed rats with 40 to 60 mg/kg of TCE liquid by gavage and observed respiratory elimination of 80% of the dose ($t_{1/2}$ = 5 hr) and elimination of the remainder via urinary metabolites. Other gavage studies using TCE in a corn oil vehicle demonstrate a much greater degree of TCE metabolism in rodents. Muller et al. (1982) gave intramuscular injections of 50 mg/kg TCE to chimpanzees, baboons, and Rhesus monkeys and observed that urinary plus fecal elimination of the (presumably metabolized) dose amounted to 40 to 60%, 11 to 28%, and 7 to 40%, respectively, of the administered dose. Other recent studies of TCE metabolism in mice and rats provide further information on the extent of TCE metabolism in these species (Buben and O'Flaherty, 1985; Stott et al., 1982; Parchman and Magee, 1982; Dekant et al., 1984; Mitoma et al., 1985; Prout et al., 1985; Rouisse and Chakrabarti, 1986). The extent of TCE metabolism in mice and rats measured in these studies is summarized in Tables 3-4 and 3-5, respectively, in terms of the total amount of TCE metabolized and the percent of this amount excreted in the form of urinary metabolites.

Humans

Many studies have been conducted using volunteers to assess the extent to which TCE is metabolized in humans. Quantification of metabolism in these studies is done by collection of urinary metabolites and/or by calculating total exhaled TCE subsequent to a known TCE exposure. Unmetabolized TCE is either distributed within body tissues, as discussed above in this section, where it remains available for subsequent excretion or metabolism, or it is excreted via exhalation with kinetics that parallel depletion of TCE concentration in blood after exposure

cessation. A small amount of metabolized TCE apparently is excreted in bile (Bartonicek, 1962) and in exhaled air as TCOH (Monster et al., 1976) in humans.

Studies have demonstrated that in humans TCE is metabolized primarily to TCA, TCOH and TCOH-G, which are excreted in urine for the most part, although some TCOH and TCA may be metabolized further. Studies of the kinetics of excretion of these urinary metabolites in volunteers have shown that subsequent to TCE exposure, urinary TCOH is first produced more quickly and in larger amounts than is urinary TCA, but that TCA production persists and eventually supersedes that for TCOH (Soucek and Vlachova, 1960; Nomiyama and Nomiyama, 1971; Muller et al., 1974; Fernandez et al., 1975; Monster et al., 1979). The observed distinction between TCOH and TCA after TCE exposure has played an important role in the development of strategies for biological monitoring of occupational TCE exposure (Guberan, 1977; Sato et al., 1977; Fernandez et al., 1977; Monster and Houtkooper, 1979).

In a number of studies the extent to which people metabolize TCE in response to a controlled respiratory exposure has been quantified by measuring total urinary metabolites generated after exposure or by measuring the total amount of unchanged TCE expired after an exposure for which an estimate of total retained TCE dose was available (Soucek and Vlachova, 1960; Ogata et al., 1971; Nomiyama and Nomiyama, 1971; Ertle et al., 1972; Muller et al., 1972; Monster et al., 1976; Fernandez et al., 1975,1977; Monster et al., 1979). The reported values for average percent of retained dose metabolized (PRDM) range from 81% to 92%. If only the studies by Monster et al. and Fernandez et al. involving a total of 18 males given respiratory exposures ranging from 280 to 1440 ppmv are considered, the reported values for average PRDM are remarkably consistent, ranging from 89% to 92% with a person-weighted average of 90.6 $\pm$ 1.9% (C.V. = 2.1%) and a corresponding individual PRDM range of 87% to 93%. These 18 individual PRDM values are not significantly correlated with either TCE exposure concentration or time-integrated TCE exposure (in ppmv-hr).

In contrast to the estimates of PRDM for humans, the values reported for percent of metabolized dose identified as urinary metabolites (PMDU) show a greater degree of inter-individual heterogeneity. The 18 individual PMDU values from the Monster et al. and Fernandez et al. studies average 66.0% $\pm$ 10.9% (C.V. = 16.6%). This inter-individual heterogeneity is only partly due to differences in study methodology (e.g., regarding urinary metabolite identification efficiency, specificity, etc.), because the separate Monster et al. (1976), Fernandez et al. (1975, 1977), and Monster et al. (1979) PMDU averages are 67.4% $\pm$ 8.5% (C.V. = 12.6%), 54.9% $\pm$ 2.1% (C.V. = 3.9%) and 75.0% $\pm$ 11.0% (C.V. = 14.7%), respectively. The high PMDU values reported by Nomiyama and Nomiyama (1971) are not consistent with the other reported values, due partly to the fact that in this study the total urinary metabolite excretion was estimated beyond day six using a first-order decay assumption (with a half-life of 1.3 to 1.5 d), and also possibly to the fact that TCE retention was estimated to be only about 35% to 36% based (apparently) on a single post-exposure measurement for exposed individuals. The fact that the PMDU values are in general significantly below 100% indicates that respired TCE is metabolized by humans either to products excreted in urine other than those considered, such as HAAE (see Dekant et al., 1984), or to expired products such as CO_2. Human values for PRDM and PMDU are similar to those obtained from mice and rats given oral (applied) TCE doses below 2000 mg/kg and 500 mg/kg, respectively. This indicates that humans exposed to very low levels of TCE may metabolize almost all of the dose received as dose approaches zero, although, as is the case for animals, detailed human data on this point are entirely lacking. However, results from a study of urinary metabolites excreted by 51 male Japanese workers regularly exposed to TCE in 10 different workshops indicate that certain TCE-metabolism or metabolite-

excretion processes may saturate at high exposure levels (Ikeda et al., 1972; Ikeda, 1977). This study showed that while the concentration of total trichloro-compounds (TTC) and trichloroethanol (TCOH) in urine increased linearly with increasing exposure levels up to 200 ppmv (8 hr/d, 6 d/wk), that of trichloroacetic acid (TCA) appears to saturate at about 200 mg/L in workers exposed to air concentrations of TCE greater than 100 ppmv.

Kostrzewski et al. (1993) measured the kinetics of TCE elimination from blood in three subjects following acute occupational TCE exposures. They also interpreted the earlier data of Monster and Sato described above deriving a tri-exponential equation for TCE elimination. The half lives corresponding to the successive elimination phases were 0.1, 0.5, and 3.6 hr, but the observation period was limited to 16 hr. For the three subjects studied the TCE elimination from venous blood, over a 128 hr observation period, was described by a one compartment model with a mean half-life of 21.7 hr. On the basis of the two data sets the authors proposed a bi-exponential relation with $t_{1/2}$ values of 0.5 and 21.7 hr for the early (first few hours) and later phases of elimination, respectively.

Pharmacokinetics & PBPK Models

Other studies of TCE metabolism in mice and rats provide further information on the extent of TCE metabolism in these species (Buben and O'Flaherty, 1985; Stott et al., 1982; Parchman and Magee, 1982; Dekant et al., 1984; Mitoma et al., 1985; Prout et al., 1985; Rouisse and Chakrabarti, 1986). All of these studies are mass-balance studies, except the studies of Buben and O'Flaherty (1985) and Rouisse and Chakrabarti (1986) on urinary metabolites of TCE in mice and rats, respectively.

The results of the studies indicate that total TCE metabolism in mice is not saturated at single gavage doses below 2000 mg/kg. Furthermore, the relationship between applied and metabolized dose for mice appears to be approximately linear over most of the dose range below this point of metabolic saturation. The Prout et al. (1985) mouse data show a fairly linear relationship between applied gavage and total metabolized doses, with slope value estimated to be 0.788 (conditional on an intercept-parameter value of 0) by linear regression (R = 0.995). Thus, the use of a Michaelis-Menten relation to describe the mouse data may be inappropriate in the applied dose range below 2000 mg/kg, despite the fact that metabolic saturation occurs above this dose level. Saturation kinetics does not necessarily imply Michaelis-Menten (or rectangular hyperbolic) kinetics (see Pang and Rowland, 1977; Andersen, 1981; O'Flaherty, 1985). However, the data of Prout et al. (1985) for both $B6C3F_1$ and Swiss-Webster mice, as well as the $B6C3F_1$ mouse data of Mitoma et al. (1985) and the NMRI mouse data of Dekant (1984), all indicate a deviation from linearity at low doses, implying an increased metabolic efficiency as applied dose approaches zero.

Lee et al. (1996) evaluated the efficiency and dose dependency of presystemic elimination of TCE in rats surgically cannulated for carotid artery (CA), jugular vein (JV), and hepatic portal vein administration. Sprague-Dawley rats (330-380 g) were dosed with TCE (0.17, 0.33, 0.71, 2, 8, 16, 64 mg/kg) over 30 s into the CA, JV, portal vein or stomach. Serial blood samples were collected for up to 12 hr and analyzed for TCE. Pharmacokinetic analysis indicated that TCE was eliminated through dose-dependent nonlinear processes. A three-compartment model with Michaelis-Menten and first order elimination was derived to fit the TCE blood data following JV administration. Total presystemic elimination of TCE was inversely related to dose, ranging from ca. 60 to < 1%. At doses below metabolic saturation, hepatic presystemic elimination of TCE accounted for approximately 45-55% of dose.

Physiologically-based pharmacokinetic (PBPK) models are based on data from many sources; they attempt to simulate actual body organs or tissue groups (e.g., liver, muscle, fat), and are essentially predictive. These features are in contrast to classical or descriptive pharmacokinetic (PK) modeling that uses rather abstract compartments and interrelations to fit to specific data sets, usually for deriving pharmacokinetic constants and parameters. PBPK modeling has been applied in many chemical risk assessments to correct for metabolic saturation of high bioassay doses, to derive improved internal dose metrics, and to improve inter-route and inter-species extrapolations. Several PBPK models have been developed for TCE. Most of the PBPK models describe only the pharmacokinetic behavior of the parent chemical (Andersen et al., 1987; Bogen et al., 1988; Koizumi, 1989; Opdam, 1989; Opdam and Smolders, 1989; Droz et al., 1989a,b; Dallas et al., 1991; Srivatsan et al., 1993; Yang et al., 1995; El-Masri et al., 1995, 1996a,b). Fisher and co-workers developed PBPK models for TCE and TCA in pregnant rats (Fisher et al., 1989), lactating rats (Fisher et al., 1990), mice (Fisher et al., 1991), and humans (Allen and Fisher, 1993; Fisher and Allen, 1993). Sato et al. (1991) investigated the effects of physiological factors such as body fat content in a human PBPK model for TCE and TCA. More recent PBPK models have included additional metabolites such as TCOH and TCA (Clewell et al., 1995), CH, TCA, DCA, TCOH, and TCOG (Abbas and Fisher, 1997; Fisher et al., 1998), and chloral, dichlorovinylcysteine (DCVC), and DCA (Page et al., 1997). Other model elaborations have involved enterohepatic recirculation of TCA and TCOH (Stenner et al., 1998).

Lipscomb et al. (1998) compared TCE metabolic parameters from human microsomal suspensions (Lipscomb et al., 1997), whole hepatocytes, and PBPK model parameters of Allen and Fisher (1993). The Vmax value for the microsomes was 1589 ± 840 pmol/min/mg protein and for hepatocytes 16.1 ± 12.9 nmol/hr/10^6 cells. When adjusted to kg^{-1} body weight these values were 6.8 ± 3.6 and 6.9 ± 5.0 mg/hr/kg, respectively. The PBPK model Vmax was 14.9 mg/hr/kg. The similarity of these values may indicate that, once delivered to the liver, factors such as protein binding, competing enzymes, or sequestration by nonendoplasmic reticular lipids have little effect on cytochrome-dependent metabolism of TCE.

PBPK models have been used to study potential effects of mixtures of chemical contaminants and effects on enzyme systems relevant to their metabolism and toxicity (Yang et al., 1995). El Masri et al. (1996a,b) studied the interaction of TCE and 1,1-DCE with respect to binding and depletion of hepatic GSH in Fischer 344 rats. To quantitatively resolve the interaction effects on GSH content from resynthesis effects they used physiologically based pharmacodynamic (PBPD) modeling. The application of TCE to rats at higher than 100 ppm obstructed the ability of DCE to bind hepatic GSH via competitive inhibition. TCE, at concentrations below 100 ppm, was not effective in inhibiting DCE from significantly depleting hepatic GSH. Similar results were obtained for DCE-induced hepatic injury as indicated by serum aspartate aminotransferase activity. The results indicate an interaction threshold at the pharmacokinetic level.

TOXICOLOGY

In this section, we review the toxic effects of TCE in animals and humans. Previous reviews of the toxicity of TCE include those by Condie (1985), Kimbrough et al. (1985), U.S. EPA (1980; 1984a,b; 1985a,b), World Health Organization (1985), Lauwerys (1983), National Research Council (1980), Cornish et al. (1977), Infante (1977), Van Duuren (1977), Waters and Black (1976), Waters et al. (1977), Walter et al. (1976), Huff (1971), Smith (1966), Defalque (1961), Atkinson (1960), and von Oettingen (1937, 1964). This review is not intended to be exhaustive, but instead, to present a current summary and update of the available literature.

Toxicological Effects in Animals and Plants

Acute Toxicity

The 14-d acute oral LD50s for TCE were 2400 mg/kg in the mouse (Tucker et al., 1982) and 4920 mg/kg in the rat (Smyth et al., 1969). Stott et al. (1982) examined the effects of orally administered TCE on rats and mice. In one group of experiments, mice were given 2400 mg/kg of TCE by gavage daily for 3 d, or 5 d/wk for 3 wk. The livers of animals from both groups exhibited altered hepatocellular morphology, centrilobular hepatocellular swelling, and necrosis. Statistically significant ($p < 0.01$) increases in liver weight and in hepatic DNA synthesis were observed, as well as a slight reduction in DNA content per gram of liver. Stott et al. (1982) documented similar effects in mice that received oral doses of 250, 500, 1200, or 2400 mg/kg-day of TCE daily for 3 wk. Rats given 1100 mg/kg of TCE by gavage 5 d/wk for 3 wk had statistically significant ($p < 0.01$) increases in liver weight and in hepatic DNA synthesis. However there were no statistically significant changes in the livers of rats that received 1100 mg/kg of TCE for 3 d.

Tucker et al. (1982) conducted an experiment in which TCE was administered to mice by gavage at 24 and 240 mg/kg per day for 14 d. A statistically significant increase in liver weight ($p < 0.05$) was observed only in animals that received 240 mg/kg-day.

In a study by Buben and O'Flaherty (1985), mice were given 100, 200, 400, 800, 1600, 2400, or 3200 mg/kg of TCE by gavage 5d/wk for 6 wk. All dose levels caused a statistically significant ($p < 0.001$) increase in the liver-weight/body-weight ratio. Glucose-6-phosphatase (G-6-P) activity was significantly lower ($p < 0.01$) in the livers of animals that received doses of 800 mg/kg or more. Liver triglycerides increased significantly ($p < 0.01$) at 2400 mg/kg and serum glutamic pyruvic transaminase (SGPT) activity increased significantly ($p < 0.05$) after treatment with 2400 mg/kg or 3200 mg/kg. The DNA content of hepatocytes from the 400 mg/kg and 1600 mg/kg treatment groups were also observed to decrease significantly ($p < 0.05$ and $p < 0.001$, respectively).

White and Carlson (1979) studied epinephrine-induced cardiac arrhythmias in rabbits and rats. Animals were pretreated with agents that induced (phenobarbital or Aroclor 1254) or inhibited (SKF 525A or Lilly 18947) microsomal enzymes. Rabbits were exposed to 3000 ppmv TCE by inhalation for 7.5 to 60 min, while rats were exposed to 25,000 ppmv TCE for 10 to 60 min. Increasing doses of epinephrine (0.5 to 4.0 μg/kg) were administered intravenously. Cardiac arrhythmias were not observed in rats treated with phenobarbital, Aroclor 1254, or Lilly 18947 (and subsequently exposed to TCE and epinephrine). However, rats pretreated with SKF 525A developed arrhythmias in response to TCE, and sensitivity to epinephrine became more pronounced over the course of an hour. In rabbits, arrhythmias were observed in response to epinephrine in all treatment groups. The effective dose of epinephrine varied with the pretreatment regimen and duration of exposure to TCE.

In a later study White and Carlson (1981) examined the effect of ethanol on epinephrine-induced cardiac arrhythmias in rabbits exposed to TCE by inhalation. A single dose of ethanol (1 g/kg, oral or intravenous) was given to rabbits 30 min before exposure to TCE (6000 ppmv, 1 hr). Epinephrine was then injected (0.5 to 3.0 μg/kg). Rabbits treated orally with ethanol and TCE

developed epinephrine-induced cardiac arrhythmias sooner and at lower doses of epinephrine than control animals. No cardiac arrhythmias occurred when TCE was administered alone.

A single dose of ethanol (1 g/kg, oral or intravenous) was given to rabbits 30 min before exposure to TCE (6000 ppmv, 1 h). Epinephrine was then injected (0.5 to 3.0 pg/kg) until arrhythmia developed. Rabbits treated orally with ethanol and TCE developed epinephrine-induced cardiac arrhythmias sooner and at lower doses of epinephrine than control rabbits. Ethanol administered by intravenous injection induced arrhythmias in rabbits more often than orally administered ethanol. No cardiac arrhythmia occurred when TCE was administered alone.

Soni et al. (1998) investigated tissue repair response as a function of dose during trichloroethylene hepatotoxicity. Male Sprague-Dawley rats (10/dose group) were in injected intraperitoneally with 250, 500, 1250, 2500, and 5000 mg/kg TCE dissolved in corn oil. Lethality between days one and three was 100% in the top dose and 50% at 2500 mg/kg. Smaller groups of 4-6 rats were similarly dosed with 0 (vehicle control), 250, 500, 1250, and 2500 mg/kg TCE in corn oil. Hepatotoxicity and tissue repair were evaluated over a 96-hr period following TCE or oil administration. Maximum liver cell necrosis was seen at 48 hr after TCE administration. Measures of liver injury such as plasma sorbitol dehydrogenase and alanine aminotransferase did not show dose-related increases probably because of inhibition by the TCE metabolite TCA. TCA was found to inhibit both enzymes in vitro. Tissue regeneration response as measured by [^{3}H]thymidine incorporation into hepatocellular DNA was stimulated maximally at 24 hr after 500 mg/kg TCE administration. At 250 mg/kg [^{3}H]thymidine incorporation peaked only after 48 hr indicating minimal injury. At higher doses tissue repair was delayed and reduced resulting in greater liver injury.

Subchronic Toxicity

Kimmerle and Eben (1973a) evaluated the toxicity of TCE to rats after acute and subchronic inhalation exposure. One group of animals was exposed to 49, 175 or 330 ppmv TCE for 4 hr, while another group was exposed to 55 ppmv of TCE 8 hr/d 5 d/wk for 14 wk. At the end of treatment, liver- and kidney-function test results were within normal limits. However, treated animals had a significant increase in relative and absolute liver weight ($p < 0.01$) compared to untreated animals.

Continuous exposure to TCE at 150 ppmv by inhalation for 30 d caused a statistically significant increase ($p < 0.05$) in the liver weights of mice, rats, and gerbils (Kjellstrand et al., 1981). Kjellstrand et al. (1983a) used the same protocol to evaluate the effects of TCE on seven different strains of mice. All strains had a significant increase in plasma butylcholinesterase activity ($p < 0.001$). In a subsequent study by Kjellstrand et al. (1983b) mice were exposed to 37, 75, 150, or 300 ppmv of TCE vapor continuously for 30 d. Statistically significant increases ($p < 0.05$) in plasma butylcholinesterase activity were found in the males, and increases in liver weight were measured in both sexes at concentrations of TCE greater than 75 ppmv.

Several animal studies have found no evidence of renal toxicity in mice or rats exposed to TCE (Nowill et al., 1954; Utesch et al., 1981; Stott et al., 1982. In contrast to these reports, Tucker et al. (1982) found a significant increase ($p < 0.05$) in the kidney weights of mice that received 5.0 mg/mL TCE in drinking water for 4 to 6 months (2.5 and 5.0 mg/mL). In addition, high-dose females (5.0 mg/mL) and males in the two highest dosage groups (2.5 and 5.0 mg/mL) excreted greater amounts of protein and ketones in their urine than controls (specific data were not published).

A series of studies by Kjellstrand et al. (1981, 1983a, l983b) has documented effects of TCE on the kidney. For example, male and female gerbils exposed to 150 ppmv TCE continuously for 30 d had a significant increase ($p < 0.05$) in kidney weight (Kjellstrand et al., 1981). Continuous exposure of NMRI mice to TCE for 30 d (37, 75, 150, or 300 ppmv) caused a statistically significant increase ($p < 0.05$) in kidney weight at 75 ppmv (males) and >150 ppmv (females) (Kjellstrand et al., 1983b). No differences in sensitivity to TCE-induced kidney toxicity were observed among seven strains of mice (Kjellstrand et al., l983a).

Prendergast et al. (1967) conducted an extensive study on dogs, guinea pigs, rats, rabbits, and monkeys, in which he exposed the animals to TCE at 189 mg/m^3 (continuously for 90 d) or to 3825 mg/m^3 8 hr/d, 5 d/wk for 6 wk. No visible signs of toxicity were noted after exposure to 189 mg/m^3. All animals exposed to 3815 mg/m^3 (710 ppm) had non-specific inflammatory changes of the lung; some rats and guinea pigs also developed lung congestion.

Haglid et al. (1981) studied the impact of TCE on the levels of the glial brain-specific protein (S100) in discrete areas of the brain. Gerbils were exposed to 60 or 320 ppmv TCE continuously for 3 months. A pronounced decrease in total soluble protein and a significant increase ($p < 0.05$) in S100 protein were measured in the hippocampus, cerebellar vermis (posterior), and brain stem of exposed animals. The DNA content of cells was significantly elevated ($p < 0.05$ to $p < 0.01$) in the cerebellar vermis and sensory motor cortex in animals exposed to 320 ppmv.

Savolainen et al. (1977) and Vainio et al. (1978) collaborated on a series of experiments in which rats were exposed to 200 ppmv TCE 6 hr/d for 5 d. Both studies reported a decrease in the brain RNA content of treated animals (statistical significance was not given). In addition, Savolainen et al. (1977) found that exposure to TCE had no significant effect on brain protein content, but that brain acid proteinase activity was higher in treated rats on the fifth day of exposure to TCE.

Honma et al. (1980) measured levels of neurotransmitters in the brain of rats after exposure to 200, 400, or 800 ppmv TCE. Following one month of treatment, biochemical effects were observed only in the rats exposed to 800 ppmv TCE. Statistically significant ($p < 0.05$) reductions occurred in the acetylcholine content of the striatum and in the norepinephrine content of the cortex and hippocampus; only slight increases of dopamine were measured in the striatum. In addition, the serotonin content of the cortex and hippocampus were slightly elevated in the treated animals.

Channel et al. (1998) observed that subchronic exposure to TCE caused lipid peroxidation and hepatocellular proliferation in male B6C3F1 mouse liver. Animals (six per dose group) were dosed orally once daily, 5d/wk for 8 wk at 0, 400, 800, 1200 mg/kg-day TCE in corn oil. Peroxisomal proliferation, cell proliferation and apoptosis were evaluated at selected times. Lipid peroxidation, measured as thiobarbituric acid-reactive substances (TBARS), was significantly elevated at the two higher doses of TCE on days 6 through 14 of the study. By day 35 all treatment groups had TBARS values insignificantly different from the vehicle controls. A significant increase in cell and peroxisomal proliferation was observed during the same period in the 1200 mg/kg-day group. The greatest elevation occurred on day six (307% vs. controls) with modest increases on days 21, 42 and 56 (77, 30, 11% vs. controls, respectively). Necrosis or an increase in apoptosis was not observed at any dose. The authors note the temporal relationship between oxidative stress and cellular response of proliferation that both occur and resolve over the same relative time period suggests that TCE-induced mitogenesis may result from an altered liver microenvironment and selective advantage for certain hepatocyte subpopulations. Further, the initial cellular response may be a characteristic of B6C3F1 mouse liver that may help explain the species and strain sensitivity to TCE-induced hepatic tumorigenesis.

