Public Health Goal for Cis- and Trans-1,2-Dichloroethylene in Drinking Water

Prepared by

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[added at end of review cycle]
Drinking Water Public Health Goal of the Office of Environmental Health Hazard Assessment

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

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

1. PHGs for acutely toxic substances shall be set at levels at which no known or anticipated adverse effects on health will occur, with an adequate margin of safety.

2. PHGs for carcinogens or other substances which can cause chronic disease shall be based solely on health effects without regard to cost impacts and shall be set at levels which OEHHA has determined do not pose any significant risk to health.

3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.

4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.

5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.

6. In cases of insufficient data to determine a level of no anticipated risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.

7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.

8. The PHG may be set at zero if necessary to satisfy the requirements listed above.

9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.

10. PHGs adopted by OEHHA shall be reviewed every five years and revised as necessary based on the availability of new scientific data.
PHGs adopted by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. Each standard adopted shall be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory in nature and represent only non-mandatory goals. By federal law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists.

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

The Office of Environmental Health Hazard Assessment (OEHHA) proposes a Public Health Goal (PHG) of 0.10 mg/L (100 µg/L, or 100 ppb) for cis-1,2-dichloroethylene (cis-1,2-DCE), and of 0.06 mg/L (60 µg/L, or 60 ppb) for trans-1,2-dichloroethylene (trans-1,2-DCE) in drinking water. These proposed PHGs are based on the most sensitive and reproducible toxic endpoints in test animals, statistically significant effects on the liver.

The proposed PHG for cis-1,2-DCE is based upon the no-observed-adverse-effect level (NOAEL) from a 90-day oral gavage study on rats conducted by McCauley et al., 1990. Sprague-Dawley rats were dosed with 0, 32, 97, 290, or 870 mg/kg-day of cis-1,2-DCE in corn oil. Significant dose-related increases in liver to body weight ratios were observed in both sexes at and above the lowest observed adverse effect level (LOAEL) of 97 mg/kg-day. The NOAEL for liver effects in this study is 32 mg/kg-day.

The current California maximum contaminant level (MCL) of 0.006 mg/L for cis-1,2-DCE is based upon an acute inhalation study conducted on six female SPF Wistar rats by Freundt and Macholz (1978). They reported that a single 8-hour exposure to 200 ppm of cis-1,2-DCE increased hexobarbital sleeping time and zoxazolamine paralysis in rats, illustrating a reversible inhibition of the liver mixed-function oxidase system.

The proposed PHG for trans-1,2-dichloroethylene (trans-1,2-DCE) is based upon the NOAEL from a 90-day drinking water study on male and female CD-1 mice conducted by Barnes et al., 1985. Treatment groups contained 140 mice of each sex and were provided trans-1,2-DCE in their drinking water at concentrations of 0, 0.1, 1.0, or 2.0 mg/mL. Based on fluid consumption, the doses were calculated to be 0, 17, 175, or 387 mg/kg-day for males, and 0, 23, 224, or 452 mg/kg-day for females. In males, a significant increase in serum alkaline phosphatase and relative liver weight were reported at and above the LOAEL of 175 mg/kg-day. The NOAEL for liver effects in this study is 17 mg/kg-day.

The current California MCL of 0.01 mg/L for trans-1,2-DCE also is based upon Barnes et al., 1985. However, it is based upon a significant increase in serum glucose levels reported at the 17 mg/kg-day dose. A review of the toxicological data calls into question the biological and toxicological significance of this increase in serum glucose levels. Specifically, the data show that even though the difference between the low- and the high-doses administered to the mice is 20-fold, there are no differences in the serum glucose levels among the three treatment doses. Additionally, the normal range of values for this strain of mice was not included by the authors to help ascertain whether the small increases are likely to represent an adverse effect. For these reasons, OEHHA concludes that the increases in serum glucose levels should not be assumed to be an adverse effect.

The United States Environmental Protection Agency (U.S. EPA) MCL for cis-1,2-DCE is currently set at 0.07 mg/L, and the MCL for trans-1,2-DCE is set at 0.1 mg/L. Both of these values are based on liver toxicity in rats. The proposed PHGs are not significantly different from these values.
INTRODUCTION

The purpose of this document is to propose Public Health Goals for the two isomeric forms of 1,2-dichloroethylene (1,2-DCE) in drinking water, cis- and trans-1,2-DCE. The focus of this document is to examine the available toxicological data on these chemicals to determine the most appropriate studies and toxic endpoints for calculating health protective levels. This evaluation also serves as a reassessment of the adequacy of the existing California MCLs for cis- and trans-1,2-DCE.

