

**Public Health Goal for
TETRACHLOROETHYLENE
In Drinking Water**

Prepared by

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PREFACE

**Drinking Water Public Health Goals
Pesticide and Environmental Toxicology Section
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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), amended 1999, 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. Section 116365 specifies that the PHG is to be based exclusively on public health considerations without regard to cost impacts. 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 upon currently available data 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 published 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 TETRACHLOROETHYLENE IN DRINKING WATER

SUMMARY

A public health goal (PHG) of 0.06 µg/L is established for tetrachloroethylene (PCE, also known as perchloroethylene) in drinking water. The PHG is based on carcinogenic effects observed in experimental animals. Exposure to PCE is carcinogenic for rodents, inducing liver cancer in mice by inhalation (NTP, 1986) or ingestion (NCI, 1977), and leukemia in rats by inhalation (NTP, 1986). Statistically significant increases in the incidence of tumors at several sites have also been observed in certain studies of workers in the dry-cleaning industry (Blair et al., 1990; Ruder et al., 1994).

For the calculation of the PHG, cancer potency estimates were made based on the recommended practices of the 1996 United States Environmental Protection Agency (U.S. EPA, 1996) proposed guidelines for carcinogenic risk assessment. According to these methods, a polynomial model is fit to the experimental data in order to establish the lower 95 percent confidence bound on the dose associated with a 10 percent increased risk of cancer (LED₁₀). The PHG was calculated assuming a *de minimis* theoretical excess individual cancer risk level of 10⁻⁶ from exposure to PCE. Cancer potency estimates were derived, using time-dependent models, from the observed incidences of hepatocellular carcinoma in male and female mice exposed orally to PCE. For water-derived inhalation exposures, estimates were derived from the incidences of hepatocellular adenoma or carcinoma in mice, and mononuclear cell leukemia in rats of both sexes exposed by inhalation to PCE. Based on these considerations, Office of Environmental Health Hazard Assessment (OEHHA) has established a PHG of 0.06 µg/L for PCE in drinking water.

An estimate of the concentration of PCE in drinking water protective against chronic toxicity other than cancer was derived based on neurobehavioral endpoints (related to delayed reaction times) observed in epidemiological studies of humans with occupational or environmental exposures to inhaled PCE. Uncertainty factors, allowing for extrapolation from LOAELs (0.29, 4.15 and 8.48 mg/kg-d) to NOAELs and for interindividual variation in the human population, ranged from 30 to 100. The geometric mean of three such estimates was used to derive an estimated health protective concentration in drinking water of 11 ppb (11 µg/L).

The U.S. EPA has established a maximum contaminant level goal (MCLG) of zero mg/L PCE. A maximum contaminant level (MCL) of 0.005 mg/L PCE has also been established (U.S. EPA, 1989). The California Department of Health Services currently lists an MCL of 0.005 mg/L (5 ppb). The OEHHA PHG incorporates several differences from the earlier U.S. EPA evaluation, including: 1) interspecies scaling according to the ³/₄ power of body weight, 2) a time-to-tumor analysis of the NCI (1977) oral mouse bioassay data, and 3) a more sophisticated human pharmacokinetic model for low-dose oral and inhalation exposures. It also is based exclusively on public health considerations, whereas the MCLs may include considerations of economic and technical feasibility.

INTRODUCTION

The California Safe Drinking Water Act of 1996 requires protection of the public from drinking water contaminants. This document is a revision and reassessment of a 1992 Office of Environmental Health Hazard Assessment (OEHHA) document entitled *Health Effects of Perchloroethylene* (DHS, 1992). The purpose of this document is to establish a PHG for perchloroethylene (tetrachloroethylene or PCE) in drinking water. In our evaluation, an extensive analysis of the available scientific literature was made and prudent assumptions were made as necessary to assure absence of adverse health effects.

PCE is a perchlorinated two-carbon olefin. Total production of PCE in the United States has been decreasing over the last decade. In 1983, production of PCE was 547 million pounds while the production decreased to 271 million pounds in 1993 (ATSDR, 1997). The primary uses of PCE are as a chemical intermediate for the production of chlorofluorocarbons and as a solvent used in cleaning operations (metal cleaning, vapor degreasing, and dry cleaning). In addition, numerous household products contain some level of PCE. Due to widespread use, PCE is a common environmental contaminant.

Every effort was made to incorporate all aspects of potential exposure. Various sources such as air (environmental and occupational), soil, and water were considered. Typical exposures to PCE from drinking water are not expected to result in any acute health effects, due to the low levels involved. Exposure from drinking water can be in the form of household airborne exposures from showering, flushing of toilets, and other contact with water.

PCE is readily absorbed through the lungs and gastrointestinal tract, and to a lesser extent, it can be absorbed through the skin. Acute and chronic neurological changes, and liver and kidney toxicity, have been reported in humans and animals exposed to PCE. However, these effects were observed with higher exposures than typical background levels in the general indoor or outdoor environment.

As in the previous assessment of PCE, the findings observed in the rodent cancer bioassays were used for the calculation of the PHG. These assays have shown that oral administration of PCE leads to an increased incidence of hepatocellular carcinoma in B6C3F1 male and female mice (National Cancer Institute, 1977). The tumor incidence was also increased in both rats (mononuclear cell leukemia) and mice (hepatocellular carcinoma) exposed to PCE by inhalation (National Toxicology Program, 1986). The California Department of Health Services (DHS) currently lists an MCL of 0.005 mg/L (5 ppb). An MCL of 0.005 mg/L PCE has also been established by the U.S. EPA (U.S. EPA, 1989).

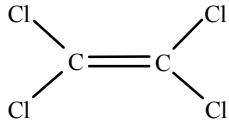
Based on considerations discussed in this document, OEHHA establishes a PHG of 0.06 ppb for PCE in water. Some of the considerations used in this calculation were interspecies scaling according to $\frac{3}{4}$ power of body weight, a time-to-tumor analysis of the NCI (1977) oral mouse bioassay data, and a more sophisticated human pharmacokinetic model for low-level oral and inhalation exposures.

CHEMICAL PROFILE

Chemical Identity

Tetrachloroethylene is a perchlorinated two-carbon olefin. The chemical formula, structure, synonyms and identification numbers are listed in Table 1 and are adopted from the International Research Agency for Research on Cancer (IARC) (IARC, 1995b).

Table 1. Chemical Identity of Tetrachloroethylene (IARC, 1995b)

Chemical name	Tetrachloroethylene
Synonyms	Perchloroethylene, Tetrachloroethene, PCE, Carbon Bichloride, Ethylene Tetrachloride
Trade names	Ankilostin, Antisol 1, Didakene, Dilatin PT, Fedal-Un, Nema, Perchlor, Percelene, PerSec, Tetlen, Tetracap, Tetraleno, Tetroguer, Tetropil
Chemical formula	C ₂ Cl ₄
Chemical structure	
Identification numbers	
Chemical Abstracts Service (CAS) Registry number:	127-18-4
NIOSH Registry of Toxic Effects of Chemical Substances (RTECS) [®] number:	KX3850000
U.S. EPA Hazardous Waste number:	K043; U210; D039
Oil and Hazardous Materials/Technical Assistance Data System (OHM/TADS) number:	7216847
Hazardous Substances Data Bank (HSDB) number:	49 403 55
National Cancer Institute (NCI) number:	NCI-C04580

Physical and Chemical Properties

Important physical and chemical properties of tetrachloroethylene are given in Table 2 (adopted from IARC, 1995b). Tetrachloroethylene is slightly soluble in water and is readily volatile.

Table 2. Physical and Chemical Properties of Tetrachloroethylene (IARC, 1995b, except as noted)

Property	Value
Molecular weight	165.83
Color	Colorless
Physical state	Liquid
Odor	Ether-like
Odor threshold	50 ppm (NIOSH, 1978) 1.0 ppm in air (ATSDR, 1993) 0.3 ppm in water (ATSDR, 1997)
Taste threshold	0.3 mg/L water (U.S. EPA, 1998)
Melting point	-19°C
Boiling point	121°C (at 760 mm Hg)
Flash point, etc.	Non-flammable
Solubility	
Water	0.15 g/L (at 25°C)
Organic solvents	Soluble in ethanol, diethyl ether, benzene
Biological fluids	Unknown
Density	1.6227 g/cm ³
Octanol-water partition coefficient (log K_{ow})	3.4
Vapor pressure	9.975 mm Hg (at 13.8°C)
Henry's law constant	1.8 x 10 ⁻² atm-m ³ /mol (ATSDR, 1997)
Conversion factor¹	1 ppm = 6.782 mg/m ³

¹Calculated assuming the ideal gas law, $PV = nRT$, where the partial molar volume at 25°C is 24.45 L/mol: then ppm = mg/m³ x MW / 24.45.

Production and Uses

The primary uses of PCE are as a chemical intermediate, primarily in the production of chlorofluorocarbons, and as a solvent, primarily for cleaning operations. The breakdown of the use of PCE is approximately 55 percent as a chemical intermediate, 25 percent in metal cleaning and vapor degreasing, 15 percent in dry-cleaning operations, and 5 percent for miscellaneous other uses (ATSDR, 1997). Numerous household products contain some level of PCE. PCE's use in the production of chlorofluorocarbons (CFCs) has declined in recent years due to reduced production of CFCs stemming from efforts to protect the stratospheric ozone layer from depletion. Solvent recovery operations and recycling have also reduced demand for PCE production.

Dry-cleaning grade PCE is supplemented with stabilizers including amines or epoxide/ester mixtures, which reduce hydrolytic decomposition.

Total production of PCE in the U.S. has been estimated at 271 million pounds in 1993, a decrease from 547 million pounds in 1983 (ATSDR, 1997). According to the U.S. EPA's 1992 Toxic Release Inventory, 68 facilities in California manufacture or process PCE, with total maximum on-site amounts ranging from 0 to 10 million pounds (ATSDR, 1997).

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Air

Environmental Exposures

The high volatility of PCE leads to considerable potential for release into the air from the various uses of the compound, particularly in cleaning operations, although releases at sites of chemical production are also possible. PCE is nearly ubiquitously present in air, with significant levels detected in areas ranging from remote to urban. Significantly higher levels have been reported in areas in close proximity to its use, such as at dry-cleaning facilities.

The California Air Resources Board (ARB) reported a statewide mean air concentration of 0.134 ppb for 1996, which represented the lowest value in a decreasing trend for reporting beginning in 1990 (highest reported mean: 0.277 ppb PCE in 1990) (ARB, 1998).

Mean U.S. ambient air concentrations compiled from over 2,500 monitoring points have shown a range from 0.16 ppb PCE in rural/remote areas to 0.79 ppb PCE in urban/suburban areas to 1.3 ppb PCE near emission sources (ATSDR, 1997, citing Brodzinsky and Singh, 1982).

In its Toxic Chemical Release Inventory (TRI), U.S. EPA reported air emissions of approximately one million pounds of PCE in 1994 (U.S. EPA, 1994a). Reported emissions to air have declined yearly from those reported in 1987 when over 5 million pounds of PCE were released. This is likely to be a considerable under-estimation of PCE releases because of limits to the required reporting to the TRI.

The half-life of PCE in air has been estimated at 96 days (ATSDR, 1997).

Occupational Exposures

As noted above, various industrial activities including dry cleaning involve the use of PCE, and significant exposures of workers may result, in addition to the release of PCE to the general environment.

As part of an industry-wide study (Ludwig et al., 1983) to assess the health effects of long-term, low-level exposures to PCE, the National Institute for Occupational Safety and Health (NIOSH) conducted industrial hygiene surveys at 44 commercial dry cleaning facilities in five states. Time-weighted average (TWA) and peak exposures to PCE were determined. Among the various jobs in a dry cleaning facility, Ludwig et al. (1983) found that the machine operators (dry cleaners) had the greatest PCE exposure. TWA exposures of machine operators ranged from 4.0 to 149.0 ppm PCE (geometric mean = 22 ppm). The geometric mean PCE exposure of the

pressers, seamstresses, and front counter workers were 3.3 ppm, 3.0 ppm and 3.1 ppm, respectively. The geometric mean 5-minute peak PCE exposure during textile transfer was 44 ppm while the mean 15-minute exposure was 33 ppm.

Investigations of PCE exposures in the workplace have also been undertaken as part of epidemiological studies of health effects; a number of such studies are described in the later sections of this report covering human health effects.

Indoor Exposures

Indoor air levels of some volatile organic compounds (VOCs) have been found to be higher than corresponding outdoor concentrations. Pellizzari et al. (1986) measured corresponding matched pairs of indoor and outdoor concentrations of several VOCs for different highly urban-industrialized residential U.S. communities. Over all the geographical areas evaluated, the outdoor air quality for the reported chemicals was better than in the residences. PCE was one chemical reported to have higher indoor medians and maximum levels than the corresponding outdoor concentrations. In some cases, the median ratios (indoor to outdoor) were greater than ten. Source or explanations for these observations were not identified.

Increases of indoor PCE air concentrations may arise due to some of the same sources responsible for the environmental and occupational exposures. These sources could include the proximity to a dry-cleaning establishment, emission of PCE from dry-cleaned clothes, or emissions of PCE for workers clothing. In addition, increased indoor air levels of PCE as a result of exhaled breath from workers have been implicated as an additional source (Wallace et al., 1991a; Thompson and Evans, 1993). Wallace et al. (1991a) found levels of PCE in indoor air on the order of 100 $\mu\text{g}/\text{m}^3$ for these homes while the average indoor level of PCE was found to be 5 to 10 $\mu\text{g}/\text{m}^3$ in non-PCE worker homes (Wallace et al. 1991b). Both Wallace et al (1991a) and Pellizzari et al. (1986) found a ten-fold increase in indoor PCE levels. These studies indicate that indoor air exposures could lead to a greater exposure to PCE than outdoor air exposures.

Soil

Contamination of soil with PCE may result from the disposal of sludge and wastewater containing PCE, particularly from recycling operations.

Water

The numerous industrial uses and its presence in consumer products may lead to the release of PCE into water. Cleaning processes have the potential to create PCE contaminated wastewater. PCE contamination of water arises primarily from the disposal of spent sludge and the storage and disposal of solvents.

PCE has been detected in most water supplies including drinking water, ground water, surface waters, and rainwater. U.S. EPA has estimated that 5.3 percent of the U.S. population (11.4 million people in 1985) may be exposed to PCE at levels in excess of 0.5 $\mu\text{g}/\text{l}$, and 0.4 percent of the population (0.87 million) may be exposed at levels in excess of 5 $\mu\text{g}/\text{l}$ (U.S. EPA, 1985, as described in IARC, 1995b).

The use of vinyl-lined asbestos-cement water pipes resulted in the contamination of the municipal water supply in Cape Cod, Massachusetts, in the late 1970s (IARC, 1995b). PCE concentrations

of 1.5 to 7750 µg/l were reported at different points of approximately 650 miles of piping used, depending on the level of water use.

Trace amounts of PCE may also be formed during the disinfection of water through chlorination (NAS, 1977).

Geographically, patterns of PCE contamination in California are usually in concert with use patterns, with the highest levels of PCE contamination occurring in the historically most heavily urbanized areas. In a state-wide sampling survey of large water systems under the Assembly Bill 1803 program, approximately 70 percent of the PCE contaminated wells were found in Los Angeles County (DHS/DIR, 1986).

The U.S. EPA TRI reported less than 12 pounds of PCE released to water for each of the years from 1987 to 1994 (U.S. EPA, 1994b).

Extent of Contribution of Tap Water to Total PCE Exposure

The National Academy of Sciences (NAS, 1982) and the U.S. EPA (U.S. EPA, 1985) have assumed that 20 percent of total exposure to organic chemicals may be attributed to drinking water. This assumption is applied when suggesting the 'no adverse response level(s)' (SNARL) for chronic effects, or when calculating U.S. EPA recommended maximum contaminant levels (RMCLs) for drinking water. The literature on PCE occurrence has been reviewed and found that tap water contaminated with PCE contributed much less than 20 percent to an individual's total exposure to PCE (Letkiewicz et al., 1982). The figures of Letkiewicz et al. (1982) for percent contribution at contamination levels of 0.5 µg/L and DHS calculations using their occurrence data and assuming 2 µg/L PCE in tap water are provided in Table 3. These figures provide an example of water contribution to total PCE exposure of an individual. They ignore the contributions from PCE found in indoor air attributable to non-tap water sources such as that arising from recently dry-cleaned clothing and from dermal and inhalation exposures which are attributable to tap water sources (e.g., exposure received while showering). PCE in indoor air was not found to be correlated with PCE tap water concentrations, because the major contributions were from environmental sources other than water (e.g., dry-cleaned clothes) (the exposure to PCE during showering and other activities of high water use was not measured) (Wallace et al., 1986). The ratio of median PCE concentrations in indoor to outdoor air has been reported to range from 2 to 27 (Hartwell et al., 1984a; Hartwell et al., 1984b).

DHS (1987) reviewed studies by Wallace et al. (1986), who measured concentrations of PCE in the air to which study participants were exposed in Los Angeles and Contra Costa counties. Personal monitors sampled over 24-hour periods, but were not placed in the bathroom while subjects showered and bathed. DHS (1987) concluded that when PCE levels in the water supply are relatively high (>10 ppb), tap water may be a predominant source of PCE exposure. However, for water sources where PCE concentrations are 0.5 ppb or less, exposures from other sources, particularly indoor air, may be more important.

Table 3. Percent Contribution of Tap Water to Total Exposure to PCE

Water concentration of PCE	Urban areas	Rural areas	Area of maximum air pollution
0.5 µg/L ^a	2.9%	4.3%	0.04%
2.0 µg/L ^b	10.7%	14.9%	0.02%

^aData reproduced from Letkiewicz et al. (1982); ignores exposures from dermal absorption and inhalation while bathing; assumes 70 kg adult ingesting 1 L/day.

^bDerived by DHS (1987) using the assumptions of Letkiewicz et al. (1982) regarding exposures.

Infants

Exposure calculations typically do not consider differences in exposure for different age groups. Because virtually all of an infant's fluid and nutritional requirements are met by breast milk and/or formula, and because, on a bodyweight basis infants consume approximately ten times the fluid volume of adults, there is the potential for greater exposure of infants to PCE through contaminated drinking water. Exposures can occur directly in formula feeding and indirectly *via* breast milk. A case of enlarged liver and obstructive jaundice was reported in an infant exposed to PCE via breast milk (Bagnell and Ellenberger, 1977). The mother of the infant regularly visited a dry-cleaning establishment to lunch with her husband who worked there as a leather and suede cleaner. One hour after visiting the husband, the mother's breast milk was found to contain 10 mg/L PCE that decreased to 3 mg/L after 24 hours. The infant's symptoms disappeared one week after cessation of breast-feeding. There are no definitive data at present to determine the amount of PCE received through breast-feeding attributable to PCE in tap water. That PCE exposure can occur via breast milk has also been demonstrated by Erickson et al. (1980) who found PCE present in all 42 samples of human milk collected in Bayonne and Jersey City (Anonymous, 1996), Pittsburgh (PA), Baton Rouge (LA) and Charleston (WV) (Erickson et al., 1980). Concentrations ranged from 0.1 to 43 µg/L with a median value of 1.25 µg/L. The mothers resided in areas with relatively high water and air concentrations of PCE.

A survey on U.S. infant dietary patterns has been conducted (Martinez and Dodd, 1983). At one month of age, approximately 50 percent of infants receive formula, 44 percent breast milk, and 6 percent breast milk plus formula. Taking into account the volatilization of PCE from tap water through boiling and the different types of infant formula used, Letkiewicz et al. (1982) estimate that 22 percent of formula-fed infants receive fluids contaminated at PCE levels found in the water supply. These data indicate that approximately 11 percent ($=0.5 \times 0.22$) of the infant population could receive up to ten times the exposure, on a mg/kg basis, of adults to PCE through drinking contaminated tap water.

Food

In its review of PCE content in food, IARC (1995b) listed the detection of PCE in numerous items including milk, meat, fish, mollusks, margarine, oils, coffee, tea, fruits and vegetables, cereals, pork and beans, baby foods, milk chocolate, baked goods, peanut butter, and nuts. In products where PCE has been detected, reported concentrations ranged from 1 to 124 µg/kg. IARC estimated daily PCE intake to be 160 µg/day (Zimmerli et al., 1982). Another estimate of

total PCE intake from all sources (including air and water as well as food) was reported to be 113-144 µg/day (IARC, 1995b; citing Bauer, 1981; von Düselen et al., 1982).