Genetic Toxicity

A range of assays, covering a wide spectrum of genetic endpoints, has been performed to assess possible genotoxic effects produced by TCE or its metabolites. DNA or chromosome-damaging effects have been evaluated in bacteria, fungi, yeast, plants, insects, rodents, and humans. The genetic endpoints measured by these assays include: forward and reverse mutation, sister chromatid exchanges, gene conversion, chromosomal aberrations, micronuclei formation, and mitotic recombination. Induction of DNA repair and covalent binding to DNA have also been examined. The U.S. EPA (1985a) health risk assessment document for TCE presents a detailed review of the earlier literature on the genotoxicity of TCE. The Genetic Activity Profile (GAP) database lists 36 entries for TCE with 12 positive results without activation and an additional two with exogenous activation (GAP version 4.01). The positive responses included reverse mutation and gene conversion in *Saccharomyces cerevisiae*, gene mutation in the plant *Tradescantia* sp., cell transformation in rat embryo cells in vitro, mouse spot test and micronucleus test in vivo, and UDS and SCE in human lymphocytes in vitro. Crebelli and Carere (1989) and more recently Fahrig et al. (1995) have also reviewed the genetic toxicity of TCE. Crebelli & Carere concluded that TCE is weakly active both in vitro, where liver microsomes produce electrophilic TCE metabolites, and also in vivo in mouse bone marrow, where high rates of micronuclei, but no structural chromosome aberrations, are found. Fahrig et al. reached somewhat similar conclusions in that the micronucleus tests were positive in mammalian cell cultures as well as bone marrow, whereas no chromosomal aberrations were found. However, Fahrig et al. noted that TCE has a very specific genotoxic activity and is not typical of a genotoxic carcinogen (Table 4). In vitro and in vivo, TCE induces recombination, including sister chromatid exchanges, and aneuploidies, including micronuclei. However, TCE appears unable to induce gene mutations or structural chromosomal aberrations. TCE was observed to induce increased DNA synthesis and mitosis in mouse liver in vivo (Dees & Travis, 1993). Despite its lack of “typical” genetic toxicity Fahrig et al. note that TCE could be involved in the expression of carcinogen-induced mutations due to its potential to induce recombination and aneuploidy. Reciprocal recombinations have been shown to play a role in inherited mutations that lead to the development of human tumors (Cavenee et al., 1983).

The genetic toxicity of TCE metabolites has also been evaluated. Chloral hydrate is able to induce chromosomal aberrations (Degrassi & Tanzarella, 1988; Furnus et al., 1990), aneuploidies (Furnus et al., 1990; Vagnarelli et al., 1990; Natarajan et al., 1993; Sbrana et al., 1993), and micronuclei (Degrassi & Tanzarella, 1988; Migliore & Nieri, 1991; Bonatti et al., 1992; Hummelen & Kirsch-Volders, 1992; Lynch & Parry, 1993; Seelbach et al., 1993) in cultured mammalian cells in vitro.

TCA was reported to induce chromosomal aberrations in human lymphocyte cultures in vitro (Kurinnyi, 1984). TCA exposure of rodents in vivo resulted in strand breaks of hepatic DNA (Nelson & Bull, 1988; Nelson et al., 1989; Chang et al., 1992). Induction of chromosomal aberrations by TCA in mouse bone marrow cells has given mixed results: positive by Bhunya & Behera (1987) and negative by Kurinnyi (1984). Bhunya & Behera (1987) reported TCA-induced increases in micronuclei frequencies in mouse bone marrow cells. Tao et al. (1996) observed the loss of heterozygosity on chromosome 6 in TCA-promoted hepatic tumors in mice. Notwithstanding the contradictory chromosomal findings, TCA clearly has genotoxic potential.

DCA was positive in the *umu* test (DNA repair) with *Salmonella typhimurium* (Ono et al., 1991), but negative in another DNA repair test in *S. typhimurium* (Waskell, 1978). DeMarini et al. (1994) found DCA active in a prophage induction test and mutagenic in *S. typhimurium* TA 100. Conflicting results have been obtained for DCA induced DNA damage as shown by the alkaline elution method (Nelson et al., 1989; Chang et al., 1992). DCA did not induce loss of heterozygosity on chromosome 6 in DCA-promoted hepatic tumors in mice (Tao et al., 1996).

Both TCA and DCA were found to induce hypomethylation of DNA in liver and tumors of female B6C3F1 mice (Tao et al., 1998). The level of 5-methylcytosine in DNA of hepatocellular adenomas for animals promoted by DCA was $2.36 \pm 0.15\%$ representing a 36% decrease compared to noninvolved liver tissue from the same animals ($p < 0.05$). Both TCA and DCA promoted clonal expansion of anchorage-independent hepatocytes in vivo and in vitro (Stauber et al., 1998). Pretreatment of male B6C3F1 mice with 0.5 g/L DCA in drinking water for two weeks resulted in a fourfold increase in in vitro colony formation above hepatocytes isolated from naïve mice. A significant ($p < 0.05$) increase was seen at the lowest exposure level of 0.02 mM DCA. In naïve animals significant increases in colony formation were seen with TCA or DCA at 0.5 mM ($p < 0.05$), with DCA showing a greater effect than TCA at higher levels (1, 2 mM ($p < 0.05$)).

TCOH was inactive for gene mutation and DNA repair tests in *S. typhimurium* (Waskell, 1978). Crebelli et al. (1985) described TCOH-induced aneuploidy in *Aspergillus nidulans*. A very weak induction of SCEs by TCOH was observed in human lymphocytes (Gu et al., 1981a,b cited in Fahrig et al., 1995).

Dichlorovinylcysteine (DCVC) is mutagenic in bacteria (Dekant et al., 1986) and induces DNA repair in the cultured kidney cell line LLC-PK_1 (Vamvakas et al., 1989). DCVC induces DNA double-strand breaks followed by increased poly(ADP-ribosyl)ation of nuclear proteins in cultured renal cells in vitro (Vamvakas et al., 1992) and in rat kidney in vivo (McLaren et al., 1994). Increased poly(ADP-ribosyl)ation may play a role in the TCE-induced kidney cancers as has been suggested for hepatocarcinogenicity of *N*-nitrosodiethylamine and benzo[a]pyrene (Denda et al., 1988). Muller et al. (1994) have investigated possible DNA adducts formed by halothioketenes and haloketenes from TCE. When chloroketene was reacted with adenine, cytosine and guanine, four adducts were identified: 1, N^2-acetylguanine; 3, N^4-acetylcytosine (two isomers); and 1, N^6-acetyladenine. Reactions with dichloroketene yielded adducts only with adenine and cytosine: N^4-dichloroacetylcytosine, N^6-dichloroacetyladenine. The results are seen to confirm earlier findings of modified DNA formed from *S*-(1,2-dichlorovinyl)-L-cysteine by the action of β-lyase (Bhattacharya & Schultz, 1972). The genetic toxicity findings for TCE and selected metabolites are summarized in Table 4.

Table 4. Summary of Genetic Toxicity Findings for TCE and its Metabolites*

Test Class	Positive Results	Negative Results
Indicator tests in vitro	• Covalent binding to DNA • Induction of C-mitoses • Induction of recombination in yeast • Weak induction of SCEs	• No induction of chromosome damage in yeast • No effects in bacteria • No induction of UDS
Mutation tests in vitro	• Induction of chromosome loss in fungi • Weakly positive in mouse lymphoma assay • Induction of aneuploidies at high concentration	• No relevant effects in bacteria • No relevant effects in fungi • No induction of chromosomal aberrations
Host-mediated assay	Induction of recombination in yeast	No induction of gene mutations in fungi
Indicator tests in vivo	• Induction of DNA strand breaks • Possible induction of sperm abnormalities • Induction of increased DNA synthesis and mitosis in liver	• Very low DNA binding capacity • No induction of SCEs • No induction of UDS
Mutation tests in somatic cells in vivo	• Weakly positive mouse spot test • Induction of micronuclei	• No induction of chromosomal aberrations
Germ cell tests		• No induction of dominant lethals • No induction of micronuclei in spermatids

Test Class	Positive Results	Negative Results
Monitoring in humans		• No relevant induction of SCEs • No induction of sperm abnormalities
Tests on metabolites:		
Chloral hydrate	• Positive in chromosomal aberration tests in vitro • Possibly positive in aneuploidy tests in vivo	
TCA	• Genotoxic potential in bacterial tests • Loss of heterozygosity on chromosome 6 in mice in vivo	• Most in vivo data inconclusive
DCA	• Some positive DNA repair and gene mutation results in bacteria	• Inconclusive data on DNA damage in vivo • No loss of heterozygosity
TCOH	• Positive aneuploidy tests in fungi • Positive SCE tests in vitro	• Negative in bacterial gene mutation tests
DCVC	• Positive in gene mutation in bacteria • Induces DNA repair in cultured kidney cells in vitro • Induction of DNA double strand breaks and poly(ADP-ribosyl)ation in kidney in vitro and in vivo	

* Adapted from Fahrig et al., 1995.

Developmental and Reproductive Toxicity

Schwetz et al. (1975) evaluated the teratogenic potential of TCE in rats and mice exposed to 300 ppmv of TCE 7 hr/d on days 6 through 15 of gestation. A statistically significant inhibition ($p < 0.05$) of maternal weight gain was observed in treated rats. The exposure had no apparent effect on the average number of implantation sites per litter, litter size, the incidence of fetal resorptions, fetal sex ratios, fetal body measurements, or on the incidence of fetal tissue or skeletal anomalies in either species.

Healy et al. (1982) exposed rats to 100 ppmv TCE (4 hr/d) during days 8 to 21 of gestation. Compared to controls, there was a significant delay ($p < 0.05$) in fetal maturation (decreased fetal weight) and in the number of resorptions in treated animals. Beliles et al. (1980) conducted a study to determine the teratogenic potential of workplace contaminants, including TCE. Rats and rabbits were exposed to 500 ppmv of TCE 7 hr/d, 5 d/wk prior to mating (3 wks) and during gestation. Separate groups of animals were exposed to TCE during gestation only. No adverse effects were noted in the offspring of rats. However, fetuses from two litters of rabbits exhibited hydrocephaly. Although the incidence of this defect was not statistically significant, the authors considered it to be of potential biological significance.

Kjellstrand et al. (1982b) studied the growth of neonatal Mongolian gerbils exposed to TCE. The exposure regimens used in the study consisted of continuous exposure to 230 ppmv TCE for 7 d (21 to 28 d of age), 14 d (14 to 28 d of age), 21 d (7 to 28 d of age), or 28 d (0 to 28 d of age). An age-related incidence of mortality was observed in the four groups (2, 13, 8, and 36%, respectively).

Slacik-Erben et al. (1980) conducted a dominant lethal assay in mice to detect spermatocyte anomalies induced by TCE. Male mice were exposed to either 50, 200 or 450 ppmv of TCE for 24 hr. Each male was then mated to 12 separate unexposed females over a 48-d period (this regimen was designed to sample effects on all stages of spermatogenesis). Females were sacrificed on day 14 of gestation. The following parameters were assessed to determine the effects of the exposure: number of implantations, fertilization rate (percentage of females with implantations in relation to the total number of mated females), post-implantation loss, pre-implantation loss, and the frequency of dominant lethal factors. None of these parameters was observed to be significantly different between the exposed and the control group.

Manson et al. (1984) administered TCE at 1,000 mg/kg-day to rats by corn oil gavage and observed indicators of maternal toxicity, significant fetal mortality, and decreased fetal weight, but no teratogenic effects. Dawson et al. (1993) exposed groups of 9-39 female rats to TCE in drinking water (1.5 or 1,100 ppm) either before pregnancy (3 mo.), before and during pregnancy (2 mo. + 21 d), or during pregnancy (21 d). Maternal toxicity was not observed. Fetal heart defects were not observed in fetuses from dams exposed only before pregnancy. Abnormal fetal heart development was observed at both concentrations in dams exposed before and during pregnancy (3% in controls; 8.2% at 0.18 mg/kg-day; 9.2% at 132 mg/kg-day). In dams exposed only during pregnancy fetal heart defects were seen only at the higher dose (10.4% vs. 3% in controls). The study is limited by widely spaced doses and lack of a useful dose-response. The study does seem to provide some support for human epidemiological findings of increased congenital heart defects and TCE exposure.

Frederiksson et al. (1993) evaluated developmental neurotoxicity in very young animals exposed to TCE. Postnatal exposure of male mice to 50 or 290 mg/kg-day TCE between the ages of 10 and 16 d resulted in a significant reduction in rearing rate at both doses when tested at 60 d. The study suggests that TCE affects brain maturation. Based on the LOAEL of 50 mg/kg-day identified in this study, ATSDR developed an acute duration oral MRL of 0.2 mg/kg-day for TCE (ATSDR, 1997).

NTP (1986) evaluated open-field activity in 21- and 45-day-old F1 rats that had been continuously exposed to TCE, in utero and throughout lactation, via maternal dietary exposure (microcapsules), at doses ranging from 75 to 300 mg/kg-day. A significant dose-related trend toward increased time required for grid traversal was observed in the 21-day-old pups. Evaluation at 45 d was unremarkable suggesting a transient effect. The 300 mg/kg-day dose was considered a NOAEL for the study.

Other studies in which rats were exposed via drinking water from 14 days before mating throughout lactation to weaning have shown neurological effects. A 40% decrease in the number of myelinated fibers was observed in 21-day-old offspring of rats given 312 mg/L TCE (37 mg/kg-day) (Isaacson & Taylor, 1989). A similar effect was seen at the higher concentration of 625 mg/L (75 mg/kg-day). Glucose uptake by the brain was reduced in 21-day-old offspring of rats given 312 mg/L TCE (Noland-Gerbec et al., 1986). Activity measurements in 60-day-old rats showed increases in offspring of rats given 312 mg/L TCE (Taylor et al., 1985).

The non-additive developmental toxicity of mixtures of trichloroethylene (TCE), di(2-ethylhexyl)phthalate (DEHP), and heptachlor has been studied in 5 x 5 x 5 designs in Fischer-344 rats. Dose levels of 0, 10.1, 32, 101, 320 mg/kg-day for TCE, 0, 24.7, 78, 247, 780 mg/kg-day for DEHP, and 0, 0.25, 0.8, 2.5, 8 mg/kg-day for heptachlor were administered by gavage on days 6-15 of gestation. The dams were allowed to deliver and the pups were weighed and examined postnatally (Narotsky et al., 1995). Three maternal and six developmental endpoints were evaluated. Several significant two-way interactions but no significant three-way interactions were observed. Maternal death exhibited no single chemical or main effects but DEHP and heptachlor were synergistic. For maternal weight gain on gestational days 6-8, main chemical effects were seen for all three agents as well as TCE-DEHP synergism and DEHP-heptachlor antagonism. Maternal weight gain on gestational days 6-20 adjusted for litter weight showed effects for TCE and heptachlor, but no interactions. Effects of all three agents were seen for full-litter resorptions and prenatal loss. The heptachlor effects were unexpected, particularly as seen with pooled data (heptachlor only plus heptachlor combinations) for each heptachlor dose, with 23% of (253) dams with resorbed litters at 8 mg/kg-day and 18% of (247) dams at 2.5 mg/kg-day vs. 12 % in the controls. For full-litter loss, the TCE-heptachlor and DEHP-heptachlor interactions were antagonistic. For prenatal loss, the TCE-DEHP interaction was synergistic. Postnatal loss showed DEHP and heptachlor effects but no interactions. Analysis of pup weights on day 1 revealed TCE and DEHP effects and DEHP-heptachlor antagonism; on day 6 DEHP and heptachlor effects and DEHP-heptachlor antagonism, and TCE-DEHP synergism were evident. The authors note that some antagonistic interactions of prenatal loss and full litter resorptions may reflect a ceiling effect and, based on heptachlor main effects, that heptachlor potentiated the other two agents. The authors thus regard all three two-way interactions to be synergistic for these related endpoints. Microphthalmia and anophthalmia incidences showed TCE and DEHP effects but no interactions. A dose related increase in micro- or anophthalmia that was statistically significant at 1,125 mg/kg-day TCE was observed. Eye defects were observed in 1%, 5.3%, 9.2%, 11.7%, and 30% of pups from dams treated with 0, 475, 633, 844, and 1,125 mg/kg-day of TCE respectively (Narotsky et al., 1995).

Gennings (1996) analyzed a subset of the Narotsky et al. data to illustrate the use of ray designs in mixtures of chemicals. Such ray designs provide a more economical way to study the effects of mixtures (Mantel, 1958; Bruden et al., 1988). Mixtures of chemicals are evaluated along rays of fixed ratios. For example, for a mixture of three chemicals with fixed ratios represented by Chemical 1:Chemical 2:Chemical 3, a 1:0:0 ratio represents a ray of Chemical 1 alone, while a 1:1:1 ratio represents a ray of equal levels of the three chemicals. A ray design for a small number of chemicals and many mixture rays can support the estimation of a response surface. However, the advantage of a ray design is that it can also be used with a mixture of many chemicals and a few mixture rays where a predictive univariate model is fit along each ray with total dose as the independent variable (Gennings, 1996).

The selected response was prenatal loss. The rays selected were one for each single chemical and one mixture ray. The dose ratios for the rays were for (DEHP:heptachlor:TCE): (1:0:0); (0:1:0); (0:0:1); and (70:1:29). A threshold model was fitted along each of the four rays simultaneously. The author concluded that departure from additivity could not be claimed along the 70:1:29 ratio mixture ray.

Zenick et al. (1984) studied the effects of TCE exposure on the reproductive function of male rats. Rats were intubated with 10, 100 or 1000 mg/kg of TCE 5 d/wk for 6 wk and then were mated with ovariectomized, hormonally primed females. At the end of 1, 5, and 10 wk after the start of the experiment, copulatory behavior and semen samples were evaluated. All dose groups exhibited a statistically significant ($p < 0.001$) increase in body weight. No significant effects were found in semen plug weights, sperm count, sperm motility, sperm morphology, or copulatory behavior. Other data of Zenick et al. (1984) indicate that male reproductive organs are able to accumulate TCE and its metabolites. Although this suggests that these substances may have the potential to interfere with normal reproductive function, Zenick et al. (1984) found little evidence of any direct effect of TCE on the male reproductive system.

Manson et al. (1984) found that TCE had no effect on the reproductive performance of female rats. Rats received 10, 100, or 1000 mg/kg of TCE daily for 6 wks (2 wks before mating, throughout mating (1 wk), and through day 21 of gestation). Females in the high-dose group gained significantly less weight than those in other groups ($p < 0.01$). The litters of these animals had a significantly greater number of deaths ($p < 0.001$) compared to controls, or to the other two treatment groups. The authors attributed the high pup mortality to materna1 TCE-induced toxicity, rather than to any direct neonatal action of TCE.

Dorfmueller et al. (1979) examined whether exposure to TCE before mating and during pregnancy was more detrimental to reproductive outcome than exposure either before mating alone or during pregnancy alone in rats. Three treatment groups were used: (1) TCE exposure before mating and during pregnancy, (2) TCE exposure before mating, and (3) TCE exposure during pregnancy. Prior to mating, animals were exposed to 1800 ppmv TCE 6 hr/d, 5 d/wk for 2 wk. Exposure during pregnancy was for 6 hr/d, 7 d/wk and continued through day 20 of gestation. Treatment had no significant effect on maternal rats, although the fetuses of rats exposed to TCE during pregnancy had an increased incidence of skeletal anomalies. The incidence was not significantly different from controls, however.

NTP (1986) conducted a continuous breeding study in which Fischer-344 rats were fed diets containing microencapsulated TCE that resulted in doses of approximately 0, 75, 150, or 300 mg/kg-day from 7 days before mating through birth of the F_2 generation. There was an increase in relative left testis/epididymis weight in the F_0 generation and a decrease in absolute left testis/epididymis weight in the F_1 generation. The findings were considered due to general

toxicity rather than specific to the reproductive system. No histopathological changes were noted. There was no effect on reproductive performance. A similar fertility study (NTP, 1985) was conducted with CD-1 mice using the same dietary concentrations of TCE (up to 750 mg/kg-day). There were no treatment related effects on mating, fertility, and reproductive performance in either F_0 or F_1 mice, but sperm motility was reduced by 45% in F_0 males and 18% in F_1 males.

TCE has not been listed as a reproductive toxicant under Proposition 65 (Safe Drinking Water and Toxic Enforcement Act of 1986).

Immunotoxicity

TCE induced a concentration-dependent decrease in the leukocyte count of dogs exposed to 200, 500, 700, 1000, 1500, or 2000 ppmv of TCE for 1 hr. In a second experiment, a group of dogs received 50 mg/kg TCE intravenously at the rate of approximately 1 mL/min through the right femoral vein. No significant differences were noted in erythrocyte counts, thrombocyte counts, or in the hematocrit values of treated dogs. Sanders et al. (1982) found a dose-related decrease in the cell-mediated immune response of mice given 24 or 240 mg/kg of TCE by gavage (daily for 14 d). In a follow-up study, the immune status in mice was evaluated after administration of 0.1, 1.0, 2.5, or 5.0 mg/mL TCE in drinking water (4 or 6 months). Humoral immunity was inhibited only at 2.5 and 5.0 mg/mL, whereas cell-mediated immunity and bone-marrow-stem cell colonization were inhibited at all four concentrations. Lymphocyte proliferation was not affected when animals were challenged with T-cell mitogens.

Wright et al. (1991) investigated the effects of TCE on hepatic and splenic lymphocytotoxic activities in Sprague-Dawley rats and B6C3F1 mice. Rats were given 0.05, 0.5, and 5.0 mmol/kg TCE i.p. for three days. Mice were similarly administered 10 mmol/kg. The highest doses resulted in decreased splenocyte count and relative spleen weights in rats and mice, respectively, and inhibition of hepatic natural killer cell (NK), natural cytotoxic cell (NC), and NPK cell activities in both rats and mice.

Kahn et al. (1995) studied TCE-induced autoimmune response in female autoimmune prone mice (MRL +/+). Three groups of mice (5 weeks old) received i.p. injections of 10 mmol/kg of TCE, 0.2 mmol/kg dichloroacetyl chloride (DCAC), or 0.1 mL corn oil. Animals were dosed every fourth day for 6 weeks and sacrificed 24 hr following the final dose. Spleen weights in the TCE and DCAC groups increased 36% with a similar increase in spleen weight/body weight ratio. Serum IgG in the TCE and DCAC groups increased 45 and 322%, respectively. Using specific ELISA assays for mice, autoimmune antibodies (anti-nuclear, anti-ssDNA, anti-cardiolipin) were detected in the sera of TCE- and DCAC-treated mice. These results suggest that TCE and its metabolite DCAC induce or accelerate autoimmune responses in female MRL +/+ mice. The similar responses to DCAC at a 50-fold lower dose than TCE indicate a metabolite-mediated mechanism for TCE-induced autoimmunity.

Neurotoxicity

Several animal studies have demonstrated behavioral changes following TCE exposure. Grandjean (1960) exposed starved rats to 200 or 600 ppmv of TCE for 3 hr and noted the reaction time to a food-motivated, preconditioned response. The average reaction time of the exposed rats was approximately the same as that of the controls. However, the total number of times an animal responded to a test stimulus was significantly greater in treated animals ($p < 0.01$) than in controls. These data indicate that TCE may cause an increase in excitability or loss

of inhibition in rats. Khorvat and Formanek (1959) observed similar effects in rats exposed to 400 ppmv of TCE for 49 d.