The U.S. EPA proposed a federal Maximum Contaminant Level Goal (MCLG) and a Maximum Contaminant Level (MCL) of 0.07 mg/L for cis-1,2-DCE, and 0.1 mg/L for trans-1,2-DCE (U.S. EPA, 1989). U.S. EPA adopted these criteria in 1991 (U.S. EPA, 1991).

The California Department of Health Services (DHS) adopted ten-fold lower MCLs in 1994 based upon recommendations from this office (then part of DHS). For cis-1,2-DCE, the California MCL is 0.006 mg/L; for trans-1,2-DCE, the MCL is 0.01 mg/L (DHS, 2001a). The California cis-1,2-DCE value is based upon an acute inhalation study on female rats conducted by Freundt and Macholz (1978), whereas the federal MCL value is based upon a subchronic ingestion study conducted on male and female rats by McCauley et al., 1990.

For trans-1,2-DCE, the federal and California MCLs are based on the same dose level in the same drinking water study (Barnes et al., 1985). The federal MCL value incorporates an uncertainty factor of 1,000, while the California MCL has an uncertainty factor of 10,000. The California MCL is based on the conclusion that the lowest level tested in this study represents the lowest observed adverse effect level (LOAEL), whereas the U.S. EPA concluded it represents the no adverse effect level (NOAEL).

The U.S. EPA Integrated Risk Information System (IRIS) has not set a chronic oral exposure Reference Dose (RfD) for cis-1,2-DCE (IRIS, 2004a). However, a chronic oral RfD of 0.02 mg/kg-day was set for trans-1,2-DCE based upon the 90-day drinking water study conducted by Barnes et al. (IRIS, 2004b).

CHEMICAL PROFILE

Chemical Identity and Structure

The two isomeric forms of 1,2-dichloroethylene (chemical formula C₂H₂Cl₂) differ only in their orientation across the double bond, as shown in Figure 1. Both chemicals, as well as their mixture, are used in industry. Common chemical names, synonyms, and the CAS Registry numbers for these are provided in Table 1.
cis-1,2-DCE \quad trans-1,2-DCE

Figure 1. Chemical Structures of cis and trans 1,2-Dichloroethylene

Table 1. Chemical Names and Identification Numbers of cis- and trans-1,2-Dichloroethylene and Their Mixture

<table>
<thead>
<tr>
<th>CIS</th>
<th>TRANS</th>
<th>MIXTURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cis-1,2-Dichloroethylene</td>
<td>Trans-1,2-Dichloroethylene</td>
<td>1,2-Dichloroethylene</td>
</tr>
<tr>
<td>(Z)-1,2-Dichloroethylene</td>
<td>1,2-Trans-Dichloroethylene</td>
<td>Cis-Trans-1,2-Dichloroethylene (Mixed Isomers)</td>
</tr>
<tr>
<td>Ethene, 1,2-dichloro-, (Z)</td>
<td>1,2-Dichloro-, (E)-Ethene</td>
<td>Cis-Trans-1,2-Dichloroethylene (Mixed Isomers)</td>
</tr>
<tr>
<td>(Z)-1,2-Dichloroethene</td>
<td>Trans-Acetylene Dichloride</td>
<td>Dioform</td>
</tr>
<tr>
<td>Cis-Dichloroethylene</td>
<td>1,2-Dichloro-, (E)-Ethylene</td>
<td>Acetylene Dichloride</td>
</tr>
<tr>
<td>Cis-1,2-Dichloroethene</td>
<td>Trans-1,2-Dichloroethene</td>
<td>Sym-Dichloroethylene</td>
</tr>
<tr>
<td>Ethylene, 1,2-Dichloro-, (Z)</td>
<td></td>
<td>1,2-Dichloroethene</td>
</tr>
<tr>
<td>NSC 6149</td>
<td>NCI-C5491</td>
<td>NCI-C56031</td>
</tr>
<tr>
<td>HSDB 5656</td>
<td>HSDB 6361</td>
<td>HSDB 6878</td>
</tr>
<tr>
<td>CASRN 156-59-2</td>
<td>CASRN 156-60-5</td>
<td>CASRN 540-59-0</td>
</tr>
</tbody>
</table>

*Data from HSDB (2002) and ATSDR (1996)*

**Physical and Chemical Properties**

1,2-DCE is a highly flammable volatile organic chemical which is a colorless liquid with a sharp, harsh odor somewhat reminiscent of chloroform. Trans-1,2-DCE is detectable to humans by odor at concentrations of 17 ppm and above in the air (Amoore and Hautala, 1983). Both isomers possess a high vapor pressure that causes them to evaporate quickly. However, each has a vapor density greater than air; therefore, 1,2-DCE in its gaseous form tends to sink toward the ground (HSDB, 2002). The isomers and the isomeric mixture are only slightly soluble in water and are sufficiently volatile that 50 percent of the compound will evaporate from stirred water at 25°C within approximately 22 minutes.
(HSDB, 2002). Both forms are expected to have high to very high mobility in soil, and are not anticipated to bioconcentrate in aquatic organisms (U.S. EPA, 2001).