Other Sources

PCE has been reported to be produced naturally in several algae of temperate, subtropical and tropical origin and in a red microalga (IARC, 1995b). IARC also reports that PCE is present in consumer products including cosmetics and cough medicine.

METABOLISM AND PHARMACOKINETICS

PCE is readily absorbed through the lungs and gastrointestinal tract and, to a lesser extent, can be absorbed through the skin. Between 50 and 70 percent of inhaled PCE is reported to be absorbed by humans (Bolanowska and Golacka, 1972; Ohtsuki et al., 1983; Imbriani et al., 1988). After oral administration to rodents, PCE is absorbed rapidly, and the percentage of dose recovered approaches 100 percent (Pegg et al., 1979). Once in the body, PCE disperses into all tissues. Steady-state tissue concentrations are a function of the absorbed dose, partitioning factors (which reflect the lipophilic nature of PCE), and rates of metabolic conversion and elimination.

A substantial proportion of PCE absorbed systemically is exhaled unchanged. This is pronounced at high doses since the metabolism of PCE appears to be saturable. Studies in which radiolabeled PCE was administered to animals have found that trichloroacetic acid is the major urinary metabolite; carbon dioxide is a commonly produced exhaled metabolite. Other urinary metabolites that have been detected in rodent studies include trichloroethanol, chloride, dichloroacetic acid, oxalic acid, ethylene glycol, S-(1,2,2 trichlorovinyl)glutathione, N-acetyl-S-(trichlorovinyl)-L-cysteine (N-Ac-TCVC), N-trichloroacetyl-aminoethanol, and N-oxalyl-aminoethanol. Several of these metabolites, including trichloroacetic acid, trichloroethanol, and N-Ac-TCVC have been observed in the urine of humans exposed to PCE (Yllner, 1961; Daniel, 1963; Dimitrieva, 1967; Ikeda and Ohtsuji, 1972; Ikeda et al., 1972; Moslen et al., 1977; Costa and Ivanetich, 1980; Monster et al., 1983; Dekant et al., 1985; Koppel et al., 1985; Green et al., 1990).

Two pathways of PCE metabolism have been identified. Which metabolites are responsible for PCE's toxic effects, including carcinogenicity, is not known and therefore the relative importance of these pathways remains unclear. Cytochrome P₄₅₀ oxidation is the first step of the most quantitatively significant metabolic pathway for PCE. An epoxide intermediate has been postulated, although this compound has not been isolated *in vivo*. More recently it has been suggested that the epoxide, if formed at all, may not be released from the cytochrome P₄₅₀ catalytic site, and that the first free product is trichloroacetyl chloride, a rearrangement product which is itself highly reactive. Trichloroacetic acid is the stable product of this pathway, and is produced by hydrolysis. The second metabolic pathway for PCE involves conjugation with glutathione. Subsequent degradation of the resulting mercapturic acids by several routes, including one catalyzed by the β-lyase enzyme in the kidney, produce further metabolites from this pathway some of which are potentially reactive.

Published studies on the absorption, distribution, metabolism, and elimination of PCE have been extensively reviewed in a previous California risk assessment document (OEHHA, 1992), and by IARC (IARC, 1995b). A recently updated Toxicological Profile (ATSDR, 1997) also reviewed the pharmacokinetics of PCE in humans and experimental animals. Since there have not been substantial changes in our understanding of these phenomena since those reviews were

undertaken, the reader is referred to these authorities for a complete description. This report will confine itself to noting some more recent findings, which confirm or extend the earlier accounts.

Metabolism

The primary route of PCE metabolism in humans and rodents occurs via oxidation. Cytochrome P₄₅₀ 2B proteins and activities were induced after exposure of male Wistar rats to 500 to 2000 mg/kg PCE p.o. in corn oil for five days, suggesting that these enzymes may be involved in PCE metabolism (Hanioka et al., 1995a; Hanioka et al., 1995b). Several Phase II enzyme activities (DT-diaphorase, glutathione-S-transferase and UDP-glucuronyl transferase) were also induced. The induction of cytochrome P₄₅₀ 2B1 and 2B2 proteins was at a level similar to that seen after phenobarbital treatment. Oxidation of PCE results in formation of trichloroacetyl chloride, possibly through an epoxide intermediate. Trichloroacetyl chloride can react with amino groups of cellular proteins or undergo hydrolysis to produce trichloroacetic acid. Trichloroacetic acid is the primary urinary metabolite of PCE in rodents and humans. This compound has been the basis for biological monitoring of workers exposed to PCE. The intermediate product, trichloroacetyl chloride, is a potentially reactive compound. N^ε-(trichloroacetyl)-L-lysine was detected in the liver of rats exposed to PCE, consistent with the formation of protein adducts by trichloroacetyl chloride (Birner et al., 1994).

Glutathione conjugation in the liver is a second metabolic pathway for PCE. In some earlier discussions of the glutathione pathway (reviewed by OEHHA, 1992) it had been asserted that this pathway was entirely absent in humans. However, recent reports have identified a derivative of this pathway, N-acetyl-S-(trichlorovinyl)-L-cysteine (N-Ac-TCVC), in the urine of dry-cleaning workers (Birner et al., 1996) and experimentally exposed volunteers (Volkel et al., 1998). N-Ac-TCVC is thought to be formed by cleavage and subsequent acetylation of the conjugate. A comparative study of the production of N-Ac-TCVC in rats and humans was recently published by this group (Volkel et al., 1998). Six volunteers were exposed to 10, 20, and 40 ppm PCE for six hours; urine was collected for the following 72 hours (Volkel et al., 1998). Wistar rats were exposed to 10, 20, 40, and 200 ppm and urine collected and analyzed in a similar manner. In humans, the cumulative quantity of TCA excreted was 100-fold higher than the quantity of N-Ac-TCVC. On a $\mu\text{mol/kg}$ basis rats excreted more of both metabolites than humans, however the ratio of TCA to N-Ac-TCVC was somewhat higher in rat urine. In addition, dichloroacetic acid was detected in rat but not human urine. The authors hypothesize that dichloroacetic acid is derived from beta-lyase cleavage of TCVC in the kidney, via a reactive dichlorothioketene intermediate. In support of this hypothesis, exposure to rats resulted in formation of a covalent protein adduct, N^ε-(dichloroacetyl)-L-lysine in kidney cells (Birner et al., 1994). The formation of sulfoxides from PCE glutathione conjugates of sulfoxides from PCE glutathione conjugates reactive electrophiles, and are cytotoxic, raising the possibility that the glutathione pathway may also play a role in the cytotoxicity and carcinogenicity of PCE at other sites in addition to the kidney.

Pharmacokinetic Models

Although the metabolic and mechanistic studies noted above have increased the understanding of PCE metabolism in both rodents and humans significantly, they have not resolved issues basic to the use of more sophisticated pharmacokinetic modeling approaches, such as whether the metabolites responsible for the observed carcinogenic effects arise via the cytochrome P₄₅₀ mediated oxidative pathway or the glutathione conjugation pathway, or both. Some information is available on human pharmacokinetics of inhaled PCE, but the consistency of these data among

themselves, and the extent to which they allow for uncertainty and variability in exposed human populations, has been subject to extensive and complex discussion (Bois et al., 1990; Hattis et al., 1993; Bois et al., 1996). The results of several pharmacokinetic models that have been used to estimate the fraction of PCE metabolized by the oxidative pathway in animals and humans are summarized below. Emphasis is placed on those models which have been used to generate dose estimates for the animal carcinogenicity bioassays, and on a recent model for human metabolism. The models discussed consider only the oxidative pathway for metabolic transformation of PCE. As discussed above, this is the major pathway in both humans and rodents, and appears to be qualitatively similar across species.

Animal Models

Bogen et al. (1987) used a steady-state metabolism model, with empirical data from metabolism studies in rodents, to predict metabolized doses of PCE for the animals in the cancer bioassays (1987). The metabolism of PCE in rats and mice was assumed to follow Michaelis-Menten kinetics. This assumption is consistent with the cytochrome P₄₅₀ enzymes mediating the major pathway of metabolism. Urinary metabolite data reported by Buben and O'Flaherty (1985) for PCE-exposed mice were used for the calculations of metabolized dose excreted in the urine (M_u) after oral exposures, using a Michaelis-Menten type equation:

$$M_u = (D V_{\max}) / (D + K_m)$$

where D = applied oral dose (from 20 to 2000 mg/kg-d), V_{max} = apparent maximum rate of metabolism and K_m = apparent Michaelis constant (all in units of mg/kg-d). In addition, the fraction of total metabolism that is excreted in the urine was estimated from mass-balance results obtained by Schumann et al. (1980). Based on these experimental data,

$$M_u / M = 0.8$$

where M = total metabolites formed and M_u = metabolites observed in urine (both in mg/kg-d). The following values of V_{max} and K_m, corrected for fraction of metabolites observed in urine, were consistent with the Buben and O'Flaherty data for mice:

$$V_{\max} = 170 \text{ mg/kg-d} \quad K_m = 660 \text{ mg/kg-d.}$$

Using these parameter values in the model, the data from the Schumann et al. (1980) study are predicted reasonably well, but the predictions of the data from another study (Mitoma et al., 1985) were not as accurate. Due to less reliable collection and quantitation of metabolites, Bogen et al. elected not to use the Mitoma data for metabolite estimates.

Bogen et al. (1987) also applied their method to predict doses for mice and rats exposed by the inhalation route. A correction for the different body weights of the experimental animals and those to be simulated was included in view of the dependence of metabolic capability and respiration rate (expressed as a volume per unit time) on body weight to the ²/₃ power. Thus:

$$M = \frac{D V_{\max} (w_1/w_2)^{1/3}}{D + K_m (w_2/w_1)^{1/3}}$$

where D = inhaled concentration in ppm, M = total metabolites formed, V_{max} = maximum rate of metabolism and K_m = apparent Michaelis constant (all in mg/kg-d). The parameter w₁ is the body weight of the animals used in the calibration experiment and w₂ is that of the animals to be simulated (e.g. those in the bioassay). Data on total metabolites formed in Sprague-Dawley rats exposed by inhalation, obtained by Pegg et al. (1979), were used to derive metabolic parameters.

Values used were $V_{\max} = 52.982$ mg/kg-d, $K_m = 273.32$ ppm, $w_1 = 0.25$ kg [the mean body weight of the rats in the Pegg et al. (1979) study], and $w_2 = 0.44$ kg for the male rats, and 0.32 kg for the female rats, in the (NTP, 1986) bioassay.

For mice, the inhalation data obtained by Schumann et al. (1980) were insufficient to calculate the required parameters, because only one inhalation exposure level was tested. Instead, the V_{\max} value obtained from the oral studies discussed above (Buben and O'Flaherty, 1985) was assumed to be applicable to the inhalation studies, and the Schumann et al. data were used for validation. The value of K_m for inhalation was then extrapolated by means of the body-weight correction noted above from the rat value of Pegg et al. (1979). Values used were $V_{\max} = 170$ mg/kg-d, $K_m = 126$ ppm, $w_1 = 0.0245$ kg [the mean body weight of the mice in the Schumann et al. study], and $w_2 = 0.037$ kg for the male mice, and 0.032 kg for the female mice, in the NTP bioassay. The metabolized doses for the cancer bioassay studies calculated using the methodology developed by Bogen et al (1987) are shown in Table 4. This is the same animal dosimetry that was used in a previous California risk assessment of inhaled PCE (OEHHA, 1992).

Table 4: Metabolized Dose of PCE in NCI (1977) and NTP (1986) Bioassays

	Applied dose	Metabolized Dose/day ^a	Corrected for 5 days/week	Corrected for weeks dosing	Correction for study length ^b
NCI Oral Study					
Male mice					
	536	76.19	54.42	47.16	30.57
	1072	105.22	75.16	65.14	42.21
Female mice					
	386	62.73	44.81	38.84	25.17
	772	91.65	65.46	56.73	36.77
NTP Inhalation Study					
Male mice, bw = 0.037 kg					
	100	60.59	43.28	43.28	43.28
	200	86.01	61.43	61.43	61.43
Female mice, bw = 0.032 kg					
	100	65.42	46.73	46.73	46.73
	200	92.10	65.78	65.78	65.78
Male rats, bw = 0.44 kg					
	200	16.56	11.83	11.83	11.83
	400	24.04	17.17	17.17	17.17
Female rats, bw = 0.32 kg					
	200	19.65	14.03	14.03	14.03
	400	28.01	20.01	20.01	20.01

^aMetabolized doses in mg/kg-d

^b Calculated as Applied Dose X (lifetime/study duration)³. The figures in this column are those tabulated by Bogen et al. (1987) and OEHHA (1992).

Other physiologically-based pharmacokinetic (PBPK) models for animals, and dosimetry for the bioassays derived from them, are also available. Chen and Blancato (1987) used metabolite

excretion data from rodents to fit a PBPK model based upon that of Ramsey and Andersen (1984). The experimental data selected were those reported by Pegg et al. (1979) and Schumann et al. (1980) for rats and mice exposed to radiolabeled PCE orally and by inhalation. Estimates of V_{max} and K_m were generated by optimizing the fit of the model to the experimental data. The resulting estimates of V_{max} and K_m , were 0.003 mg/min and 1.472 mg/liter for mice and 0.0059 mg/min and 2.938 mg/L for rats, respectively (note that these values are not directly comparable to those derived by Bogen et al. (1987), because of different units). Based on these metabolic parameters, the PBPK model of Chen and Blancato was used to estimate metabolized doses for the carcinogenesis bioassays (Table 5). The doses predicted are quite similar to those generated by Bogen et al. (1987), but are somewhat higher in all cases. Both approaches result in a higher percentage of PCE metabolized at lower applied doses and thus a less than proportional increase in dose of metabolites for a doubling of exposure level as administered in the bioassays.

A PBPK model of inhalation exposure to PCE was also developed by Bois et al. (1990). Parameter estimates for rat, mice, and humans were drawn from the literature, except for the metabolic parameters, which were obtained by fitting. The results of four experimental studies in mice and four in rats were used in the fitting process. The metabolized doses predicted by the model for the NTP rat bioassay are quite similar to those reported by Bogen et al. and Chen and Blancato, but the doses derived for mice diverge somewhat (Table 5).

As shown in Table 5, the three independent efforts produced dose estimates for the bioassay exposures that are in good agreement. Because the approach of Bogen et al. (1987) is the only source which provides estimates for both the NTP and NCI studies, in both rats and mice, these estimates will be used for analysis and route-to-route comparisons of the carcinogenesis bioassay data in rodents in the dose response assessment section of this report.

Dallas and colleagues obtained additional data on uptake and distribution of PCE in rats after exposure by inhalation and oral routes, and intraarterial infusion, and used this to refine their PBPK model of PCE distribution (Dallas et al., 1994a; Dallas et al., 1994b; Dallas et al., 1994c; Dallas et al., 1995). This model explicitly included estimates of exposure of organ systems, such as the brain, which are sites of toxicity endpoints of interest to these authors. They also demonstrated the feasibility in principle of route-to-route extrapolation using the PBPK modeling approach. This new approach is important since it improves the validation of the model by incorporating new experimental data on specific organs in animals. The Dallas et al. studies did not assess metabolite production.

Table 5: Metabolized Doses in NCI and NTP bioassays predicted by three different models

Study	Species/ Sex	Administered Dose or Exposure Concentration	Predicted Dose ¹				
			Bogen et al. (1987)	Chen and Blancato (1987)	Chen and Blancato (adjusted) ²	Bois et al. (1990 ³) (adjusted) ⁴	Bois et al. (adjusted) ⁴
<i>NCI (1977) Mouse</i>							
	male	536 mg/kg-d	30.6	56.3	36.5		
		1,072 mg/kg-d	42.2	75.3	48.8		
	female	386 mg/kg-d	25.2	40.6	26.3		
		772 mg/kg-d	36.8	57.5	37.3		
<i>NTP (1986) Mouse</i>							
	male	100 ppm	43.3	47.2		7.3	22.1
		200 ppm	61.4	66.3		12.7	38.4
	female	100 ppm	46.7	55.0		7.3	22.1
		200 ppm	65.8	76.8		12.7	38.4
<i>Rat</i>							
	male	200 ppm	11.8			9.8	13.5
		400 ppm	17.2			13.9	19.1
	female	200 ppm	14.0			9.8	13.5
		400 ppm	20.0			13.9	19.1

¹Dose units are mg metabolized/kg-d, lifetime TWA

²Adjusted for study length with conversion factor: (90weeks/104weeks)³ (Bogen et al., 1987)

³Bois et al. did not report separate estimates for males and females

⁴Bois et al. predictions were adjusted from the published units of mg/d-kg^{2/3} to mg/kg-d

Pharmacokinetic Models of PCE Exposure in Humans

A PBPK model of PCE uptake, metabolism and elimination in humans was developed by Bois and colleagues (Bois et al., 1996). To account for interindividual variation, a population level statistical model was linked to the PBPK model during the fitting process. Prior estimates of the population parameter distributions were based on literature values. Empirical data from the human exposure studies of Monster et al. (Monster et al., 1979) were used for calibration simulations, carried out using a Markov chain Monte Carlo simulation approach with Bayesian updating. The fitted posterior distributions of model parameters were then used to make predictions of metabolized doses for specific exposure scenarios. At higher exposure concentrations (50 ppm in air), the average fraction metabolized predicted by the fitted parameters was low (mean 1.7, 95 percent confidence limits 0.52 - 4.1 percent). This is in line with what has been observed in several empirical studies of occupationally exposed workers (OEHHA, 1992; ATSDR, 1997) as well as human exposure data that were not used in model fitting (e.g. Volkel et al., 1998) and the results of several other PBPK model predictions (Hattis et al., 1990 and 1993). However at a low exposure level (1 ppb in air), such as might be

encountered in environmental inhalation exposures to PCE, the predicted proportion of PCE metabolized was much higher (mean 36, 95 percent confidence limits 15 – 58 percent). Saturation of metabolism in continuously exposed humans was predicted to begin at exposure concentrations between 1 and 10 ppm. Unfortunately, measured human data on metabolite excretion at low exposure levels are not available.

Relatively little has been done to explore the kinetics of PCE in humans following oral exposure; the published models have been primarily concerned with inhalation exposures. However, the parameter values derived from fitting Bois and colleagues' model to inhalation data have also been used to predict the fraction of PCE metabolized under conditions of oral exposure (F.Y. Bois, personal communication). A compartment for uptake from the gastrointestinal tract to the liver was added to the published model for this purpose. As was done for inhalation exposure, 5,000 simulations were performed using random draws from the fitted distributions for population parameter values. Under simulated conditions of exposure to 1µg/L in drinking water assuming intake of 2 L/day and complete absorption, the fraction metabolized was 54 percent (95 percent confidence interval 28-78 percent). This is higher than the corresponding estimate for exposure to low concentrations by inhalation. The difference between routes is biologically plausible, since absorption is more efficient by the oral route and PCE absorbed through the gut is subjected directly to metabolic processes in the liver before entering systemic circulation (and thus enabling exhalatory clearance).

An alternative approach to full pharmacokinetic modeling for determining the fraction of PCE metabolized at low exposure levels in humans was presented by McKone and Bogen (Bogen and McKone, 1988; McKone and Bogen, 1992). Assuming that at low exposure levels metabolism can be described by a linear function (the V_{max}/K_m ratio), these investigators derived a formula from the Ramsey-Anderson PBPK model at steady state:

$$\text{Fraction metabolized, oral} = \left[1 + \frac{1}{K} \left(\frac{P_b}{Q_a} + \frac{1}{Q_l} \right)^{-1} \right]^{-1}$$

K is the V_{max}/K_m ratio, P_b is the blood/air partition coefficient, Q_a is alveolar flow, and Q_l is blood flow to the liver. Using their estimated parameter values with this approach, McKone and Bogen reported that 34 percent of an oral dose of PCE that is below metabolic saturation is predicted to be metabolized (range 5 – 63 percent) (McKone and Bogen, 1992). Alternatively, if the point estimates of parameter values from the fitted human model of Bois et al. (1996) are substituted (except following McKone and Bogen for the alveolar ventilation rate of 354 L/hr), the above formula produces an estimate of 87 percent metabolized. This estimate is somewhat higher than the upper 95 percent confidence limit resulting from simulations in the Bois et al. PBPK model (78 percent), but shows reasonable agreement.