Goldberg et al. (1964a) found that rats exposed to TCE (200, 560, 1568, or 4380 ppmv, 4 hr/d for 10 d) exhibited a specific inhibition of the avoidance response. This effect was not clearly concentration dependent, however. Furthermore, animals exposed to 1568 ppmv showed "some evidence" of ataxia, while gross ataxia was observed in animals treated with 4380 ppmv TCE. Test results also indicated a slight increase in learning ability following exposure at 200 ppmv, while all other concentrations inhibited learning ability.

To develop exposure protocols that were representative of episodes of TCE "sniffing," Utesch et al. (1981) exposed rats to high concentrations of TCE (i.e., 9000, 12,000, 14,000, or 15,000 ppmv) for up to 15 min. Animals displayed signs of CNS depression, such as difficulty in locomotion and loss of the righting reflex. With the exception of animals exposed to 15,000 ppmv, recovery was rapid. In high-dose animals, the effects of exposure persisted for several hours. In a separate experiment, the coupling of ethanol exposures and/or fasting regimens with exposure to TCE had no marked effects on neurological responses.

Subchronic exposure of rats to TCE at 2600, 5000, or 8000 ppmv 30 min/d, 6 d/wk for 80 d caused a statistically significant ($p < 0.05$) decrease in open-field ambulation performance and response time (Ikeda et al., 1980b). In a study conducted by Battig and Grandjean (1963), rats that were exposed to 400 ppmv TCE 8 hr/d, 5d/wk for 44 wk showed a decrease in swimming performance, exploratory activity, and learning ability (Hebb test or conditioned-avoidance response test). Mikiskova and Mikiska (1966) demonstrated that TCE can also cause CNS depression with intraperitoneal (IP) administration. Guinea pigs given a single IP dose of 880 mg/kg (6.7 mmol/kg body weight) developed ataxia, a loss of muscle tone, and hyperalgesia.

Eighteen female Sprague-Dawley rats were divided into three groups of six and administered an oil vehicle, TCE or dichloroacetylene (DCAC) by oil gavage, 5d/wk for 10 wk, then examined for impairment of the trigeminal nerve. The daily doses were 2.5 g/kg for TCE and 17 mg/kg for DCAC. Significant decreases of the internode length and of the mean fiber diameter were seen in the DCAC group, with diminished but not significant effects in the TCE group (Barret et al., 1992).

Arito et al. (1994) exposed rats by inhalation to 0, 50, 100, and 300 ppm TCE for 8hr/d, 5d/wk, 6 weeks. The endpoints of interest were reduced heart rate and wakefulness indicative of central nervous system (CNS) toxicity. A LOAEL of 50 ppm was identified.

Chronic Toxicity

Histopathological changes in the GI tract were not seen in intermediate- and chronic-duration studies in rats and mice treated by oil gavage (NCI, 1976; NTP, 1988, 1990; Maltoni et al., 1986) or by chronic inhalation of TCE in rats (Maltoni et al., 1988). Ingestion of TCE in drinking water for six months resulted in minor hematological changes in mice, including a 16% decrease in the red blood cell count in males exposed to 660 mg/kg (Tucker et al., 1982). Liver enlargement is the primary effect seen in TCE-exposed animals after oral or inhalation exposure. Many of the studies were limited by lack or inadequate scope of pathological examinations, lack of measurement of hepatic enzymes, and/or failure to evaluate liver function indices (ATSDR, 1997). Renal enlargement has been associated with acute or intermediate duration exposures to TCE. Chronic experiments have also exhibited kidney toxicity. Administration of high doses of TCE by gavage for 78 weeks to Osborne-Mendel rats and $B6C3F_1$ mice resulted in treatment

related nephropathy with degenerative changes in the tubular epithelium (NCI, 1976). In cancer bioassays in rats and mice, renal effects included toxic nephrosis (cytomegaly) at 500 and 1000 mg/kg-day (NTP, 1983, 1990) and cytomegaly of the renal tubules and toxic nephropathy (NTP, 1988). Additional chronic effects in animals are discussed in the Carcinogenicity and Dose-Response sections below and in recent reviews (ATSDR, 1997; Gist and Burg, 1995).

Biochemical Toxicity

Moslen et al. (1977a, 1977b) examined the effect of microsomal enzyme induction on TCE-induced liver damage. Hepatic damage occurred in rats anesthetized with TCE following pretreatment with five different inducers of microsomal enzymes. Animals were given 400 μmol/kg doses, in corn oil, of 3-methycholanthrene (3-MC), phenobarbital, hexachlorobenzene, spironolactone, pregnenolone-16-a-carbonitrile, or 150 to 300 μmole/kg of Aroclor 1254 by gavage, daily for 7 d. Rats from all treatment groups were subsequently exposed to 1% TCE for 2 hr by inhalation. In vehicle control animals (corn oil pretreatment) exposure to TCE did not cause hepatic injury. Moslen et al. (1977a) noted a striking increase in SGOT activity ($p < 0.01$ to $p < 0.001$) accompanied by hepatic necrosis in all other animals (except those pretreated with spironolactone). In a separate study, Moslen et al. (1977b) evaluated the effects of TCE on hepatic enzyme activity in rats pretreated with phenobarbital. Rats were given an oral dose of 400 μmol of phenobarbital or 5 mL/kg of vehicle daily for 7 d followed by a 2-hr exposure to TCE (1% by volume in air). Liver homogenates from phenobarbital-treated animals had significantly lower levels of cytochrome P-450 ($p < 0.001$) and cytochrome b_5 ($p < 0.05$) compared to controls. Phenobarbital pretreatment caused hepatic glutathione (GSH) levels to decrease to half of control levels during the exposure, but GSH increased to above normal levels 8 hr after the end of treatment. Moslen et al. (1977b) also reported a marked increase in the rate of NADH-cytochrome c reduction following exposure to phenobarbital and TCE, but did not find any significant changes in the activity of other microsomal enzymes (N-demethylase aminopyrine, N-demethylase ethylmorphine, G-6-P, and zoxazolamine hydroxylase).

Carlson (1974) studied the effects of TCE in rats treated with 3-MC or phenobarbital. In one phase of this study, animals were exposed to 6900, 7800, 10,400, 12,000, or 16,000 ppmv TCE for 2-hr. Forty-eight hours later, half of these animals were given an intraperitoneal (IP) injection of 40 mg/kg 3-MC (the remaining animals served as controls). A separate group of rats received four IP injections of phenobarbital (50 mg/kg) daily for 4 d prior to a 2-hr exposure to 10,400 ppmv TCE. Isocitrate dehydrogenase activity was significantly greater ($p < 0.05$) in animals exposed to 7800 ppmv TCE, both with and without 3-MC treatment. Carlson (1974) also measured a significant increase ($p < 0.05$) in SGPT and SGOT activity in animals exposed to 6900 or 10,400 ppmv TCE. Treatment with 3-MC did not appear to affect the levels of these enzymes. Pretreatment with phenobarbital followed by exposure to 10,400 ppmv TCE caused a significant decrease ($p < 0.05$) in G-6-P activity.

Norpoth et al. (1974) measured a statistically significant ($p < 0.05$) increase in cytochrome P-450 content in the liver homogenates of rats exposed to 470 ppmv of TCE 3 hr/d for 10 d. Aminopyrine demethylase activity was not significantly affected by this treatment. Vainio et al. (1978) exposed rats to TCE at 7.9 μmol/L 6 hr/d for 4 or 5 days. No effects were observed after 4 d. However, exposure to TCE for 5 d was associated with an increase in hepatic cytochrome P-450 content (the statistical significance of this increase was not given). Exposure to 500 to 1000 ppmv of TCE 18 hr/d for three months produced no measurable effect on the liver function of rats, rabbits, or one dog (Nowill et al., 1954).

A correlation has been established between sleep prolongation after anesthetization and microscopic hepatic derangement. Plaa et al. (1958) attempted to define an ED_{50} for TCE-induced hepatic damage by using prolongation of sleeping time as an index. Mice were injected subcutaneously with 749, 1130, 1314, 1840, or 2627 mg/kg of TCE (these doses were associated with "varying degrees of centrilobular necrosis"). Plaa et al. (1958) then measured the duration of the resulting anesthesia and used these data to develop a dose-response curve. An ED_{50} of 1445 mg/kg was estimated from this curve.

Danni et al. (1981) studied the ability of TCE to induce peroxidation of liver microsomal lipids. Rats were given a single 678 mg/kg dose of TCE by gavage; hepatic lipids from these animals were analyzed for signs of peroxidation. Lipid peroxidation in unsaturated fatty acids produces conjugated dienes, which can be measured spectrophotometrically. However, no evidence of lipid peroxidation was found. In a parallel study, male and female rats received 170 mg/kg TCE 48 hr after an i.p. injection of 5 or 8 mg/kg of phenobarbital. Statistically significant increases in hepatic triglycerides were measured in male and female rats ($p < 0.025$ and $p < 0.005$ respectively) at both doses of phenobarbital. Rats that received only TCE showed no measurable adverse effects. A third group of rats were given 85 or 339 mg/kg TCE orally. No effect was found on hepatic or serum lipoproteins.

Rats exposed to TCE, either by gavage or inhalation, excreted large amounts of formic acid in urine (Green et al., 1998). Following a single 6-hr inhalation exposure to 500 ppm TCE, the excretion of formic acid was similar to that seen after a 500 mg/kg oral dose of formic acid. Formate excretion from TCE reached a maximum on day two and had a half-life of 4-5 days, whereas urinary excretion of administered formic acid was complete in 24 hr. Formate is not a metabolite of TCE but rather results from inhibition of formate clearance by TCE metabolites. Long term exposure to formic acid is known to cause kidney damage and may contribute to TCE-induced kidney toxicity seen in long-term studies with TCE.

Carcinogenicity

In a recent risk assessment of TCE by Bogen & Gold (1997), 35 long-term, chronic exposure experiments of TCE reported in the Carcinogenic Potency Database (Gold and Zeiger, 1997) were summarized. These studies included dosing by gavage or inhalation in several strains of rats and mice, and in hamsters, and are listed in Table 5 below. The main tumor findings were liver carcinomas in male mice by inhalation and in male and female mice by gavage administration, and lung carcinomas in female mice by inhalation. In rats, kidney tubular cell carcinomas were seen in males by inhalation and gavage administration of TCE. Benign testicular tumors were also seen in rats by inhalation and gavage administration of TCE.

Table 5. TCE Rodent Bioassay Results Summary

Species Route	Tumor Site/ Strain	Sex	Exposure/ Experi-ment (wk)	Nonzero doses/ 100	Tumor Incidences Control (first value), Malignant	Tumor Incidences Benign + Malignant Numerator	Ref.
Mouse	**Liver**						
Inhala-tion (ppm)	B6C3F1	F	78/154	1, 3, 6	3/88, 4/89, 4/88, 9/85 (p = 0.05)		1
		M	78/154	1, 3, 6	1/59, 1/31, 3/38, 6/37 **(**)**		1
		M	78/154	1, 3, 6	17/77, 19/47, 27/67, 21/63		1
	Han: NMRI	F	78/129	1, 5	0/29 0/30, 0/28	(0, 0, 0)	2
		M	78/129	1, 5	1/30, 0/29, 0/30		2
	IC	F	104/107	0.5, 1.5, 4.5	0/49, 0/50, 0/50, 0/46	(0, 0, 0, 1)	3
	Swiss	F	78/145	1, 3, 6	0/84, 0/89, 0/86, 1/86		1
		M	78/145	1, 3, 6	4/66, 2/53, 8/59, 13/61 **(**)**		1
Gavage mg/kg-day	B6C3F1	F	78/90	9,18	0/20, 4/50, 11/50 **(**)**	(0, 4, 11) **(**)**	4
		M	78/90	12, 24	1/20, 26/50, 30/50 **(***)**	(1, 26, 30) **(***)**	4
		F	103/105	10	2/50, 13/50 **(***)**	(6, 22) **(***)**	5
		M	103/105	10	8/50, 31/50 **(***)** **(p < 1E-9)**	(14, 39) **(***)** **(p < 1E-7)**	5
Mouse	**Lung**						
Inhala-tion (ppm)	B6C3F1	F	78/154	1, 3, 6	0/90, 1/90, 0/89, 0/87	(2, 6, 7, 14) **(**)**	1
		M	78/154	1, 3, 6	0/85, 0/86, 0/88, 0/88	(1, 2, 2, 1)	1
		M	78/135	1, 3, 6	0/90, 0/89, 0/90, 1/90	(12, 6, 7, 7)	1

Species Route	Tumor Site/ Strain	Sex	Exposure/ Experi-ment (wk)	Nonzero doses/ 100	Tumor Incidences Control (first value), Malignant	Tumor Incidences Benign + Malignant Numerator	Ref.
	Han: NMRI	F	78/129	1,5	1/29, 3/30, 0/28		2
		M	78/129	1, 5	5/30, 3/29, 1/30		2
	IC	F	104/107	0.5, 1.5, 4.5	1/49, 3/50, 8/50, 7/46 **(*)**	(6, 5, 13, 11)	3
	Swiss	F	78/145	1, 3, 6	2/88, 0/89, 0/88, 2/88	(15, 12, 12, 16)	1
		M	78/145	1, 3, 6	0/78, 0/73, 0/78, 1/74	(10, 5, 12, 12)	1
Gav-age, mg/kg-day	B6C3F1	F	78/90	9, 18	0/20, 2/50, 2/50	(1, 4, 7)	4
		M	78/90	12, 24	0/20, 0/50, 1/50	(0, 5, 2)	4
		F	103/105	10	1/50, 0/50	(1, 4)	5
		M	103/105	10	3/50, 1/50 **(p = 0.65)**	(7, 6) **(p = 0.089)**	5
Rat Inhala-tion (ppm)	**Kidney tubular cell car-cinoma**	F	104/159	1, 3, 6	0/101, 0/89, 0/88, 1/88	(0, 1, 0, 1)	1
		M	104/159	1, 3, 6	0/87, 0/86, 0/80, 3/85 **(*)**		1
	Sprague Dawley	F	104/159	1, 3, 6	0/38, 0/39, 0/39, 0/39	(0, 0, 0, 0)	1
		M	104/159	1, 3, 6	0/33, 0/32, 0/36, 1/37	(0, 0, 0, 1)	1
		F	104/107	0.5, 1.5,	0/50, 0/50, 0/47, 1/51	(0, 0, 0, 1)	3

Species Route	Tumor Site/ Strain	Sex	Exposure/ Experi-ment (wk)	Nonzero doses/ 100	Tumor Incidences Control (first value), Malignant	Tumor Incidences Benign + Malignant Numerator	Ref.
				4.5			
	Han: WIST	F	78/156	1, 5	0/28, 0/30, 0/30	(0, 0, 1)	2
	Han: WIST	M	78/156	1, 5	0/29, 0/30,1/30		2
Gavage mg/kg-day	ACI	F	103/104	5, 10	0/50, 1/50, 1/50	(0, 3, 1)	6
	ACI	M	103/104	5, 10	0/50, 1/50, 0/50	(0, 1, 0)	6
	Aug	F	103/104	5, 10	0/50, 2/50, 0/50	(1, 4, 0)	6
	Aug	M	103/104	5, 10	0/50, 1/50, 0/50	(0, 2, 1)	6
	Fischer 344	F	103/103	5, 10	0/50, 0/50, 1/50	(0, 0, 1)	5
	Fischer 344	M	103/103	5, 10	0/50, 0/50, 3/50 **(*)**	(0, 2, 3) **(**)**	5
	Mar-shall	F	103/104	5, 10	0/50, 1/50, 1/50	(1, 2, 1)	6
	Mar-shall	M	103/104	5, 10	0/50, 0/50, 1/50	(0, 1, 1)	6
	Osborne-Mendel	F	78/110	5, 10	0/20, 0/50, 0/50	(0, 0, 0)	4
	Osborne-Mendel	M	78/110	5, 10	0/20, 1/50, 0/50	(0, 1, 0)	4
	Osborne-Mendel	F	103/104	5, 10	0/50, 0/50, 0/50	(0, 0, 1)	6
	Osborne-Mendel	M	103/104	5, 10	0/50, 0/50, 1/50	(0, 6, 2)	6
	Sprague-Dawley	F	52/140	0.5, 2.5	0/30, 0/29, 0/26	(0, 0, 0)	1
	Sprague-Dawley	M	52/140	0.5, 2.5	0/22, 0/24, 0/21 **(p = 0.11)**	(0, 0, 0) **(p = 0.0065)**	1

Species Route	Tumor Site/ Strain	Sex	Exposure/ Experi-ment (wk)	Nonzero doses/ 100	Tumor Incidences Control (first value), Malignant	Tumor Incidences Benign + Malignant Numerator	Ref.
Rat Inhala-tion (ppm)	**Testis** **Tumor** **Benign**	M	104/159	1, 3, 6	5/81, 11/73, 24/71, 22/76 **(***)**		1
	Sprague -Dawley	M	104/159	1, 3, 6	1/33, 5/32, 6/36, 9/37 **(*)**		1
	Han: WIST	M	78/156	1, 5	4/29, 0/30, 3/30		2
Gavage mg/kg-day	ACI	M	103/104	5, 10	36/50, 23/50, 17/50		6
	Aug	M	103/104	5, 10	34/50, 30/50, 26/50		6
	Fischer 344	M	103/103	5, 10	46/50, 47/50, 32/50		5
	Mar-shall	M	103/104	5, 10	17/50, 21/50, 32/50 **(***)**		6
	Osborne -Mendel	M	78/110	5, 10	0/20, 0/50, 0/50		4
	Osborne -Mendel	M	103/104	5, 10	0/50, 0/50, 1/50		6
	Sprague -Dawley	M	52/104	0.5, 2.5	0/30, 0/30, 1/30 **(p = 0.00002)**		1
Ham-ster Inhala-tion (ppm)	**All tumor bearing animals** Syrian Golden	F	78/129	1, 5	2/30, 3/29, 3/30		2
		M	78/129	1, 5	6/30, 2/30, 4/30		2
	Hepato-cellular	F	78/129	1, 5	1/30, 0/29, 0/30	(1, 1, 0)	2

Species Route	Tumor Site/ Strain	Sex	Exposure/ Experi-ment (wk)	Nonzero doses/ 100	Tumor Incidences Control (first value), Malignant	Tumor Incidences Benign + Malignant Numerator	Ref.
	carcino ma Syrian Golden	M	78/129	1, 5	1/30, 0/30, 0/30	(1, 0, 0)	2

Note: Adapted from Bogen and Gold (1997). In the first three columns are given the species, exposure route and exposure units, tumor site and strain of animal used. In the fourth and fifth columns are the exposure periods and study length and the doses divided by 100 (e.g., 100, 300, and 600 ppm are listed as 1,3,6). The sixth and seventh columns give the quantal tumor incidences and statistical significance for malignant and benign + malignant tumors respectively. The benign + malignant are given as numerators only since the denominators are the same. The final column gives the reference to the study cited. Doses, Inhalation = ppm in air 7 hr/d, 5d/wk; Gavage = mg/kg-day by gavage in oil 5d/wk; Studies, 1= Maltoni et al. (1986), 2 = Henschler et al. (1980), 3 = Fukuda et al. (1983), 4 = NCI (1976), 5 = NTP (1990), 6 = NTP (1988); Study specific p values test the null hypothesis that the dose-response slope is zero, tests for NCI and NTP studies are based on life-table analysis, and for other studies from Gold et al. (1984), asterisks indicate level of rejection of the null hypothesis, $p < 0.05$ (*), $p < 0.01$ (**), $p < 0.001$ (***) unless otherwise specified. A global analysis of each tumor site using Fisher's chi-square test (Fisher, 1973) was also performed by Bogen and Gold and p values are given in parentheses following each site.

National Cancer Institute, 1976

The National Cancer Institute (NCI, 1976) study was the first major long-term cancer bioassay of TCE and has led to several other investigations. TCE was administered by gavage 5 d/wk for 78 wk to B6C3F1 mice and Osborne-Mendel rats of both sexes. The industrial grade of TCE used contained 1,2-epoxybutane (0.19%) ethyl acetate (0.04%), epichlorohydrin (0.09%), N-methylpyrrole (0.02%), and diisobutylene (6.03%) as stabilizers.

Following the dosing period, the animals were observed for 12 wk and they were sacrificed in the 90th (mice) or 110th (rats) wk. When the study began, the mice and rats were 5 wk and 7 wk of age, respectively. Dose groups consisted of 50 male and 50 female mice and rats. Twenty animals made up each matched control group. Investigators also reported the tumor incidence in groups of colony controls.

Preliminary acute and subchronic tests were used to determine a maximum tolerated dose (MTD) that could be given to the high-dose groups in chronic studies; the low-dose groups received half of the MTD. Male mice received initial daily doses of 2000 mg/kg of body weight in the high-

dose group and 1000 mg/kg in the low-dose group. Dose levels were increased during the course of the study resulting in corresponding experimental time-weighted average (TWA) doses of

2339 and 1169 mg/kg. Initial doses to female mice were 1400 and 700 mg/kg, and the corresponding experimental TWA doses were 1739 and 869 mg/kg. Dose levels to rats were lowered during the study because of poor survival and decreasing body weights. High-dose groups of both sexes initially received 1300 mg/kg, but a lower TWA dose of 1097 mg/kg. The low-dose groups initially received 650 mg/kg, but a lower TWA dose of 549 mg/kg.

The incidences of hepatocellular carcinoma in female mice were 0/20, 4/50, and 11/50 ($p < 0.01$) for control, mid and high dose respectively. For male mice the incidences were 1/20, 26/50 ($p < 0.001$), and 30/50 ($p < 0.001$), respectively. Tests for linear trend on age-adjusted data were highly significant for hepatocellular carcinoma in males ($p < 0.001$) and females ($p < 0.002$). Metastases of the liver cancer to the lung were observed in four low-dose and three high-dose males. The first hepatocellular carcinoma was observed among the high-dose males at 27 wk and among the low-dose males at 81 wk.

In contrast to the positive results in the mouse study, analysis of tumor incidences in rats showed no significant difference in specific or total tumors between treated and control groups. High-dose male rats exhibited significantly ($p = 0.001$) decreased survival relative to that of controls. The response in rats to carbon tetrachloride, the positive control compound, appeared relatively low.

Questions have been raised about the possible impact of the epichlorohydrin (ECH) impurity in the TCE used in the NCI mouse and rat bioassays. The presence of this contaminant may have directly contributed to tumor induction observed in the NCI mice. ECH is a direct-acting alkylating agent and is mutagenic (Kucerova et al., 1977; Bridges, 1978). Van Duuren et al. (1974) demonstrated that ECH was carcinogenic in mice when injected subcutaneously. A subsequent study by Laskin et al. (1980) showed that ECH induced neoplastic nasal cavity lesions in rats. Most of these tumors were carcinomas of the squamous epithelium. Interestingly, 30-d exposures to 100 ppmv produced a much greater incidence of cancer than lifetime exposures of 30 ppmv (exposures were 6 hr/d, 5 d/wk). Results from studies by Konishi et al. (1980) and Kawabata (1981) also showed that ECH fed discontinuously to rats in drinking water at a concentration of 1500 ppm (a lifetime TWA dose of approximately 40.2 mg/kg-day) induced a significantly increased incidence of papillomas and squamous cell carcinomas of the forestomach above that of control animals.

The estimated quantity of ECH present in the TCE used in the NCI study is equivalent to lifetime TWA doses of 1.3 and 0.97 mg/kg-day for high-dose male and female mice, respectively. These doses are only 3.2% and 2.4%, respectively, of the dose that elicited squamous cell carcinomas in rats referred to above. Furthermore, ECH appears to initiate tumors at sites by a localized tumorigenic action where it is in direct contact with tissue, such as nasal or forestomach squamous-cell epithelium (U.S. EPA, 1984b). No animal in the NCI mouse bioassay developed tumors at these sites.