Table 2. Physical and Chemical Properties of cis- and trans-1,2 DCE and Their Mixture

<table>
<thead>
<tr>
<th>Property</th>
<th>Cis</th>
<th>Trans</th>
<th>Mixture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Weight</td>
<td>96.94</td>
<td>96.94</td>
<td>96.94</td>
</tr>
<tr>
<td>Physical State</td>
<td>Liquid</td>
<td>Liquid</td>
<td>Liquid</td>
</tr>
<tr>
<td>Odor</td>
<td>Sharp, harsh</td>
<td>Sharp, harsh</td>
<td>Sharp, harsh</td>
</tr>
<tr>
<td>Odor threshold in air</td>
<td></td>
<td></td>
<td>17 ppm</td>
</tr>
<tr>
<td>Melting point</td>
<td>-80.5 °C</td>
<td>-50 °C</td>
<td>-57 °C</td>
</tr>
<tr>
<td>Boiling point</td>
<td>60 °C</td>
<td>48 °C</td>
<td>48 – 60 °C</td>
</tr>
<tr>
<td>Flash point</td>
<td>6 °C</td>
<td>2 – 4 °C</td>
<td>2 – 4 °C</td>
</tr>
<tr>
<td>Flammability limits</td>
<td>9.7 - 12.8%</td>
<td>9.7 - 12.8%</td>
<td>5.6 – 12.8%</td>
</tr>
<tr>
<td>Solubility - Water</td>
<td>3.5 mg/mL @ 25°C</td>
<td>6.3 mg/mL @ 25°C</td>
<td>1 mg/mL @ 21°C</td>
</tr>
<tr>
<td>Density</td>
<td>1.28 g/mL @ 20°C</td>
<td>1.28 g/mL @ 20°C</td>
<td>1.28 g/mL @ 20°C</td>
</tr>
<tr>
<td>Partition coefficients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Octanol-water (K_{ow})</td>
<td>72</td>
<td>115</td>
<td>72</td>
</tr>
<tr>
<td>Log K_{ow}</td>
<td>1.86</td>
<td>2.06</td>
<td>1.86</td>
</tr>
<tr>
<td>Soil Sorption</td>
<td>36</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Bioconcentration</td>
<td>15-22</td>
<td>15-22</td>
<td></td>
</tr>
<tr>
<td>Vapor pressure</td>
<td>273 mm Hg @ 30°C</td>
<td>395 mm Hg @ 30°C</td>
<td></td>
</tr>
<tr>
<td>Henry’s law constant</td>
<td>0.034 atm-m³/mole</td>
<td>0.067 atm-m³/mole</td>
<td></td>
</tr>
<tr>
<td>Conversion factor</td>
<td>1 ppm = 3.96 mg/m³</td>
<td>1 ppm = 3.96 mg/m³</td>
<td>1 ppm = 3.96 mg/m³</td>
</tr>
</tbody>
</table>

Adapted from HSDB (2002) and ATSDR (1996)

**Production and Uses**

The isomeric mixture and both cis- and trans-1,2-DCE are used as chemical intermediates in the synthesis of chlorinated solvents and compounds. 1,2-DCE has also been used as a solvent for waxes, resins, perfumes, dyes, lacquers, thermoplastics, fats, and phenols. It is used in the extraction of oils and fats from fish and meat, and has been used as an extraction solvent for organic materials such as decaffeinated coffee. The trans isomer is more widely used in industry than the cis isomer or the commercial mixture (ATSDR, 1996).
Sources

An important source of cis- and trans-1,2-DCE in the environment is the anaerobic degradation of chlorinated solvents commonly found in municipal and industrial landfills, including tetrachloroethylene (PERC), trichloroethylene, 1,1,1-trichloroethane (TCE), and 1,1,2,2-tetrachloroethane (Parsons et al., 1984; Smith and Dragun, 1984).