A similar formula was derived for the maximal fraction metabolized at steady state during inhalation exposure. This formula is also an appropriate approximation for dermal exposure, since a dermally absorbed dose is delivered to systemic circulation, as is an inhaled dose, and is not subject to first pass effects:

$$\text{Fraction metabolized, inhalation} = \left[1 + \frac{Q_a}{P_b} \left(\frac{1}{K} + \frac{1}{Q_l} \right) \right]^{-1}$$

Using this equation, and taking into account a range of possible V_{\max} and K_m values, McKone and Bogen (1992) estimated that the average fraction of inhaled PCE metabolized in humans could range from 0.04 to 0.46 (geometric mean 0.25). Using the fitted parameter estimates of Bois et al. (1996) results in a revised estimate of 0.59, very close to the upper confidence limit of 0.58 that resulted from simulations of inhalation exposure in the Bois et al. PBPK model.

Bogen and McKone also theorized that as the inhaled or ingested concentration approaches zero, metabolism of the dose becomes very rapid, such that V_{\max} can be considered to approach infinity. Under this assumption, they argued that metabolism of respired or dermal doses would be subject to a theoretical physiological upper limit of 73 percent metabolized (Bogen and McKone, 1988; McKone and Bogen, 1992). Substituting the parameter estimates derived from the fitted human PBPK model of Bois et al. into the formula of Bogen and McKone, this theoretical maximum becomes 68 percent. For ingested PCE, the assumption of infinite metabolism as exposure level approaches zero results in a theoretical upper limit of 100 percent metabolized fraction.

For the purposes of determining a PHG, the 95 percent upper confidence limits on the fractions predicted at low dose by the human PBPK model will be used to determine human doses. However, the agreement between these figures and those derived from the approach of Bogen and colleagues provides added confidence in their relevance.

Bois et al. (1996) noted a 30-fold variation in the fraction metabolized in a sample of 25,000 simulations, and a two-fold difference in the maximal metabolic rate within the study population of six males. Findings of substantial interindividual variability have been noted in several other studies. For example, Jang and colleagues reported that TCA in urine was significantly lower in a sample of six Asians in comparison to a sample of six Caucasians (Jang et al., 1997a), indicating potential ethnic differences. Another study reported a two-fold spread in PCE blood concentrations in a small study group (Opdam, 1989). Metabolism of other compounds by cytochrome P₄₅₀ 2B enzymes has also been found to vary. The use of upper confidence limits on the fraction metabolized in humans is reasonable considering the extensive interindividual variability in pharmacokinetics expected in the diverse California population.

Issues in PCE Pharmacokinetics and Other Studies

Hattis and colleagues reviewed several modeling efforts for PCE with particular reference to uncertainties in predictions of low-dose metabolism rates (Hattis et al., 1990). Bois et al. also examined the issue of uncertainty, and investigated sensitivity of pharmacokinetic and cancer risk predictions to key pharmacokinetic parameters (Bois et al., 1990). They established that the most important parameters are K_m and V_{\max} for the metabolism of PCE, and the partition coefficients for distribution of PCE between blood, air, and various tissue compartments. Hattis et al. (1993) reported that the value for one of these parameters, the coefficient for partitioning of

PCE between blood and air, used by most investigators is likely to be too low; a value between 15 and 18 for humans was recommended. The fitted estimate of the partition coefficient in the Bois

et al. human model, 16, falls within this range. Bois et al. (1990) also showed that the precise details of model structure with regard to grouping of tissues did not have a major effect on model predictions; in fact a model based on single body compartment with Michaelis-Menten metabolism and reversible pulmonary exchange was adequate to fit the data they examined. Subsequently, it was argued that parameter uncertainty was not an important source of variation in model output (Gearhart et al., 1993). This conclusion was disputed by Bois et al. (1996), who pointed out that although the variability and/or uncertainty attributable to a single parameter might not be extremely large, the overall uncertainty and variability of the result was considerable due to the combined effect of uncertainty and variability in all the parameters of the model.

Hattis and colleagues examined a large number of different PBPK models and found anomalies in the model fits to human PCE exposure data which they suggested were due to either heterogeneity of the fat compartment, or diffusion of PCE between fat and muscle compartments (Hattis et al., 1993). However it does not appear, based on the work by Bois et al. (1990), that they make a large difference to the prediction of the extent of metabolism of inhaled PCE by humans exposed at very low doses.

In addition to the model developed by Bogen and colleagues (1987) and those evaluated by Hattis et al. (1993), Gearhart et al. (1993) and Bois et al. (1990; 1996), several other PBPK models for PCE have been proposed. These include a model developed by Rao and Brown (1993) specifically to address uptake of PCE as a result of showering and bathing in contaminated water. Byczkowski and colleagues described a computerized simulation of their experimental findings on the transfer in milk of PCE from exposed lactating rats to their pups (Byczkowski et al., 1994; Byczkowski and Fisher, 1995). Jang and Droz applied a PBPK model to their data from experimental exposures of six Asian and six Caucasian volunteers (Jang and Droz, 1997b), but the results are not directly comparable to other human PBPK models, since metabolism was assumed to follow linear kinetics.

Reitz and colleagues reported experimental studies on intraarterial and inhalation exposure of rats and mice *in vivo*, and also various measurements *in vitro* with rodent and human tissues and extracts, in order to determine parameters for incorporation into a refined PBPK model (Reitz et al., 1996). The model was used to fit experimental data in rodents, and measured results from human occupational exposure studies, and to predict tissue concentrations at various times during and after inhalation exposure. The authors concluded that their enhanced model with improved experimental and fitted parameter estimates was successful in fitting the experimental data available in rodents exposed to PCE. They also attempted to refine parameter estimates for humans based on the data sets available to earlier authors. This latter attempt is somewhat frustrated by the inconsistencies between different results noted previously (Hattis et al., 1993; OEHHA, 1992). However, two overall conclusions were reached by Reitz et al. (1996) which are important for the purpose of this report:

1. Their various model predictions, and the available experimental data, are consistent with the fraction of oral dose metabolized in experimental animals as originally estimated by Chen and Blancato (1987) and therefore with the Bogen et al. (1987) approach used in this document for dose-response modeling of the animal cancer data.
2. The estimates of fraction metabolized by humans exposed by inhalation at high and low doses are still somewhat uncertain, but not inconsistent with earlier estimates as reported by Hattis (1990). Although Reitz et al. (1996) do not cite the work of Bois et al. (1996), it appears that the range of values proposed is consistent with Bois' estimates of the mean values and confidence bounds at high and low doses.

TOXICOLOGY

Estimates of human health risks resulting from exposure to a toxic substance may be based on evidence of effects in humans exposed to the chemical, when data are available. Frequently, however, specific human data are absent or inadequate for this purpose. In this case, estimates of human health risks are based on an assessment of animal dose-response data. The toxicity of PCE was reviewed previously by OEHHA (1992), and prior to that evaluation by IARC (1979), Reichert (1983), WHO (1984), and the U.S. EPA (1980, 1982, 1984, 1985a, 1985b). Also, ATSDR (1993) compiled a Toxicological Profile for PCE, which was recently updated (ATSDR, 1997). This section provides a further update to these reviews, with emphasis on the endpoints and specific studies used in the later sections of this report to determine a recommended PHG level.

Toxicological Effects in Animals

In this section, animal PCE toxicity studies are reviewed, including data from bioassays conducted to evaluate the carcinogenicity of PCE. Bioassay results are also used as the basis of the quantitative assessment of carcinogenic potency. The bioassay results are therefore described individually in this report. However not all the non-neoplastic toxicity endpoints are of significance for the determination of the PHG (as noted in the following section on Calculation of the PHG). Therefore, except where relevant for calculation of the PHG, or for recent reports not covered by the reviewers noted above, these non-neoplastic effects will be described in general terms only. The reader is referred to these reviews, and particularly those by OEHHA (1992) and Isacson et al. (1985), for further details.

Acute Toxicity

Acute lethality, particularly after inhalation exposures to high concentrations of PCE, typically results either from the CNS depression or from cardiac sensitization to adrenaline resulting in arrhythmia. These effects are seen with many other volatile halogenated compounds, but PCE is apparently one of the more potent of the common solvents. (In the series of halogenated C₁-C₃ alkanes and alkenes, cardiac sensitization and anesthetic potency are determined by various physical parameters related to molecular weight.) There is no evidence of substantial interspecies variations in susceptibility, other than variations in the effects of different exposure concentrations and time due to interspecies pharmacokinetic variations.

Liver and kidney damage after PCE exposures (by various routes) has been described by various authors. Some experiments have shown such effects after single inhalation, oral or intraperitoneal doses. The nature of the effects is similar to (although more limited than) those seen in subacute or subchronic repeated dose experiments, described below.

Significant exposure levels for acute exposures (ATSDR, 1997) are shown in Table 6.

Subacute and Chronic Toxicity

Liver toxicity has been observed after treatment with PCE by various routes. This has been revealed by increases in liver-specific transaminase levels in serum, by observation of various histological effects (swelling, vacuolation, centrilobular necrosis, hyperplasia) and by biochemical changes (decrease in the adenosine triphosphate (ATP) content, increase in the content of lipids and triglycerides) indicative of damage to hepatocytes. Mice are generally

substantially more susceptible than rats to this effect. After exposure to PCE, increased numbers of peroxisomes and increased peroxisomal cyanide-insensitive palmitoyl CoA oxidation were reported in mouse liver, but not in rat liver. In mice, liver weight increases and induction of cytochrome P₄₅₀ after repeated PCE treatment have been reported.

In the bioassay of tetrachloroethylene by gavage (NCI, 1977) described in the section on carcinogenicity, there was no reported increase in any non-carcinogenic hepatic lesions in either mice or female rats. However, in the inhalation bioassay (NTP, 1986), male and female mice of both exposure groups showed dose related liver degeneration and necrosis. Under the conditions of this study, rats did not develop hepatic lesions in response to exposure to PCE.

Kidney damage after oral, intraperitoneal or inhalation PCE exposure has been reported in rodents (especially male rats) and dogs (ATSDR, 1997). With shorter treatment regimens and lower doses this may be limited to functional impairments, increases in kidney weight and modest histological alterations. However, more extensive histological changes are seen after extended exposures at high doses, including desquamation of tubular epithelium and intratubular casts. In male rats, hyaline droplet formation has been reported. This was described as an α 2u globulin nephropathy by the original authors (Green et al., 1990; Bergamaschi et al., 1992) and by ATSDR (1997). However, there appears to be some doubt as to whether the findings in male rat are fully compatible with this explanation. In any case, there must be other mechanisms by which PCE produces renal toxicity, since nephropathy (which may be severe or fatal after chronic exposures at high doses) is observed in female rats and both sexes of mice, none of which are susceptible to α 2u globulin nephropathy. The observations by Birner et al. (1994) of a glutathione-based metabolic route (which may be active in the kidney) to a reactive intermediate are described in the section on Metabolism. This may indicate an additional possible mechanism for renal toxicity of PCE.

The NCI cancer bioassay of PCE by gavage (NCI, 1977) documented a high incidence of toxic nephropathy in mice and rats for all dose groups. Toxic nephropathy was defined as degenerative changes in the proximal convoluted tubule, fatty degeneration, and necrosis of the tubular epithelium. In the inhalation bioassay (NTP, 1986), kidney casts, nephrosis, and tubular cell karyomegaly were reported in mice. In rats, a dose-related increase of renal tubular cell karyomegaly was reported in both sexes. Male rats exhibited a dose-related increase in renal tubular cell hyperplasia; one high-dose female was also affected.

Table 6: Significant Exposure Levels for Acute Exposure to Perchloroethylene

Species, Strain, Sex	Route	Level, Type	Effect
Rat			
Sprague-Dawley, M	Oral (single dose)	3005 mg/kg, LD ₅₀	Lethality
Sprague-Dawley, F	Oral (single dose)	3835 mg/kg, LD ₅₀	Lethality
Fischer 344, M/F	Inhalation (4 h)	3768 ppm, LC ₅₀	Lethality
Fischer 344, F	Oral (single dose)	500 mg/kg, NOAEL 1500 mg/kg, LOAEL	Lacrimation, gait disturbance, decreased motor activity
Wistar, M	Oral (5 days)	1000 mg/kg, NOAEL	Decreased body weight gain
Fischer 344, F	Inhalation (6 h/d, 5d/wk, 2 wk)	875 ppm, NOAEL 1750 ppm, LOAEL	Decreased body weight gain
Various, M/F	Oral (5-10 days)	500 mg/kg, NOAEL 1000 mg/kg, LOAEL	Increased liver weight, liver enzyme induction
Mouse			
Swiss-Webster, M	Oral (single dose)	8139 mg/kg, LD ₅₀	Lethality
?, M/F	Inhalation (4 h)	5200 ppm, LC ₅₀	Lethality
?, F	Inhalation (4 h)	200 ppm, LOAEL	Liver fatty degeneration
B6C3F ₁ , M	Oral (10 days)	1000 mg/kg, LOAEL	Hepatic and renal peroxisome proliferation
B6C3F ₁ , M/F	Oral (11 days)	100 mg/kg, LOAEL	Hepatocellular swelling
B6C3F ₁ , M/F	Inhalation (6 h/d, 5d/wk, 2 wk)	400 ppm, LOAEL	Liver fatty changes, peroxisome proliferation

Source: ATSDR (1977), citing Isacson et al. (1985)

Developmental and Reproductive Toxicity

Developmental and reproductive effects of PCE were reviewed by OEHHA (1992), IARC (1985a,b) and ATSDR (1997). The teratogenic activity of PCE has been studied in rats (Schwetz et al., 1974; Schwetz et al., 1975; Beliles et al., 1980; Nelson et al., 1980), mice (Schwetz et al., 1975) and rabbits (Beliles et al., 1980). Maternal exposure levels ranged from 100 to 1800 ppm PCE. Tinston (1995, in an unpublished report cited by ATSDR, 1997) undertook a multigeneration study in rats exposed to PCE. At 1000 ppm there were some decreases in litter size and survival during lactation, but these were not seen at 300 ppm.

Although some minor effects have been seen in the progeny in these studies, PCE is not generally considered a rodent teratogen. Developmental toxicity, in the form of morphological abnormalities, was also observed in an *in vitro* study in which ten-day old embryos from Sprague-Dawley rats were removed to culture medium containing PCE (Saillenfait et al., 1995). There are some possible effects of PCE on the developing nervous system following exposure to PCE *in utero* (Nelson et al., 1980) or neonatally (Fredriksson et al., 1993). In general, however,

investigations of developmental effects of PCE have shown evidence of maternal toxicity, rather than specific adverse effects on the progeny.

Immunotoxicity

Kroneld and associates conducted *in vitro* experiments using isolated human peripheral blood lymphocytes (Kroneld, 1987). Lymphocytes were exposed to PCE at concentrations of 0.2, 1.6, 16, 160 µg/L. Significant decreases in ³H-thymidine intake were noted at concentrations of 1.6 µg/L and greater.

Groups of 140 female CD-1 mice were exposed to 0, 25 or 50 ppm PCE for three hours (Aranyi et al., 1986). Challenge by inhaled *Streptococcus zooepidemicus* resulted in significantly increased mortality in animals exposed to 50 ppm PCE relative to controls. Pulmonary bactericidal activity against *Klebsiella pneumoniae* was significantly decreased in mice exposed to 50 ppm PCE. However, the significance of the effects observed is unclear because the mortality observed in the control animals in the 25 ppm experiment was greater than that of PCE-exposed animals in the 50 ppm experiment. Furthermore, exposure to 25 ppm PCE for three hours per day for five days did not result in changes in *Streptococcus* mortality or pulmonary bactericidal activity.

Miyano and associates (1987) reported that PCE caused decreased cell viability in mouse spleen cell cultures (Miyano and Nakano, 1987). Lipopolysaccharide-stimulated B-lymphocyte transformation and Con A-stimulated T-lymphocyte transformation were also inhibited by PCE.

Neurotoxicity

Acute high exposure to PCE typically induces CNS depression. Initial depression can progress to loss of consciousness, anesthesia, and respiratory failure with prolonged or massive exposure. Chronic exposures at lower levels have been reported to result in alterations in biochemical parameters in the central nervous system. These effects were reviewed by ATSDR (1997) and OEHHA (1992). The following account describes a small number of recent studies of PCE neurotoxicity in animals, which were not cited by Alewife et al. (1992) or in the recent review by ATSDR (1997).

Wang et al. (1993) exposed rats to PCE (300 – 600 ppm) by inhalation for 4–12 weeks. Total brain weight increase was inhibited at 600 ppm for 4 or 12 weeks, and tissue weight, total protein and DNA were reduced in specific regions after 12 weeks at this concentration. Studies of specific biochemical markers indicated reductions in numbers of brain cells, probably glial cells rather than neurons, and interference with the metabolism of cytoskeletal proteins in both types of cell.

Umezu et al. (1997) examined the effects of intraperitoneal injections of PCE on the behavior of mice. Loss of righting reflex was noted, with an ED₅₀ of 4209 mg PCE/kg. Inhibition of operant behavior was noted at 2000 mg PCE/kg. Negative effects were noted on conflict behavior in two tests at 250-500 mg/kg. The study also examined the effects of trichloroethylene, which were similar to those of PCE.

Mattson et al. (1998) examined various neurotoxicological end-points in rats during and following inhalation of 50 – 800 ppm PCE for 6 hours/day, 5 days/week for 13 weeks. Long-latency flash evoked potentials (FEPs) in the visual cortex were found to have greater amplitude in the group exposed to 800 ppm PCE. The authors described the toxicological significance of this finding as “unknown.” Other neurotoxicological parameters (FEPs in the cerebellum;

auditory, somatosensory, or caudal nerve evoked potentials; clinical or histopathological observations) showed no dose-related effects. The NOEL for amplitude changes in visual cortex FEPs was 200 ppm.

Genetic Toxicity

A number of investigators have reported data on the genetic toxicity of PCE, using microorganisms, mammalian cells in culture, and a variety of genetic assays *in vivo* in mammals and in *Drosophila*. The genetic toxicity of PCE has been extensively reviewed by OEHHHA (1992), by IARC (1995b) and by ATSDR (1997), and the reader is referred to these sources for details of the studies. The reviewers generally concluded that the evidence for genotoxicity of PCE is negative, or at most, equivocal. However, this may be related to the difficulty in designing a test system with appropriate sensitivity and metabolic activation, rather than necessarily indicating the absence of a role for genotoxicity in the overall toxic and carcinogenic effects of PCE.

The results in the majority of cases for the assays measuring forward or reverse mutations in prokaryotes (*Salmonella typhimurium*, *Escherichia coli*) *in vitro* have been negative. A few positive results were obtained which were apparently associated with the presence of mutagenic impurities or stabilizers in the PCE, or were of doubtful significance. Some positive or equivocal results were obtained with eukaryotic systems *in vitro*, including mitotic recombination in *Saccharomyces* and induction of unscheduled DNA synthesis in cultured mammalian cells, but most results in these types of test systems were also negative. Some reports of effects *in vivo* (DNA single strand breakage in liver, micronucleus induction and altered sperm morphology, in rodents) have appeared. However, these results are often hard to interpret, and are not considered to provide clear evidence of direct genotoxicity of PCE or its metabolites.

A recent study examined the effect of oral PCE exposure (800 mg/kg-d, five days per week for up to 76 weeks) on proto-oncogenes in the livers of mice (Anna et al., 1994). Oncogene mutations were examined in the spontaneously occurring tumors (hepatocellular adenomas and carcinomas) found in control mice, and in those from exposed mice. The frequency of mutations at codon 61 of the H-*ras* gene was significantly reduced in exposed mice, and a possible shift in the spectrum of mutations at this codon was noted. The frequencies of other mutations in the H-*ras* gene, and the K-*ras* gene were very low in concurrent or historical controls. On the other hand, in tumors from exposed mice these mutations contributed 4 and 13 percent respectively of the total observed *ras* mutations.