National Toxicology Program, 1983

In order to clarify the question of contaminant effects in the 1976 NCI mouse study the National Toxicology Program (NTP, 1983) initiated a repeat series of carcinogenicity studies in mice and rats. Dosing by gavage began when mice (B6C3Fl) and rats (F344/N) of both sexes were 8 wk of age. The TCE used contained no epichlorohydrin and was stabilized with 8 ppm diisopropylamine. Treated mice and high-dose rats received 1000 mg/kg 5 d/wk. Low-dose rats

received 500 mg/kg 5 d/wk. The dosing period lasted for 103 wk. Survivors were killed within 4 wk after treatment. The incidences of renal tubular-cell adenocarcinoma in male rats dosed with either 500 mg/kg (0/49) or 1000 mg/kg (3/49) were not significant when compared to that of controls (3/49). However, high-dose male rats that survived until the end of the experiment exhibited a statistically significant higher incidence (3/16) of renal tubular-cell adenocarcinoma than that of the controls (0/33) ($p = 0.028$) using the "Life Table" or "Incidental Tumor" tests referenced in NTP (1983). These kidney tumors are considered uncommon occurrences in F344/N rats. Only three of 748 (0.4%) male rats from historical vehicle gavage control groups have exhibited such tumors. The incidence of mesotheliomas of the peritoneum among the low dose rats (5/50, 10%) significantly ($p<0.05$) exceeded concurrent (1/50, 2%) and historical controls (16/752, 2.1%). However, toxic nephrosis that significantly reduced equivocal results that were considered "inadequate to evaluate the presence or absence of a carcinogenic response" of these rats to TCE (NTP, 1983).

Significantly higher incidences of hepatocellular carcinoma in dosed male mice (13/49, $p < 0.05$) relative to those of their controls (8/48 and 2/48, respectively) confirmed the positive results of the 1976 NCI mouse study. Dosed female mice were also found to have a statistically significant ($p< 0.05$) increase in the incidence of hepatocellular adenomas (8/49) relative to that of controls (2/48).

National Toxicology Program, 1988

In the 1987 National Toxicology Program study (NTP, 1988), four strains of rat (ACI, August, Marshall and Osborne-Mendel) received high (1000 mg/kg) or low (500 mg/kg) daily doses of TCE in corn oil by gavage 5 d/wk for 103 wk. The TCE used contained no epichlorohydrin. Test groups consisted of 50 animals of each sex. Male Osborne-Mendel rats exhibited a statistically significant higher incidence of renal cell adenomas (6/50) at the lower dose vs. controls (0/50) ($p = 0.007$). Male Marshall rats exhibited a statistically significant higher incidence of testicular interstitial cell tumors at the higher dose (32/48) vs. the controls (17/46) ($p = 0.002$). The incidence of these proliferative testicular lesions was also high in control groups of ACI rats (36/49), but dosed ACI rats showed a (nonsignificant) decrease in incidence (23/49 in the low-dose rats, 17/49 in the high-dose rats). Therefore, the biological significance of the dose-related increase observed in this study is in question (DHS, 1990; Bogen et al., 1988).

Consistent negative dose-response trends were observed in the incidence of adrenal pheochromocytomas in male ACI, female Marshall, and male and female August and Osborne-Mendel rats in this study. Results of audits conducted in the Fall of 1983 and the Spring of 1984 (the in-life portion of the study was completed many years before the final report was issued) revealed that the documentation of animal breeding, animal identity, clinical observations, environmental conditions, and analytical chemistry data were inadequate to support any meaningful interpretation of the reported tumor incidence data (NTP, 1988).

National Toxicology Program, 1990 (NTP, 1990)

Carcinogenesis bioassays of epichlorohydrin-free TCE were conducted by corn oil gavage in groups of 50 male and 50 female F344/N rats and B6C3F1 mice. Dose levels were 500 and 1,000 mg/kg for rats and 1,000 mg/kg for mice. TCE was administered five times per week for 103 weeks, and surviving animals were sacrificed between weeks 103 and 107. Groups of 50 rats and 50 mice of each sex received corn oil by gavage and served as vehicle controls. Groups of 50 male and 50 female rats were used as untreated controls. Survival of treated animals was less than that of vehicle controls. Mean body weights of treated animals were also lower than

control animals, except female mice which were comparable. Cytomegaly (toxic nephrosis) of the kidney was seen in 96/98 male and in 97/97 female rats given TCE, and in none of the vehicle controls. Cytomegaly was observed in 45/50 male mice and 48/49 female mice given TCE, and in none in the vehicle controls. Renal tubular cell adenocarcinomas were found in three high dose male rats killed at the end of the study (0/33, 0/20, and 3/16, 19%, $p < 0.05$). Renal cell adenocarcinomas are considered uncommon in F344/N rats with a 0.4% historical incidence in vehicle gavage controls. Additional renal tumors in TCE-treated male rats included one transitional cell carcinoma of the renal pelvis at the high dose and two tubular cell adenomas in low dose and one carcinoma of the renal pelvis in a high dose animal. No renal neoplasms were seen in vehicle control rats. In female rats, one tubular cell adenocarcinoma was found in the high dose group. The results in male rats were considered equivocal for detecting a carcinogenic response because both TCE-treated groups showed significantly reduced survival compared to the vehicle control (35/50, 70%; 20/50, 40%; 16/50, 32%) and because 20% of the animals in the high dose group were lost due to gavage dosing errors (NTP, 1990).

TCE administration to mice caused increased incidences of hepatocellular carcinomas in males (8/48 vs.31/50, $p < 0.001$) and in females (2/48 vs. 13/49, $p < 0.005$). Hepatocellular carcinomas metastasized to the lungs in five dosed male mice and one control male; none was observed in female mice. The incidence of hepatocellular adenomas was increased in male mice (7/48 vs. 14/50) and in female mice (4/48 vs. 16/49, $p < 0.05$). Under the conditions of the studies, TCE caused renal tubular cell neoplasms in male F344/N rats, produced toxic nephrosis in both sexes, and shortened survival time of males. The significance of these findings is compromised by inadequate survival. No evidence of carcinogenicity was seen in female F344/N rats. TCE was carcinogenic for B6C3F1 mice causing increased hepatocellular carcinomas in males and females and increased hepatocellular adenomas in females.

Henschler et al., 1980

Henschler et al. (1980) exposed three species of rodents (Han:NMRI mice, Han:WIST rats, and Syrian hamsters) to concentrations of pure TCE at 100 and 500 ppmv for 6 hr/d, 5 d/wk, for 78 wk. The ages of the animals when placed on study were not given. Surviving mice and hamsters were sacrificed at the 130th wk. Rats were not sacrificed until the 156th wk. Neither rats, hamsters nor male mice were observed to have significantly increased tumor incidence. Dosed female mice, however, exhibited significantly ($p < 0.05$) higher incidences of malignant lymphoma relative to that of the controls (100 ppmv, 17/30; 500 ppmv, 18/28; controls, 9/29). The time-to-tumor occurrence also decreased in a dose-related fashion. Henschler et al. (1980) cited three studies that describe a high spontaneous incidence of malignant lymphoma in female NMRI mice. The authors also referenced several studies that attribute the development of murine lymphoma to immunosuppressive agents that allow lymphoma induction by specific in-born viruses. In its review of this study, the U.S. EPA also suggests that immunosuppression by TCE or some other nonspecific agent provides a possible interpretation of the positive results of this study (U.S. EPA, l985a).

Fukuda et al., 1983

In a study by Fukuda et al. (1983), females of two species (Sprague-Dawley rats and ICR mice) were exposed to concentrations of 50, 150, and 450 ppmv of reagent grade TCE for 7 h/d, 5 d/wk, for 104 wk. The surviving animals were killed in the 107th wk. Animals of both species were 7 wk old when placed on the study. Size of the test groups varied between 49 and 51. Chemical analysis revealed the test sample to contain TCE (99.824%) along with carbon tetrachloride (0.128%), benzene (0.019%), epichlorohydrin (0.019%), and l,l,2-trichloroethane

(0.010%) in the vapor phase. The incidence of lung adenocarcinomas among mice in the two higher exposure groups (150 ppmv, 8/50; 450 ppmv, 7/46) was significantly ($p < 0.05$) higher in both groups than that in the low dose (3/50) or controls (1/49). The incidence of total lung tumors (adenomas and adenocarcinomas combined) in exposed mice was not significantly different (6/50,13/50,11/46) from that of the controls (6/49). Statistical analysis of the tumor incidences among rats showed no significant increases or trends.

Henschler et al., 1984

Henschler et al. (1984) tested different samples of TCE with or without epichlorohydrin (ECH) and/or 1,2-epoxybutane for carcinogenicity in groups of 50 5-wk-old male or female ICR/Ha-Swiss mice. Treated animals received one large dose of TCE with or without epoxides (males: 2400 mg/kg; females: 1800 mg/kg) by corn oil gavage 5 d/wk times a week for 18 months. Dosing was interrupted during weeks 35 to 40, 65, and 69 to 78. All doses were reduced to half the initial amount after the 40th wk. We calculated experimental TWA daily doses of 1900 mg/kg for males and 1400 mg/kg for females by dividing the sum of the product of the number of days dosed and the administered dose by the number of days dosed. After the dosing period (61 doses in 78 wk), the mice were observed for 26 wk and then sacrificed during the 104th wk. Mice dosed with purified, amine-stabilized TCE did not exhibit a statistically significant increase in the incidence of any tumor type. The administration of TCE with ECH (0.6%, equivalent to lifetime TWA ECH doses of 8.1 and 6.0 mg/kg-day for males and females, respectively), or both ECH (0.25%) and 1,2-epoxybutane (0.25%) was associated with a significant ($p<0.05$) increase in forestomach papillomas or carcinomas in both sexes. In particular, the incidence of these tumors in the control mice in this experiment versus that in the mice exposed to ECH-stabilized TCE was 1/50 vs. 8/50 in males and 1/50 vs. 12/50 in females. The latter response in dosed females was the most significant ($p = 0.0002$, using an age-adjusted chi-squared test) increase in tumor incidence observed in the Henschler et al. (1984) study. The administration of TCE with 1,2-epoxybutane (0.8%) was associated with a significant ($p < 0.05$) increase in squamous cell carcinomas in males.

Maltoni et al., 1986

Maltoni et al. (1986) reported the results of a series of eight TCE carcinogenicity experiments performed between 1976 and 1983. This project employed nearly 4,000 mice and rats that were observed until spontaneous death. Inhalation was the primary route of administration. The statistically and biologically significant results of these bioassays (BT301, 302, 303, 304, 304-bis, 305, 306, and 306-bis) are summarized below.

BT301 was the only noninhalation experiment in the project. TCE was administered by stomach tube to Sprague-Dawley rats at dose levels of 50 or 250 mg/kg, 4 to 5 d/wk, for 52 wk. Dosing began when the rats were 13-wk old. Thirty rats of each sex were in each dosing group. The TCE was epoxide free and contained 50 ppmv or less each of 1,2-dichloroethylene, chloroform, carbon tetrachloride and 1,1,2-trichloroethane. A dose-related higher frequency of leukemia was observed in treated males, but this increase was not statistically significant.

The U.S. EPA (1985a) reviewed this bioassay and remarked that the dosing period of 52 wk was below potential lifetime exposures. They also stated that the older rats (13-wk old) would give no indication of the carcinogenic potential of TCE in developing animals.

Maltoni et al. (1986) conducted two short-term inhalation bioassays with Sprague-Dawley rats (BT302) and Swiss mice (BT303). The animals were exposed to 100 or 600 ppm TCE for 7 hr/d, 5 d/wk, for 8 wk. No statistically significant effect was observed. Treated male mice

exhibited an increase in the incidence of hepatomas over that of the controls, but the increase was not statistically significant at a 95% confidence level.

BT304 and BT304-bis were both similar long-term inhalation experiments whose results were combined and evaluated together. Sprague-Dawley rats were exposed to either 100, 300, or 600 ppm TCE for 7 hr/d, 5 d/wk, for 104 wk. A statistically significant exposure-related increase in the incidence of Leydig cell tumors of the testes was observed in treated rats: 31/130 (23.8%) at 600 ppm ($p < 0.01$), 30/130 (23.1%) at 300 ppm ($p < 0.01$), 16/130 (12.3%) at 100 ppm ($p < 0.05$), and 6/135 the (4.4%) in the control group.

In experiment BT305 Swiss mice (90/sex/dose group) were exposed to TCE at a concentration of 100, 300, or 600 ppm for 7 h/d, 5 d/wk, for 78 wk. Males exposed to the two higher levels showed pulmonary tumors (27/90 at 600 ppm, $p < 0.01$; 23/90 at 300 ppm, $p < 0.05$) relative to that of the control group (11/90). The increased incidence of pulmonary tumors included a slight increase in adenomas and adenocarcinomas, but the statistical significance of the increase in pulmonary tumors was clearly due to an increase in the number of animals with adenomatous hyperplasia or early adenomas (i.e., borderline adenomas). Males exposed to 600 ppm TCE also had a higher frequency of hepatomas (13/90, $p < 0.05$) than that of controls (4/90). Females did not show any significant response to TCE exposure in this bioassay.

BT306 and BT306-bis were both conducted with $B6C3F_1$ mice (90/sex/dose group) under similar conditions. BT306-bis was added due to early high mortality in BT306 males. Animals were exposed to 100, 300, or 600 ppm TCE for 7 hr/d, 5 d/wk for 78 wk. The increase in the total numbers of malignant tumors in female mice was significant at all three dose levels: 64.4% at 600 ppm ($p < 0.01$); 58.9% at 300 ppm ($p < 0.01$); 57.8% at 100 ppm ($p < 0.05$); and 46.7% in the controls. A dose-related increase in the incidence of pulmonary tumors was observed in females, but was significant ($p < 0.01$) only at 600 ppm (14/87) relative to that in the control group (2/90). The pulmonary tumors included no adenocarcinomas but consisted primarily of adenomas. When males and females were considered together, a slight increase in the incidence of hepatomas was observed in treated animals and was significant ($p < 0.01$) at 600 ppm (15/180; controls: 4/180). Males in BT306 (poor survival group) showed significant increases in hepatoma (1/59 control, 1/31, 3/38, 6/37, $p < 0.01$). Males in BT306-bis (normal survival) didn't show significant increases in hepatoma (17/77 control, 19/47, 27/67, 21/63). Combined males from these two groups showed significant differences in hepatoma at all dose levels by Fisher's exact test and a significant Mantel-Haenszel trend test [18/136 control, 20/78 ($p = 0.02$), 30/105 ($p = 0.0027$), 27/100 ($p = 0.0066$), trend ($p = 0.0024$)].

Maltoni et al. (1986) reported statistically significant increases in pulmonary tumors (benign and malignant combined) and hepatomas (malignant) in treated mice and testicular tumors (benign and malignant combined) in treated rats. An increased incidence of renal tubular cell adenocarcinoma was also observed in treated rats. Although the incidence of this neoplasia was not statistically significant, Maltoni et al. (1986) considered the appearance of these tumors to be biologically significant because of their rarity in control animals (0/460).

Summary of Evidence of Carcinogenicity in Animals

The results of the rodent bioassays summarized in Table 5 indicate that TCE induces tumors in different tissues in mice and rats, and no tumors in hamsters. The principal findings are: 1) liver carcinomas in male mice by inhalation and in both sexes by gavage administration; 2) lung carcinomas in female mice by inhalation; and 3) kidney tubular carcinoma in male rats by

inhalation and gavage dosing. Results in both rats and mice are inconsistent across experiments and at each site and some tests are negative. The strongest evidence for carcinogenicity is in $B6C3F_1$ mouse liver with TCE administered by gavage.

The results of the NCI (1976) bioassay of TCE administered by gavage show that oral exposure was associated with a statistically significant ($p < 0.01$) increased incidence of hepatocellular carcinoma in both sexes of $B6C3F_1$ mice. Factors such as dose-related increases of hepatocellular carcinoma in both sexes, a decrease in the time to tumor among males, and the occurrence of metastases to the lung in dosed mice support the NCI conclusion that TCE was hepatocarcinogenic in that strain of mouse under the conditions of the experiment.

In the repeat experiment (NTP, 1983), oral administration of epoxide-free TCE was observed to be associated with increased incidences of hepatocellular carcinoma in both sexes, and of hepatocellular adenomas in females, confirming the results of the mouse bioassay by NCI (1976). An increased incidence of malignant lymphoma was observed in TCE-exposed female Han:NHRI mice (Henschler et al., 1980). The EPA (U.S. EPA, 1985a) concluded that the biological significance of this observation is unclear because these tumors have a high rate of spontaneous occurrence, which may have increased as an indirect result of TCE dosing, possibly mediated by immunological sensitivity to the exposure regimen.

In rats there is evidence of kidney carcinogenicity when TCE is administered by gavage, but not by inhalation. When the multiple tests were analyzed together the incidence of malignant tumors of the kidney tubules was not statistically significant ($p = 0.11$). Nearly all the significant results appeared in bioassays reported by the NTP (1983, 1988) that are considered by the NTP to be "inadequate" studies of carcinogenicity. However, under the conditions of these studies, the administration of TCE was deemed by NTP to be "associated" with an increased incidence of renal tubular cell adenocarcinoma in the male F344/N rat (NTP, 1983), renal tubular cell adenoma in the male Osborne-Mendel rat, and testicular interstitial cell tumor in the male Marshall rat (NTP, 1988). Malignant tumors in mouse lung were significantly increased ($p = 0.001$) in only one of 12 experiments. When analyzed as a group neither malignant or combined benign and malignant lung tumors were significantly increased ($p > 0.05$). Increases in benign tumors of the testis occurred in some rat strains but not in others (Bogen and Gold, 1997).

"Sufficient" evidence of carcinogenicity in animals is described by the U.S. EPA as evidence "which indicates that there is an increased incidence of malignant tumors or combined malignant and benign tumors: (a) in multiple species or strains; or (b) in multiple experiments (e.g., with different routes of administration or using different dose levels); or (c) to an unusual degree in a single experiment with regard to high incidence, unusual site or tumor type, or early age at onset" (U.S. EPA, 1986b).

Based on only the positive results of the NCI (1976) bioassay, IARC (1979) determined that there was "limited evidence" that TCE is carcinogenic in animals. Upon additional review of the data of Henschler et al. (1980), IARC's classification of evidence for carcinogenicity of TCE to animals remained "limited" (IARC, 1984). In the latest evaluation IARC concluded that there is sufficient evidence in experimental animals for the carcinogenicity of TCE (IARC, 1995). Based on the increased incidences of malignant liver tumors in $B6C3F_1$ mice in two studies (NCI, 1976; NTP, 1983), the increased incidence of malignant lymphoma in NMRI mice (Henschler et al., 1980), and the increased incidence of renal tumors in rats (NTP, 1983), the U.S. EPA (1985a) concluded that the above results constitute "sufficient" evidence for carcinogenicity in animals.

The results reported by Fukuda et al. (1983) and Maltoni et al. (1986) provide unambiguous support for the U.S. EPA classification of "sufficient" evidence of carcinogenicity in animals because they showed statistically significant increases in malignant pulmonary tumors and liver tumors in treated mice. The evidence is enhanced by the addition of a tumor type (lung adenocarcinomas from Fukuda et al., 1983) distinct from those observed in previous studies. Results from both studies further strengthen the classification by introducing the inhalation route of exposure, and by using different strains of mice.

An increase in renal tubular cell adenocarcinomas found in treated Sprague-Dawley rats that was not statistically significant (Maltoni et al., 1986) may support the biological significance of the similar results observed in the NTP (1983) study. Significant carcinogenic responses were observed in male $B6C3F_1$ mice exposed to high concentrations of the TCE metabolites, trichloroacetic acid (TCA) or dichloroacetic acid (DCA) in drinking water (Herren-Freund et al., 1987; Pereira, 1996).

Toxicological Effects in Humans

Acute Toxicity

Kleinfeld and Tabershaw (1954) reported the death of an individual following accidental ingestion of an unspecified quantity of TCE. Prior to his death, the individual developed jaundice (elevated bilirubin levels); at autopsy, evidence of severe centrilobular necrosis was found. Liver failure following TCE exposure was also implicated in a case reported by Joron et al. (1955). TCE caused hepatitis and jaundice in an individual exposed to 27 to 294 ppmv in air. Liver damage progressed to massive liver necrosis, which was ultimately fatal. Reports of recent TCE poisonings have included pharmacokinetic modeling of tissue concentrations (Perbellini et al., 1991; Ford et al., 1995). In the latter study the most recent fatal case analyzed gave model predictions of TCE exposure concentrations in the 500-10,000 ppm range. Blood TCE was 174 mg/L and brain TCE was 809 mg/kg. Previous fatalities analyzed showed values of 3-110 mg/L and 2-270 mg/kg, respectively.

Bruning et al. (1998) evaluated clinical symptoms, toxicokinetics, metabolism, and biochemical parameters for renal damage in a 17-year old male who ingested about 70 mL of TCE. The patient developed fever, tremor, general motor restlessness, and sinus tachycardia and lost consciousness five hr after TCE ingestion. Medical management included hyperventilation and diuresis. The highest TCE concentration in blood (4 mg/L) was observed 13 hr after TCE ingestion. TCOH, TCA, *N*-acetyl-*S*-(1,2-dichlorovinyl)-L-cysteine, and *N*-acetyl-*S*-(2,2-dichlorovinyl)-L-cysteine were quantified in urine samples. Chloroacetic and dichloroacetic acids were also found in urine. Normal levels of protein and glucose were seen in urine but α_1- and β_2-microglobulin as well as β-NAG were significantly increased. These increases are indicative of renal tubule damage. Also seen via SDS-PAGE of urinary proteins were a number of low-molecular-mass proteins between 10,000 and 50,000 Da, clearly indicating renal tubular damage.

Baerg and Kimberg (1970) described three cases of intentional intermittent exposure to TCE-containing products that resulted in drowsiness, headache, vomiting, fever, chills, abdominal pain, jaundice, abnormal hepatic function, and hepatic necrosis. In two of the three cases, hepatic damage occurred after inhalation of Carbona, a cleaning fluid (Carbona is composed of 44% TCE and 56% petroleum distillates).

Occupational exposure to TCE from heated degreasing tanks was described by Thiele et al. (1982). A worker reportedly became inebriated after periods of exposure to TCE fumes from the tank. In addition to these intermittent exposures, the individual was inadvertently trapped several times in tanks that contained residual TCE. Upon switching jobs, this worker was exposed to l,l,l-trichloroethane and began to suffer from fatigue, weight loss, anorexia, icterus, and abdominal swelling. Results from liver tests were abnormal, and the worker was diagnosed as having hepatic cirrhosis. There was no history of alcohol consumption or hepatitis, and Thiele et al. (1982) attributed the cirrhosis to repeated exposure to chlorinated hydrocarbons.

The U.S. EPA (1985a) and the World Health Organization (1985) have reviewed a number of early occupational and medical reports on the hepatotoxicity of TCE. Exposure to TCE has not consistently produced liver damage. Of 248 patients anesthetized with TCE, none had evidence of hepatic injury (Brittain, 1948). However, lethal hepatic failure has occurred in some instances following TCE-induced anesthesia (Ayre, 1945; Dodds, 1945; Elam, 1949; Werch et al., 1955).

Accidental or occupational exposure to TCE has also caused liver disease, necrosis, and hepatic failure. For example, Cotter (1950) found that accidental exposure to TCE induced hyperglobulinemia and hypercalcemia. Secchi et al. (1968) reviewed seven cases of poisoning caused by ingestion of TCE. Liver damage was documented in three of these individuals. The authors noted, however, that this damage may have been due to the presence of contaminants. Phoon et al. (1984) described jaundice, hepatomegaly, and abnormal liver function in five individuals occupationally exposed to TCE for 2 to 5 wk (unknown concentration). One of these workers eventually died from liver failure.