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Air

The California Air Resources Board (CARB) does not list cis-, trans-1,2-DCE or the isomeric mixture as Toxic Air Contaminants. Therefore, these chemicals are not monitored as part of the Ambient Air Quality Data program (CARB, 1998). However, landfill gases from 20 California landfills have been shown to contain detectable levels of 1,2-DCE (Wood and Porter, 1987). 1,2-DCE is produced by anaerobic biodegradation of trichloroethylene, tetrachloroethylene and other short-chain organochlorine compounds in landfills (ATSDR, 1996). Levels of 1,2-DCE in the air may be higher in and around landfills that contain 1,2-DCE and its precursors, especially if the landfill is not equipped with a vapor recovery system that captures 1,2-DCE.

Other sources of ambient exposure to 1,2-DCE include process and fugitive emissions from the production of 1,2-DCE and its use as a chemical intermediate; evaporation from waste water streams, landfills, and solvents; emissions from combustion or heating of polyvinyl chloride and other vinyl copolymers; evaporation from sludge; and leaching from landfills. Most of the 1,2-DCE released in the environment will eventually enter the atmosphere or groundwater, where it is subject to further biotic or abiotic degradation processes.

In the air 1,2-DCE is primarily removed through photochemical reactions which generate oxygenated species. The estimated atmospheric lifetimes for cis- and trans-1,2-DCE due to photochemical reactions are 12 and 5 days, respectively (Goodman et al., 1986).

Soil

Cis- and trans-1,2-DCE are released to soil and sediments from the disposal and leaching of wastes containing these compounds. They also may be formed in landfills, aquifers, or sediments as anaerobic bacteria biodegrade tetrachloroethylene (PERC), trichloroethylene, 1,1,1-trichloroethane (TCE), 1,1,2,2-tetrachloroethane and other chlorinated solvents commonly found in municipal and industrial landfills (Parsons et al., 1984; Smith and Dragun, 1984). Parsons et al. (1984) demonstrated that sediment microcosms convert tetrachloroethylene to 1,2-DCE with a preponderance of the cis isomer being formed.
Water

In the United States, trans-1,2-DCE has been detected in surface water at concentrations ranging from 0.43 ppb to 1,307 ppb. Similar data are not available for cis-1,2-DCE in surface water (ATSDR, 1996). A rainwater sample in Los Angeles had a concentration of 0.23 ppb 1,2-DCE. The specific isomer was not identified (ASTDR, 1996). Reported concentrations of trans-1,2-DCE in U.S. groundwater ranged from 0.25 ppb to 500,000 ppb. For cis-1,2-DCE, groundwater concentrations ranged from 0.5 ppb to 20,000 ppb (ATSDR, 1996). Trans-1,2-DCE has been found in industrial and commercial wastewater in a range of less than 10 ppb to 2266 ppb (ATSDR, 1996). Of the surface drinking water supplies in the U.S., less than 5 percent had detectable 1,2-DCE levels, but 21 percent of community systems relying on groundwater had detectable levels of 1,2-DCE (ATSDR, 1996). Cis-1,2-DCE was found in 199 out of 12,773 drinking water samples taken between 1984 and 2001, based on a detection limit for the purposes of reporting (DLR) of 0.5 ppb (DHS, 2002). Trans-1,2-DCE was found in 23 out of 15,308 drinking water samples taken between 1984 and 2001, based on a DLR of 0.5 ppb (DHS, 2002).

Food

No information was found regarding concentrations of 1,2-DCE in food or food sources. However, because of the high volatility of 1,2-DCE, no significant retention of this chemical would be expected in foodstuffs.

Other Sources

No information was found regarding other sources of 1,2-DCE.

METABOLISM AND PHARMACOKINETICS

Absorption

1,2-DCE is a volatile, lipophilic molecule capable of passing easily through the respiratory, gastrointestinal, and dermal systems. Due to its small molecular size and lipophilicity, it is thought to pass through membranes by simple or passive diffusion. It is readily absorbed though the lungs, with systemic retention estimates as high as 75 percent (ATSDR, 1996). Systemic retention at equilibrium for the inhalation route is likely to be about 50 percent, as measured for other volatile organic chemicals (Raabe 1986, 1988). Gastric absorption of 100 percent is expected. Dermal absorption from soil or liquid phase films is expected to be low, based on the high volatility of 1,2-DCE (U.S. EPA, 1992). However, its lipophilicity and water solubility should result in relatively efficient dermal penetration from a water phase (Hall et al., 1989). Humans showering with water contaminated with cis-1,2-DCE and vinyl chloride were shown to absorb these compounds (Pleil and Lindstom, 1997). The results were qualitative and were
determined by sampling exhaled breath. In occupational settings, the most common routes of exposure are inhalation and dermal contact (HSDB, 1995).