Several metabolites of PCE are known to be mutagenic. Tetrachloroethylene oxide (PCE oxide) is believed to be the first intermediate formed by microsomal oxidation of PCE. PCE oxide was found to be mutagenic to *Salmonella typhimurium* TA1535 (without metabolic activation) but not to *E. coli* WP2 uvrA. PCE oxide gave positive results in a differential growth inhibition test using the DNA-polymerase-deficient strain, pol A 1 of *E. coli* (Kline et al., 1982).

Trichloroacetic acid (TCA) is excreted in the urine of rodents and humans exposed to PCE. In an Ames test conducted with metabolic activation, TCA (0.45 mg/plate) and trichloroethanol (7.5 mg/plate) were not mutagenic to *S. typhimurium* strains TA98 and TA100. There is some indication, however, that trichloroethanol can induce sister-chromatid exchange in cultured human lymphocytes (Gu et al., 1981), although this potential metabolite has not been consistently detected in humans. TCA may also contribute to "non-genotoxic" mechanisms of liver carcinogenesis in rodents, since it is known to be carcinogenic in mice (Herren-Freund et al., 1987) and to induce peroxisome proliferation (Odum et al., 1988).

The proposed metabolism of PCE to a glutathione conjugate by the mercapturic acid pathway and beta-lyase, resulting in formation of a genotoxic metabolite, is discussed further in the section in this report on Metabolism. The PCE glutathione conjugate S-(1,2,2-trichlorovinyl)glutathione (TCVG) was found to be mutagenic in *S. typhimurium* TA 100 when a suitable metabolic activation system was included in the assay (Vamvakas et al., 1989). TCVG incubated with rat kidney particulate fraction containing high concentrations of gamma-glutamyl transpeptidase (GGT) and dipeptidases was highly mutagenic. PCE was not mutagenic in the absence of metabolic activation, or under conditions supporting oxidative metabolism. PCE was, however, mutagenic in the Ames assay upon incubation purified with rat liver glutathione (GSH) S-transferases, GSH and rat kidney fractions. Under these conditions, it was expected that TCVG would be formed in the mixture. TCVG was formed from PCE in isolated perfused rat liver and excreted in bile, and this bile was mutagenic in the presence of kidney particulate fractions. Serine borate, an inhibitor of GGT, or aminooxyacetic acid, an inhibitor of β -lyase, reduced mutagenicity.

Carcinogenicity

The National Toxicology Program has conducted two lifetime bioassays on PCE (NCI, 1977; NTP, 1986). Additionally, three other studies have addressed the question of PCE carcinogenicity (Theiss et al., 1977; Rampy et al., 1978; VanDuuren et al., 1979).

Gavage studies

Mouse (NCI, 1977)

The National Cancer Institute conducted a long-term study (NCI, 1977) in which B6C3F₁ mice were administered PCE in corn oil by gavage, 5 days/week (78 weeks + an additional 12 week observation period). Mice were 25 days old at initial treatment. The time-weighted average daily doses of PCE were 536 and 1,072 mg/kg for male mice, 386 and 722 mg/kg for female mice, 471 and 941 mg/kg for male rats, and 474 and 949 mg/kg for female rats. A statistically significant increase ($P < 0.001$, Fisher Exact test) in hepatocellular carcinoma was observed in both males (controls 2/17; 536 mg/kg-d 32/49; 1072 mg/kg-d 27/48) and females (controls 0/20; 386 mg/kg--d 19/48; 772 mg/kg-d 19/48). Incidences of hepatocellular carcinoma in concurrent groups of untreated mice were 2/17 (males) and 2/20 (females). The NCI concluded that under the conditions of this study, PCE was a liver carcinogen to B6C3F₁ mice of both sexes.

Questions have been raised about the purity of PCE used in the NCI mouse and rat gavage bioassays. The PCE was produced by Aldrich Chemical Co. and had a purity of 99 percent. However, epichlorohydrin (ECH) was apparently used as a stabilizer. It has been suggested that the presence of this contaminant may have directly contributed to tumor induction. ECH is a direct-acting alkylating agent and is mutagenic (Kucerova et al., 1997; Bridges, 1978). VanDuuren and associates demonstrated that ECH was carcinogenic in mice when injected subcutaneously (VanDuuren et al., 1974). A subsequent study by Laskin and colleagues showed that ECH induced neoplastic lesions of the nasal cavity of rats (Laskin et al., 1980). Most of these tumors were carcinomas of the squamous epithelium. A study by Konishi and co-workers and Kawabata also showed that ECH fed discontinuously to rats in drinking water at a concentration of 1500 ppm (and at a lifetime TWA dose of approximately 40.2 mg/kg-d) induced a significantly increased incidence of papillomas and squamous cell carcinomas of the forestomach above that of control animals (Konishi et al., 1980; Kawabata, 1981).

The exact quantity of ECH present in the PCE used in the NCI study is not known, but it has been estimated that high-dose male mice received 0.42 mg/kg-d (U.S. EPA, 1985a). This represents one percent of the dose that elicited squamous cell carcinomas in rats. Furthermore, ECH appears to initiate tumors by a localized tumorigenic reaction at sites where it is in direct contact with tissue, such as nasal or forestomach squamous-cell epithelium (U.S. EPA, 1984). No animal in the NCI bioassay developed tumors at these sites. ECH is among the weakest of the more than 50 suspect carcinogens evaluated by the EPA Carcinogen Assessment Group, having an estimated upper-bound carcinogenic potency, or effect per unit dose at low doses, to humans of $9.9 \times 10^{-3} \text{ (mg/kg-d)}^{-1}$, based on increased nasal cavity tumor incidence in rats exposed to ECH via drinking water (U.S. EPA, 1984). Using the methodology of the U.S. EPA, the equivalent potency to mice would be $9.9 \times 10^{-3} \times (\text{fm}/\text{fh})$, where fm and fh are the fractions of body weight consumed as water by mice and humans, respectively (U.S. EPA, 1984). The potency for ECH to mice is therefore estimated to be $0.058 \text{ (mg/kg-d)}^{-1}$. Using this potency estimate, the highest dosed animals (high-dose male mice) in the NCI bioassays would be expected to incur an increased cancer risk of $(0.42) \times (0.058) = 0.024$, or less than 2.5 percent (NCI, 1977). Therefore, it is unlikely that ECH contributed significantly to the observed increased tumor incidence in PCE-exposed mice in the NCI bioassay (NCI, 1977).

Rat (NCI, 1977)

Male and female Osborne-Mendel rats received 471 mg/kg-d or 941 mg/kg-d, and 474 mg/kg-d or 949 mg/kg-d PCE, respectively, by gavage in corn oil (78 weeks + an additional 32 week observation period). Early mortality occurred in all groups of rats dosed with PCE. Half of the high-dose males had died by week 44 and half of the high-dose females died by week 66. The survival time of control animals ranged from 88 to 102 weeks. The NCI determined that there was a statistically significant association ($p < 0.001$) between increased dosage of PCE and increased mortality. The early mortality observed in rats and its statistical association with dose of PCE indicate that the doses given to rats in this bioassay were inappropriately high. Because the optimum dosages were not used and because significant early mortality occurred, these results preclude making conclusions regarding the carcinogenicity of PCE in rats.

Inhalation studies

Mouse (NTP, 1986)

A study of the carcinogenic potential of PCE by inhalation in mice was conducted by Battelle Pacific Northwest laboratories for the National Toxicology Program (NTP, 1986). In this experiment, B6C3F₁ mice were exposed to 99.9 percent pure PCE by inhalation, 6 hours/day, 5 days/week for 103 weeks at concentrations of 0, 100, or 200 ppm. Hepatocellular adenoma and hepatocellular carcinoma in males, and hepatocellular carcinoma in females were observed. The incidences of hepatocellular carcinoma relative to controls were significant ($P < 0.01$, Fisher Exact test) for mid- and high-dose males (controls 7/49; 100 ppm 25/49; 200 ppm 26/50) and females (controls 1/48; 100 ppm 13/50; 200 ppm 36/50). The NTP determined that, under the conditions of this study, there was "clear evidence of carcinogenicity" of PCE for both sexes of B6C3F₁ mice.

Rat (NTP, 1986)

In parallel to the mouse study, a PCE inhalation study in rats was conducted (NTP, 1986). In this experiment, F344/N rats were exposed to 99.9 percent pure PCE by inhalation, 6 hours/day,

5 days/week for 103 weeks at concentrations of 0, 200, or 400 ppm. Treated male rats had lower survival rates than control animals (controls, 23/50 animals; 200 ppm, 20/50; 400 ppm, 12/50). Survival rates among female rats showed little variation (controls, 23/50 animals; 200 ppm, 21/50; 400 ppm, 24/50). A statistically significant increase in mononuclear cell leukemia was observed in mid- and high-dose males (controls 28/50; 200 ppm 37/50; 400 ppm 37/50) and females (controls 18/50; 200 ppm 30/50; 400 ppm 29/50). In males, increases in renal tubular cell adenomas (controls 1/49; 200 ppm 3/49; 400 ppm 2/50) and tubular cell adenocarcinomas (controls 0/49; 200 ppm 0/49; 400 ppm 2/50) were observed. Although these increases were not statistically significant according to NTP (1986), subsequent commentators and investigators have generally concluded that the results have toxicological significance in view of the low historical incidence of such tumors in F344 rats (Green et al., 1990; Birner et al., 1994). The combined incidence of tubular cell adenoma or adenocarcinoma was: controls, 1/49; 200 ppm, 3/49; 400 ppm, 4/50. The NTP determined that, under the conditions of this study, there was “clear evidence of carcinogenicity” of PCE for male F344/N rats, and “some evidence of carcinogenicity” of PCE for female F344/N rats.

Rat (Rampy et al., 1978)

Male and female Sprague-Dawley rats were exposed to 300 or 600 ppm PCE by inhalation for 6 hours/day, 5 days/week for 12 months. Animals were then observed for an 18-month follow-up period. High-dose males had slightly greater mortality than did controls. No treatment-related tumors were observed in either male or female rats. Interpretation of this study is limited by the short duration of the exposure and by the fact that it was reported only as an abstract.

Other Routes

Mouse i.p. study (Theiss et al., 1977)

Six to eight weeks old male A/St mice were given 80, 200, or 400 mg/kg of PCE in tricapyrylin by intraperitoneal injection three times per week. Each group received 14, 24, or 48 injections. Animals were sacrificed 24 weeks after the first injection and examined histologically for the presence of pulmonary tumors. No treatment-related tumors were observed.

Mouse dermal studies (VanDuuren et al., 1979)

ICR/Ha Swiss mice were treated with 163 mg PCE applied once to surface skin. Fourteen days after treatment, phorbol myristate acetate, a promoter, was applied to the same area three times a week for 428 to 576 days. A second group received 54 mg PCE by topical application three times a week for 440 to 594 days. No treatment-related tumors were observed in either male or female mice.

Summary of Evidence of Carcinogenicity in Animals

The NCI bioassay of PCE found that administration of PCE by gavage was associated with a statistically significant increased incidence ($p < 0.001$) of hepatocellular carcinoma (NCI, 1977). This increase was documented in low and high-dose PCE-treated B6C3F₁ mice of both sexes. A decrease in the time to first tumor development was also observed in treated mice of both sexes and both dose groups. Early mortality prevented an analysis of PCE's carcinogenic potential in

rats. The NCI concluded that under the conditions of this study, PCE was a liver carcinogen to B6C3F₁ mice of both sexes (NCI, 1977).

The final report of the NTP inhalation bioassay on PCE was released in 1986 (NTP, 1986). The NTP determined that, under the conditions of this study, there was "clear evidence of carcinogenicity" of PCE for male F344/N rats, "some evidence of carcinogenicity" of PCE for female F344/N rats, and "clear evidence of carcinogenicity" of PCE for both sexes of B6C3F₁ mice. In rats, these conclusions were based on an increased incidence of mononuclear cell leukemia in males and females. Male rats also developed renal tubular cell neoplasms (a rare type of tumor). The evaluation of carcinogenicity in mice was based on an increased incidence of hepatocellular adenoma and hepatocellular carcinoma in males, and an increased incidence of hepatocellular carcinoma in females.

In 1979, IARC reviewed the NCI study on PCE as well as the animal carcinogenicity studies of Rampy and associates (Rampy et al., 1978) and Theiss and colleagues (1977). Only two short-term assays were evaluated (Greim et al., 1975; Cerna and Kypenova, 1977). At this time, IARC determined that there was "limited evidence" that PCE was carcinogenic in mice (IARC, 1979). Recently, IARC re-evaluated the evidence of carcinogenicity of PCE, including the NTP (1986) data. The working group concluded that there was "sufficient evidence" that PCE is carcinogenic to animals (IARC, 1995b).

Toxicological Effects in Humans

Acute and Subacute Toxicity

Numerous case reports of short-term exposure to PCE, studies of occupationally exposed workers and experimental studies of human volunteers have demonstrated acute toxicity of PCE to humans (reviewed in Isacson et al. (1985); OEHHA (1992); OEHHA (1999)). The reader is referred to these sources for additional details. It does not appear likely that the acute toxicity described would be important at the exposure levels anticipated as a result of exposures to PCE contaminated drinking water. The effects described in humans resemble the acute toxicity of PCE in animals. Symptoms associated with effects on the central nervous system predominate: nausea, speech difficulty, lightheadedness, anesthesia, and eye and throat irritation have been observed. In most cases, effect levels are at or above 100 ppm. Hepatic necrosis and hepatitis have also been reported occasionally, particularly following substantial oral doses (ca. 0.12 mL/kg).

Neurotoxicity

Human and animal studies of acute and chronic duration have shown that, like many other solvents, the nervous system is a critical target organ for the effects of PCE. Recent reviews by the ATSDR (1997) and OEHHA, (1992) have surveyed many of the available studies. Selected findings of these documents are noted below; the discussion is supplemented with more recent data not available at the time of the earlier reviews.

Acute exposure has been studied in short-term experimental studies in humans. At very high concentrations, anaesthetic effects occur; these effects are generally thought to be reversible (ATSDR, 1997). At lower exposure concentrations (ranging from 50-600 ppm) for acute exposure periods (10 minutes to 1 week) a variety of CNS symptoms such as dizziness, ataxia, loss of coordination, balance, and increased latency of visual evoked potentials have been

reported (ATSDR, 1997). Effects on visual evoked potentials, coordination, and vigilance were noted in 15 male volunteers exposed to 50 ppm for 4 hr/day, 4 days, in comparison to a similar group exposed to 10 ppm (Altmann et al., 1992). Based on this study, ATSDR considered 10 ppm to be an acute NOAEL for PCE.

Subchronic exposure to volunteers (0, 25, or 100 ppm for 5.5 hours/day for 11 weeks) resulted in significant decreases in an index of coordination at 100 ppm. Exposure to 100 ppm for 4 weeks caused alterations in EEG patterns, suggesting a state of drowsiness similar to the first stages of anesthesia (Stewart et al., 1977, 1981, as cited in ATSDR, 1997).

Chronic effects of PCE exposure on the nervous system have been studied in occupationally exposed workers, mostly dry-cleaners, and in one study of environmental exposure to residents in the vicinity of dry-cleaning shops. A wide variety of tests for neurotoxicity have been performed. The most important effects appear to be neurobehavioral and cognitive effects such as longer response times and decreased memory functions. Visual effects including dyschromatopsia (acquired color vision loss) are also potentially important neurotoxic endpoints in humans. Effects on the peripheral nervous system, such as would be detected in tests of motor functions, appear to be less frequently affected by PCE exposure than central nervous system endpoints.

Delayed reaction times to different stimuli types have been observed in a number of tests conducted in people with exposure to PCE. In a study of 60 female dry-cleaning workers with an average employment duration of 10.1 years, Ferroni and colleagues found statistically significantly longer simple reaction times and longer reaction time in tests of shape comparison (Ferroni et al., 1992). Exposure was determined by 4-hour air samples taken in each workplace at two different times of year (median 15 ppm), and by blood concentration of PCE (median 145 µg/L). Delayed reactions were also reported in an earlier study of German workers exposed to an average of 30 ppm PCE (Seeber, 1989). While the effects were statistically significant in low exposure (average exposure level 12 ppm for 141 months) and high exposure (54 ppm, 127 months) groups, there were no significant differences between the two exposure groups for any of the test results reported. A recent paper reported that laundry operators exposed to PCE had significantly delayed vocal reaction time to words displayed on a computer screen compared to unexposed controls (Spinatonda et al., 1997). The duration of the response was also shorter, particularly for meaningless words. Average exposure was 8 ppm; years of employment were not given. Altmann and colleagues tested a number of cognitive and psychomotor functions in a group of 14 people with at least one year of residence neighboring a dry-cleaning shop (Altmann et al., 1995). The median air concentration in the home was 0.2 ppm, average residence duration was 10.6 years, and blood concentrations averaged 17.8 µg/L. Significant differences from controls in simple reaction time, visual memory for shapes and a vigilance were observed. The findings remained significant after adjustment for age, education, and gender. This study is limited by the small sample size, but appears to identify the lowest exposure level at which chronic effects of PCE exposure have been reported. In contrast to these findings, Lauwerys and colleagues (1983) did not find effects on reaction time in two tests administered to workers exposed to an average of 21 ppm for 6.4 years.

Adverse effects on memory, particularly visual memory, have been reported in PCE-exposed people. Echevarria and colleagues followed up on clinical findings in four patients examined for PCE-induced encephalopathy with a field study in workers (Echeverria et al., 1995). The clinical findings on the four patients included decrements in memory, motor, attention, and visuospatial functions; these findings were used to design a field study of 65 dry-cleaning workers in PCE-only shops. Exposure was determined by PCE measurements in breath and air. Two exposure levels were noted: low (11 ppm) and high (41 ppm). Both current exposure and lifetime cumulative exposure (accounting for other occupational and hobby exposure) were used

as explanatory variables in the analysis of results from a variety of neurobehavioral tests. Visually-mediated functions, particularly those associated with short-term memory for visual designs, were significantly associated with cumulative exposure, but not current exposure. These effects were also associated with alcohol intake, emphasizing the importance of controlling for alcohol in studies of this kind. In the aforementioned study of environmentally exposed subjects (Altmann et al., 1995), a test for visual memory showed differences between exposed subjects and unexposed controls.

Other outcome measures that have been assessed in neurotoxicity studies of chronic PCE exposure include tests for attention, cognitive function, verbal skills, and motor function. Lauwerys and colleagues (1983) did not find any differences between their exposed workers and controls in a test of attention, whereas Seeber et al. (1989) reported a significant difference in an attention task. Echevarria and colleagues concluded that there were few effects on verbal and cognitive functions, and proposed that PCE may target parts of the limbic and frontal systems dealing with visual response and memory (Echevarria et al., 1995).

Mood changes and other subjective symptoms were reported with increased prevalence in exposed groups in two studies (Lauwerys et al., 1983; Cai et al., 1991). However, findings of similar symptoms were not significant in the paper of Lauwerys et al. (1983) and effects on emotional lability were restricted to the low exposure group in a third study (Seeber, 1989). Motor functions also appear to be relatively unaffected in chronic studies. One positive result for a finger tapping test was reported (Ferroni et al., 1992). Another study appears to have been negative, although only selected results were reported (Seeber, 1989). Altmann et al. (1995) reported no effect in a finger-tapping test in subjects with low environmental exposure.

Acquired dyschromatopsia has been observed in several studies of occupational exposure to organic solvents at relatively low levels, as well as in alcoholics, and may be a sensitive indicator of PCE neurotoxicity. The mechanism of acquired dyschromatopsia is not known, but could involve direct effects on cone cells in the retina or axonopathy of the optic nerve. Mergler found evidence that solvent-induced loss of color vision is due to neural rather than direct ocular damage (Mergler et al., 1987).