Renal damage following TCE exposure is relatively uncommon. However, Baerg and Kimberg (1970) diagnosed acute tubular necrosis in two individuals with a history of repeated inhalation of Carbona. These authors cited a number of other case reports that also implicated TCE exposure in renal damage. Gutch et al. (1965) documented hyperkalemia and elevated blood urea nitrogen levels in an individual occupationally exposed to TCE (≥ 2 hr). A kidney biopsy revealed abnormalities of the glomeruli and tubular degeneration. An acute occupational exposure to TCE (unknown concentration) reportedly caused oliguria and hepatorenal insufficiency (Suciu and Olinici, 1983). Kleinfeld and Tabershaw (1954) reported that one of five deaths they attributed to TCE exposure was caused by acute renal failure.

The use of TCE as a surgical anesthetic has provided a number of case reports that have documented its adverse effects on the cardiovascular system. TCE's cardiotoxicity has been reviewed by Norris and Stuart (1957), Defalgue (1961), and by the U.S. EPA (1985a). In addition, the World Health Organization (WHO, 1985) published a comprehensive review of foreign-language articles on the cardiovascular effects of TCE in humans. These effects reportedly include cardiac arrest, atrial and ventricular extrasystole, tachycardia, and ventricular fibrillation.

Inhalation or ingestion of TCE has resulted in a number of instances of sudden death, presumably due to heart failure. There are also case reports of nonlethal cardiac arrest due to TCE exposure. For the most part, the concentration of TCE and the duration of exposure that caused these effects have not been clearly established (Kleinfeld and Tabershaw, 1954; Bernstine, 1954; Norris and Stuart, 1957; Dhuner et al., 1957; James, 1963; Defalque, 1961; U.S.EPA, 1985a). TCE can cause sensitization of the cardiac muscle to epinephrine. Concurrent administration of TCE and epinephrine has caused arrhythmia and tachycardia (reportedly fatal in some instances) (Defalque, 1961; U.S. EPA, 1985a).

When used as an inhalation anesthetic, TCE vapor was "slightly irritating" to the respiratory tract of patients (Atkinson, 1960; U.S. EPA, 1985a). However, the primary respiratory problem associated with the medical use of TCE has been a pronounced increase in the rate of respiration (tachypnea). Although Atkinson (1960) stated that the magnitude of this effect was dose related, the effective concentrations of TCE were not given. TCE-induced tachypnea has commonly been associated with the onset of shallow respiration. Coleridge et al. (1968) attempted to determine the physiologic basis for TCE-induced alterations in respiration. Earlier work (cited by Coleridge et al., 1968) had indicated that an increase in excitability of the pulmonary stretch receptors may be responsible for the decrease in depth of respiration during TCE anesthesia. This study found that the frequency of discharge of the pulmonary stretch receptors increased when cats and dogs were exposed to 1.0 or 3.0% TCE for five minutes. In concurrent experiments, TCE did not produce any change in the impulse frequency of the pulmonary endings of vagal nerve fibers.

Subchronic Toxicity

McCunney (1988) reports various effects of TCE exposures varying from a few days to 18 months. The cases studied represent diverse manifestations of TCE toxicity secondary to acute and subchronic exposures. Encephalopathy characterized by impaired short term memory, a sense of inebriation, irritability, and personality changes developed after low dose exposure, primarily by dermal absorption. Urinary TCA levels dropped within one week of removal from the worksite, indicating a half-life of 40 hr. Symptoms persisted even at lower TCA levels suggesting other toxic metabolites with longer residence contributed to the symptoms. Chloral hydrate, an intermediary metabolite of TCE, has hypnotic effects. Air measurements were repeatedly within recommended limits (e.g., < 25 ppm). Hepatitis from exposure to TCE in occupational settings is extremely rare. In a review of 288 cases of industrial poisoning by TCE only five showed symptoms of hepatic toxicity. When TCE was used as an anesthetic, numerous cases were reported. Hepatitis has also been attributed to the inhalation of spot remover that contained 45% TCE. Of ten cases reported, five showed liver function abnormalities, two exhibiting proteinuria and a rise in blood urea nitrogen. A review of cases of TCE-associated hepatitis indicates that dose had little effect on development or prognosis. In nine of twelve hepatitis cases there was renal impairment. Liver biopsies of TCE induced hepatitis usually show centrilobular necrosis in both fatal and non-fatal cases.

Although rare, serious skin diseases secondary to occupational TCE exposures have been reported (Nakayama et al., 1988; Yanez Diaz et al., 1992).

Genetic Toxicity

The demonstration of TCE-induced genetic toxicity in humans has been largely inconclusive. Four studies of SCE tests in peripheral lymphocyte cultures from exposed workers show no or only minor effects on SCE frequencies (Seiji et al., 1990; Nagaya et al., 1989; Gu et al., 1981a,b cited in Fahrig et al., 1995; Brandom et al., 1990).

Three studies have been conducted that measured chromosomal effects on humans occupationally exposed to TCE. Peripheral lymphocytes were scored for hypodiploid cells and chromosome breaks by Konietzko et al. (1978) and for sister chromatid exchanges (SCE) by Gu et al. (1981a,b). The incidence of hypodiploid cells (cells containing less than the diploid number of chromosomes) was found to be higher in the exposed group of 28 workers compared

to an unmatched control group (l0.9% ± 4.4% and 6.5% ± 3.2%, respectively). Konietzko et al. (1978) also found a greater frequency of chromosome breaks in cells from the exposed group. Although this increase was not considered biologically significant, no statistical evaluation of the data was provided.

Gu et al. (1981a,b) compared an occupationally exposed group of six workers to a control group of nine individuals and reported a statistically significant ($p < 0.01$) increase in SCE in cultured peripheral lymphocytes (9.0 ± 0.4 vs. 7.9 ± 0.2, respectively). Exposed workers showed a positive correlation between the average number of SCE/cell and levels of trichloroacetic acid and trichloroethanol in the blood. These studies indicate that TCE or a metabolite may cause chromosomal aberrations or SCE in chronically exposed humans. However, exposure to additional compounds, including TCE contaminants, cannot be ruled out as possible causative agents in these studies.

Rasmussen et al. (1988) evaluated genotoxicity in 15 metal workers exposed to TCE. For workers exposed to high doses of TCE there was no difference (vs. unexposed) with respect to sperm count and morphology, and a small (insignificant) increase of two fluorescent Y-bodies (an indicator of two Y chromosomes) in spermatozoa. In contrast, there was a highly significant increase in the frequency of structural aberrations (breaks, gaps, translocations, deletions, inversions) and hyperdiploid cells in cultured lymphocytes from TCE degreasers. Of 1261 metaphases analyzed, 21.7 % exhibited gaps (vs. 2.8%, $p < 0.001$), 1.9% breaks (vs. 0.85%, $p < 0.001$), sum of translocations, deletions and inversions 1.35% (vs. 0.15%, $p < 0.001$), and hyperdiploid cells 0.79% (vs. 0.24%, $p <0.0013$). Chromosomal aberrations in cultured circulating lymphocytes are a reliable indicator of mutagenic exposure. Lymphocytes reflect cumulative exposure, having half lives between 12 mo. and 20 yr. Urinary TCA was also measured in the TCE exposed degreasers with a mean value of 3.7 mg/L (range 0.02-26.9). The cumulative exposure for the group averaged 4.6 yr (range 0.8-22.0). The authors noted the lack of an adequate negative control group so these findings are inconclusive.

Developmental and Reproductive Toxicity

Tola et al. (1980) conducted an epidemiologic study on the mortality of Finnish workers exposed to TCE. As part of this study, these investigators consulted the Finnish Registry of Congenital Malformations. No malformed babies had been born to women exposed to TCE during the 13 yr covered by this study. Based on the national incidence, three malformed infants would have been expected.

A survey of 80,938 live births and 594 fetal deaths in an area of New Jersey with TCE-contaminated public drinking water (mean concentration of 55 ppb) found an association between TCE concentrations >10 ppb and oral clefts, CNS defects, neural tube defects, and major cardiac defects (Bove et al., 1995). Small numbers of cases and exposure classifications are limitations of the study. A study of subjects exposed to solvent contaminated well water including 267 ppb TCE in Massachusetts suggests that the combination of eye and ear anomalies and the combination of CNS, chromosomal, and oral cleft in newborns were associated with contaminated water exposure (Lagakos et al., 1986). The groupings for statistical analysis have been questioned on the basis of a lack of connection in embryological development. Additional studies of the same population (MDPH, 1994) indicated increased prevalence in choanal atresia, a rare respiratory effect, and hypospadias/congenital chordee. A small increase in eye defects was seen but there was no relation between TCE exposure and heart defects. In an Arizona population exposed to TCE (6-239 ppb), dichloroethylene, and chromium in drinking water

wells, an association was found between contaminated water and congenital heart disease in children whose parents were exposed in the month before conception and the first trimester of pregnancy (Goldberg et al., 1990). The rate of heart defects in the exposed group was about 2.5 times higher than among children from the unexposed referent group. A study in Michigan communities exposed to chlorinated solvents including up to 14,890 ppb TCE in drinking water found no increase in congenital defects (Freni & Bloomer, 1988). The size of the study population was small, however.

Taskinen et al. (1989) conducted a nested case-control study of 120 cases of spontaneous abortion (SAB) and 251 controls in a file of 6000 Finnish workers biologically monitored for solvent exposure. No association was found between parental occupational exposure to TCE and SAB (crude odds ratio (OR), 1.0; 95% C.I. 0.6-2.0). Pregnancies occurring among 3265 women biologically monitored for solvent exposure in 1965-83 were identified in a Finnish database (Lindbohm et al., 1990). Only one pregnancy per woman was included, resulting in 120 cases of SAB; 336 age-matched controls were randomly selected from women who had normal births during the study period. The OR for SAB, adjusted for previous SABs, parity, smoking, alcohol use, and exposure to other solvents, was 0.6 (95% C.I., 0.2-2.3) for exposure to TCE.

Windham et al. (1991) compared 852 cases of SAB in Santa Clara Co., CA with 1618 controls randomly selected from county residents. All participants were surveyed about occupational use of 18 solvents and products used during the first 20 weeks of pregnancy. An excess risk for SAB was observed for women who reported exposure to TCE (crude OR, 3.1; 95% C.I., 0.92-10.4). Four of the seven women exposed to TCE also reported PCE exposure.

Information on 7316 pregnancies was obtained from a hospital discharge register of 9186 women identified as working in Finnish laboratories (Taskinen et al., 1994). The pregnancies resulted in 5663 births, 687 SABs and 966 induced abortions. A case referent study was conducted within the cohort. The 206 women with only one SAB and 329 randomly selected normal birth controls were included in the study. The OR for SAB and exposure to TCE was 1.6 (95% C.I., 0.5-4.8) adjusted for employment, smoking, alcohol consumption, parity, previous miscarriages, failed birth control, and febrile disease during pregnancy. The OR for exposure to halogenated solvents as a group were 0.6 (0.4-1.1) for exposure 1-2 d/wk and 1.8 (0.9-3.7) for 3-5 d/wk.

Chia et al. (1996) evaluated semen parameters of workers exposed to TCE. Eighty-five workers were analyzed for volume, sperm density, viability, motility, and morphology. Urine samples were analyzed for TCA. Personal monitoring of 12 subjects showed a mean air concentration of 29.6 ppm (range 9-131). The mean urine TCA was 22.4 mg/g creatinine (range 0.8-136.4). One of the sperm parameters to show a significant difference between low (< 25 mg/g urine TCA) and high exposure subjects was sperm density at 56.9 million/mL vs. 63.6 million/mL ($p = 0.044$). The authors also report an apparent dose-response relation between TCA in urine and hyperzoospermia or sperm densities > 120 million/mL. The prevalence ratios vs. the low exposure group were: 50 to <75, 2.36 (0.92-6.07); 75 to <100, 3.00 (1.00-9.02); ≥100 mg TCA/g creatinine, 3.58 (1.09-11.80). Hyperzoospermia has been implicated in infertility.

Endocrine Toxicity

Goh et al. (1998) examined serum levels of insulin and selected adrenal steroid hormones in men chronically exposed to low doses of TCE. Eighty-five workers had urine collected and analyzed for TCA (UTCA) and on the same day blood samples were analyzed for serum testosterone, sex hormone-binding globulin (SHBG), androstenedione, cortisol, aldosterone, and insulin. The

mean environmental concentration of TCE was 29.6 ppm and the mean UTCA was 22.4 mg/g creatinine (range 0.8-136.4). No significant alterations in adrenal steroid hormone production were noted. However, UTCA was significantly correlated with serum insulin levels. Insulin and SHBG responded in tandem with the highest levels found in workers exposed for less than two years, while levels of both were significantly lower in those exposed for more than 2 years. A triphasic response in insulin levels vs. duration of TCE exposure was observed. An initial acute rise (41 mIU/L) was followed by a fall to normal levels (12 mIU/L) in those exposed 2-4 yr and then a more gradual rise in those exposed 4-6 yr (16 mIU/L), and >6 yr (20 mIU/L). The mechanism of this dynamic response is unknown but may be related to TCE-associated increases in SHBG. Although none of the subjects had a history of diabetes, the clinical significance of such transient TCE-induced insulin levels is unknown and needs further study.

Immunotoxicity

Kilburn &Warshaw (1992) investigated the prevalence of symptoms of systemic lupus erythematosus (SLE) and of fluorescent antinuclear antibodies associated with chronic exposure to TCE and other chemical contaminants in well water. Criteria for recognition of SLE were applied to 362 subjects exposed to TCE, trichloroethane, inorganic chromium, and other chemicals in a contaminated aquifer in Tucson, AZ. TCE concentrations in the affected wells ranged from 6-500 ppb for a period of up to 25 years. Antinuclear antibodies were measured by fluorescence in serum (FANA). Frequencies of each of 10 criteria symptoms were higher in the exposed subjects than in any comparison group (AZ control group, published studies, laboratory controls) except those with clinical SLE. The number of subjects with four or more symptoms was 2.3 times higher than referent subjects. FANA titers >1: 80 were about 2.3 times higher in exposed women but equivalent in men and laboratory controls. The symptom criteria and FANA were rank correlated with a coefficient of 0.125, $r^2 = 0.0205$ ($p < 0.059$). In control men and women neither correlation was significant. The study indicates an association between exposure to chemical contaminants, particularly TCE, in drinking water and the development of symptoms of SLE in a manner similar to drug-induced lupus or scleroderma.

Neurotoxicity

TCE is a central nervous system (CNS) depressant and has been used as an anesthetic and analgesic. TCE's popularity as an anesthetic declined with the accumulation of evidence that documented severe (and occasionally fatal) neurotoxic effects (Defalque, 1961; Atkinson, 1960; Tomasini and Sartorelli, 1971; Thierstein et al., 1960; Nomura, 1962). Occupational exposure to TCE has resulted in nausea, headache, loss of appetite, weakness, dizziness, ataxia, and tremors (Longley and Jones, 1963; Milby, 1968; Mitchell and Parsons-Smith, 1969; Okawa and Bodner, 1973). Acute exposure to high concentrations of TCE has caused irreversible nerve damage (Mitchell and Parsons-Smith, 1969; Buxton and Hayward, 1967; Barret et al., 1982) and death (Kleinfeld and Tabershaw, 1954; James, 1963; Buxton and Hayward, 1967). Evidence from experimental human and animal studies indicates that TCE induces a variety of adverse effects on the CNS.

In a controlled experiment conducted by Salvini et al. (1971), six individuals were exposed to 110 ppmv of TCE vapor for two 4-hr periods. Volunteers had a statistically significant ($p < 0.001$) reduction in performance on various psychophysiological function tests, such as perceptiveness, immediate memory, and complex reaction time. In an attempt to remove a

source of bias, the experiment was repeated with six workers familiar with the odor of TCE. Similar decrements in test performance were also noted in these individuals.

Vernon and Ferguson (1969) evaluated the effects of TCE exposure (100 to 1000 ppmv TCE for two hr) on the psychophysiologic performance of eight volunteers. Exposure to 1000 ppmv TCE caused a statistically significant ($p < 0.05$) decrease in performance on the Howard-Dolman, steadiness, and pegboard tests. Stopps and McLaughlin (1967) also reported a decline in psychophysiologic test performance following exposure to 500 ppmv TCE for approximately three hr.

Triebig et al. (1982) did not detect any change in motor or sensory nerve-conduction velocity in persons occupationally exposed to TCE (400 ppmv, 1 month to 36 yr). However, other reports have documented trigeminal nerve impairment in workers who were chronically exposed to TCE (exposure concentration and duration were not provided) (Barret et al., 1982; Mitchell and Parsons-Smith, 1969).

Alcohol intolerance associated with exposure to TCE has been described by Defalque (1961) and Muller et al. (1975). The experimental data of Muller et al. (1975) indicate that simultaneous exposure to TCE and ethanol results in a marked inhibition of TCE's metabolism. This leads to an accumulation of TCE in blood, which increases the extent of CNS depression.

Buxton and Hayward (1967) described an industrial incident involving four men who were exposed to TCE (actual concentrations are not known). Of the four men, two developed severe multiple cranial nerve palsies, and one of them died after 51 d. An autopsy revealed damage to the brainstem, cerebral cortex, and spinal cord. Cavanagh & Buxton (1989) have suggested that cranial neuropathy of TCE may result from reactivating a latent herpes virus.

Rasmussen et al. (1993) conducted a historical cohort study of 99 metal degreasers whose occupational exposures were mainly to TCE. Cumulative exposure to solvents was categorized in three groups where the mean full time exposure was: low, 0.5 yr; medium, 2.1 yr; and high, 11.0 yr. The dominant exposure for 70 workers was TCE with a mean exposure time of 7.1 yr and 35 hr/wk and for 25 workers Freon 113 (CFC 113) 4.2 yr and 15.1 hr/wk. Present and recent TCE exposures were assessed by blood and urine analyses of TCA and TCOH metabolites. The mean urinary TCA in the highly exposed group was 7.1 mg/L with a maximum of 26.1 mg/L. Historical data during the 1947-87 period indicate a fairly constant and high exposure level corresponding to a urinary TCA of 40-60 mg/L from the mid 1950's to the mid 1970's, the period relevant to the study population. A variety of neurological tests was performed to assess cranial nerve, olfactory nerve, and facial nerve functions, coordination and vibration threshold. The most marked finding was a highly significant dose-response relation between solvent exposure and motor dyscoordination. No significant cranial nerve dysfunction was found.

Kilburn & Warshaw (1993) studied neurobehavioral impairment in a population of human subjects exposed to TCE (6-500 ppb) and other contaminants in their drinking water for 1-25 yr. The 170 well-water exposed subjects were compared to 68 referent subjects for neurophysiological (NPH) and neuropsychological (NPS) tests. Also, 113 histology technicians were referents for the blink latency test. Exposed subjects were statistically significantly impaired when compared to referents for NPH tests. The impairments included sway speed with eyes open and closed, blink reflex latency, eye closure speed, and two-choice visual reaction time. NPS status was significantly impaired for Culture Fair (intelligence) scores, recall of stories, visual recall, digit span, block design, recognition of fingertip numbers, grooved pegboard, and Trail making A and B. Profile of Mood States (POMS) scores were also elevated. In a subsequent study 116 subjects exposed to TCE and polychlorinated biphenyls (PCBs) via

contaminated well water were compared to 46 reference subjects with uncontaminated water in two tests of balance or postural sway (Kilburn et al., 1994). A head and trunk tracking device and a force platform were used simultaneously. Speed, mean radius, and distance of sway were equally reproducible by both methods. Correlation coefficients were 0.672 with eyes closed and 0.588 with eyes open. The balance of the exposed group was significantly worse than that of the referent group by both head tracking (1.50 ± 0.71 cm/s vs. 1.27 ± 0.36 cm/s, $p < 0.034$) and the force platform (4.93 ± 1.56 N vs. 4.29 ± 1.14 N, $p < 0.013$) with the eyes closed. The differences were also significant with the eyes open. Exposure information in this study is sketchy; well water analyses for PCBs in the 1980's claimed values up to 3500 ppm and TCE concentrations exceeded the federal MCL of 5 ppb. Subjects in the exposed group lived in the area with contaminated water for at least four years between 1956 and 1981.

White et al. (1997) also examined residents exposed to TCE in well water for neurobehavioral effects. Three groups of subjects were studied. The first group in Woburn, MA was exposed to water initially showing concentrations of 267 ppb TCE, 21 ppb PCE, 12 ppb chloroform, 29 ppb dichloroethylene, and 23 ppb trichlorotrifluoroethane. The mean TCE concentrations of wells during the two-year study were: 256 ppb (range 184-400 ppb) and 111 ppb (range 63-188 ppb). A total of 28 subjects were assessed. Exposure durations were < 1 to 12 yr. The second group from Alpha, OH was exposed to well water with up to 760 ppb TCE and up to 2569 ppb 1,1,1-trichloroethane. Three subjects also had PCE (16.5 ppb), *cis*-1,2-dichloroethane (23.9 ppb), and 1,1-dichloroethane (21.7 ppb) in their well water. Twelve subjects were assessed for exposures of 5-17 yr duration. The third group of 14 subjects from Minnesota (MN) were exposed to TCE concentrations in well water ranging from 1220 to 2440 ppb for periods of 0.25 to 25 yr. For the MA group peripheral nerve conduction studies generally were normal although subclinical peripheral neuropathy was indicated in several patients. Neuropsychological assessment of the MA group showed that the behavioral domain most commonly affected was memory with 89% of subjects showing impairments on at least one memory test. In the OH group evidence of peripheral nerve involvement included nerve-conduction abnormalities greater than 2 SD from the mean in 3/12 subjects. Blink reflex in this group was normal. Neuropsychological assessment of this group showed that the most commonly affected domain was attention/executive function in 10/12 (83%). Digit Span, Wisconsin Card Sorting Test, and Visual Spans were especially difficult for these patients. Memory was abnormal in 7/12 (58%). In the MN group peripheral neuropathy was diagnosed in 5/14 (36%) subjects. A family of six underwent neuropsychological assessment. All six showed signs of impaired memory. All six also performed below expectation on tests of attention/executive functions. The children in the family had long term developmental exposure to TCE and academic testing and language were carefully assessed. The mother had normal test results and no evidence of academic disability and the father had reading difficulty due to a childhood head injury. All four children performed below average. Three of the children showed naming deficits on the Boston Naming Test. All six were diagnosed with TCE-induced encephalopathy. The authors caution that the results presented are from a clinical/diagnostic study and not a prospective epidemiological investigation. Nevertheless the results suggest that chronic environmental exposure to solvents at ppb concentrations can be associated with significant behavioral deficits as measured by neuropsychological tests. The data also indicate that the younger the individual is at the time of exposure, the greater is the range of neuropsychological deficits detected.

Chronic Toxicity

Information from medium to long term TCE exposures via inhalation and dermal routes is presented elsewhere in this report and in ATSDR (1997). These studies indicate that the nervous system is the most sensitive target. The studies also indicate that the liver and kidneys are targets of TCE chronic toxicity. The liver effects noted include liver enlargement and increases of serum levels of liver enzymes. The kidney effects include increased *N*-acetyl-β-D-glucoaminidase. Other chronic effects include cardiovascular, immunological, and cancer (see next section).

Carcinogenicity

The evidence of TCE-induced cancers in humans has been reviewed in depth by IARC (1995). Three cohort studies were considered to be relevant to TCE evaluation. Two of these studies in Sweden and Finland (Axelson et al., 1994; Anttila et al., 1995) involved people who had been monitored for exposure to TCE by measurement of TCA in urine. The third study in the U.S. (Spirtas et al., 1991) covered workers exposed to TCE during maintenance of military aircraft and missiles, some of whom were also exposed to other solvents. A fourth cohort study included all workers in an aircraft manufacturing company in the U.S. (Garabrant et al., 1988). This study was considered less relevant, since only one-third of the workers had jobs that exposed them to TCE. In none of the available cohort studies was it possible to control for potential confounding factors, such as social class (with regard to cervical cancer) and smoking (with regard to urinary bladder cancer).