**Distribution**

1,2-DCE is anticipated to be distributed throughout the body, with potentially higher concentrations in fat due to its lipophilicity (el-Masri et al., 1996). It is anticipated that it can readily penetrate the brain and cross the placenta.

**Metabolism**

1,2-DCE is metabolized similarly to other small-chlorinated solvents. Primary metabolism occurs in the liver by oxidation of the double bond, then further oxidation to acid metabolites with or without dechlorination. When 1,2-DCE was incubated with microsomes from rat liver, dichloroethanol, dichloroacetaldehyde, and dichloroacetic acid were detected (Costa and Ivanetich, 1982). Figure 2 illustrates this metabolic pathway (redrawn from ATSDR, 1996).

![Figure 2. Postulated Metabolic Scheme for 1, 2-Dichloroethylene](image)

Similarities and differences have been observed in the metabolism of cis- and trans-1,2-DCE. Both isomers have been shown to bind to the active site of hepatic cytochrome P450 (Freundt and Macholz, 1978; Costa and Ivanetich, 1982). This was associated with competitive inhibition of the metabolism of other cytochrome P450 substrates in rat liver (Freundt and Macholz, 1978). In addition, other researchers have reported depletion and
induction of various liver enzymes (Hanioka et al., 1998; Matthews et al., 1998; Paolini et al., 1995; Thornton-Manning et al., 1994). The cis isomer displayed a four-fold greater rate of turnover in the hepatic microsomes in vitro than did the trans isomer. Further, the metabolic rates of formation of dichloroethanol and dichloroacetic acid differ between the two isomers (Costa and Ivanetich, 1984).

1,2-DCE has been shown to inhibit its own metabolism by inactivating the cytochrome isozyme that catalyses 1,2-DCE oxidation (Lily et al., 1998). Nonetheless, metabolism is quite rapid and (combined with exhalation of the intact chemical) results in a blood half-life of less than one hour (Barton et al., 1995; Gargas et al., 1990).

Excretion

1,2-DCE is partially eliminated through exhalation of the intact chemical (Matthews et al., 1997); most of the remainder will be excreted as urinary metabolites. The primary urinary excretion products will be monochloro- and dichloroacetic acid metabolites with and without conjugation. No fecal excretion is expected.

TOXICOLOGY

Toxicological Effects in Animals and Plants

Acute Toxicity

Cis

McCauley et al. (1990) conducted a 14-day oral gavage experiment on cis-1,2-DCE using ten male and ten female Sprague-Dawley rats per group. The study was subsequently published in the peer-reviewed scientific literature (McCauley et al., 1995). Cis-1,2-DCE was administered daily by corn oil gavage at 0, 1.0, 3.0, 10.0 and 20.0 mmol/kg-day (equivalent to 0, 97, 290, 970 and 1900 mg/kg-day, respectively).

A significant dose-related increase in relative liver weight was observed in both males and females at and above the lowest observed adverse effect level (LOAEL) dose of 97 mg/kg-day. Significant dose-related increases in absolute liver weight were reported in females at and above the LOAEL dose, while males had significant increases in absolute liver weight at and above the 970 mg/kg-day dose level. In females, decreased hematocrit values and erythrocyte counts were reported at doses of 290 mg/kg-day and above. A statistically significant increase in relative and absolute kidney weight was also reported for females at and above 970 mg/kg-day, and the blood urea nitrogen (BUN) levels were significantly decreased in females at the highest dose level.

Freundt and Macholz (1978) reported that a single 8-hour inhalation exposure to cis- or trans-1,2-DCE at 200 ppm increased hexobarbital sleeping time and zoxazolamine paralysis time in female Wistar rats. Dose to the rats is estimated as 198 mg/kg, based on a conversion factor of 3.96 mg/m$^3$ per ppm, 0.30 m$^3$/day breathing rate times 8/24 hours of exposure for an adult female rat weighing 0.2 kg, with a net inhalation retention estimated to be 50 percent (Raabe, 1986). These effects were stronger from the cis
isomer than the trans isomer and were interpreted as indicating that both cis and trans-1,2-DCE reversibly inhibit the mixed function oxidase system. This conclusion was supported by in vitro studies in a rat liver microsomal enzyme system.