In 1992, Nakatsuka and colleagues reported on a study of color vision in groups of workers exposed to toluene, PCE alone or PCE in combination with trichloroethylene (Nakatsuka et al., 1992). Color vision was somewhat worse in control subjects as compared to any of the exposed groups. However, other authors have pointed out that this study failed to control for alcohol intake, an important factor for color vision outcomes (Valic et al., 1997). Further, there is some question about whether the test administered was sufficiently sensitive (Gobba et al., 1998). Color vision was tested in a group of dry-cleaning workers, using a desaturated color test and a sensitive measurement scale (Cavalleri et al., 1994). Subjects were selected from workers with low alcohol intake. Exposure assessed by personal sampling for a full shift. A statistically significant increase in color confusion was observed in exposed subjects, mostly affecting blue-yellow discernment. When the data for ironers with lower exposure (4.8 ppm, range 0.5-11.3) were analyzed separately from data for dry-cleaners (7.3 ppm, range 0.4-31.2), the dry-cleaning workers were found to have a significant increase in dyschromatopsia that was not observed in ironers. The same group of workers was followed up two years later (Gobba et al., 1998). Exposure in one group had been 1.7 ppm and increased to 4.4 ppm, whereas in the other group, exposure had been 3.0 ppm and had decreased to 0.7 ppm. Color confusion index had worsened in the subgroup that had experienced an increase in exposure level, and no improvement was observed in the subgroup with decreased exposure level. Thus, PCE effects on color vision appear to be cumulative and persistent.

A third study considered potential interactive effects of alcohol and solvent exposure (Valic et al., 1997). Exposure to PCE and/or trichloroethylene was determined by urinary TCA levels; most of the 31 PCE/TCE subjects were classified as having “mild exposure”. Neither cumulative exposure to solvents (toluene, xylene, TCE, PCE) nor TCA in urine were correlated with color confusion in Lanthony’s d-15 test. However, there was a significant increase in color confusion in workers co-exposed to solvents and high alcohol intake, with the TCE/PCE group showing the most pronounced effect.

In conclusion, neurobehavioral and cognitive effects, including effects on visual perception, are sensitive to relatively low PCE exposures; changes in function have been measured in workers at exposure levels below current occupational standards.

Reproductive and Developmental Toxicity

Adverse effects on fertility and pregnancy outcomes have been described in several studies of men and women occupationally exposed to PCE. Since earlier reviews by ATSDR (1997) and IARC (1995 a, b, c) were published, one further study on pregnancy outcomes was identified that is pertinent to the current review (Doyle et al., 1997). The reader is referred to the previous assessments for more complete review of studies published before 1997.

Serum prolactin levels were significantly increased relative to controls in a group of women with occupational exposure to PCE (Ferroni et al., 1992). In another study, it was noted that women with potential exposure to PCE in laundry/dry-cleaning reported menstrual disorders, including PMS, menorrhagia, and dysmenorrhea more frequently than women in the same work who were considered unexposed (Zielhuis et al., 1989). Two studies have reported a possible association between dry-cleaning work and reduced fertility, although the small number of study subjects in both cases limits the usefulness of the results. In a study comparing infertile to fertile couples, the women in infertile couples were more likely to have exposure to dry-cleaning chemicals; specific exposures were not assessed (Rachootin and Olsen, 1983). In a second study, couples in which the men were employed in dry-cleaning were compared to couples in which the men were employed in laundries (Eskenazi et al., 1991a). Men who worked as dry-cleaners and their partners experienced a longer time to conception and were more likely to have sought treatment for infertility than laundry workers. Minor differences in sperm morphology and motility were also found, and were related to the concentration of PCE in expired air (Eskenazi et al., 1991b).

Spontaneous abortion among women with employment in laundry or dry-cleaning was investigated in studies in four Nordic countries, reported together by Olsen and colleagues (Olsen et al., 1990). Spontaneous abortion was increased slightly in workers classified as having low exposure to PCE and further increased in the high exposure group (OR 2.9, 95 percent CI 0.98-8.4). The association in the overall cohort was largely due to an increased risk of spontaneous abortion in Finnish women (Kyyrönen et al., 1989). In that study, an odds ratio of 3.4 (CI 1.0-11.2) was observed. A survey of occupational exposures among cases of spontaneous abortion found a significant association with employment in laundry/dry-cleaning (Lindbohm et al., 1984). A much smaller study of 67 Italian dry-cleaning workers noted a marginally significant increased risk of spontaneous abortion in comparison to women who worked in the home (Bosco et al., 1987). A Canadian study did not find an association, except for a weak effect on past pregnancies (McDonald et al., 1986). A significant effect of exposure to PCE during the first 20 weeks of pregnancy was reported in a study of spontaneous abortion in women exposed to PCE and other solvents in California (OR 4.7, 95 percent CI 1.1-21.1) (Windham et al., 1991). However, the results are based upon only seven cases with PCE exposure, four of which were also exposed to trichloroethylene. A recent retrospective study reported reproductive outcomes in 7305 women with employment history that included dry-cleaning or laundry in the

UK (Doyle et al., 1997). An odds ratio for spontaneous abortion of 1.67 (95 percent CI 1.17-2.36), adjusted for age, previous pregnancies and year, was observed for women who worked as dry-cleaner operators versus those who did not report any work in dry-cleaning or laundry during pregnancy or the three months preceding.

Spontaneous abortion has also been studied with paternal exposure as the descriptor of interest. A case control study nested in a cohort of male workers biomonitoring for solvent exposure in Finland did not find an association between PCE exposure in men and spontaneous abortion in their wives (Taskinen et al., 1989).

Several of the above-cited studies have also assessed the rates of stillbirth, congenital malformation, and low birth weight in children born to women with potential exposure to PCE. No significant associations have been observed. Thus there is evidence from several studies that employment in occupations that potentially involve PCE exposure can have adverse effects on pregnancy; the most marked effect reported to date is increased spontaneous abortion. It is likely that these effects are most pronounced when exposure coincides with the early stages of pregnancy; only one study focussed on exposure during this period. Fertility may also be impacted in exposed men and women, although the available data are quite limited.

Genetic Toxicity

The genetic toxicity of PCE exposure in humans has not been adequately evaluated. A small study of factory workers exposed to high (92 ppm PCE [geometric mean]) or low (10-40 ppm) found no evidence of cytogenetic damage to lymphocytes or altered cell cycle kinetics (Ikeda et al., 1980). Air concentrations of PCE were also reflected in trichloro-compound content from urinalysis. No differences between either group and concurrent controls were observed with respect to lymphocyte damage. No increase in sister chromatid exchanges in lymphocytes was found in a study of 27 subjects exposed to PCE compared with control subjects matched by age, sex, smoking habits, and place of residence (Seiji et al., 1990).

Immunotoxicity

Groups of "exposed" (n=21) and "unexposed" (n=16) workers in a dry-cleaning plant were examined for differences in numerous immunological parameters (Andrýs et al., 1997). Both groups were also compared with long-term laboratory reference values. Exposure was measured at time-weighted average concentrations of 11-752 mg/m³. While immunological parameters of metabolic activity did not tend to fall outside the normal range for either group, the exposed group did have statistically significantly different levels for several metabolic activity parameters relative to the in-plant control group (phagocytes, α_2 -macroglobulin, C3 and C4 complement component, salivary secretory IgA, blast transformation test). Both plant groups also showed some departure from the long-term reference values (α_2 -macroglobulin, C3, percent lymphocytes).

Chronic Toxicity (Other Endpoints)

The neurotoxic and reproductive effects of PCE have been discussed above. Other effects of chronic exposure include indicators of renal and hepatic toxicity. The literature previous to 1997 was adequately summarized by ATSDR (1997).

As discussed in the section on animal toxicology, above, the kidney is a target organ for cancer and other toxic effects in rodents exposed to PCE. While effects were often weak, changes in at

least one renal-effect parameter were observed in six of eight studies of nephrotoxicity associated with PCE exposure (ATSDR, 1997). An additional study, recently published, reported a nearly two-fold increase in the mean urinary concentration of retino-binding protein in a group of exposed workers as compared to an unexposed group (Verplanke et al., 1999). No significant differences were seen in the concentration of albumin or the activities of alanine aminopeptidase, beta-galactosidase, or N-acetyl-glucosaminidase. Exposure was assessed by concentration of PCE in exhaled air and a work history that included hours spent in particular tasks. The exposed and control groups were similar in sex age, mass smoking, and alcohol intake. The geometric mean of daily exposure to PCE was estimated to be 1.2 ppm, with employment ranging from 0.1 to 32 years, lower exposure than that estimated in other studies of nephrotoxicity. This confirms that pre-clinical toxic effects on the kidney may occur at relatively low exposure to PCE.

Hepatic effects, as indicated by alterations in serum levels of liver enzymes, have been assessed in several studies of workers, with mostly negative results (ATSDR, 1997). One study used ultrasound analysis to assess morphological changes in liver of dry-cleaning workers (Brodkin et al., 1995). Significant differences in exposed and unexposed groups were found by ultrasound, yet no changes in blood clinical chemistry markers were noted. No new studies of chronic liver toxicity were located that have not been previously reviewed.

Carcinogenicity

There are a number of reviews of cancer epidemiology for humans exposed to PCE (ATSDR, 1997; IARC, 1995a,b; OEHHA, 1992; U.S. EPA, 1985). The epidemiological studies are primarily concerned with inhalation exposure in occupational settings, particularly in the dry-cleaning workers. A recent working group convened by the International Agency for Research on Cancer evaluated the carcinogenicity of PCE and of dry-cleaning occupations and concluded that the evidence for carcinogenicity is limited for both (IARC, 1995a, b). While the available studies of human carcinogenicity do not provide an adequate basis for quantitative analysis of PCE risk, the limited findings in humans lend support to the sufficient evidence of cancer in animals, resulting in an overall evaluation of PCE as a probable human carcinogen, group 2A (IARC, 1995b). Detailed reviews of available epidemiological studies can be found in the documents cited above; a brief summary of findings follows. References to work published since the IARC document was prepared are included in the findings below.

A number of occupational cohort studies have examined the potential relationship between inhalation exposure to PCE and various cancer types. The most significant tumor endpoints that have emerged from the epidemiological studies are esophageal, lymphohematopoietic, and female genital cancers. Cancer of the bladder, liver, kidney, lung, and breast have also been associated with PCE exposure in at least one study. The majority of occupational studies with relevance to PCE exposure concern the dry-cleaning industry in the U.S. (most recent updates in Blair et al., 1990 and Ruder et al., 1994) or laundry and dry-cleaning occupations in Nordic countries (Lyng and Thygesen, 1990). A cohort of chemical industry workers (Olsen et al., 1989), air force base employees (Spirtas et al., 1991) and a study of Finnish workers in a variety of occupations have also provided important information (Anttila et al., 1995). This report emphasizes the results of cohort studies, but results of descriptive mortality and case-control studies are included where pertinent. Interpretation of the majority of the epidemiology studies of PCE is hampered by concomitant exposure to other solvents in the studied industries, limited treatment of risks of smoking and alcohol intake, and/or poor definition of occupational history in death certificate-based studies. Other issues with these studies include low exposure levels (e.g. Anttila et al.,

1995) making detection of an effect unlikely, and numbers of exposed cases too low for quantitative assessment.

A statistically significant excess of mortality from cancer of the esophagus (SMR 2.1) was observed in two U.S. cohorts of dry-cleaning workers (Blair et al., 1990; Ruder et al., 1994). In the Blair study, significant excess was found only in black men. Ruder and colleagues defined a sub-cohort for whom PCE was the primary solvent exposure; in this group an SMR of 2.6 for esophageal cancer was observed, but the excess was not statistically significant. Three other cohort studies of PCE-exposed workers did not provide data on esophageal cancer. One population-based study of esophageal cancer cases did not identify any cases with history of employment in laundry or dry-cleaning; however, only 99 cases were examined (Siemiatycki, 1991, as cited by IARC, 1995). Another population-based case control study of esophageal cancer reported an elevated, non-significant odds ratio (3.6; 95 percent CI: 0.5-27.0) for ever having worked in dry cleaning (Vaughan et al., 1997). Excesses of esophageal cancer have been identified in two mortality studies that included dry cleaners (Walker et al., 1997; Office of Population Censuses and Surveys, 1986, as cited by IARC, 1995a). One of these, a recent mortality study based on the NIOSH national occupational mortality surveillance database, found a statistically-significant excess of esophageal cancer in black men aged 15-65 employed in laundry or dry-cleaning (Walker et al., 1997). Non-significant excesses were observed in other race/sex categories. The inclusion of laundry workers, presumably without PCE exposure, in the study would be expected to reduce the likelihood of observing an association. This study was not yet available when IARC reviewed the evidence for PCE carcinogenicity. While the association between occupational exposure to PCE and esophageal cancer has been perhaps the most consistent cancer finding, potential confounding by combined smoking and alcohol consumption, a risk factor for this cancer, has not been fully accounted for (Weiss, 1995). Further, there is not yet an explanation for the greater susceptibility in black men suggested in two studies.

No consistent pattern has been observed for the association of PCE with lymphohematopoietic cancers in humans, but several reports have noted increased risks. This class of cancers is of particular interest in light of the increased leukemia rate in rats exposed to PCE. Olsen and colleagues (1989) reported an elevated SMR for leukemia/aleukemia in a cohort of chemical workers; the SMR was statistically significant when local cancer rates were used for comparison. However, there were only 11 total cancer deaths in the cohort of 2610 subjects, and exposure was not limited to PCE. A drinking water study also reported increased relative risk of leukemia in the group with the highest exposure to PCE (90th percentile of exposure); however the result was based on only two cases (Aschengrau et al., 1993). Elevated risks of non-Hodgkin's lymphoma (NHL) have been reported in three cohort studies (Blair et al., 1990; Anttila et al., 1995; Spirtas et al., 1991). In contrast, a case control study and a recent mortality study did not find any association between PCE and NHL (Siemiatycki et al., 1991; Walker et al., 1997). A second case-control study of NHL found an increased OR of 2.0 for employment in laundry or dry cleaning, after adjustment for smoking, although the association was not statistically significant. The New Jersey Department of Health conducted a study of 18 organic chemicals in drinking water in 75 towns (Cohn et al., 1994). Incidence rates of high-grade lymphoma were elevated in females from the towns with the highest concentrations of PCE in drinking water. After stratifying towns into 0, 0.1-5.0 and >5.0 ppb exposure levels, the relative risk of high-grade NHL was significantly higher in the highest exposure stratum compared to controls. However, PCE levels in drinking water were also highly correlated with trichloroethylene levels, so whether the lymphoma risk was due to PCE is not clear.

Three cohort studies have indicated that occupational exposure to PCE may be associated with cervical or other female genital cancers (Blair et al., 1990; Anttila et al., 1995; Ruder et al., 1994). However, in an earlier study of mortality in female laundry and dry-cleaning workers (which

solvents were used was not known), the increased risk of cervical cancer observed in the first analysis was no longer apparent when workers in other low-wage jobs were used as a reference group (Katz and Jowett, 1981). This has raised the question of whether significant confounding by socio-economic status could have occurred in the analysis of the cohort studies.

Both of the major U.S. dry cleaner cohorts (Ruder et al, 1994; Blair et al., 1990) reported an increased risk of bladder cancer. One study defined a subcohort of workers whose exposures were primarily to PCE; the bladder cancer risk was not elevated in the subcohort. Two Nordic laundry/dry-cleaning cohorts did not experience excess bladder cancer (Lynge and Thygesen, 1990; Malzer and Weiner, 1984). Two proportionate mortality studies of laundry and dry cleaning workers reported some increases in bladder cancer risk (Katz and Jowett, 1981; Office of Population Censuses and Surveys, 1986, as cited by IARC, 1995a), as did a study of a population in Massachusetts exposed via drinking water (Aschengrau et al., 1993). A significant increased risk of bladder cancer was reported in non-whites employed 6 months or longer in dry-cleaning (Silverman et al., 1989). A recent occupational surveillance study in Canada concluded that the elevated odds ratio for bladder cancer observed in laundry/dry-cleaning workers (after adjustment for smoking, coffee drinking, and other possible risk factors) merited further surveillance follow-up (Teschke et al., 1997). Whether smoking and/or exposure to other solvents could play a key role in bladder cancer observed in these studies is not clear (Weiss, 1995). IARC concluded that the risk for cancer of the bladder “may be increased by employment in dry-cleaning”, but also that “little or no information was available” about the specific relation to PCE from the majority of bladder cancer studies (IARC, 1995b).

Liver and kidney have been identified as target tissues for tumor formation in studies of animals exposed to PCE. However, these sites have not been consistently reported in epidemiological studies. Among 8567 female laundry and dry-cleaning workers identified from an occupational cancer registry, liver cancer incidence was significantly higher than the comparison population (standardized incidence ratio 3.4, 95 percent CI 1.4-7.0) (Lynge and Thygesen, 1990). An update of the study, with ten additional cases, reported an SIR of 2.7 (95 percent CI 1.5-4.5) (Lynge, 1994). However, a nested case control study indicated that the excess risk occurred in laundry, not dry-cleaning workers (Lynge et al., 1995). Kidney cancer was elevated in some studies of dry-cleaning workers, but the findings were not consistent across studies. A recent review of the evidence for renal cell cancer, in which the results of at least 13 studies were considered, concluded that there is “little evidence of an increased risk of renal-cell cancer” with exposure to PCE (McLaughlin and Blot, 1997).

A recent article has found an association between PCE exposure and lung cancer among individuals residentially exposed to high cumulative levels of PCE-contaminated drinking water. Paulu et al. (1999) reported moderately elevated adjusted odds ratios (3.7, 3.3, 6.2, and 19.3) for lung cancer among those individuals whose exposure level was above the 90th percentile without a latent period or with 5, 7, and 9 years of latency, respectively. The controlled variables for this analysis included age of diagnosis or index year, vital status at interview, sex, occupational exposure to PCE, benzene, and other solvents, usual number of cigarettes smoked, history of cigar or pipe use, living with a smoker, and occupational history associated with lung cancer.

Most studies that assessed breast cancer reported no effects or reduced risks in women with occupational exposure to PCE. Aschengrau and colleagues recently reported preliminary results of a breast cancer case-control study in women exposed to PCE in drinking water (Aschengrau et al., 1998). While there was no overall association between PCE exposure and breast cancer, significantly elevated odds ratios were observed for the most highly exposed women when seven or nine years latency was assumed. A larger study is underway. A recent survey of mortality based on NIOSH records identified elevated risks of breast cancer in men formerly employed in laundry/dry-cleaning work (Walker et al., 1997). The risks were based on only two cases in black

men and four in white men, but these are very rare cancers and the proportional mortality ratios were statistically significant.

In conclusion, epidemiological studies provide evidence that PCE is possibly carcinogenic in humans. Especially important tumor sites are the esophagus and lymphatic system, but available data are quite limited in terms of the ability to quantify these cancer risks. This is particularly the case for risks associated with oral exposure to PCE, since the majority of the human data, and the most quantitatively informative studies, concern occupational exposure by the inhalation route. Most of the evidence for human carcinogenicity is based on solvent exposures in the dry-cleaning industry, of which PCE is a major but not exclusive component. Studies of solvent exposures in other industries also implicate PCE as a possible risk factor for human cancer, but typically involve exposure to multiple solvents and other potentially carcinogenic agents.

The epidemiological studies performed have relatively low power to detect an effect, and uncertain dose quantitation in most cases. Because of this, both the potential of PCE to induce human cancers, as well as quantitative estimates of the human risk associated with particular levels of exposure, must be inferred from animal data. In Appendix 1 of this report, the predictions made using the animal data are compared to the observations in some of the more quantitatively reliable epidemiology studies. In general, the upper bound predictions of excess human cancers due to PCE exposure do not exceed the increased cancer incidences observed to be associated with PCE exposure in the studies. However, any such conclusions must be regarded as tentative in view of the difficulties in interpreting the human data.

DOSE-RESPONSE ASSESSMENT

Non-Cancer Effects

Studies of non-cancer toxicity in humans associated with chronic exposure to PCE derive primarily from the occupational health literature, and involve the inhalation exposure route. No studies addressing chronic effects of ingested PCE in humans were identified. Several studies in workers exposed by inhalation have identified neurotoxic effects associated with relatively low chronic exposures in humans (see Neurotoxicity section); these appear to be the most sensitive endpoints for chronic non-cancer toxicity in humans. One study of renal toxicity indicators found significant effects in a group of workers calculated exposure levels in the low ppm range (Verplanke et al., 1999). This study is more difficult to use for risk assessment, however, because the exposure estimates were calculated based on pre-shift exhaled air concentrations of PCE; no measurements of workplace air were available for validation of the computed exposure levels.