The results of the three better cohort studies consistently indicated an excess relative risk for cancer of the liver and biliary tract, with a total of 23 observed vs. 12.87 expected. The results for liver cancer only in the Finnish and U.S. studies were 7 observed vs. 4.00 expected. With respect to non-Hodgkin's lymphoma the results of the three cohort studies were consistent: a modest increase in relative risk with 27 cases observed vs. 18.9 expected. A twofold risk for cervical cancer was observed in two cohort studies. The occurrence of kidney cancer was not elevated in the cohort studies. However a study of German workers exposed to TCE yielded five cases of renal cancer vs. none in a comparison group (IARC, 1995). The incidence of urinary bladder cancer was not increased in the two cohort studies from Sweden and Finland. However, slightly increased numbers of deaths were seen in the two U.S. cohorts. The incidence of bladder cancer was not increased in subjects assumed to be exposed to TCE in a case-control study from Montreal, Canada (IARC, 1995).

Morgan et al. (1998) investigated mortality rates in a cohort of 20,508 aerospace workers followed up over the period 1950-1993. Of these, 4733 workers had occupational exposures to TCE. TCE was also present in some washing and drinking water at the work site. Standardized mortality ratios (SMRs) were calculated for the entire cohort and the TCE exposed subcohort. SMRs for nonmalignant respiratory diseases were near or less than 1.00 for TCE exposure groups. Elevated SMRs for ovarian cancer were observed for workers with peak TCE exposure at medium and high levels, relative risk (RR) = 2.74, 95% C.I. = 0.84-8.99, and among women with high cumulative exposure (RR = 7.09, 95% C.I. = 2.15-23.54). Among those workers with peak exposures at medium and high levels, slightly elevated SMRs were seen for kidney cancer (RR = 1.89, 95% C.I. = 0.85-4.23); urinary bladder (RR = 1.41, 95% C.I. = 0.52-3.81);

and prostate cancer (RR = 1.47, 95% = 0.85-2.55). For kidney cancer the cumulative low and high exposure groups gave (RR = 0.31, 95% C.I. = 0.04-2.36) and (RR = 1.59, 95% C.I. = 0.68-3.71), respectively. A meta-analysis of four occupational studies including Anttila et al. (1995), Axelson et al. (1994), and Spirtas et al. (1991) gave the following meta-SMRs: liver cancer, 1.32; prostate cancer, 1.09; kidney cancer, 1.09; bladder cancer, 1.15; and non-Hodgkin's lymphoma, 1.25. However, small numbers of cases (except for prostate cancer), even aggregated across four studies, limits the interpretation of these findings. Other limitations include narrowly defined exposure groups, lack of data on potential confounders such as smoking, diet, and exposure to other solvents, and no direct measure of personal exposure.

Blair et al. (1998) reported an extended followup of mortality and cancer incidence of 14,457 aircraft maintenance workers exposed to TCE and other organic solvents and chemicals. Workers exposed to TCE showed non-significant excesses for non-Hodgkin's lymphoma (RR = 2.0), and cancers of the esophagus (RR = 5.6), colon (RR = 1.4), primary liver (RR = 1.7), breast (RR = 1.8), cervix (RR = 1.8), kidney (RR = 1.6), and bone (RR = 2.1). None of these cancers showed an exposure-response relation. The authors conclude that the findings do not support a causal link with TCE due to lack of significance and dose-response. The study has a number of limitations including lack of information on lifestyle and other non-occupational risk factors for various diseases, such as tobacco use and diet.

Henschler et al. (1995a,b) conducted a retrospective cohort study in a cardboard factory in Germany where workers in one part of the plant were exposed to TCE. The study group consisted of 169 men who had been exposed to TCE for at least one year. The average observation period was 34 years. By the close of the study 50 members of the study group had died, 16 from malignant neoplasms. In 2/16 cases, kidney cancer was the cause of death (SMR = 3.28, vs. local population). Five workers were diagnosed with kidney cancer: four with renal cell cancer and one with a urothelial cancer of the renal pelvis. The standardized incidence ratio (SIR) was 7.77 (95% CI:2.50-18.59). After the close of the observation period, two additional kidney tumors (one renal and one urothelial) were diagnosed in the study group. The control group consisted of 190 unexposed workers from the same plant. By the close of the study 52 members of this group had died, 16 from malignant neoplasms, but none from kidney cancer. No case of kidney cancer was diagnosed in the control group. For the 7 cases of kidney cancer the average exposure duration was 15.2 years (range 3-19.4). Comparisons with cancer registries in Denmark and the former German Democratic Republic gave SIR values of 11.15 (95% CI: 4.49-23.00) and 13.53 (95% CI: 5.44-27.89) respectively. The statistical significance (internal study comparison) was $p < 0.005$ (Mantel-Haenszel test) and $p < 0.006$ (Binomial test). No exposure data were obtained but the authors summarized: "all workers enrolled in the study were repeatedly, in part continuously, exposed over long periods of time both via the lungs and through the skin to moderate to very high TCE concentrations, and extremely high exposure episodes occurred at regular weekly to biweekly intervals, when the major cleaning operations were conducted." The occupational threshold limit values of 100 ppm (U.S.) and 50 ppm (German) were probably exceeded during episodic exposures. "The workers often left the work area 'to get fresh air and to recover from drowsiness and headaches'" (Henschler et al., 1995a). This is the only study of kidney cancer in humans that claims a causal link with TCE exposure.

A recent case-control study by Bruning et al. (1997b) investigated the role of glutathione-S-transferase (GST) polymorphisms on the incidence of renal cell cancer in two occupational groups exposed to high levels of TCE. Forty-five cases with histologically verified renal cell cancer and TCE exposure were studied. The reference group was 48 workers from the same region with similar occupational exposures to TCE but free of any cancer. GSTM1 and GSTT1

genotypes were determined by internal standard controlled polymerase chain reaction. Among the 45 cancer patients, 27 carried at least one functional GSTM1 gene (GSTM1+) and 18 at least one functional GSTT1 gene (GSTT1+). Among the 48 reference workers, 17 were GSTM1+ and 31 were GSTT1+. Odds ratios for renal cell cancer were 2.7 for GSTM1+ individuals (95% CI, 1.18-6.33; $p < 0.02$) and 4.2 for GSTT1+ individuals (95% CI, 1.16-14.91, $p < 0.05$), respectively. The data indicate a higher risk for development of renal cell cancer if TCE-exposed persons carry either the GSTT1 or GSTM1 gene. The GSTM1 isozyme is thought to detoxify epoxides of aromatic (polycyclic) hydrocarbons while the GSTT1 is primarily involved in the metabolism of some aliphatic epoxides and halogenated hydrocarbons (Their et al., 1996). The nephrocarcinogenicity of TCE has been attributed to metabolites derived from the glutathione dependent pathway (Henschler et al., 1995a). These results tend to support this view of the mode of action of TCE-induced kidney cancer at least in humans.

Cancer occurrence in populations exposed to drinking water contaminated with various concentrations of TCE has been compared in several studies. The interpretation of these studies is complicated by methodological problems. Lagakos et al. (1986) studied childhood leukemia in a community in Massachusetts where water from two wells was contaminated with TCE. In 1979 the well showed a TCE concentration of 267 ppb. Twenty cases of childhood leukemia were diagnosed in 1964-83 and were associated with exposure to water in the two contaminated wells vs. the community at random (observed 21.1 vs. expected 10.6, $p = 0.03$). A study in New Jersey during 1979-87 included 75 towns (Cohn et al., 1994). TCE concentrations were measured during 1984-85, and an average level assigned to each town, the highest being 67 ppb. The water supply of six towns contained > 5 ppb TCE (average, 23.4 ppb). Women in these towns had significantly higher total incidence of leukemia than inhabitants of towns with average TCE concentrations in drinking water < 0.1 ppb (relative risk, 1.4; 95% CI, 1.1-1.9); no effect was seen in men (1.1, 0.84-1.4). The risk among women was particularly elevated for acute lymphocytic leukemia, chronic lymphocytic leukemia, and chronic myelogenous leukemia. The risk for acute lymphocytic leukemia in children was also significantly increased in females but not in males. Increased risks for non-Hodgkin's lymphoma were also seen in the towns with the highest TCE contamination (1.2, 0.94-1.5 for males; 1.4, 1.1-1.7 for females). Other human studies are also reviewed by IARC (1995).

Overall the most important human observations are the elevated risk for liver and biliary tract cancer, the moderately elevated risk for non-Hodgkin's lymphoma, the suggested marginally increased risk for non-Hodgkin's lymphoma in areas with TCE-contaminated drinking water (IARC, 1995), and finally the recent occupational findings of renal cell carcinomas in cardboard workers exposed to TCE (Henschler et al., 1995a,b). The IARC (1995) concluded that "*there is limited evidence in humans for the carcinogenicity of trichloroethylene*." A strikingly different assessment of these studies was provided by McLaughlin and Blot (1997) who concluded: "although exposure to TCE and PCE can induce cancers in some species of rodents, it is not clear that these solvents pose a risk for renal-cell cancer in humans." Their critique of the Henschler et al. (1995a) study included the following points: (a) they claim that some cases (3) were identified prior to the initiation of the study and should be excluded, reducing the observations to non-significance; (b) that the occurrence of the much rarer urothelial cancer cases indicates a different mode of action than assumed for renal cell cancer and either undercuts a chief conclusion of the study or reveals a confounding exposure to another agent or non-occupational factors; and (c) a possible discrepancy in the reported incidence and mortality rates for kidney cancer. Notwithstanding these criticisms as to whether the Henschler et al. (1995a) study is a true cohort or a cluster analysis, it is impossible to ignore these findings (see authors' response to published critiques, Henschler et al., 1995b). Assumptions about the mode(s) of

action of TCE in humans extrapolated from current knowledge of work in rodents are uncertain and cannot be used to exclude potentially relevant public health findings relating to TCE exposures even when the latter are somewhat poorly defined.

DOSE-RESPONSE ASSESSMENT

The risk assessment of TCE with respect to induced tumors has witnessed enormous change in the last decade. A summary of some risk assessments reviewed for this document (Table 6) reveals differences in virtually safe concentrations of TCE in drinking water of over eight (8) orders of magnitude. According to the U.S. EPA's proposed 1996 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996), the preferred approach for dose response assessment is one based on a relevant biologically based model or a case-specific model for tumor responses in both the observed range and in the extrapolated range. The default procedure, in the absence of specific models, is to fit the data in the observed range with a curve-fitting model. The choice between a nonlinear extrapolation, a linear extrapolation, or a combination of linear and nonlinear is based on the view of the mode of action (MOA) as, for example, when the MOA clearly indicates linearity through direct alterations in DNA. A linear default approach is recommended when MOA information is insufficient to support a nonlinear approach. From the curve-fitting model the point of departure for low dose extrapolation is the 95% lower bound on the dose yielding a 10% tumor incidence, the so-called LED_{10}. A nonlinear approach is used when adequate data on the MOA show that linearity is not the most reasonable judgment and there is sufficient evidence to support a nonlinear MOA, e.g., a clearly nonlinear overall dose response or a sharp reduction in tumor incidence with decreasing dose. In this case the default approach would employ either a margin of exposure (MOE) analysis using an LED_{10} from tumor data or related biological response data as the point of departure, or if a specific numerical value is required the LED_{10} could be used as a benchmark dose or LOAEL. Evidence of a receptor mediated MOA per se may not be sufficient to justify a nonlinear MOE approach. Factors to be considered in determining the margin of exposure for the analysis include: the dose response slope at the LED_{10}; the severity of the effect chosen; extent of human variability; the persistence in the body following exposure; interspecies differences in sensitivity, and distinguishing pharmacodynamic differences from pharmacokinetic factors which may already be included in a human equivalent LED. Where a MOE approach is adopted it is still useful to show the comparable value if the linear approach had been used.

An important task for the TCE risk assessor is to evaluate the evidence supporting claims of a nonlinear MOA. This is particularly critical in view of the differences in magnitude of assessed risks by nonlinear and linear approaches and the fact that the consequences of underestimation versus overestimation of risk are not equal.

Mode of Action

Noncarcinogenic Effects

The acute toxicity of TCE in rodents and humans is low. After repeated high doses of TCE to rodents, damage is seen in liver and kidney (mice and rats) and in lung (mice only). TCE is a more potent peroxisome proliferator in livers of mice than of rats. Repeated exposure of humans to TCE in the workplace appears to have some toxic effects on kidney or liver (see discussion

above). Available data show no consistent effect of TCE on the human reproductive system. TCE is metabolized to TCA in the placenta or fetus of many species but there is little evidence of toxic effects in developing rats or mice (IARC, 1995).

Carcinogenic Effects

Orally administered TCE induces benign and malignant liver tumors in mice but not in rats. In two oral studies, the incidence of uncommonly occurring renal-cell tumors was significantly increased in male rats. In one study an increased incidence of testicular interstitial-cell tumors was seen. Of four inhalation studies in mice, one showed increased incidence of lymphomas, one showed increased incidence of liver tumors, and three showed increased incidences of lung tumors. One of three TCE inhalation studies in the rat showed an increased incidence of testicular tumors and a marginal increase of renal-cell tumors in males (IARC, 1995). No increased tumor incidences were found in hamsters with TCE inhalation exposures. No skin tumors or local sarcomas were observed after topical or s.c. injection of TCE or trichloroethylene oxide in mice (IARC,1995).

TCE is rapidly absorbed by oral and respiratory routes in rodents. The metabolic fate of TCE is largely via cytochrome P450 oxidation leading to the formation of chloroacetic acids. Mice show consistently more oxidative biotransformation than rats. A minor pathway in rodents and humans involves the production of mercapturic acids. [1,2-^{14}C]TCE or metabolites were found to bind to mouse liver protein and DNA in a linear dose-dependent manner in vivo (Kautiainen et al., 1997). Most genetic toxicity studies of TCE are negative or inconclusive. Pure TCE apparently does cause an induction of micronuclei and DNA single-strand breaks/alkaline labile sites. In mammalian cells in vitro pure TCE induced cell transformation, sister chromatid exchange and gene mutation, but not chromosomal aberrations. In one study with human cells in vitro impure TCE slightly increased SCE frequencies and unscheduled DNA synthesis. In fungi TCE induced aneuploidy, gene mutation and mitotic recombination and induced gene conversion with exogenous metabolic activation. Humans exposed to TCE occupationally or in drinking water may have elevated risk for cancer of the liver and biliary tract, for renal tumors, and for non-Hodgkin's lymphoma (IARC, 1995; Henschler et al., 1995a).

The following elements need to be considered in the development of the MOA of TCE:

- While TCE does not have a typical genotoxic profile for a mutagenic or direct-acting carcinogen, it (or its metabolites) does have some genotoxic ability to damage chromosomes, e.g., as indicated by micronuclei tests. Thus a genotoxic MOA, albeit atypical, cannot be ruled out on the basis of current data;
- While the evidence of TCE induced cancer in humans is limited, the possible target sites reflect some of the findings in animal bioassays, i.e., liver tumors, renal tumors, and lymphoma;
- The demonstration of dose dependent mouse liver DNA and protein adducts with doses as low as 2.0 μg/kg equivalent to ~ 4 adducts/10^{11} base pairs;
- Rodent species and strain susceptibility to TCE induced tumors seems to be related to the degree of metabolic transformation of TCE;
- The principal products of TCE metabolism, the chloroacetic acids, are cytotoxic and carcinogenic. In particular TCA may play a key role in the tumorigenicity of TCE;

- Other minor products such as chloral hydrate, DCVC and other TCE conjugates may also play a role in cytotoxicity and tumorigenicity of TCE;
- Since TCE induces tumors at more than one site, there may well be more than one MOA operating;
- While TCE-induced tumors in rodents were observed in studies with necessarily high doses, in some cases showing toxicity, it remains to be established that the tumors at all sites were a direct result of the cell/tissue toxicity and not the result of parallel exposure to one or more genotoxic metabolites;
- Evidence of carcinogenicity from human epidemiological studies, while limited, would have resulted from exposures with little on no overt toxicity;
- The only human cancer with a claimed causal link to TCE exposure, kidney cancer in male cardboard workers, was also observed in male rats exposed to TCE.
- The role of glutathione-*S*-transferase polymorphisms may be important in assessing variability in human renal cell cancer risk from TCE exposures;
- The shape of the dose-response curves for cytotoxic effects may figure in the carcinogenic process, i.e., hepatic cytomegaly, nephropathy etc.

<u>Liver</u>

Bogen & Gold (1997) have summarized the key findings supporting a cytotoxic MOA and non-linear dose response for TCE-induced liver tumors in mice. They noted that:

- TCE-induced cytotoxicity occurs primarily in the liver, the main site of TCE metabolism;
- Liver toxicity positively correlates with the total amount of TCE metabolized;
- Liver and kidney weights were increased and liver-related serum enzymes (SGPT) were elevated as indicators of toxicity;
- Toxic effects were noted at doses lower than those given in the cancer bioassays;
- The main TCE metabolites (chloral hydrate, TCA, DCA) all induce liver cancer in mice when given in buffered drinking water;
- TCE is hepatocarcinogenic in mice but not rats correlating with species differences in the rate of TCE metabolism; mouse strain differences in carcinogenic susceptibility also correlate with metabolism;
- TCA or DCA administered in water caused lipoperoxidative-stress-induced cell killing in liver (similar to that of CCl_4) at doses of 300 mg/kg and higher;
- Substantial peroxisome proliferation is observed in mice, but the effect is weaker in rats;
- Acute and subchronic TCE administration in corn oil gavage significantly increases S-phase-DNA synthesis and proliferation in mouse hepatocytes;
- In mice exposed to either TCA or DCA in drinking water, hepatocellular DNA-labeling index was significantly elevated after 5 days, but not 12 or 33 d of exposure;
- DCA or TCA induced hepatocellular carcinomas in $B6C3F_1$ mice have a *ras* oncogene mutation frequency approximating those seen in spontaneous tumors, indicating tumor promotion rather than initiation.

Kidney

For kidney cancer Bogen & Gold (1997) give the following supporting evidence for a cytotoxic mode of action:

- Most rats chronically exposed to TCE in the NCI and NTP bioassays developed toxic nephrosis and greater than 90% of rats (and mice) developed cytomegaly, which was most evident in male rats;
- Kidney tumors were increased only in male rats and this presumably correlates with greater cytomegaly in males;
- The dichlorovinylcysteine TCE conjugates (1,2-DCVC and 2,2-DCVC) and the corresponding mercapturic acids (1,2-DCV-Nac and 2,2-DCV-Nac) are all rodent (and possible human) nephrotoxicants that can produce proximal tubular necrosis and other lesions in rat kidney after conversion to reactive mutagenic intermediates by cytosolic cysteine conjugate β-lyase (Goeptar, 1995);
- 1,2-DCVC induces *c-fos* and *c-myc* proto-oncogene expression in cultured rat kidney cells which indicates direct mitogenic action for this TCE metabolite similar to the tumor promoter 12-*O*-tetradecanoylphorbolacetate;
- TCE-conjugation metabolites like DCV-Nac occur as minor metabolites in rodents and in human workers exposed to TCE;
- TCE conjugation with cysteine and GSH become significant upon saturation of the main oxidative cytochrome P450 metabolic pathway in rats, but not in mice highly exposed to TCE.

Lung

As noted above lung tumors were induced in female mice by inhalation exposure to TCE. Odum et al. (1992) studied inhalation toxicity of TCE in female mice. A specific lesion, characterized by vacuolization of Clara cells, was only seen in mice. Mice exposed to 100 ppm chloral had a similar lesion. Only mild effects were seen with inhaled TCOH and none with intraperitoneally administered TCA (500 mg/kg). These results suggest that acute lung toxicity of TCE may be due to accumulation of chloral in Clara cells, the result of low glucuronidation capacity and low metabolism to TCOH. Since chloral is also genotoxic, the toxicity observed with intermittent exposures is likely to exacerbate any genotoxic effect through compensatory cell proliferation. Green et al. (1997) studied the activity of TCE metabolizing enzymes in mouse, rat and human lung. Metabolism of TCE to chloral was significant in the mouse lung, 23-fold lower in rat lung, and non-detectable in human lung microsomes. Immunolocalization of cytochrome P450 2E1 in lung sections showed high concentrations in mouse lung Clara cells with lesser amounts in type II cells. Low levels of enzyme were detected in rat lung, but not in human lung sections.

Dose-response approach

The three tumor types mentioned above have complex modes of action with contributions from: (1) non-genotoxic processes related to cytotoxicity; (2) possibly receptor-mediated mitogenic stimulation; (3) genotoxic metabolites such as chloral, DCVC and related metabolites, and; (4) possibly reactive oxygen species related to peroxisomal induction in the liver. While the role of cytotoxicity seems to play an important role in TCE induced cancer in rodents, particularly liver cancer, it is uncertain what role it plays in human cancers induced by TCE at exposure levels below those expected to cause frank toxicity. The demonstration of linear dose-dependent DNA

adducts by environmentally relevant doses of [^{14}C]TCE in mice, in vivo, would tend to support a genotoxic MOA, at least in mice. The potential role of several mutagenic and/or carcinogenic metabolites of TCE cannot be ignored, particularly in renal cell carcinoma, with additional supporting evidence of human GST isozyme dependence and DNA adducts formed from genotoxic DCVC metabolites. Bruning et al. (1997a) have found evidence supporting the role of *VHL* tumor suppressor gene mutations in TCE-induced renal cell cancer in humans.

For liver cancer the preferred approach is to apply both linear and non-linear methods. For the rodent data the dose metric of AUC TCA + AUC DCA based on current rodent PBPK modeling is probably a reasonable approach, although a metric based on the metabolism of TCE (AMET) should also be evaluated to account for a possible epoxide mediated dose response. The LED_{10} point of departure would be used: a) to calculate a potency or Carcinogen Slope Factor (CSF) for low dose extrapolation (linear method); and b) as a LOAEL with appropriate uncertainty factors to calculate a virtually safe dose or water concentration of TCE (non-linear method).

For kidney cancer the linear approach would appear to be the most appropriate notwithstanding the arguments in favor of a wholly cytotoxic MOA, or arguments based on the potential role of α-2μ-globulin a male rat specific factor (Goldsworthy et al., 1988). As noted above there is enough evidence indicating the importance of TCE glutathione conjugates in human TCE-induced renal cancer to justify this approach. A preferred dose metric would be based on prolonged exposure to DCVC and possibly other TCE-conjugates, i.e., AUC DCVC or total TCE metabolized via the GST pathway (e.g., TCOG and related metabolites in urine).

For lung cancer the relative importance of cytotoxicity and genotoxicity in rodents is uncertain as is the implication for human cancer since TCE-induced lung cancer has not yet been observed in humans. In this case as in liver both linear and non-linear approaches based on chloral hydrate dose metrics seem appropriate. There is considerable uncertainty about the comparability of TCE pharmacodynamics in humans vs. rodents.

The best approach, not mentioned above, would be to use the available human data to develop a safe water concentration for TCE. Unfortunately the current epidemiological database, with very limited exposure and dose response information, allows only rough, at best semi-quantitative, estimates. Human risk estimates should include the possibility of subpopulations at greater risk due to GST polymorphisms.