**Trans**

Barnes et al. (1985) evaluated the acute toxicity of trans-1,2-DCE in CD-1 mice following a single oral gavage in one of nine doses ranging from 800 to 3,500 mg/kg. The 14-day LD50 was 2,100 mg/kg in males and 2,400 mg/kg in females.

Freundt et al. (1977) exposed groups of six female rats (SPF Wistar) to trans-1,2-DCE in an inhalation chamber. A single eight-hour exposure was conducted on four groups at 0, 200, 1,000 and 3,000 ppm. These chamber concentrations correspond to approximate doses of 0, 198, 990 and 2,970 mg/kg, respectively [calculated as above]. Slight to severe fatty degeneration of the hepatic lobules and Kupffer cells (highly phagocytic macrophages that protect the systemic circulation from gastrointestinal bacteria) was seen in all dosing groups except controls. At exposure levels of 200 and 1,000 ppm (198 and 990 mg/kg), a significant decrease in the number of leucocytes was reported. Additionally, a reduction in the number of erythrocytes was observed at 1,000 ppm (990 mg/kg), but these effects were not seen at higher concentrations. At 3,000 ppm (2,970 mg/kg), there was evidence of fibrous swelling and hyperemia of cardiac muscle. A lowest observed adverse effect level (LOAEL) of 198 mg/kg was established for this acute exposure study, based on hepatic effects.

Freundt and Macholz (1978) reported that a single 8-hour inhalation exposure to cis- or trans-1,2-DCE at 200 ppm (198 mg/kg) increased hexobarbital sleeping time and zoxazolamine paralysis time in adult female rats, illustrating that 1,2-DCE exposure reversibly inhibits the liver mixed function oxidase system. Effects from exposure to the cis isomer were stronger than from the trans isomer. A LOAEL of 198 mg/kg-day was established for these enzymatic effects.

**Mixture**

A significant increase in rat kidney weight was reported from a 14-day oral gavage exposure to a 50 percent mixture of the 1,2-DCE isomers at a dose of 480 mg/kg-day (McMillan, 1986).

**Subchronic Toxicity**

**Cis**

McCauley et al. (1990) conducted a 90-day oral gavage study of cis-1,2-DCE in corn oil using ten male and ten female Sprague-Dawley rats at doses of 0, 0.33, 1.0, 3.0 or 9.0 mmol/kg-day. These values equate to 0, 32, 97, 290 and 870 mg/kg-day, respectively.

A statistically significant increase in kidney to body weight ratios was reported in males at all subchronic dose levels. However, the effect does not appear to be strongly dose-related and the underlying histological and clinical chemistry do not provide evidence of renal toxicity. In fact, the authors noted that the changes in kidney-to-body weight ratio in males are interesting, “but in light of the negative histopathological findings, these effects are difficult to interpret.” The authors hypothesized that “the significant increase
in kidney-to-body weight ratio may be due at least in part to decreased body weight gain.” They also concluded that the relatively consistent but non-dose-related and non-significant kidney weight gain “may require further experimentation to better understand this observation.” No significant effect on absolute kidney weights or kidney-to-body weight ratio was reported in females, although these measures did show modest, non-significant increases. Data for these two endpoints are presented in Tables 3 and 4.

Table 3. Relative Kidney Weight (Percent Body Weight)

<table>
<thead>
<tr>
<th>Gender</th>
<th>Control (SD)</th>
<th>32 mg/kg</th>
<th>97 mg/kg</th>
<th>290 mg/kg</th>
<th>870 mg/kg</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>0.70 (0.06)</td>
<td>0.80* (0.06)</td>
<td>0.83* (0.06)</td>
<td>0.83* (0.10)</td>
<td>0.89* (0.06)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>0.69 (0.06)</td>
<td>0.71 (0.05)</td>
<td>0.82 (0.23)</td>
<td>0.85 (0.21)</td>
<td>0.85 (0.06)</td>
<td>NS</td>
</tr>
</tbody>
</table>

* = Significantly different from controls; NS = Not significant; SD = Standard Deviation

Table 4. Absolute Kidney Weight (Grams)

<table>
<thead>
<tr>
<th>Gender</th>
<th>Control (SD)</th>
<th>32 mg/kg</th>
<th>97 mg/kg</th>
<th>290 mg/kg</th>
<th>870 mg/kg</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>4.02 (0.56)</td>
<td>4.40 (0.57)</td>
<td>4.70 (0.59)</td>
<td>4.30 (0.77)</td>
<td>4.58 (0.74)</td>
<td>NS</td>
</tr>
<tr>
<td>Female</td>
<td>2.18 (0.22)</td>
<td>2.24 (0.29)</td>
<td>2.53 (1.01)</td>
<td>2.55 (0.49)</td>
<td>2.55 (0.37)</td>
<td>NS</td>
</tr>
</tbody>
</table>