Three recent studies have reported statistically significant increased reaction times in neurobehavioral tests in people with PCE exposure compared to control subjects (Altmann et al., 1995; Ferroni et al., 1992; Spinatonda et al., 1997). None of these studies identify a no-observed-adverse-effect-level (NOAEL) for chronic neurotoxicity in humans.

An alternative endpoint for non-cancer risk assessment is reduction in color vision, which has been investigated in two groups of exposed workers, and followed up in one of these (see neurotoxicity section, above). An advantage of using the color vision data is that one study reported results for two subgroups with different exposure levels, thus providing some dose-response information (Cavalleri et al., 1994). A statistically significant effect was seen in the higher exposure group (mean 7.3 ppm, SD 8.2) and not in the 16 workers exposed to the lower concentration (mean 4.8 ppm, SD 3.5), thus suggesting a possible NOAEL. However, the number of subjects is too low to clearly define a NOAEL. Also, the exposure ranges of the group

with no effect and the group with a significant effect overlap, making the difference in results between the groups somewhat less convincing. In addition, the effect of PCE on color vision has not been confirmed in other studies.

Therefore, the selected endpoint of concern for determining a health protective drinking water level for non-cancer toxicity is delayed reaction time. The average daily dose associated with the exposure level and duration in each of the three studies cited above is estimated below. These doses provide estimates of the human LOAEL in each study. Since PCE itself is considered to be the relevant compound for neurotoxicity, metabolic models are not needed and the dose calculations are based on PCE concentrations. Exposures reported in ppm are converted to mg/m^3 (see Table 2 for conversion factor). Default breathing rates of $20 \text{ m}^3/\text{day}$ and $10 \text{ m}^3/\text{workshift}$ are assumed, and an inhalation absorption factor of 0.7 is used below to account for incomplete uptake of PCE by this route. Body weights are assumed to be 60 kg for females and 70 for males, and working time to be 5 days per week (non-working periods, e.g. vacations, are unspecified, but are assumed not to affect the critical dose rate for development of chronic toxicity).

Altmann et al. 1995:

Fourteen subjects with environmental exposure to PCE (median indoor air concentration $1.36 \text{ mg}/\text{m}^3$; average duration 10.6 yr.) had decreases in measures of simple reaction time, vigilance and visual memory for shapes compared to 23 age and gender matched controls.

$$1.36 \text{ mg}/\text{m}^3 \times 20 \text{ m}^3/\text{d} \times 0.7 = 19 \text{ mg}/\text{d}$$

$$\text{Using } 65 \text{ kg body weight for mixed gender study subjects} = 0.29 \text{ mg}/\text{kg}\text{-d}$$

Spinatonda et al, 1997:

Vocal reaction time (to visual stimuli) was increased in 35 workers with median exposure to $53.9 \text{ mg}/\text{m}^3$ PCE in comparison to 39 controls matched for age and education.

$$53.9 \text{ mg}/\text{m}^3 \times 10 \text{ m}^3/\text{d} \times 5/7 \times 0.7 = 270 \text{ mg}/\text{d}$$

$$\text{Gender not specified, assume } 65 \text{ kg average body weight} = 4.15 \text{ mg}/\text{kg}\text{-d}$$

Ferroni et al, 1992:

60 female dry-cleaning workers with median exposure to 15ppm PCE for an average duration of 10.1 years had significant differences in simple reaction time, vigilance, and finger tapping compared to 30 controls comparable in age, gender, and vocabulary test scores.

$$15 \text{ ppm} \times 6.78 \text{ mg}/\text{m}^3 \times 10 \text{ m}^3/\text{d} \times 5/7 \times 0.7 = 509 \text{ mg}/\text{d}$$

$$\text{Using average body weight of } 60 \text{ kg} = 8.48 \text{ mg}/\text{kg}\text{-d}$$

It appears that no single study is sufficiently reliable to be used as the primary basis for a health protective standard for chronic non-cancer effects. The Altmann et al. (1995) study was based on an environmentally rather than occupationally exposed population, and appears to define the lowest lowest-observed-adverse-effect-level (LOAEL). It might therefore be selected as the most health protective basis for risk assessment. However, the results are based on only 14 exposed subjects. The study by Spinatonda et al. (1997) is somewhat larger (35 subjects), although this is still quite small, and the population studied was occupationally exposed, which may be less

predictive of the general population due to the “healthy worker” effect. The sample size in the Ferroni et al. (1992) occupational study is larger, however the reporting of the study results is rather sparse on details. To account for the different strengths and weaknesses of the three studies, a geometric mean of the estimates of a human health protective concentration (after application of uncertainty factors appropriate to each study) will be used below in the risk assessment calculations.

Carcinogenic Effects

Selection of Data for Estimation of PCE Carcinogenic Potency

The bioassay used as the basis of an oral potency estimate for this report is the National Cancer Institute (NCI) study of mice exposed to PCE by gavage (NCI, 1977). The EPA used this gavage study as the basis of a carcinogenic potency assessment in 1985 (U.S. EPA, 1985), and used studies of mice and rats exposed to PCE by inhalation by National Toxicology Program (NTP, 1986) to update this assessment in 1986 (U.S. EPA, 1986). Both the NCI and NTP studies were used in the risk assessment prepared for the California Air Resources Board (OEHHA, 1992). In each of the reported bioassays PCE caused a significantly increased tumor incidence. Since human epidemiological data suitable for dose-response assessment are not available, these two bioassay data sets represent the only long-term animal exposure studies with well-defined, exposure-response data that indicate a positive carcinogenic response for PCE in animals. The current objective of calculating a public health goal for drinking water exposure to PCE is best addressed by using the gavage study. Since the human exposure is also by the oral route, the uncertainties of route-to route extrapolation are thus avoided. However, the findings of the more recent NTP inhalation study provide important supporting data. Because of this, the analysis of the inhalation study as performed by OEHHA (1992) is included for comparison.

In the mouse gavage study (NCI, 1977), incidence of hepatocellular carcinomas increased with dose for both males and females. Table 7 gives the tumor incidence data (see U.S. EPA, 1985a). In contrast to the overall tumor incidence data given earlier (in the description of the animal carcinogenicity studies), the incidence of tumors in Table 7 is reported as that in animals which survived at least until the appearance of the first carcinoma in each study. This appeared at week 24 for female mice and at week 41 for male mice in the NCI study. The mortality-adjusted incidence data are used here in preference to unadjusted incidence data to partially correct for the influence of competing mortality risks.

Also shown in Table 7 are tumor incidence data from the inhalation studies (NTP, 1986) in the rat and mouse. Mononuclear-cell leukemia was the only tumor type observed to be significantly increased in rats at either the low or high dose levels. Again, in order to partially correct for competing mortality, the incidence values appearing in the table refer to animals surviving at least until the appearance of the first mononuclear-cell leukemia, at week 53 for males and at week 60 for females.

The tumor types observed to be significantly increased in the mice exposed by inhalation are hepatocellular carcinoma and hepatocellular adenoma. Since these two tumor types are of the same cellular origin, it is conventional to combine them for purposes of potency estimation. The incidence rates (carcinoma only, and adenoma or carcinoma) in the table are reported for animals surviving at least until the appearance of the first hepatocellular carcinoma, which was at week 60 for males and week 67 for females.

Estimation of Carcinogenic Potency

Dose Adjustments

Adjustments to the experimental exposures are required to calculate the lifetime daily exposure levels. Thus, for inhalation exposures, the reported dose must be multiplied by:

- H/24: where H is the hours of exposure per day. This converts the exposure period to a time weighted average for 24 hours daily continuous exposure.
- D/7: where D is the number of days exposed per week. This converts the dosing schedule to a time weighted average for a continuous (7 days/week) exposure.
- L_e/L : where L_e is the length of the experimental exposure and L is the lifespan of the animal (the longer of L_e or 24 months). This converts the experimental protocol to a continuous lifetime exposure.

Respiration rate is observed to be proportional to body surface area (or, approximately, to body weight to the two-thirds power) (Guyton, 1947; Adolph, 1949; U.S. EPA, 1980; Anderson et al., 1983; Calabrese, 1983). Therefore, assuming 1 ppm PCE = 6.78 mg/m³, and standard values (Anderson et al., 1983) for mouse and rat respired volume per day at the “average” body weights for the experimental animals (see Table 7) :

Total respired dose (averaged over time):

$$\text{(for mice)} = \text{Applied dose} \times (6/24) \times (5/7) \times 0.0345 \times (\text{body weight of mouse}/0.025)^{2/3} \times 6.78 / \text{body weight}$$

$$\text{(for rats)} = \text{Applied dose} \times (6/24) \times (5/7) \times 0.105 \times (\text{body weight of rat}/0.113)^{2/3} \times 6.78/\text{body weight}$$

In the NCI study, PCE in corn oil was administered by gastric intubation to male and female B6C3F₁ mice for 5 days/week for 78-weeks, beginning at about 5 weeks of age, followed by 12 additional weeks of pre-sacrifice observation (NCI, 1977). In the NTP inhalation rat study, groups of fifty 8- to 9-week-old male and female F344/N rats were exposed to PCE by inhalation at 0, 200, or 400 ppm for 6 hours/day, 5 days/week over 2 years (NTP, 1986). In the NTP inhalation mouse study, groups of fifty 8- to 9-week-old male and female B6C3F₁ mice were exposed to PCE by inhalation at 0, 100, or 200 ppm for 6 hours/day, 5 days/week over 2 years (NTP, 1986). Table 7 shows the average administered daily doses (in units of mg/kg), for the male and female vehicle control, low- and high-dose groups in the NCI oral study, and the exposure concentrations in the mouse and rat inhalation studies, alongside the tumor incidences data for each group. The dose corrections noted above were used to convert the experimental dose values to time-weighted average doses for the oral study, and total respired doses (averaged over time) for the inhalation studies.

Table 7: Dose-Response Data For Selected Cancer Bioassays of PCE

Study, species (strain)	Sex and weight	Administered dose or conc.	TWA Applied dose (mg/kg-d)	Tumor Type	Tumor Incidence ^a
NCI, 1977	Male	0 (mg/kg-d)	0	hepatocellular	2/20

Mice (B6C3F ₁)	0.030	536 ^b	215.0 ^d	carcinoma	32/48
		1072 ^b	430.1 ^d		27/45
	Female	0	0	hepatocellular	0/20
	0.025	386 ^b	154.9 ^d	carcinoma	19/48
		772 ^b	309.7 ^d		19/45
NTP, 1986	Male	0 (ppm)	0	hepatocellular	7/49
Mice (B6C3F ₁)	0.037	100 ^c	146.6 ^e	carcinoma	25/47
		200 ^c	293.2 ^e		26/50
	Female	0	0	hepatocellular	1/44
	0.032	100 ^c	153.9 ^e	carcinoma	13/42
		200 ^c	307.8 ^e		36/47
	Male	0	0	hepatocellular	16/49
	0.037	100 ^c	146.6 ^e	adenoma or carcinoma	31/47
		200 ^c	293.2 ^e		40/50
	Female	0	0	hepatocellular	4/44
	0.032	100 ^c	153.9 ^e	adenoma or carcinoma	17/42
		200 ^c	307.8 ^e		38/47
NTP, 1986	Male	0	0	mononuclear-	28/50
Rats (F344/N)	0.44	200 ^c	143.0 ^e	cell leukemia	37/48
		400 ^c	286.0 ^e		37/50
	Female	0	0	mononuclear-	18/49
	0.32	200 ^c	159.0 ^e	cell leukemia	30/50
		400 ^c	318.1 ^e		29/50

^aTumor-incidence denominator excludes animals dying before the first corresponding tumor type observed in each study.

^bAverage daily gavage dose in mg/kg-d, for a 5 d/wk exposure over 78 wk of a 90-wk bioassay.

^cAverage administered inhalation exposure in ppm 6 h/d, 5 d/wk over 2-years.

^dTime-weighted average (TWA) dose (following Anderson et al., 1983).

^eTotal respired dose averaged over time (following Anderson et al., 1983).

Selection of pharmacokinetic models

Pharmacokinetic analyses have been used to estimate the “effective” dose for use in risk assessment calculations. In the case of PCE, the relevant quantity is considered to be the amount of PCE metabolized. Ideally, a pharmacokinetic model could be used to extrapolate dose measures to low-level exposures of humans. Although some more recent publications have expressed disagreements or uncertainties over the pharmacokinetic modeling of human exposures, the calculation of effective dose in the animal studies has not been seriously challenged. In the earlier section on metabolism and pharmacokinetics, available models for use in determining effective dose in the two bioassay studies were discussed. Dose estimates resulting from three different approaches (Bogen et al., 1987; Bois et al., 1990; Chen and Blancato, 1987) were compared; all three are in reasonably good agreement. The methodology of Bogen et al. (1987) was retained, since this is the only model that provided dose estimates for mice and rats exposed by both inhalation and orally. The calculations were repeated to separate out the adjustments for dose frequency, dose duration and study duration, which are dealt with separately by the program used for potency calculations.

Selection of extrapolation model

According to the proposed guidelines for carcinogen risk assessment (U.S. EPA, 1996), the type of extrapolation employed for a given chemical depends on the existence of data supporting linearity or non-linearity, or a biologically-based or case-specific model. When data are not sufficient to construct a case-specific model, and are not inconsistent with linearity, the default is to use a linear extrapolation. In the case of PCE, although there are significant uncertainties as to the actual mode of action, several lines of evidence suggest that a linear low-dose extrapolation assumption is reasonable. Although only limited genotoxicity has been reported for pure PCE, this may be because of the well-known difficulties in testing highly volatile materials, and the failure to include appropriate metabolic systems in many experiments. At least two classes of identified metabolites (tetrachloroethylene epoxide, and the halothioketenes produced by β -lyase action on the mercapturic acids) are considered to have mutagenic activity. On the other hand, metabolites such as trichloroacetic acid are known rodent carcinogens, which are often argued to operate by a mechanism other than direct genotoxicity via covalent modification of DNA. Various indirect mechanisms involving cytotoxicity or modulation of genetic control systems are also argued as important in carcinogenesis by halocarbons, especially when the target tissue is mouse liver. However, these counter-proposals are hypothetical, and attempts to identify positively what an alternative mechanism might be have been unsuccessful. On balance therefore, it is assumed for the purposes of risk assessment that PCE is acting as a directly genotoxic carcinogen. In this case a linear low-dose extrapolation model is appropriate, and a constrained polynomial (“multistage”) model is suitable when fitting tumor incidence data in the observed range.

Earlier guidelines for cancer risk assessment, including those formerly used by OEHHA (DHS, 1985) have required the use of the linearized multistage (LMS) model to estimate an upper bound on the low-dose potency (q_1^*). This was used, for example, in the previous PCE risk assessment prepared by California (OEHHA, 1992). However, more recent OEHHA methodologies, and the proposed U.S. EPA (1996) guidelines for carcinogen risk assessment, recommend a linear extrapolation approach based on the 95 percent lower bound on the dose which produces a 10 percent tumor incidence (LED_{10}). A multistage polynomial is used to fit data in the observable range, unless some other dose-response curve is specifically indicated by available data. As noted above, for PCE this curve-fitting approach is appropriate.

Interspecies extrapolation

A numerical adjustment must be made to convert the q_1^* calculated from the animal data to a q_1^* relevant to humans. Cross-species scaling of carcinogen doses by the $3/4$ power of body weight is adopted as proposed by the U.S. EPA (1996), instead of the previous use of the $2/3$ power (OEHHA, 1994). Therefore, to convert the animal potency value to an estimated human potency, a scaling factor equal to the ratio of human to animal body weight is raised to the $1/4$ power is applied:

$$q_1^* (\text{human}) = q_1^* (\text{animal}) \times (\text{human body weight/animal body weight})^{1/4}$$

That is, for example, $(70 \text{ kg}/0.034 \text{ kg})^{1/4}$, or 6.74 for mice. The scaling factor is used to account for interspecies differences in dose rate and response rate. Thus, even if a pharmacokinetic model is used to account for dose differences between species, scaling may still be necessary to account for potential interspecies differences in sensitivity to the resulting internal doses.

For inhalation exposures, U.S. EPA has at times in the past assumed equivalence between different species for exposures to a given atmospheric concentration. This provides roughly

similar dose scaling in effect, due to the way that breathing rate and related parameters affecting uptake scale with body weight. More recently, physiologically based pharmacokinetic modeling has been seen as a preferable approach to both dose estimation and inter-species scaling of inhalation exposures, where data are available to support this.

The potency calculations selected for use in setting a Public Health Goal, below, are based on a dose metric defined as the fraction of PCE metabolized in the bioassay animals. Scaling by the 3/4 power of body weight method discussed above is used to convert the risk estimates from animal to human. The resulting oral and inhalation potencies in Tables 10-12 are expressed in units of (mg PCE metabolized/kg-d)⁻¹. For those potencies, application to human risk estimation requires conversion of the fraction metabolized back to external exposure units for humans. This latter computation is subsumed in the computations of exposure factors, as explained below, but has the same effect on the PHG as correcting the q₁* values.

Potency estimates

In all cases the Tox_Risk (v. 3.1, KS Crump Division, Clement International Corp., Ruston, LA) program was used to fit the multistage model to the quantal data sets. The q₁* cancer potencies or the 95 percent upper bound on the linear slope at low dose (LMS) were calculated directly by the program. Carcinogen slope factors (CSFs) are based on the LED₁₀ (the 95 percent lower bound on the dose that is predicted to give a 10 percent tumor incidence). The carcinogen slope factor (CSF) is 0.1/LED₁₀, in units of (mg/kg/day)⁻¹. For the curve fitting to estimate the LED₁₀, we have employed a p ≥ 0.05 criterion for the χ² goodness of fit statistic of the optimized polynomial.

Quantal analysis with applied dose metric

In Table 8 are summarized the cancer potency values derived by both the LED₁₀ method (and the LMS model, for comparison with earlier results) from the data sets in the NCI (1977) oral study, using the time-weighted average applied dose as the dose metric. The potency estimates for hepatocellular carcinoma in male and female mice are quite similar whether based on the q₁* or the CSF. However, the fit of the time-independent version of the polynomial model to the data is not good in either case. The χ² goodness of fit criterion is barely met in the case of the female mouse data, and failed for the male mouse data.

Table 8: PCE Mouse Oral Study - Administered Dose as Dose Metric

Study	Sex	Tumor site and type	q ₁ * (mg/kg-d) ⁻¹	LED ₁₀ mg/kg-d	CSF (mg/kg-d) ⁻¹
NCI, 1977	male	Hepatocellular Carcinoma	0.024	4.38	0.023
	female	Hepatocellular Carcinoma	0.022	4.86	0.021

The q₁* values quoted here differ significantly from earlier estimates (e.g. by OEHHA, 1992) due to different methodology, in particular the use of the ¾ rather than 2/3 power of body weight for interspecies scaling. When this difference is allowed for, the present calculations agree with the

values reported (as q_{mouse} values) by Bogen et al. (1987) and (OEHHA, 1992) for the female mice Table 9. For the male mice OEHHA (1992) followed Bogen et al. (1987) in ignoring the high dose group data in their calculation because of the poor fit.

Table 9: q_1^* Values in the NCI Oral Mouse Study of PCE

Methodology	$q_1^*_{\text{mouse}}$ (mg/kg-d) ⁻¹		Scaling index	$q_1^*_{\text{human}}$ (mg/kg-d) ⁻¹	
	Males	Females		Males	Females
This report	0.0035	0.0030	2/3	0.046	0.042
			3/4	0.024	0.022
Bogen et al. (1987)	0.0064	0.0030	2/3	0.085	0.042

Quantal analysis with metabolized dose metric

Use of the metabolized dose (determined as described in the section on pharmacokinetic models, and shown in Table 6) as the dose metric allows comparison of potencies derived from oral and inhalation studies. Accordingly, in Table 10 the cancer potency values derived by the LED₁₀ method and the LMS model using metabolized dose are shown for both the NCI (1977) oral study in mice, and the NTP (1986) inhalation study in mice and rats. As in the case of the applied dose analysis, the figures for q_1^* are in agreement with those reported by OEHHA (1992) after allowing for the use of a different interspecies scaling index, apart from the male mice in the NCI (1997) gavage experiment. In addition, the differences between the LMS model results and the CSFs derived from the LED₁₀ approach are not large. Note that the units are in mg-metabolized, and so they are not directly comparable to the potencies derived from the applied dose metric, above.