Table 6. Summary of TCE Cancer Risk Assessments to Determine Virtually Safe Lifetime Concentrations in Air and/or Drinking Water.[1]

Study	Dose Metric Used	Nonlinear/MOE Approach	Linear/LMS Approach
Page et al., 1997; Clewell et al., 1995	PBPK metrics incl. mg DCVC/ kg kidney/d MOE = 1000	Lung: 9-6000 ppb air; 900-600,000 ppb in water Liver: 12.5-88 ppb air; 56-390 ppb in water Kidney: 36-15,000 ppb air; 540-225,00 in water	Lung: 0.06-41 ppb air; 6-4000 ppb in water Liver: 0.05-0.35 ppb in air; 0.8-5.6 ppb in water Kidney: 0.64-300 ppb in air; 9.6-4500 ppb in water
Bogen & Gold, 1997	PBPK peak concentration metrics: Liver, Max(C_{TCA}) ppm; Kidney, Max(B)/Km	16 ppb in air continuous; 700 ppb in air brief; 210 ppm in water at 2 L/day intake	
Cronin et al.,1995	PBPK/Monte Carlo: Liver AMET mg/kg-day, AUCTCA mg-hr/L/day		AMET: Intermittent inhalation exposure: 25-120 ppb in air Continuous inhalation exposure: 5-26 ppb in air Drinking water: 5-69 ppb in water AUCTCA: Intermittent inhalation exposure: 0.07-13.3 ppb in air Continuous inhalation exposure: 0.01-6.3 ppb in air Drinking water: 0.09-5.3 ppb

Study	Dose Metric Used	Nonlinear/MOE Approach	Linear/LMS Approach
Fisher & Allen,1993	PBPK metrics: AMET, AUCTCA		AMET:15-69 ppb in air; 7-39 ppb water AUCTCA: 0.1-0.2 ppb in air; 4 ppt in water
Brown et al.,1990		227 µg/d MOE=10,000	
DHS,1990	See Bogen et al. below		0.1-1.7 ppb in water 0.022-0.22 ppb in air
	TCA oral		Liver: 9.0 ppb in water
	DCA oral		Liver: 0.25 ppb in water
Fan, 1988			5 ppb in water
Bogen et al., 1988	PBPK adjusted metabolized doses, 7.0 Leq/d water intake for multiroute exposure, range of 6 studies analyzed.		Liver: 0.28-1.0 ppb in water Kidney: 2.5 ppb in water Lymph: 0.1 ppb in water Lung: 0.53 ppb in water
	TCA oral DCA oral		Liver: 0.56 ppb in water
			Liver: 0.15 ppb in

Study	Dose Metric Used	Nonlinear/MOE Approach	Linear/LMS Approach
U.S. EPA, 1986			water 0.33 ppb in water
U.S. EPA, 1985	Values adjusted for partial lifetime, 2 L/d water intake		1.8-6.0 ppb in water

1 Notes: Page et al. ranges are for best and worst case estimates; MOE is margin of exposure; AMET is TCE metabolized dose metric; AUC is the area under the blood concentration x time curve or tissue concentration x time curve; Max(C_{TCA}) is the peak concentration of TCA in blood plasma; Max(B)/Km peak concentration metric which, when >>1, indicates saturation of oxidative TCE metabolism. This metric is a measure of effective kidney cytotoxic dose. PBPK/Monte Carlo, a probabilistic simulation of model parameters, was incorporated into a risk assessment using a PBPK model; the values in the table above are ranges from the analysis of male and female mice; LMS is the linearized multistage model of low dose extrapolation of cancer risk.

Noncarcinogenic Effects

The results of a number of studies discussed in this section are summarized in Table 7.

Animal Studies

Clewell et al. (1997) have incorporated PBPK modeling into a noncancer risk assessment of TCE employing benchmark doses (BD) based on animal data sets. For intermediate term inhalation exposure Clewell et al. (1997) used the data of Arito et al. (1994) on CNS effects (decreased wakefulness, reduced heart rate) in rats. The animals were exposed to 0, 50, 100, and 300 ppm; 8 hr/d, 5 d/wk, for 6 wk. The continuous data were fitted with a polynomial model and the Weibull (power) model. The dose metrics chosen were peak concentration or the AUC of TCE in the blood. The lowest benchmark dose based on a 10% response (BD_{10}) was 56 ppm, which exceeded the LOAEL of 50 ppm determined by pairwise significance testing. This was due to poor fitting of the model to the data. Excluding the highest dose, an improved BD_{10} of 31 ppm for decreased wakefulness was obtained. The continuous equivalent of this value is 7 ppm (31 ppm x 8/24 hr x 5/7 d). The authors considered the 7 ppm a NOAEL and applied a UF of 30 to obtain a minimum risk level as defined by the ATSDR (MRL) of 0.25 ppm.

For an intermediate term oral BD the teratogenicity data of Dawson et al. (1993) were used. Rats were given 0, 1.5 or 1100 ppm in drinking water. The observed critical toxic endpoint was cardiac abnormalities. Female rats were exposed either before and during pregnancy (80-90d), during pregnancy only (18-20d), or before pregnancy only (80-100d). A study LOAEL of 0.18 mg/kg-day was identified for the 1.5 ppm group exposed before and during pregnancy. There was no apparent dose response relationship. Also the reporting of this study is unclear. For example, the number of animals per test group was not specified (116/9 groups assumed) and the number of fetuses per maternal rat are much higher (5.4 vs. 17.6) than in a previous study using

similar methods (Dawson et al., 1990). Also the results are not reported by litter, making it impossible to test for litter effects. The quantal responses for the heart abnormalities were: control, 7/238, 2.9%; 1.5 ppm TCE, 21/257, 8.2%; 1100 ppm TCE 40/436, 9.2%. Notwithstanding the difficulties presented by these study data, Clewell attempted to analyze the quantal data. The dose metrics employed were the AUC of TCE and TCA in blood. The models used in fitting the data were the polynomial and the Weibull. Modeling of the administered dose yielded the lowest BD_{10} of 65 mg/kg-day, well above the LOAEL, again due to poor fit by the models. Removing the top dose gave an improved BD_{10} of 0.24 mg/kg-day. The use of the PBPK dose metrics did not linearize the data and probably represents saturation of response rather than nonlinear pharmacokinetics. Without the high dose the BD_{10} values of 0.0027 mg hr/L (AUC TCE) and 2.26 mg hr/L (AUC TCA) were obtained. With a PBPK model for continuous human exposure the target dose metrics are produced by doses of 0.018 mg/kg-day TCE and 0.009 mg/kg-day TCA. The authors employed an uncertainty factor of 3 to account for human variability to give an MRL range of 0.003-0.006 mg/kg-day for TCE. They assumed that the human PBPK model would account for interspecies differences. It might be argued that the uncertainties inherent in the problem data set should also rate an uncertainty factor. Also in view of the severity of effect (teratogenicity), the human BD_{10} value of 0.009 mg/kg-day probably represents a LOAEL, not a NOAEL. The authors caution against quantitative use of these data due to shortcomings in reporting of the original study data. The study and analysis are included here for the sake of completeness and because there are relatively few studies of this type in the literature.

Haag-Gronlund et al. (1995) applied the benchmark dose method to a risk assessment of TCE. They used polynomial models for both quantal and continuous data sets. Toxicity data on liver, kidney and CNS effects, and tumor data were selected for evaluation. Benchmark doses were estimated at the 1%, 5%, and 10% response levels. For kidney effects in the NTP (1988) rat study, BD_{10} values for cytomegaly ranged from 11-24 mg/kg-day for different sexes and strains of rat. The BD_{10}s for nephropathy ranged from 50-210 mg/kg-day. These values are lower than the study LOEL of 500 mg/kg-day. The lowest BD_{10} values for liver, kidney, and CNS effects in inhalation experiments (Henschler et al., 1980; Fukuda et al., 1983; Maltoni et al., 1988) were 23, 122, and 10 ppm respectively. Overall, all NOELs were higher than the BD_{01}, and 42% of the NOELs and 93% of the LOELs were higher than the BD_{10}. The authors noted that the polynomial regression models often failed to fit the experimental data at the desired level of significance in the X^2 "goodness of fit" test ($p > 0.05$).

Barton & Das (1996) conducted a similar assessment for chronic noncancer effects from oral exposures to TCE. Four dose response models for quantal data and one for continuous data were employed. The analysis considered liver effects, kidney toxicity, and developmental effects. For liver endpoints the BD_{05} values ranged from 82-289 mg/kg-day. The lowest value was based on liver weight/body weight ratio changes (LW/BW) in $B6C3F_1$ mice (Elcombe et al., 1985) and the highest value on LW/BW in F344 rats (Melnick et al., 1987). For kidney, toxicity data from NTP (1988) and Maltoni et al. (1986) were evaluated. For rat kidney cytomegaly, BD_{05} values with superior fits ($p > 0.1$) ranged from 0.14 to 24 mg/kg-day for 8 data sets. For toxic nephrosis, BD_{05}s ranged from 5 to 276 mg/kg-day. For eye defects (Narotsky et al., 1995) in rats, BD_{05}s ranged from 231 to 308 mg/kg-day and the BD_{01}s ranged from 48 to 60 mg/kg-day. The authors noted high model dependence in the BD values generated. They used the LOAEL of 10 mg/kg-day and the BD of 82 mg/kg-day for liver effects in a calculation of safe drinking water concentrations of 1 and 10 ppm, respectively. The kidney LOAEL and developmental NOAEL gave similar values.

Table 7. Benchmark Dose Estimates and LOAELs for TCE and Noncancer Endpoints

Study	Species	Duration & Exposure Route	Site Toxic Endpoint LOAEL	BD10 or BD05*	Authors' Suggested UF
Clewell et al., 1997	Rat	Subchronic Inhalation	CNS Decreased wakefulness 50 ppm	7 ppm	30
	Rat	Subchronic Oral	Cardiac abnormalities in offspring 0.18 mg/kg-day	0.24 mg/kg-day 0.009-0.018 mg/kg-day in human PBPK	10 3
Haag-Gronlund et al., 1995	Rat	Chronic Oral	Kidney Cytomegaly 500 mg/kg-day	11-24 mg/kg-day	100
	Rat	Chronic Oral	Kidney Nephropathy 500 mg/kg-day	50-210 mg/kg-day	100
	Mouse	Chronic Inhalation	Tumors Lung 100 ppm Liver 100 ppm	141 ppm 594 ppm	5000
	Mouse	Chronic Inhalation	Liver effects 35 ppm Kidney effects 75 ppm CNS effects 25 ppm	23 ppm 122 ppm 10 ppm	1000

Study	Species	Duration & Exposure Route	Site Toxic Endpoint LOAEL	BD10 or BD05*	Authors' Suggested UF
Barton & Das, 1996	Mouse	Chronic Oral	Liver LW/BW 100-800 mg/kg-day	82-289 mg/kg-day*	300
	Mouse	Chronic Oral	Kidney Cytomegaly 500 mg/kg-day	0.14-24 mg/kg-day*	1000
	Mouse	Chronic Oral	Kidney Toxic nephrosis 250 mg/kg-day	5-276 mg/kg-day*	1000
	Rat	Short term Gestation days 6-15 Oral	Eye defects 101 mg/kg-day	231-308 mg/kg-day*	1000
Kahn et al., 1995	Mouse	Subchronic Intra-peritoneal	Autoimmune response 328 mg/kg-day single dose frank effect?	none	10,000
Chia et al., 1997	Human	Subchronic Inhalation	Endocrine effects trends: DHEAS ↑; SHBG ↓; serum testosterone ↓ 5.4 mg/kg-day	none	100
Chia et al., 1996	Human	Subchronic Inhalation	Increased hyperzoospermia	ED_{10} = 0.2** mg TCA excreted/kg-day	30

Study	Species	Duration & Exposure Route	Site Toxic Endpoint LOAEL	BD10 or BD05*	Authors' Suggested UF
Isaacson & Taylor, 1989	Rat	Subacute Oral in drinking water	Developmental effect, decrease in myelinated fibers in the hippocampus LOAEL = 37 mg/kg-day		10,000
Maltoni et al., 1986	Rat	Subchronic Oral	Kidney toxicity NOAEL = 50 mg/kg-day		300
Fredriksson et al., 1993	Mouse	Subacute Oral	Developmental effect, reduced rearing at 60 d LOAEL = 50 mg/kg-day		3000

Note: DHEAS = dehydroepiandrosterone sulfate; SHBG = sex hormone binding globulin; ** estimated by linear regression of % hyperzoospermia vs. level of TCE exposure indicated by urinary TCA in mg/g creatinine. The TCA dose metric was adjusted to mg/kg-day assuming excretion of 25 mg creatinine/kg/day and 70 kg body weight. The regression was % hyperzoospermia = 0.06 + 0.204(mg TCA/kg-day), $R^2 = 0.98$. BD_{05} values indicated by *

Human Studies

Clewell et al. (1997) also evaluated the data of Stewart et al. (1970) on humans exposed to 200 ppm TCE for 7 hr/d for 5 days. The endpoint was behavioral effects (mental fatigue and sleepiness). A LOAEL of 200 ppm was reported for the study. Clewell et al. (1997) concluded that benchmark modeling could not be performed on the study due to inadequate reporting of the data. Using human PBPK modeling of the LOAEL (200 ppm x 7 hr), a blood peak concentration and AUC TCE target dose metrics were estimated. These metrics were then divided by a 30 UF to obtain target dose metrics for the MRL. The PBPK model was then run with varying continuous exposure conditions until the target dose metrics were obtained. These values were reached at 8 ppm for the peak TCE concentration and two ppm for AUCTCE. These MRLs are much higher than the current acute MRL value of 0.1 ppm. This disparity is due to differences in calculating human equivalence since the latter depends on ratios of pulmonary ventilation and body weight whereas the former PBPK-based estimate is essentially based on the ratio of blood/air partition coefficients for TCE.

Carcinogenic Effects

Animal Studies

The data sets selected for dose response analysis were the liver tumors in the NCI (1976) study in $B6C3F_1$ mice, the liver and lung tumors from Maltoni et al. (1986) in $B6C3F_1$ mice, and the lung tumors from Fukuda et al. (1983) in ICR mice. The NCI study used oral gavage administration of TCE while the other two studies used inhalation exposure. Each of these data sets had at least two non-zero dose groups.

For the dose response assessment of TCE in mice the PBPK modeling results of Abbas and Fisher (1997) were employed to estimate the following dose metrics: AUC of chloral hydrate (CH) for lung tumors and AUC of TCA+DCA for liver tumors. Abbas and Fisher's results are based on male $B6C3F_1$ mice dosed orally with 300, 600, 1200, and 2000 mg/kg TCE. The model predictions for CH in lung and the dose metric of AUC CH in mg hr/L d were regressed against applied dose to give the relation AUC CH = 0.05496 (mg/kg-day) - 3.46, R= 0.9976. The AUC values were estimated by triangulation from the tabular Cmax values and the graphs of CH lung concentration vs. time in the paper as AUC (mg hr/L d) = Cmax-0.1 Cmax mg x 20 hr/2 L d. A similar process on the liver TCA + DCA AUC produced the following relation: AUC TCA +DCA = 0.476 (mg/kg-day) + 191.2, R = 0.92. For values below 300 mg/kg-day the relation was forced through the origin with a slope of 0.575 (mg/kg-day)/(mg hr/L d). Using these relationships, bioassay doses could be converted to AUC dose metrics adjusted for lifetime exposure, converted back to oral equivalents and fitted to the tumor incidence data. The metrics are summarized in Table 8 and the results of the analysis are shown in Table 9.

Using the AUC TCA+DCA metric, the human equivalent LED_{10} values for liver tumors in both sexes in two studies by two routes of administration vary by 15 fold, i.e., 4.5-70 mg/kg-day. For lung tumors with the AUC CH metric the LED_{10} values from two inhalation studies varied by a factor of two, i.e., 12-28 mg/kg-day. The geometric mean (Gmean) CSF for the four liver data sets is 4.9×10^{-3} $(mg/kg\text{-}day)^{-1}$ and for the two lung data sets is 5.5×10^{-3} $(mg/kg\text{-}day)^{-1}$. If the total TCE metabolism dose metric (AMET) (Cronin et al., 1995) is used, the LED_{10} values are lower at 1.3-29.1 mg/kg-day (CSFs of 0.021, 0.0047, 0.077, 0.0034 in Table 9) corresponding to a higher geometric mean CSF of 0.013 $(mg/kg\text{-}day)^{-1}$. The three geometric mean CSFs vary by less than a factor of three. Since the AMET dose metric gave a better fit on 2/4 data sets and fit all four with acceptable significance ($p > 0.05$), the CSF based on this metric, namely 0.013 $(mg/kg\text{-}day)^{-1}$, is considered the most appropriate for use in calculating possible PHG values. While carcinogenic potencies based on the linearized multistage model (LMS) varied somewhat from CSFs depending on the specific data set, the geometric mean potency estimate for liver tumors with the AMET dose metric was identical to that derived from the CSFs. Different authors have published different quantal responses for some of the data sets listed in Table 8, particularly for the Maltoni et al. (1986) liver tumor data. The calculations noted above were performed on the Maltoni mouse liver tumor values noted by Bogen & Gold (1997) (Table 5) and Fisher & Allen (1993) for both dose metrics. While the latter are used in the current analysis, the Bogen & Gold values gave only slightly higher CSFs of 6.1×10^{-3} $(mg/kg\text{-}day)^{-1}$ for the AUC based Gmean and 0.014 $(mg/kg\text{-}day)^{-1}$ for the AMET based Gmean.

Not included in Table 9 are the dose response results from the combined male mouse groups from Maltoni et al. (1986) (BT306 and BT306-bis). For the AMET dose metric this combined

data set gave a CSF of 0.01 (mg/kg-day)$^{-1}$ with adequate fit statistics. The AUC metric did not give an adequate fit with this data set (chi squared = 8.24, p = 0.02). These are not considered significant differences from the values given above in the context of this risk assessment. . The CSF value of 0.013 (mg/kg-day)$^{-1}$ is consistent with previous estimates of carcinogenic potency from OEHHA (DHS, 1990ab; Cal/EPA, 1994).

Table 8. Summary of Dose Metrics and Doses Used in the TCE Cancer Dose Response

Study, Site	Sex, Species	Dose Metric [a]	Oral or Oral Equivalent Continuous Lifetime Doses mg/kg-day
NCI, 1976	Male Mouse	AUC TCA + DCA	0, 172.4, 697.3
Liver Tumors			
	Female Mouse	AUC TCA + DCA	0, 139.4, 456.7
	Male Mouse	AMET	0, 69.2, 84.0
	Female Mouse	AMET	0, 57.7, 73.1
Maltoni et al. 1986	Male Mouse	AUC TCA + DCA	0, 50.6, 88.9, 542.5
Liver Tumors	Female Mouse		
	Male Mouse	AMET	0, 58.7, 150.6, 190
	Female Mouse	AMET	0, 58.4, 125.5, 155.5
Lung Tumors	Female Mouse	AUC CH	0, 67.7, 82.0, 103.8
Fukuda et al. 1983	Female Mouse	AUC CH	0, 27.6, 115.4, 571.9

Note:[a] AUC TCA + DCA is the area under the liver concentration x time curve for the sum of TCA and DCA; AMET is the total amount of TCE metabolized by the liver; AUC CH is the area under the curve for the chloral hydrate metabolite in the lung.

Table 9. Carcinogenic Dose Response Estimates for TCE Based on PBPK Dose Metrics and Mouse Bioassays

Study, sex, route, site	Applied Doses[a]	AUC or AMET Lifetime Dose Metrics	Quantal Tumor Incidence; **X^2, p, k** [d]	ED_{10}/LED_{10} mg/kg-day Human equivalent[e]	**CSF** [f] q_1* [g] $(mg/kg\text{-}day)^{-1}$
NCI, 1976 female, gavage, liver	0, 869, 1739 mg/kg-day	[b] 0, 242*, 408.6 mg hr/L d;	0/20, 4/50,11/50; **0.03, 0.87, 2**;	29.1/10.2	**9.8×10^{-3}** 5.7×10^{-3}
		[c] 0, 57.7, 73.1 mg/kg-day	**1.16, 0.28, 2**	8.1/4.8	**2.1×10^{-2}** 2.4×10^{-2}
male, gavage, liver tumors	0, 1169, 2339 mg/kg-day	[b] 0, 299.8*, 523, mg hr/L d;	1/20, 26/50,30/50; **9.34, 0.002, 2;**	13.3/4.5	**2.2×10^{-2}** 1.3×10^{-2}
		[c] 0, 69.2, 84.0 mg/kg-day	**0, 1, 2**	2.0/1.3	**0.077** 0.089
Maltoni et al., 1986, female, inhalation, liver tumors (Fisher & Allen, 1993)	0, 100, 300, 600 ppm	[b] 0, 134, 255, 436 mg hr/L d;	2/90, 3/90, 4/89, 9/87; **0.12, 0.94, 3**	102/53.6	**1.9×10^{-3}** 2.1×10^{-3}
		[c] 0, 58.4, 125.5, 155.5 mg/kg-day	**0.63, 0.73, 3**	27.2/21.4	**4.7×10^{-3}** 4.3×10^{-3}
(Bogen & Gold,1997)		[b]0, 134, 255, 436 mg hr/L d	3/88, 4/89, 4/88, 9/85; **0.03, 0.99, 3;**	116/57.2	**1.7×10^{-3}** 2.0×10^{-3}
		[c]0, 58.4, 125.5, 155.5 mg/kg-day	**0.89, 0.64, 3**	27.8/22.7	**4.4×10^{-3}** 4.2×10^{-3}
male,	0, 100,	[b] 0, 134, 255,	1/85, 1/86, 3/88,	144/71.4	**1.4×10^{-3}**

Study, sex, route, site	Applied Doses[a]	AUC or AMET Lifetime Dose Metrics	Quantal Tumor Incidence; **X^2, p, k** [d]	ED_{10}/LED_{10} mg/kg-day Human equivalent[e]	**CSF** [f] q_1* [g] $(mg/kg\text{-}day)^{-1}$
inhalation, liver tumors (Fisher & Allen, 1993)	300, 600 ppm	436 mg hr/L d;	6/88; **0.76, 0.69, 3**		1.6×10^{-3}
		[c] 0, 58.7, 150.6, 190.0 mg/kg-day	**0.07, 0.97, 3**	356/29.4	**3.4×10^{-3}** 2.6×10^{-3}
(Bogen & Gold, 1997)		[b]0, 134, 255, 436 mg hr/L d	1/59, 1/31, 3/38, 6/37; **0.86, 0.65, 3**	51.0/27.0	**3.7×10^{-3}** 4.2×10^{-3}
		[c]0, 58.7, 150.6, 190.0	**0.14, 0.71, 3**	25.9/16.1	**6.2×10^{-3}** 7.0×10^{-3}
female, inhalation, lung tumors	0, 100, 300, 600 ppm	0, 4.75, 19.1, 40.8 mg hr/L d	2/90, 6/90, 7/89, 14/87; **0.22, 0.90, 3**	14.4/12.0	**8.3×10^{-3}** 9.0×10^{-3}
Fukuda et al., 1983, female, inhalation, lung tumors	0, 50, 150, 450 ppm	0,1.52*, 9.8, 34.9 mg hr/L d	1/49, 3/50, 8/50, 7/46; **5.2, 0.07, 3**	62.1/27.8*	**3.6×10^{-3}** 3.8×10^{-3}
Gmean Liver AUC [b]				48.8/20.4	**4.9×10^{-3}** 4.5×10^{-3}
				38.9/16.3	**6.1×10^{-3}** 5.0×10^{-3}
Gmean Liver AMET [c]				19.9/7.9	**0.013** 0.012
				10.4/6.9	**0.014** 0.016
Gmean				29.9/18.3	**5.5×10^{-3}**

Study, sex, route, site	Applied Doses[a]	AUC or AMET Lifetime Dose Metrics	Quantal Tumor Incidence; **X^2**, **p**, **k** [d]	ED_{10}/LED_{10} mg/kg-day Human equivalent[e]	**CSF** [f] q_1* [g] $(mg/kg\text{-}day)^{-1}$
Lung AUC [b]					5.9×10^{-3}

Notes:

[a] Unadjusted applied doses.