* = Significantly different from controls; NS = Not significant; SD = Standard Deviation

At 97 mg/kg-day and above, statistically significant dose-related increases in relative liver weight ratios were reported in male and females. The increases ranged from 14 percent at the lower dose to 33 percent at the highest dose for both sexes. In females, a statistically significant increase in absolute liver weights was reported at the highest dose tested. Data for relative and absolute liver weight are presented in Tables 5 and 6, respectively. The histological examination did not discern any specific hepatic injury. Nevertheless, the clinical chemistry results show that BUN levels were significantly decreased in males at the highest dose level, suggesting hepatocellular insufficiency. The authors concluded that, “there was a consistent, dose-related increase in both liver weight and liver-to-body weight ratios in both sexes” and that this effect, given the negative histology, “may be a hypertrophy and hyperplasia similar to that induced by phenobarbital.”
Table 5. Relative Liver Weight (Percent Body Weight)

<table>
<thead>
<tr>
<th>Gender</th>
<th>Control (SD)</th>
<th>32 mg/kg</th>
<th>97 mg/kg</th>
<th>290 mg/kg</th>
<th>870 mg/kg</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>2.85 (0.26)</td>
<td>3.15 (0.27)</td>
<td>3.28* (0.18)</td>
<td>3.34* (0.44)</td>
<td>3.75* (0.20)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>2.82 (0.19)</td>
<td>2.91 (0.18)</td>
<td>3.21* (0.22)</td>
<td>3.36* (0.18)</td>
<td>3.67* (0.27)</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

* = Significantly different from controls; NS = Not significant; SD = Standard Deviation

Table 6. Absolute Liver Weight (Grams)

<table>
<thead>
<tr>
<th>Gender</th>
<th>Control (SD)</th>
<th>32 mg/kg</th>
<th>97 mg/kg</th>
<th>290 mg/kg</th>
<th>870 mg/kg</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>16.6 (3.07)</td>
<td>17.6 (3.12)</td>
<td>18.7 (2.09)</td>
<td>17.5 (3.71)</td>
<td>19.1 (1.92)</td>
<td>NS</td>
</tr>
<tr>
<td>Female</td>
<td>8.89 (0.81)</td>
<td>9.16 (0.56)</td>
<td>9.80 (1.55)</td>
<td>10.2 (0.89)</td>
<td>11.0* (1.34)</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

* = Significantly different from controls; NS = Not significant; SD = Standard Deviation

A significant decrease in hematocrit levels was observed in males at doses of 97 mg/kg-day and above, and in females at doses of 290 mg/kg-day and higher. Slight decreases in SGOT were also observed in the female rats at 290 mg/kg-day.

OEHHA concludes that the LOAEL for liver effects in this study of 97 mg/kg-day based on significant dose-related increases in relative liver weight in both sexes is the most robust endpoint for risk assessment. While there is a significant increase in relative kidney weights in males at all doses in the subchronic study, the data are not as convincing as those for adverse liver effects. Specifically, the McCauley study showed that in both acute and subchronic exposures both males and females displayed dose-related, significant increases in relative liver weights. In the acute study, significant dose-related relative-liver-weight increases were seen at all dose levels (97, 290, 970 and 1,900 mg/kg-day) in both sexes. In the subchronic study, increases were seen at the three highest levels (98, 290 and 870 mg/kg-day). Females in the acute study had significant, dose-related increases in absolute liver weights at all doses; males did at the two highest doses. BUN levels were significantly decreased in females at the highest dose in the acute study. In the subchronic study, absolute liver weights were significantly increased in females at the highest dose, and BUN levels were significantly decreased in males at the highest dose. These data taken together provide substantial evidence that cis-1, 2-DCE exposure causes adverse effects on the liver.
Conversely, kidney effects were absent in males in the acute (14-day) study at doses up to 1900 mg/kg-day; in females, absolute and relative kidney weights were significant at only the two highest doses (970 and 1,900 mg/kg-day). In the subchronic study, kidney effects were absent in females, while males had relative kidney weights increased at all dose levels. However, males had no significant change at any dose for absolute kidney weights in either the acute or the subchronic studies, and no histopathological evidence of kidney damage. Decreased BUN may reflect effects on the liver or on the kidney, so this observation does not substantiate potential kidney effects. The irregularity of the kidney changes brings into question the toxicological significance of the effect, and raises the question of whether an anomalous excursion occurred in males in the subchronic study, which might be attributable to other causes. That doubt cannot be said for liver effects which are consistent, dose-related, and reported in both sexes in both studies. For these reasons, OEHHA concludes that the LOAEL of 97 mg/kg-day and the NOAEL of 32 mg/kg-day based on adverse effects in the liver in the subchronic study is the preferred endpoint for risk assessment. However, a calculation based on the possible LOAEL of 32 mg/kg-day for male rate kidney effects is also presented for comparison.