Table 10: Rat and Mouse Studies of PCE - Metabolized Dose as Dose Metric

Study	Species, Sex	Tumor site and type	q_1^* (mg-metab/ kg-d) ⁻¹	LED ₁₀ mg-metab/ kg-d	CSF (mg-metab/ kg-d) ⁻¹
NCI, 1977 (oral)	Mouse, male	Hepatocellular Carcinoma	0.22	0.48	0.21
	Mouse, female	Hepatocellular Carcinoma	0.16	0.65	0.15
NTP, 1986 (inhalation)	Mouse, male	Hepatocellular Adenoma or Carcinoma	0.16	0.66	0.15
	Mouse, female	Hepatocellular Adenoma or Carcinoma	0.071	1.32	0.076
NTP, 1986 (inhalation)	Rat, male	Mononuclear Cell Leukemia	0.23	0.46	0.22
	Rat, female	Mononuclear Cell Leukemia	0.15	0.69	0.15

Time-to Tumor analysis

The impact of mortality in the bioassays is significant, especially in the NCI (1977) oral mouse study. The use of the pharmacokinetic correction in the quantal analysis reported above results in an improved fit of the model to the data points, within acceptable limits for both sexes. However, the fit is still not good. Evidently, the approximate correction for mortality based on time to first appearance of the tumor is insufficiently accurate in this case. Interpretation of this study is further complicated by the fact that the dose given to both high and low dose groups was increased after 11 weeks. Both the mortality and the variation in dose rate are accommodated by a time-to-tumor model, so this analysis was used for all data sets. The time-to-tumor analysis had been previously used, and preferred, by OEHHA (1992) for the NTP (1986) study. However the individual animal data are not provided in the publicly available technical report of the oral study (NCI, 1977). These latter data were obtained specially for this analysis (Dr. L. Gold, personal communication to Dr. A.G. Salmon, 1998).

In order to determine the metabolized dose at different stages of the experiment, the pharmacokinetic model developed by Bogen et al. (1987) was applied to the dose rates for the individual experiment segments as shown in Table 11.

Table 11: Metabolized Dose in Individual Segments of the NCI (1977) PCE Bioassay

	Applied dose (mg/kg-d)	Metabolized Dose (mg-metab/kg-d)	Corrected for 5 d/week
Males: Low dose			
Weeks 1-11 (11 weeks)	450	68.92	49.23
Weeks 12-78 (67 weeks)	550	77.27	55.19
Males: High dose			
Weeks 1-11 (11 weeks)	900	98.08	70.05
Weeks 12-78 (67 weeks)	1100	106.25	75.89
Females: Low dose			
Weeks 1-11 (11 weeks)	300	53.13	37.95
Weeks 12-78 (67 weeks)	400	64.15	45.82
Females: High dose			
Weeks 1-11 (11 weeks)	600	80.95	57.82
Weeks 12-78 (67 weeks)	800	93.15	66.54

The calculations were made using the model and source data described earlier. These dose rates and the individual tumor and mortality data were fit to the multistage in dose, Weibull in time model provided by Tox_Risk v. 3.5. This program is designed to provide an estimate of q_1^* according to the previously standard linearized multistage dose extrapolation model. It was also used to provide an estimate of the end-of-life LED_{10} at 104 weeks, a value comparable to the LED_{10} estimate obtained with the quantal polynomial model after adjustment for non-standard experimental durations. Results of these calculations are shown in Table 12. Again, the resulting dose and risk figures are based on mg-metabolized.

Tox_Risk does not report quality of fit measures for this model comparable to the χ^2 goodness of fit criterion reported for the quantal models. However, the fit of the time dependent models to the data appears to be adequate by inspection of the graphical output and other informal criteria. Potency values reported here for the NTP inhalation studies in rats and mice are similar to those reported by OEHHA (1992), allowing for the incorporation of the $3/4$ power of bodyweight factor for interspecies scaling¹. Use of the time-to-tumor model, the explicit inclusion of the varied dose rates, and the pharmacokinetic model result in potency estimates between two and five times higher than the quantal analyses of the same data sets. This reflects the better allowance for the substantial intercurrent mortality in this study when using the time-dependent model. The fits to

¹ However, it should be noted that Bogen et al. (1987) used the Weibull 82 program for their time-dependent calculations [which were the source of the numbers reported by OEHHA (1992)]. There are differences in methodology between this earlier program and Tox_Risk v 3.5. The earlier authors do not report time-dependent calculations for the NCI oral study. The program used by Bogen et al. does not allow for the simultaneous application of a multistage time-to tumor model and allowance for varying dose rates during the study. However this option is available with the more recent software (and the more powerful hardware now used to run it).

the data also appear to be more satisfactory. Because of these considerations, the full time-dependent analysis used here is the preferred approach for obtaining a potency estimate from the NCI (1977) oral data sets.

Table 12: Rat and Mouse Studies - Metabolized Dose of PCE, Time Dependent Model

Study	Species, Sex	Tumor site and type	q_1^* (mg-metab/ kg-d) ⁻¹	LED ₁₀ (mg-metab /kg-d)	CSF (mg-metab/ kg-d) ⁻¹
NCI, 1977 (oral)	Mouse, male	Hepatocellular Carcinoma	0.42	0.25	0.40
	Mouse, female	Hepatocellular Carcinoma	0.78	0.13	0.74
NTP, 1986 (inhalation)	Mouse, male	Hepatocellular Adenoma or Carcinoma	0.20	0.53	0.19
	Mouse, female	Hepatocellular Adenoma or Carcinoma	0.062	1.4	0.071
NTP, 1986 (inhalation)	Rat, male	Mononuclear Cell Leukemia	0.26	0.40	0.25
	Rat, female	Mononuclear Cell Leukemia	0.18	0.58	0.17

The estimates obtained using the time-dependent methodology and the metabolized dose metric are consistent within one order of magnitude, regardless of route or species. Apart from the low estimate obtained in the female mice in the NTP (1986) inhalation study, they are all consistent within a factor of five. In view of the overall uncertainties involved in the estimation methodology, it is reasonable to regard all these estimates as consistent with one another.

Carcinogen risk assessment guidelines used by OEHHA normally recommend selection of human cancer potency estimates based on the most sensitive study, site, and species. This applies unless there is evidence to indicate that the most sensitive site(s) are not relevant to human cancer induction, or represent data sets with unusually wide error bounds. However, the selection of a potency value may take into account the appropriateness of the route of exposure in the various studies, and a geometric mean of several estimates may be chosen where several similar values are available. In this case, the values from the NCI oral (gavage) study are preferred both because of appropriateness of the route to a public health goal for drinking water, and by the most sensitive study/site/species criterion. The values for male and female mice are not regarded as significantly different, so the geometric mean of the two values may be chosen. The preferred value for the oral cancer potency is therefore a CSF of 0.54 (mg-metabolized/kg-d)⁻¹ for liver carcinomas in male and female mice in the gavage studies by NCI (1977).

The oral cancer potency is the result of primary interest from the standpoint of drinking water consumption. However, as described below, some inhalation and dermal exposure is expected to result from contamination of a public water supply with PCE. In addition to the estimate of oral carcinogenic potency, estimates based on inhalation studies were produced. Although these

estimates are not so different as to be clearly inconsistent with the oral estimate, it is appropriate to make use of this route-specific information, since it appears to be of at least as high quality as the estimate for the oral route. As in the oral case, the estimates calculated using the metabolized dose basis do not differ greatly (by a factor of 3.5 between the highest and lowest values). The geometric mean of these four values was chosen, giving a preferred value for the inhalation CSF of $0.15 \text{ (mg-metabolized/kg-d)}^{-1}$. This is based on liver carcinomas or adenomas in male and female mice, and mononuclear cell leukemia male and female rats, in the NTP inhalation studies.

There is no direct evidence as to the appropriate potency estimate to be used for dermal exposures. This route has been considered analogous to inhalation exposure in that the toxicant enters the general circulation directly, rather than via the portal circulation and the liver as for oral exposures. So by default the inhalation value will be used for this route also.

The oral and inhalation potency estimates are expressed as risk per mg of PCE metabolized/kg-d. To apply these potencies to human exposures, a conversion from metabolized dose back to external exposure is needed. As noted earlier in the section on Pharmacokinetics, the most recent and reliable estimates of the percentage of ingested and inhaled doses (and the associated inter-individual variability) that are metabolized by humans in low exposure conditions were derived by Bois et al. (1996, and in a personal communication from Dr. Bois). Based on that model, at low exposure levels such as could occur in ambient media (1 ppb in air or water), the predicted mean proportion of PCE metabolized was 54 percent (95 percent confidence limits 28 – 79 percent) for the oral route, and 36 percent (95 percent confidence limits 15–58 percent) for inhaled PCE. In order to protect sensitive sub-populations and individuals adequately, it is appropriate to use the 95 percent upper confidence limit of these values in determining the public health goal for PCE.

Conversion between metabolized dose and external doses is carried out by correcting the exposure factors, below, rather than correcting the CSF values. Both approaches result in the same adjustment of the PHG estimates.

CALCULATION OF PHG

Calculations of concentrations of chemical contaminants in drinking water associated with negligible risks for carcinogens or non-carcinogens 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 that may result in dermal and inhalation exposures.

Exposure Factors

Bogen et al. (1987) showed that significant inhalation and dermal absorption of PCE from tap water occurs during bathing and other periods of high domestic water use. The amount of PCE absorbed from water in this way is uncertain due to the variability of use patterns, and uncertainties in physical and biological models. The ratio of the amount inhaled to the amount ingested was estimated to range from one to six (Cothorn et al., 1984; Andelman, 1985; Foster and Chrostowski, 1986; McKone, 1987; Bogen et al., 1987). Data on dermal absorption are more limited, although it has been suggested that dermal exposure may contribute a dose up to that equivalent to drinking two liters per day of water or more (Brown et al., 1984). Various other sources, not related to the drinking water supply, may also contribute substantially to human environmental exposure to PCE, as noted in the earlier section on exposure.

The CalTOX exposure model² was used to examine the likely exposures to PCE from drinking water contamination by all routes, including inhalation and dermal absorption as well as ingestion. This uses a range of calculated, measured or assumed parameters to describe the movement of a contaminant between different environmental media, and a standardized series of exposure assumptions to estimate the exposure impact from these media. Data specific to PCE are included with the program in the “Datacal” module. For particular individuals, the physiological parameters such as body size and area, volume of water consumed as tap water, or other fluids, and volume of air inhaled per day are obviously highly variable depending on climate and level of exercise. Exposures as a result of bathing, showering and other indirect routes related to water contamination also may vary considerably, depending on building type, occupancy periods and behavior. CalTOX uses assumed values and distributions for these inputs, which are considered representative of average California residents, and provides uncertainty estimates on the results. In order to estimate relative route and media contributions for PCE the model was specified for “Average Residential Exposure in California.” Relative contributions from inhalation, dermal absorption and ingestion were unchanged for initial applied concentrations (to root and vadose zones) of 1 – 100 ppm PCE. These model inputs resulted in contamination levels of water and other media covering ranges considered typical of low-level environmental contamination. Volume of drinking water consumed was referred to the “standard” value of 2.0 L/day used in other PHG calculations, rather than to a model-specific consumption rate estimate. The resulting predictions of route-specific exposure, expressed in terms of liter equivalents per day, are shown in the second column of Table 13. Alternative physiological or behavioral parameters input to the model resulted in some variation in the result, but this remained broadly similar for most plausible inputs. Inputs of the body size, consumption and breathing parameters for a 70 kg male used by Bogen et al. (1987) resulted in a 6 percent lower contribution from inhalation, due mainly to the assumption of a lower breathing rate during exercise. However, this difference was not considered significant in view of the overall uncertainties in the result.

Table 13 also converts the exposure volumes to human dose of metabolites, using the fraction of PCE metabolized predicted by the pharmacokinetic model of Bois et al. (1996). A discussion of the pharmacokinetic model, the findings, and rationale for its use was presented in the earlier section of this document on pharmacokinetics. The fraction metabolized for PCE taken up by the dermal route was considered to follow the same kinetics as respired doses, since both are delivered to the systemic circulation and are not subject to first-pass effects in the liver. It is important to note that the metabolism of PCE in humans is not predicted to be linear with exposure. The conversion between exposure and metabolized dose used in Table 13 was developed for continuous exposure to 1 ppb by inhalation and intake of drinking water containing 1 µg/L. It should be noted that, because of the non-linear relationship between exposure and metabolism in humans (Bois et al, 1996), use of the same adjustment factors for high exposure scenarios would not be appropriate.

Table 13: Exposure to PCE in Water for an Average California Resident

Route of PCE Exposure from	Avg. Dose (mg/kg-d)	Exposure: Vol. Equiv.	Fraction Metabolized	Metabolized: Vol. equiv.	% of Total
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² CalTOX™ 2.3 (beta): Eight-Compartment Multimedia Exposure Model. Copyright (c) 1996 Regents of the University of California and California Department of Toxic Substances Control.

Water		(L/day)	(UCL)	(L/day)	Dose
INHALATION	1.27 x 10 ⁻⁶	3.54	0.58	2.05	50.0%
INGESTION:					
Water	7.16 x 10 ⁻⁷	2.00	0.79	1.58	38.5%
Produce, meat, etc.	2.48 x 10 ⁻⁸	0.07			
Total ingestion	7.41 x 10 ⁻⁷	2.07	0.79	1.64	40.0%
DERMAL UPTAKE	2.51 x 10 ⁻⁷	0.70	0.58	0.41	10.0%
DOSE SUM	2.26 x 10 ⁻⁶	6.31		4.1	100.0%

Bogen and colleagues (1987) calculated "best estimates" of 2.2, 2.8 and 2.2 liter equivalents (for the 70 kg 'reference' adult) associated with exposures by the oral, inhalation and dermal routes, respectively (before adjustment for percentages metabolized). Their estimate of the relative input by inhalation is similar to that generated by the CalTOX model, and the estimate of dermal uptake is higher by a factor of 3. This latter difference clearly represents a difference in assumptions either about the likely exposure scenario, or about the extent of dermal uptake of PCE. CalTOX includes a more extensive range of information about exposures to California residents than was available to Bogen et al. at the time of their assessment. It also may benefit from physical parameters and process models of dermal uptake which have been validated for a number of different organic solvents, particularly since (as noted previously) the data on dermal uptake of PCE are relatively sparse. The CalTOX results will therefore be used, yielding an equivalent uptake of 2.07 L/day orally and 4.24 L/day by dermal or inhalation routes. It should however be noted that there is a substantial range of both variability and uncertainty for these values, which should be taken into account in evaluating specific exposure situations. Where more specific, measured data are available it would be preferable to use them.

Noncarcinogenic Effects

The estimated daily doses at which three different studies identified delayed response time in neurobehavioral tests will form the basis of the calculation below. Because a NOAEL was not defined (only one exposure group was reported in these studies) an uncertainty factor is required in each case; a factor of 10 is appropriate for extrapolation to a presumed no-effect level for the cognitive and visual effects noted in study subjects. Exposure durations in all studies averaged eight years or greater, and therefore no uncertainty factor is applied below to correct for less than lifetime exposure. It should be noted that there may have been subjects with considerably less than the average exposure time, however. An additional uncertainty factor of ten is needed to account for the interindividual variability in the diverse California population, compared to the adult and relatively healthy workers in the occupational study cohorts. In the Altmann et al. (1995) study the exposed group was environmentally rather than occupationally exposed. Although this group may therefore be less selected than an occupational cohort, it is likely that due to its small size, and other selective influences in the study design, it still does not reflect the true diversity of the total California population. An uncertainty factor of 3 is therefore included in this case.

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

$$C = \frac{\text{LOAEL (mg/kg-d)} \times 70 \text{ kg} \times \text{RSC}}{\text{UF} \times \text{L/day}} = \text{mg/L}$$

where,

- LOAEL = lowest-observed-adverse-effect-level,
 RSC = relative source contribution (3 percent, based on data cited in Table 3 for urban areas with 0.5 µg/L PCE in drinking water),
 UF = uncertainty factors (10 to account for use of a LOAEL rather than NOAEL, and 10 or 3 for potentially sensitive human subpopulations, as described above),
 L/day = adult daily water consumption rate. (As described in the section on exposure factors, 6.31 L/d is the estimated intake by all routes of PCE present in tap water).

Using the LOAEL for each study, and substituting the values for the RSC, UF, and intake rate into the above equation, estimates of the concentration of PCE in drinking water protective against the chronic neurotoxic endpoints observed in the cited studies are derived:

Altmann et al. (1995):

$$C = \frac{0.29 \text{ mg/kg-d} \times 70 \text{ kg} \times 0.03}{30 \times 6.31 \text{ L/day}} = 3.22 \times 10^{-3} \text{ mg/L}$$

Spinatonda et al. (1997)

$$C = \frac{4.15 \text{ mg/kg-d} \times 70 \text{ kg} \times 0.03}{100 \times 6.31 \text{ L/day}} = 1.38 \times 10^{-2} \text{ mg/L}$$

Ferroni et al. (1992)

$$C = \frac{8.48 \text{ mg/kg-d} \times 70 \text{ kg} \times 0.03}{100 \times 6.31 \text{ L/day}} = 2.82 \times 10^{-2} \text{ mg/L}$$

The geometric mean of these estimates is 1.1×10^{-2} mg/L, or 11 ppb. The protective concentration derived below for cancer is significantly lower, and therefore the drinking water concentration proposed below to protect against carcinogenic effects is also protective against non-cancer chronic toxicity. A reference dose (RfD) of 0.01 mg/kg-d was previously established by the U.S. EPA (IRIS, 1988). The LOAELs reported here yield an estimated safe dose level, as the geometric mean of the three results, of 0.032 mg/kg-d, after application of the previously chosen uncertainty factors. This is higher than the U.S. EPA RfD, but OEHHA considers the human data to be preferable for risk assessment purposes. The RfD was based on a NOAEL for hepatotoxicity in mice exposed to PCE by oral gavage for only 6 weeks. While there is significant uncertainty concerning the actual exposure levels in the epidemiological studies, a NOAEL is not available, and inter-route extrapolation is required to use the human data, it is important to eliminate the additional uncertainty that comes from interspecies extrapolation.

Carcinogenic Effects

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

$$C = \frac{BW \times R}{\sum_{(\text{all routes})} (q_1^* \text{ or CSF} \times \text{L/day})} = \text{mg/L}$$

where,

BW = adult body weight (a default of 70 kg),

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

q_1^* or CSF = cancer slope factor, q_1^* is the upper 95 percent confidence limit on the cancer potency slope calculated by the LMS model, and CSF is a potency derived from the lower 95 percent confidence limit on the 10 percent tumor dose (LED_{10}). $CSF = 10 \text{ percent} / LED_{10}$. Both potency estimates are converted to human equivalent [in $(\text{mg-metab/kg-d})^{-1}$] using $BW^{3/4}$ scaling,

L/day = daily volume of water consumed by an adult. A default of 2 L/day is used for direct oral consumption, but this may be modified to allow for indirect oral exposures from drinking water and percentage metabolized. Other routes are represented by equivalent daily water consumption volumes, again corrected for the metabolized fraction, and appropriate CSF or q_1^* values.

The potency estimates for carcinogens are calculated by both methods because a substantial part of our current experience-base is with the LMS model. The new methodology, which is based on the LED_{10} and is similar to that proposed by U.S. EPA (1996) in its proposed guidelines for carcinogen risk assessment, has only been in regular use for the past three years. It may therefore present problems of interpretation, particularly when comparisons with earlier risk estimates are necessary. 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 percent lower bound (LED_{10}), the point from which the low dose extrapolation is made (U.S. EPA, 1996). In the specific case of PCE considered here the two methods show no major divergences in results, reinforcing the confidence in use of the LED_{10} methodology, which is considered generally preferable from a theoretical viewpoint.