[b] AUC dose metrics from linear regressions of AUC values for CH (lung) or TCA+DCA (liver) vs. oral mg/kg-day (Abbas & Fisher, 1997); inhalation applied doses first converted to mg/kg-day (DHS, 1990), adjustments made to AUC doses to produce lifetime average daily AUC doses (DHS, 1990). Lifetime AUCs were converted back to oral mg/kg-day equivalent using regression (* in three low doses the slope was forced through zero) and the oral equivalent AUC doses were then fit to the tumor incidence data using Tox_Risk v.3.5.

[c] AMET dose metric from Cronin et al. (1995) is the total amount of TCE metabolized, in mg/kg-day, converted to a continuous lifetime daily dose.

[d] Quantal tumor responses for respective doses, fit statistics by Tox_Risk v. 3.5 using multistage polynomial in bold face, values of p greater than 0.05 are considered acceptable fits.

[e] LED_{10} human equivalents are produced by the Tox_Risk v. 3.5 program using $(\text{body weight})^{3/4}$ interspecies scaling.

[f] Carcinogen slope factor (CSF) is calculated as $0.1/LED_{10}$.

[g] q_1* carcinogenic potency determined by the linearized multistage model (Tox_Risk v.3.5). For Maltoni et al. (1986) data sets quantal tumor responses as reported by Fisher & Allen (1993) and by Bogen & Gold (1997) were analyzed and included in separate Gmeans.

Human Studies

The study of Henschler et al. (1995a) on kidney cancer in TCE exposed cardboard workers may provide a useful estimate of TCE carcinogenic potency, although there are few exposure or dose-response data as such. If we assume continuous exposure to TCE during the working hours at the German threshold limit value of 50 ppm for the average exposure duration of 15.2 yr, it seems unlikely that the total TCE intake would be seriously underestimated notwithstanding episodic exposures to several times this value. If we also assume 50% of inhaled TCE is absorbed we can estimate the daily continuous intake of TCE as follows:

$50 \text{ ppm} \times 5.37 \text{ mg/m}^3\text{/ppm} \times 20 \text{ m}^3\text{/d}/70 \text{ kg} \times 5 \text{ d}/7 \text{ d} \times 8 \text{ hr}/24 \text{ hr} \times 0.5 = 9.13 \text{ mg/kg-day}$.

The kidney cancer incidence in the Henschler et al. study was 7/169 = 0.0414. The background rate of kidney cancer based on the standardized incidence ratio (SIR = observed kidney cancers/expected kidney cancers) of 13.53 from the German Cancer Registry was about 0.003, indicating a TCE-induced incidence of 0.038. Adjusting this value to an incidence resulting from a 70 yr lifetime exposure gives 0.038 x (70/15.2) = 0.175. Assuming linearity of dose-response a potency estimate of 0.175/9.13 = 0.019 $(mg/kg\text{-}day)^{-1}$ is obtained.

Bruning et al. (1997b) have studied the influence of glutathione transferase (GST) polymorphisms on risk of kidney cancer in workers with long-term high occupational exposure to TCE (see study summary above). Their data indicate that persons with the combined genotypes for GSTM1 and GSTT1 (+/+), representing about 40% of the European (Caucasian) population, are at higher risk of developing kidney cancer from TCE exposures. The odds ratio (OR) for the (+/+) combined genotype vs. the other combinations (-/+, +/-, -/-) was 3.75. If we assume the study population in Henschler et al. was balanced with a 40% (+/+) frequency, then the relative potency in this sensitive sub-population would be about 0.035 $(mg/kg\text{-}day)^{-1}$ vs. 0.009 $(mg/kg\text{-}day)^{-1}$ for the other genotype combinations. Similarly the 47% of the population with GSTM1 (+/+, +/-) had an OR of 2.74 and an average TCE potency of 0.03 $(mg/kg\text{-}day)^{-1}$ compared to the 85% subpopulation with the GSTT1 (+/+, -/+) with an OR of 4.16 and a potency of 0.017 $(mg/kg\text{-}day)^{-1}$. The frequency of the genotypes in the Bruning et al. study of 93 subjects was: (+/+) 40 %; (-/+) 45%; (+/-) 7.5%; and (-/-) 7.5%.

CALCULATION OF PHG

Calculations of concentrations of chemical contaminants in drinking water associated with negligible risks for carcinogens or noncarcinogens must take into account the toxicity of the chemical itself, as well as the potential exposure of individuals using the water. Tap water is used directly as drinking water and for preparing foods and beverages. It is also used for bathing or showering, and in washing, flushing toilets and other household uses resulting in potential dermal and inhalation exposures.

Noncarcinogenic Effects

Calculation of a public health-protective concentration (C, in mg/L) for TCE in drinking water for noncarcinogenic endpoints follows the general equation:

$$C = \frac{NOAEL/LOAEL \times BW \times RSC}{UF \times W}$$

where,

NOAEL/LOAEL	=	No-observed-adverse-effect-level or lowest-observed-adverse-effect-level, or an appropriate benchmark dose (e.g., BD_{10})
BW	=	Adult body weight (a default of 70 kg for average human, 60 kg for female, and 10 kg for a child)
RSC	=	Relative source contribution (a default of 20%, 40%, or 80%).

UF	=	Uncertainty factors (typical defaults of 10 to account for LOAEL to NOAEL, 10 for inter-species extrapolation, 10 for subchronic study to lifetime exposure, and 10 for inter-individual variation in sensitivity to toxic chemicals)
W	=	Adult daily water consumption rate; default of 2.0 L/day for a 70 kg adult and 1.0 L/day for a 10 kg child. Higher liter equivalents/day (Leq/day) are used to account for inhalation and dermal exposures to volatile organic compounds (VOCs) through showering, bathing, flushing of toilets and other typical household uses of tap water.

In Table 10, the value of C in the equation above was calculated for a number of selected noncancer toxic endpoints (see Table 6 above for details). In these calculations a relative source contribution of 20% (0.2) was used since TCE residues have been measured in a number of food products. In addition a multi-route tap water intake value of 7.1 Leq/day (Bogen et al., 1988; Bogen et al., 1992) was used to account for ingestion, dermal and inhalation exposures from typical household uses of TCE contaminated tap water. This value was based on the equivalent lifetime daily fluid intake by a 70 kg adult or the sum of 2.2 L ingestion absorption, 2.9 Leq inhalation absorption, and 2.0 Leq dermal absorption. Bogen et al. (1988) also give upper bound estimates of 3.8 L, 11.9 Leq, and 2.6 Leq respectively for a total upper bound exposure of 18.3 Leq/day. Note that the earlier mentioned study of Weisel and Jo (p. 14) measured showering and bathing exposures only and not other household exposures which would be expected to add to the inhalation exposure. Their results would indicate lower estimates of 2 L, 3 Leq and 3 Leq (8 Leq total) and upper estimates of 2 L, 6 Leq, and 6 Leq (14 Leq total) for ingestion, inhalation and dermal intakes, respectively. An alternative analysis was performed using CalTOX™, a multimedia total exposure model (v. 1.5, DTSC, 1994). For tap water containing 5 ppb TCE the CalTOX model predicts lower dermal and inhalation doses relative to ingestion, namely 12% dermal, 40% inhalation, and 48% ingestion, at 0.022 L/kg-day tap water ingestion. Overall the estimates of Bogen et al. (1988) seem best suited to use in this calculation. Other assumptions are given in Table 10 below.

Among the studies listed in Table 10 the kidney nephropathy endpoint in a chronic rat study is judged to be the most reliable and relevant for human risk assessment because the kidney is an important target of TCE toxic action. The value of C based on this endpoint could be rounded to 1 mg/L or 1 ppm:

$$C = \frac{50 \text{ mg/kg-day} \times 70 \text{ kg} \times 0.2}{100 \times 7.1 \text{ Leq/day}} = 0.986 \text{ mg/L} = 1.0 \text{ mg/L (rounded)} = 1.0 \text{ ppm}$$

In this calculation we employ the BD_{10} as a chronic NOAEL with 10-fold uncertainty factors (UF) for interspecies and interindividual differences. No additional uncertainty factor is added for potential carcinogenicity in the kidney. A relative source contribution default of 0.2 (20%) and the total water intake from ingestion, dermal and inhalation exposures of 7.1 Leq/day are applied.

Table 10. Estimated Health Protective Drinking Water Concentrations [C] Based on Noncancer Toxicity Endpoints

Study	Species Duration Route	Toxicity Endpoint	BD10/05 or LOAEL/ NOAEL	Uncertainty Factor (UF)	C, mg/L, ppm
Chia et al., 1996	Human, subchronic inhalation	Hyperzoo-spermia	0.2 mg/kg-day [a]	30	0.013
Clewell et al., 1997	Rat, subchronic oral	Cardiac abnormalities	0.009 mg/kg-day [b]	3-10	0.0017-0.005
Haag-Gronlund et al., 1995	Rat, chronic oral	Kidney nephropathy	50 mg/kg-day [c]	100	0.98
Barton & Das, 1996	Mouse, subchronic oral	Liver effects, LW/BW	82 mg/kg/d [c]	1000	0.16
Barton & Das, 1996	Rat subacute oral	Eye defects	101 mg/kg-day [d]	1000	0.17

Notes: [a] ED_{10} based on linear regression of urinary TCA vs. % hyperzoospermia; [b] BD_{05} value includes human pharmacokinetic adjustment; [c] BD_{10}; [d] LOAEL.

Carcinogenic Effects

For carcinogens, the following general equation can be used to calculate the public health-protective concentration (C) for a carcinogenic chemical in drinking water (in mg/L):

$$C = \frac{BW \times R}{CSF \times W} = \text{mg/L}$$

where,

BW = Adult body weight (a default of 70 kg)

R = De minimis level for theoretical lifetime excess individual cancer risk (a default of 10^{-6})

CSF	=	Cancer slope factor, CSF, is a potency derived from the lower 95% confidence limit on the 10% tumor dose (LED_{10}). CSF = 0.1/ LED_{10}. The q_1*, included for comparison, is the upper 95% confidence limit on the low dose slope calculated by the LMS model. Both potency estimates are converted to human equivalent [in $(mg/kg\text{-}day)^{-1}$] using $BW^{3/4}$ scaling from the animal data.
W	=	Daily volume of water consumed by an adult. A default of 2.0 L/day is used for a 70 kg adult and 1.0 L/day for a 10 kg child. Larger values of L equivalents/day (Leq/day) are used to account for multi-route exposures to volatile organic chemicals (VOCs).

The purpose of comparing two potency estimates for a carcinogen is based on the fact that our current experience-base is largely with the LMS model whereas the new methodology, proposed by U.S. EPA (1996) in its draft guidelines for carcinogen risk assessment, is based on the LED_{10} which has a more limited experience-base. The LMS model focuses on the linear low dose extrapolation, and analysts (e.g., U.S. EPA) have often accepted relatively poor fits to the observed tumor incidence data. The new method places a higher premium on fitting the observed data to estimate the ED_{10} and the 95% lower bound (LED_{10}), the point from which the low dose extrapolation is made (U.S. EPA, 1996).

Using the Gmean CSF from the AMET dose metric for mouse liver tumors of 0.013 $(mg/kg\text{-}day)^{-1}$ from the NCI (1976) and the Maltoni et al. (1986) studies, and a value of 7.1 Leq/day for water consumption, the water concentration corresponding to a negligible cancer risk, C, is calculated as follows:

$$C = \frac{70\ kg \times 10^{-6}}{0.013\ (mg/kg\text{-}d)^{-1} \times 7.1\ Leq/day} = 7.6 \times 10^{-4}\ mg/L$$

$$= 0.8\ ppb$$

If we assumed that the dose response is nonlinear we could treat the LED_{10} for liver tumors as a chronic LOAEL. In this case appropriate uncertainty factors would be 10 for LOAEL to NOAEL, 3 for interspecies extrapolation (since the LED_{10} estimate incorporates an interspecies adjustment), 10 for interindividual variation, and 10 for severity of effect, possibly cancer, giving a total UF of 3,000. Note that the relative source contribution (RSC) is included in this calculation.

$$C = \frac{7.9\ mg/kg\text{-}d \times 70\ kg \times 0.2}{3{,}000 \times 7.1\ Leq/day} = 5.2 \times 10^{-3}\ mg/L$$

$$= 5\ ppb$$

Since the values for the cancer endpoint are lower than the values calculated for noncancer endpoints in Table 10, the PHG should be based on the more health protective cancer endpoint. Of the dose response approaches for the cancer endpoint, the linear default is appropriate to use for TCE because the nonlinear MOA is insufficiently supported by the data, and in view of the specifications of the PHG, namely in cases when "the currently available scientific data is insufficient to determine the amount of a contaminant that creates no significant risk to public health, the public health goal shall be set at a level that is protective of public health." Thus **the value of 0.8 ppb is the PHG for TCE**. This value is lower than current state and federal MCLs of 5 ppb and is identical to the value calculated from current Cal/EPA oral and inhalation potencies for TCE of 0.015 and 0.01 $(mg/kg\text{-}day)^{-1}$ respectively, namely 0.8 ppb (Cal/EPA, 1994). It is also similar to the estimate based on the occurrence of kidney cancer in human cardboard workers with occupational exposures at or above the German TLV. This study would indicate a health-protective water concentration of 0.5 ppb (range 0.3 -1.1 ppb), albeit with less certainty than the mouse based value, based on an estimated potency of 0.019 (range 0.009 to 0.035) $(mg/kg\text{-}day)^{-1}$ (Henschler et al., 1995a).

RISK CHARACTERIZATION

The PHG of 0.8 ppb was calculated from the cancer slope factor (CSF) of 0.013 $(mg/kg\text{-}day)^{-1}$ based on the geometric mean of CSF values of liver tumors from the NCI (1976) and Maltoni et al. (1986) studies using the AMET dose metric. In calculating the PHG, a de minimis theoretical excess individual cancer risk level of 10^{-6} was assumed. The corresponding levels for cancer risk levels of 10^{-5} or 10^{-4} are 8 and 80 ppb, respectively.

Some of the uncertainties involved in the present assessment can be listed as follows:

- <u>CSF based on the LED_{10} vs. the q_1* based on the linearized multistage model</u>. Since the Gmeans for the tumor site and dose metric of choice, i.e., liver by AMET, are identical, there is no difference between the methods. For lung tumors the CSF is 7% lower and for liver tumors using AUC metric the CSF is 23% higher. For the sum of lung and liver by AUC the CSF is 5% higher than a LMS based potency. Typically CSF and q_1* values differ by 5-10%.

- <u>Use of the AMET dose metric based CSF vs. the AUC-based values</u>. The difference is a 2.5-fold greater estimate of theoretical extra lifetime risk for a single site. However if the sum of liver and lung tumors by AUC is chosen the difference is only 17% higher. The AUC values are based on estimates made from published graphs of blood or tissue concentrations of metabolites versus time and are thus less accurate than the published AMET values. The AUC values are probably underestimates by 10% or more.

- <u>Use of an average value vs. a CSF based on the most sensitive tumor site</u>. The highest CSF calculated was 0.077 and the lowest was 0.0014 $(mg/kg\text{-}day)^{-1}$, a 55-fold range. The selected value was six-fold less than the highest individual value and nine-fold higher than the lowest individual value.

- <u>Use of $(\text{body weight})^{3/4}$ interspecies scaling vs. $(\text{body weight})^{2/3}$ scaling, no scaling, or the use of a human PBPK model.</u> Scaling from mouse to human using the ¾ power increases the CSF value about 6.5-fold vs no scaling. Previous scaling using the 2/3 power would increase the value by 13-fold. The scaling factor is used to account for metabolic and tumor response differences between rodents and humans where humans are generally considered the more sensitive species. Calculations made by Fisher (1993) using a human PBPK model and the

AMET dose metric as described above yielded a safe drinking water concentration of 7 ppb (see also Fisher & Allen, 1993; Allen & Fisher, 1993). The methods of Fisher and Allen only address pharmacokinetic differences in the interspecies extrapolation and not possible pharmacodynamic differences or significant interindividual differences (see Fisher et al., 1998).

- Use of linear dose response for cancer risk assessment vs. a nonlinear approach. If instead of the linear approach we applied the nonlinear approach as described above we would obtain a value of 5 ppb or six-fold higher than the proposed value of 0.8 ppb. In this calculation an uncertainty factor of 3,000 was applied to the LED_{10} of 8 mg/kg-day (see above).
- Use of animal data vs. human data. The estimates based on human data including sensitive subpopulations with specific GST polymorphisms range from three-fold higher to two-fold lower CSFs vs the mouse based values. However the human exposure estimates are too uncertain to rely on fully but are in fair agreement with the mouse based CSF. In view of the uncertainty in the human exposure data, it is an open question whether mouse liver-based CSF estimates adequately protect humans against TCE-induced renal cancer. In general, tumor concordance between species is poor. In addition there may be other sensitivity factors besides GST polymorphisms related to age and disease conditions. Also the GST polymorphisms have only been studied in limited subpopulations.
- Stochastic Analysis. A number of the factors noted above were included in a stochastic analysis to forecast a PHG distribution based on distributions of the component variates. Included in the analysis were: adult human body weight, a lognormal distribution with a mean and standard deviation of 71.0 ± 15.9 kg (range 45-115 kg); relative source contribution, a triangular distribution, minimum = 0.1, maximum = 0.8, likeliest = 0.2; water consumption (multiroute) in Leq/day, triangular distribution, min. =1.0 L/day, max. = 18 Leq/day, likeliest = 7.1 Leq/day; and a fixed CSF of 0.013 $(mg/kg\text{-}day)^{-1}$. The Monte Carlo analysis was performed using Microsoft Excel v. 4.0 and Crystal Ball v. 4.0 (Decisioneering). The forecast mean values based on 20,000 trials with Latin hypercube sampling were: PHG = 0.28 ppb; body weight = 71.17 kg; RSC = 0.37; water intake = 8.8 Leq/day. Fifty percent of the forecast PHG values fell between 0.14 and 0.35 ppb and the 95th percentile of the distribution was 0.7 ppb. Note that the stochastic analysis includes the RSC, unlike the calculation noted in the text above. If interspecies scaling power (triangular distribution, min. = 0.67, max = 1.0, likeliest = 0.75) and LED_{10} values for all cancer sites (triangular distribution, min. = 1.3, max. = 71.4, likeliest = 7.9 mg/kg-day) were included in the Monte Carlo simulation, the forecast PHG values were: mean = 0.9 ppb, median = 0.58 ppb, with 50% of the predicted values falling between 0.29 and 1.1 ppb. If the calculation was extended to include the range of ED_{10} values, the forecast values were 4.2 ppb, 2.5 ppb, and 1.1-5.2 ppb, respectively. Current OEHHA recommendations for stochastic analysis apply only to exposure variates (OEHHA, 1997). Overall the results of this brief stochastic analysis are similar to the range of safe water concentrations in the main analysis above, i.e., about 0.5 to 5.0 ppb.

TCE may have synergistic or antagonistic interactions with other chemicals (e.g., DEHP or 1,1-DCE) but these effects were noted at higher doses, unlikely to be relevant to drinking water exposures to TCE. However this is an area of limited data and further studies need to be conducted with other common water contaminants.

TCE is a volatile organic chemical (VOC) and can be expected to result in oral and dermal doses related to showering, bathing, flushing toilets and other typical household uses of tap water. An estimate of such exposures is included in the calculation of the PHG. The range of estimates from Bogen et al. (1988) is 2.2 L/day for ingestion of water only, to 18.3 Leq/day for the upper bound on the sum of ingestion (3.8 L/day), inhalation, and dermal absorption. Predictions of the CalTOX™ program ranged from total intakes of 4.2 Leq/day for average exposure to 26.5 Leq/d for high exposure. For these calculations water ingestion values were 1.36 L/day (CalTOX default), 1.68 L/day (high point estimate, OEHHA, 1997), and 2.29 L/day, the average for lactating women (Ershow et al., 1991). The body weight was 62 kg (CalTOX default) and it was assumed that 50% of inhaled dose was absorbed and 100% of ingestion and dermal doses were absorbed.

The relative source contribution (RSC) chosen for TCE is the 20% default, indicating anticipated exposure via other sources besides drinking water, notably ambient air and food. A larger RSC, based on a more detailed exposure assessment, would possibly give a higher PHG value. OEHHA scientists have determined that the 80% default is not appropriate for use in the case of TCE.

For PHGs, our use of the RSC has, with a few exceptions, followed U.S. EPA drinking water risk assessment methodology. U.S. EPA has treated carcinogens differently from noncarcinogens with respect to the use of RSCs. For noncarcinogens, RfDs (in mg/kg-day), drinking water equivalent levels (DWELs, in mg/L) and MCLGs (in mg/L) are calculated using uncertainty factors (UFs), body weights and water consumption rates (L/day) and the RSC respectively. The RSC defaults are 20% for agents with expected non-water sources or 80% for agents whose anticipated exposure is mainly from water (0.2, 0.8) other values are used depending on the strength of scientific evidence supporting them.

For approaches that use low-dose extrapolation based on quantitative risk assessment, U.S. EPA does not factor in an RSC. The use of low-dose extrapolation is considered by U.S. EPA to be adequately health-protective without the additional source contributions. In developing PHGs, we have adopted the assumption that RSCs should not be factored in for carcinogens grouped in U.S. EPA categories A and B, and for C carcinogens for which we have calculated a cancer potency based on low-dose extrapolation. This is an area of uncertainty and scientific debate and it is not clear how this assumption impacts the overall health risk assessment.

OTHER REGULATORY STANDARDS

The U.S. EPA has established a National Primary Drinking Water Standard or maximum contaminant level (MCL) of 0.005 mg/L (5 ppb) and a maximum contaminant level goal (MCLG) of zero mg/L for TCE. They have also set a drinking water equivalent level (DWEL) of 0.3 mg/L and a 1E-4 cancer risk level of 0.3 mg/L. U.S. EPA (1985a) has classified TCE as a probable human carcinogen, B2. Subsequently U.S. EPA's Science Advisory Board concluded that TCE was on a continuum between a possible human carcinogen, C, and a probable human carcinogen, B2. U.S. EPA is currently reassessing TCE for oral and inhalation reference doses, cancer classification, etc.

The California Department of Health Services (DHS) has promulgated a California primary drinking water standard (MCL) of 0.005 mg/L (5 ppb) for TCE (Section 64444, California Health & Safety Code). Under Proposition 65 risk specific intake levels of 50 μg/day for ingestion and 80 μg/d for inhalation have been established for TCE (DHS, 1990; OEHHA, 1996).

The Agency for Toxic Substances and Disease Registry (ATSDR) has derived an acute duration inhalation MRL of 2 ppm with an uncertainty factor of 30 for TCE based on neurological effects in humans (Stewart et al., 1970), and an intermediate duration MRL of 0.1 ppm with an uncertainty factor of 300, based on neurological effects in rats (Arito et al., 1994). An acute duration oral MRL of 0.2 mg/kg-day with an uncertainty factor of 300 was derived based on developmental effects in mice (Fredriksson et al., 1993; ATSDR, 1997).

The International Agency for Research on Cancer (IARC) designated TCE as Group 2A, probably carcinogenic to humans (IARC, 1995).

The World Health Organization (WHO) has set a drinking water guidance level of 0.03 mg/L based on the carcinogenic endpoint (WHO, 1984).

The American Conference of Governmental Hygienists (ACGIH) has recommended a TLV TWA of 50 ppm TCE and a STEL of 100 ppm TCE (ACGIH, 1996).

U.S. EPA has set the following Ambient Water Quality Criteria for Protection of Human Health: for consumption of water and aquatic organisms, 2.7 μg/L for 10^{-6} lifetime risk. For ingestion of organisms only, 80.7 μg/L for 10^{-6} lifetime risk.

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