For the carcinogenic endpoint and the linear approach based on the oral and inhalation CSFs of 0.54 and $0.15 (\text{mg/kg-d})^{-1}$ the water concentration equivalent to a negligible lifetime theoretical cancer risk of 10^{-6} can be calculated as follows:

$$C = \frac{1 \times 10^{-6} \times 70 \text{ kg}}{(0.54 \times 1.64 \text{ L/d}) + (0.15 \times 2.46 \text{ Leq/d})} = 5.6 \times 10^{-5} \text{ mg/L} = 0.06 \text{ ppb (rounded)}$$

where 1.64 L/d is the estimate of water and other oral ingestion (corrected for percentage metabolized), and 2.46 Leq/d is the estimate of inhalation and dermal exposure equivalents from showering, bathing, flushing toilets and other household activities using PCE contaminated water derived above, using CalTOX, and corrected for percent metabolized. The PHG is therefore 0.06 ppb, based on the induction of hepatocellular carcinoma in male and female mice exposed orally to PCE (and, for water-derived inhalation exposures, on the induction of hepatocellular adenoma or carcinoma in mice, and mononuclear cell leukemia in rats, exposed by inhalation to PCE).

RISK CHARACTERIZATION

PCE is used as a chemical intermediate, and as a solvent, primarily for cleaning operations (metal cleaning and vapor degreasing, dry-cleaning). Many household products contain some PCE. This results in opportunities for airborne exposures, particularly near the site of PCE-using industrial or dry-cleaning activities, and when handling recently-dry-cleaned clothing. Drinking water exposures may occur as a result of environmental releases of PCE from leaking storage tanks, from industrial wastes, and through spills on site or during transportation. The public health risks of exposure to PCE can be characterized as follows:

Acute and Chronic Health Effects

Typical exposures to PCE in drinking water are not expected to result in any acute health effects, due to the low levels involved. This includes household airborne exposures from showering, flushing toilets, etc. Various health complaints, including neurological changes, have been reported as a result of exposures to inhaled PCE in a domestic context. However, these involved exposures to higher levels than expected in a typical household situation. These levels resulted from, for example, proximity to commercial dry-cleaning operations, or improper handling and storage of recently dry-cleaned clothing or furnishings. Acute and chronic neurological changes, and liver and kidney toxicity, have also been reported in humans and animals exposed to PCE. However, the effective levels for these changes do not indicate that humans exposed to typical background levels in the general indoor or outdoor environment are at significant risk of experiencing such effects.

Carcinogenic Effects

Some studies have suggested a positive relationship between working in the dry-cleaning industry and cancer. Although interpretation of these results is complicated, due (among other issues) to concurrent exposures to other potentially carcinogenic agents, they are considered to provide limited evidence of a carcinogenic effect of PCE in humans. In animal studies, inhalation exposure to PCE produced increased incidences of mononuclear cell leukemia in male and female rats, kidney tumors in male rats, and liver tumors in mice. Oral administration of PCE produced liver tumors in mice. A summary of our evaluation is given below.

- OEHHA considers PCE to be an animal carcinogen and a possible human carcinogen.
- Three separate cancer bioassays (two in mice, one in rats) have shown PCE induced tumors at several sites, in two species, in both sexes, by oral and inhalation routes of exposure.
- A fourth bioassay (in rats, with oral exposure) was non-positive as a result of severe non-neoplastic toxic effects, and therefore neither confirms nor conflicts with the other data.
- Another small inhalation experiment in male rats was also non-positive, but due to the study design appears to have had limited power to detect any carcinogenic effect. Two other studies (one using intraperitoneal injection, and the other skin exposure) also found no dose-related tumors. However, due to the route differences and restriction of the sites examined (which did not include sites found positive in other studies) these also neither confirm nor conflict with the results of the positive studies.
- The cancer study results in mice show consistency, in that liver tumors were induced by PCE exposures via both oral and inhalation routes.

- The oral studies in male and female mice were considered adequate for risk assessment of drinking water exposures to PCE. This is despite the early mortality in the studies, which was accommodated by using time-to-tumor data and a time-dependent dose response model.
- The inhalation studies in rats and mice were also considered adequate for risk assessment of exposures by the inhalation route.
- There is some evidence of cancer in humans as a result of PCE exposures, but the equivocal nature of this evidence (especially its confounding by concurrent exposure to other potentially carcinogenic chemical exposures), and its unsuitability for quantitative risk assessment, are significant limitations. There is also uncertainty as to the relevance to human cancer causation of the tumors induced by PCE in rodents. However, the occurrence of tumors in animals at several sites adds considerably to the weight of evidence supporting the conclusion that PCE should be considered a possible human carcinogen.
- Site concordance between the various species in which positive or suggestive results have been obtained is not observed, but this is not necessarily expected except in cases where certain special site-specific mechanisms have been demonstrated.
- PCE genotoxicity data is mostly negative or equivocal. On the other hand, a minor metabolic pathway involving glutathione conjugation, leading to a highly mutagenic intermediate, has been identified. The standard mutagenicity assays usually fail to demonstrate this effect. It has been hypothesized that this route is important in the production of the kidney toxicity and tumors observed in rats. The significance of these observations for the observed carcinogenic effects of PCE at other sites, and in other species including humans, is unclear. It is possible, although unproven, that entirely different mechanisms, including non-genotoxic effects such as protein-deposition nephropathies, or interactions of PCE or its metabolites with growth-regulating receptors, may also contribute to the effects observed in the rat kidney.
- The mechanisms by which exposure to PCE leads to the observed liver tumors in mice, and leukemia in rats, are unknown. In the case of the liver tumors it is possible that non-genotoxic mechanisms (such as those involving interactions with a peroxisome proliferator activated receptor) contribute to the effects observed, but this is unproven. Directly genotoxic mechanisms involving activation of PCE to reactive metabolites have also been proposed, but the nature of these metabolites has not been clearly established. Such mechanisms might involve either oxidative metabolism or glutathione conjugation, but neither of these possibilities has been definitively shown to contribute to toxic effects in the liver or hematopoietic system.
- It appears probable that metabolism of PCE is required for carcinogenicity. The evidence is not however sufficient to demonstrate the relevance of the hypothetical specific modes of action, whether genotoxic or otherwise, at the sites where carcinogenesis is observed (in either animals or humans). In the absence of such evidence, dose metrics based on the overall extent of metabolism of parent compound, PCE, were chosen for the dose-response assessment.
- Lack of knowledge of the mode(s) of action of PCE or its metabolites in causing cancer in rats and mice, and the implication of these processes for human disease, is a limitation of this risk assessment.
- Cancer potency estimates derived from different studies, species, sites, and routes of administration are similar, although some differences between the oral and inhalation routes are observed.
- The PHG of 0.06 ppb is based primarily on an average of the quantitatively similar CSFs for liver tumors in male and female mice exposed to PCE by the oral route. A slightly different (but still broadly consistent) CSF was derived for the inhaled component of exposures

derived from drinking water contamination with PCE. This latter value was based on the average of CSFs for liver tumors in male and female mice, and leukemias in male and female rats, exposed to PCE by the inhalation route. If the PHG value were based on individual tumor sites (specific to the oral and inhalation routes) instead of an average, the values would range from 0.04 to 0.09 ppb.

- The CSFs are upper-bound estimates defined by the 95 percent confidence limit on the ED₁₀. It is theoretically possible that the true value of the cancer potency of PCE in humans could exceed these values, but that is considered unlikely. It is plausible that the true value of the human cancer potency for PCE has a lower bound of zero, based on statistical and biological uncertainties including interspecies extrapolation and mode of action.
- The estimate of multi-route exposure employed in the PHG calculation was 6.31 Leq/day (of which 4.1 Leq/day is metabolized). Use of an alternative exposure model (in which the total exposure is 7.2 Leq/day) employed in earlier risk assessments would yield a health protective level of 0.051 ppb, using the same metabolized dose conversion and slope factors as the basis of the estimate. Estimates of the health protective levels based on other data and assumptions (including median rather than upper bound estimates of the percentage of inhaled or ingested PCE that is metabolized) might be as high as approximately 0.1 ppb. However, these estimates are not recommended since they fail to make appropriate allowance for the expected inter-individual variation in the human population.
- The estimate of additional exposure via the inhalation route is 3.54 Leq/day (of which 2.05 Leq/day are metabolized). This is higher than the default value of two Leq/day suggested by U.S. EPA (based on average estimated showering exposures of a number of typical VOCs). This estimate reflects the greater volatility and lower water solubility of PCE, compared to some other VOCs commonly found in drinking water, and is based on reasonable extrapolations from the known physical properties of PCE.

According to this analysis, the health protective concentration of PCE in water associated with a negligible theoretical extra lifetime cancer risk is 0.06 ppb. This includes an estimate of inhalation exposure from showering in PCE contaminated water, flushing toilets, and other household activities involving tap water. The primary sources of uncertainty in the development of the PHG for PCE in drinking water are also the general issues of uncertainty in any risk assessment, particularly inter- and intra-species extrapolation, extrapolation from high to low doses, and issues relating to possible human exposure. A more formal analysis of the uncertainties used in our approach is possible, but would not affect the PHG and has therefore not been included.

The PHG of 0.06 ppb was calculated based on the carcinogenic potency of PCE. 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 0.6 and 6 ppb, respectively.

For PHGs, OEHHA's use of the relative source contribution (RSC) has followed U.S. EPA drinking water risk assessment methodology, with a few exceptions. U.S. EPA has treated carcinogens differently from noncarcinogens with respect to the use of RSCs. For noncarcinogens, RfDs (in mg/kg-d), DWELs (in mg/L) and MCLGs (in mg/L) are calculated using UFs, body weights and DWC (in Leq/day) and RSC, respectively. The typical RSC range is 20 to 80 percent (0.2 to 0.8), depending on the scientific evidence. In this case, evidence indicated an RSC below this range could be justified based on exposure to PCE from multiple sources. However, this was not used for development of the PHG, since the PHG was based on carcinogenicity.

U.S. EPA follows a general procedure in promulgating MCLGs:

- For Groups A and B (strong evidence of carcinogenicity), MCLGs are set to zero;
- For Group C (limited evidence of carcinogenicity), **either** an RfD approach is used (as with a noncarcinogen) but an additional UF of one to ten (usually 10) is applied to account for the limited evidence of carcinogenicity, **or** a quantitative method (calculation of potency and low-dose extrapolation) is used and the MCLG is set in the 10^{-5} to 10^{-6} cancer risk range;
- For Group D (inadequate or no animal evidence of carcinogenicity), an RfD approach is used to promulgate the MCLG.

For approaches that use low-dose extrapolation based on quantitative risk assessment, U.S. EPA does not factor in a 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 assumed 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 value based on low-dose extrapolation. (U.S. EPA has categorized PCE as a probable/possible Group B/C) carcinogen, and OEHHA has indicated in this risk assessment that it is appropriate to calculate a cancer potency by low-dose extrapolation.) This is an area of uncertainty and scientific discussion, and it is unclear how this assumption impacts the overall health risk assessment.

OTHER REGULATORY STANDARDS

The U.S. EPA has established a Maximum Contaminant Level Goal (MCLG) of zero mg/L PCE. A Maximum Contaminant Level (MCL) of 0.005 mg/L PCE has also been established which U.S. EPA believes would protect against the potential health problems identified in its report and is “the lowest level to which water systems can reasonably be required to remove this contaminant should it occur in drinking water” (U.S. EPA, 1989).

The California Department of Health Services currently lists a Maximum Contaminant Level of 0.005 mg/L (5 ppb). This is based in part on the earlier Proposed Maximum Contaminant Level document (DHS, 1987), which proposed a Maximum Contaminant Level of 2 ppb PCE. This concentration in drinking water was calculated to be associated with exposure producing a *de minimis* excess cancer risk value of one case in one million persons. Both the DHS (1987) assessment and the health risk assessments by U.S. EPA (1984, 1986) used similar data sets to those examined in the present analysis. The *de minimis* level (0.7 ppb) indicated by the U.S. EPA analysis is approximately 10-fold higher than that presented here. (However, the cancer risk assessment of PCE is no longer presented in U.S. EPA’s IRIS database.) The difference results primarily from the use in this document of 1) interspecies scaling according to $\frac{3}{4}$ power of body weight, 2) a time-to-tumor analysis of the NCI (1977) oral mouse bioassay data, and 3) a more sophisticated human pharmacokinetic model for low-level oral and inhalation exposures. The DHS (1987) document also did not use the time dependent analysis of the oral study. In addition, the final value presented was an average of estimates obtained using a wide range of different assumptions about exposure, uptake, and interspecies scaling, some of which were not included for consideration by either U.S. EPA (1984, 1986) or the present authors. The DHS and U.S. EPA MCL standards reflect risk management choices in addition to the health protective levels.

The California Air Resources Board has identified PCE as a Toxic Air Contaminant, with an upper bound estimate of the human lifetime risk of carcinogenicity of between 2 and 72×10^{-6} per ppb exposure (best value 54×10^{-6} /ppb). Various other regulatory standards for occupational and environmental exposures to PCE exist, but these are primarily designed to

address the hazards of short-term exposures to PCE rather than long-term environmental exposures such as those from polluted air or drinking water. The current U.S. EPA and California standards (RfD of 0.01 mg/kg-d; the California Hot Spots program inhalation chronic REL is based on this number) for non-cancer health effects are based on extrapolation from liver toxicity in mice. The protective non-cancer level established in this document is derived using human data and is approximately three times higher (equivalent to 0.032 mg/kg-d).

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APPENDIX 1: COMPARISON OF EXCESS CANCERS PREDICTED BY ANIMAL- DERIVED POTENCY FOR PCE TO COHORT DATA

The data from two cohort studies (Ruder et al, 1994; Blair et al, 1990) are considered. Both are mortality studies of members of dry-cleaning unions in U.S. cities. A number of limitations of both studies have been noted in IARC, 1995b, the main part of this document, and other analyses. Nonetheless, these two studies comprise the best available human data on carcinogenicity of PCE.

Assumptions

Exposure levels

No measurements of exposure levels are available for either of the cohort studies. A study conducted by the National Institute of Occupational and Industrial Health (NIOSH) in 1977-1979 measured exposure to workers performing four task categories in 44 U.S. dry-cleaning operations (Ludwig et al, 1983). Assuming exposure conditions were similar, the results of the NIOSH survey can be used to provide surrogate data for the dry cleaners in the Ruder and Blair studies. This also assumes that the distribution of dry vs. wet transfer shops in the cohorts was similar to that in the NIOSH study. Taking the geometric means (GM) for each of the four job categories described by Ludwig et al. (1983), time-weighted average (TWA) exposure to PCE for various dry-cleaning jobs is:

Operators	22.0 ppm
Pressers	3.3 ppm
Seamstress	3.0 ppm
Counter	3.1 ppm
GM:	5.1 ppm (35 mg/m ³)

The GM over all four job categories (35 mg/m³) is used in this analysis to represent typical exposure in the cohorts. The GM is not likely to significantly underestimate exposure, because most workers in dry-cleaning operations perform the lower exposure tasks. Ludwig et al. (1983) reported that a "typical workforce" consisted of one operator, and six pressers, seamstresses, and counter clerks. Further, the Blair study reported similar standard mortality ratios (SMRs) in both the high and mid exposure groups, indicating that excess risks are not likely to be restricted to the minority of workers with the highest TWA exposure levels. In that study, the highest SMRs were found in the largest group, those exposed to intermediate levels of PCE.

Exposure duration

The duration of exposure is estimated by the years of union membership, following the assumptions made in the analyses of the epidemiologic cohorts performed by the original authors.

Fraction metabolized

This analysis assumes that it is the metabolites of PCE that are likely to be associated with human cancers in exposed workers. Therefore, the exposures above were converted to metabolized doses, using the results of the human pharmacokinetic model of Bois et al. (1996). Based on visual estimation from the graph presented by Bois et al (1996), the mean fraction of inhaled PCE metabolized at 5 ppm is 12 percent of inhaled dose (95 percent CI: 5 - 30 percent). Both the mean and upper 95 percent confidence bound on the metabolized fraction are used below.

Body weightThe Blair cohort was 75 percent women and the Ruder cohort was 65 percent women. A bodyweight of 65 kg (average of male and female default bodyweights) is assumed in dose estimation for both cohorts.

Dose estimation

Application of the above assumptions results in an estimated average daily dose for workers in both cohorts of 0.46 mg-metabolites/kg-d:

$$35 \text{ mg/m}^3 \times 10 \text{ m}^3/\text{d} \times 5 \text{ d}/7 \text{ d} \times 0.12 \times 1/65 \text{ kg} = 0.46 \text{ mg-metab/kg-d}$$

Or, using the upper bound on metabolite production, the daily dose becomes:

$$35 \text{ mg/m}^3 \times 10 \text{ m}^3/\text{d} \times 5 \text{ d}/7 \text{ d} \times 0.3 \times 1/65 \text{ kg} = 0.15 \text{ mg-metab/kg-d}$$

Potency

The lifetime cancer risk due to a daily dose from inhalation exposure was derived from animal data, as described in the documentation for the PHG. The upper bound potency estimate for exposure by inhalation was $0.15 \text{ (mg-metab/kg-d)}^{-1}$. Using this value, the cancer risk for one year is assumed to be:

$$\text{Risk per year at } 1 \text{ mg-metab/kg-d} = 0.15/70 \text{ yr} = 0.002$$

To make a prediction of the expected number of excess cancers due to PCE exposure in the epidemiological cohorts, the total person-years of exposure to 1 mg-metab/kg-d is multiplied by this annualized risk estimate.

Predictions for the Ruder et al. (1994) data set:

1701 workers at risk

Mean duration of exposure = 9.6 years

Total "Dose-Years" = 1701 workers x 9.6 years x 0.46 mg-metab/kg-d = 7,512.
(Using the mean estimate of the fraction of inhaled PCE converted to metabolites.)

Predicted excess cancers due to PCE exposure, derived from animal potency estimates:

$$7,512 \times 0.002 = \mathbf{15 \text{ excess cancers.}}$$

If the upper bound on metabolite production is used in place of the average, "dose years" increase to 18,780 and **38 excess cancers** are predicted.

To compare what the animal-derived potency estimates predict for the cohort to the reported results of the cohort analysis, we select the SMR for total cancer, because the inhalation potency for the rodent model is taken to be indicative of any human cancer. In

the Ruder cohort, the SMR was 1.23, based on 209 deaths observed, 170 expected. This means **39 excess cancers** occurred in the study cohort during the period of observation. Thus, the cancer potency based on rodents shows a slight under-prediction, but reasonable agreement with the human data in this very rough analysis.

It should be noted that the predictions for the cohort made using the animal potency assume a lifetime of follow-up; the actual years of observation of these cohorts was considerably less. Given the same exposures, but follow-up increased to lifetime, more excess cancers might be expected from in the cohort data, somewhat increasing the tendency of the animal-derived potency to underestimate.

Predictions for the Blair et al. (1990) data set:

5365 workers at risk.

Mean duration of exposure = 6.6 years

Total "Dose-Years" = 5365 workers x 6.6 years x 0.46 mg-metab/kg-d = 16,288
(Based upon the mean estimate of the fraction of inhaled PCE converted to metabolites.)

Predicted excess cancers due to PCE exposure, using animal potency:

$$16,288 \text{ TDY} \times 0.002 = \mathbf{33 \text{ excess cancers}}$$

Using the upper bound on the human metabolized dose, the "dose years" for this cohort are 40,720 and **81 excess cancers** are predicted.

For comparison, the SMR for total cancers reported in the study was 1.16, based on 294 observed, 254 expected, indicating that **40 excess cancers** occurred in the study cohort. For this cohort, the animal potency agrees well with the observed SMR for cancer.

Conclusions

The number of cancers due to PCE exposure that is predicted by the animal-derived inhalation potency shows reasonable agreement with the number of excess cancers actually observed for both the PCE-exposed cohorts. While the analysis is necessarily quite crude, and is based on rough average estimates for a considerable number of variables, it may provide some confidence that the potency derived from rodent bioassay data used to set the PHG is not overly conservative. It was concluded in the PHG that the epidemiological data are not adequate to produce a quantitative estimate of the risk of PCE, and the same limitations apply here.