Trans

Barnes et al. (1985) conducted a 90-day drinking water study of trans-1,2-DCE on groups containing 140 male and 140 female CD-1 mice at concentrations of 0, 0.1, 1.0, or 2.0 mg/mL. Based on fluid consumption, the doses were 0, 17, 175, or 387 mg/kg-day for males, and 0, 23, 224, or 452 mg/kg-day for females. There were no differences in fluid consumption among the various groups of mice and at the termination of the 90-day experiment, no DCE-induced changes in terminal body weight or gross pathology were noted in either sex at any dose level.

A significant increase in glucose levels was reported at all dose levels for both male and female mice. However, a review of the data calls into question the biological and toxicological significance of these increases in serum glucose levels. Specifically, the data show that despite a 20-fold difference between the low- and the high-dose levels administered to the mice, there are no dose-related differences in the serum glucose levels (see Table 7). The normal range of values for this strain of mice was not included by the authors to ascertain that this was anomalous to the extent that it could be classified as a compound-related toxic effect, and transient 20-30 percent changes in glucose levels are not unusual. Further, increased levels of serum glucose in animals are associated with a number of causes, including postprandial effects and stress typically seen in test animals (Benjamin, 1984). Finally, the glucose concentrations, while significantly increased compared with control levels, are all well within the range of measured values in control mice because the range is so large (Charles River, 2000). For these reasons, OEHHA does not consider the apparent increases in serum glucose levels in the study to indicate an adverse effect suitable for estimating a safe dose.
Table 7. Serum Glucose Levels in Mice after 90-Day Exposure to Trans-1,2-DCE in Drinking Water (Barnes et al., 1985)

<table>
<thead>
<tr>
<th>Serum Glucose Levels in mg percent +/-SE (percent increase)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water Concentration of trans-1,2-DCE</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>Males</td>
</tr>
<tr>
<td>Females</td>
</tr>
<tr>
<td>N</td>
</tr>
</tbody>
</table>

*Significance level p <0.05

In male mice, there were significant increases in serum alkaline phosphatase levels at the 175 and 387 mg/kg-day levels. In addition, liver glutathione concentrations were decreased at the highest dose. In females, the thymus weight, calculated as percent body weight, was significantly decreased at both 224 and 452 mg/kg-day, while the lung weight was depressed at the highest dose only. The levels of serum glutamic-pyruvic transaminase (SGPT) and glutamic-oxaloacetic transaminase (SGOT) were decreased at the two higher doses. In addition, the hepatic levels of aniline hydroxylase were decreased at all three dose levels, but the levels of cytochromes P-450 and b5, microsomal protein, and aminopyrine N-demethylase were not affected by any dose of trans-1,2-DCE. There is uncertainty about the toxicological significance of the increases in blood glucose and decreases in SGOT, SGPT, and aniline hydroxylase. However, the increased serum alkaline phosphatase and an increase in relative liver weight (8 percent) in males indicate hepatic effects at 175 mg/kg-day. These hepatotoxic effects mark the LOAEL for this study at 175 mg-kg-day and the NOAEL at 17 mg/kg-day. McCauley et al. (1990) reported liver effects at comparable doses using cis-1,2-DCE, thus providing supporting evidence that 1,2-DCE affects the liver.

Freundt et al. (1977) exposed female SPF Wistar rats to air containing trans-1,2-DCE at 200 ppm (198 mg/kg-day) for 8 hours/day, 5 days/week for 1, 2, 8, or 16 weeks. Some rats in each group showed fatty infiltration in the liver lobules and Kupffer cells. At 8 and 16 weeks of exposure, severe pneumonic infiltration was observed.

Hayes et al. (1987) reported the results of administration of trans-1,2-DCE in drinking water to groups of 10 male and 10 female Sprague-Dawley rats, 22 to 30 days old, for 90 days. Solvent concentrations in the water were monitored, and average concentrations and doses were calculated by the authors. The average daily doses of trans-1,2-DCE were estimated as 0, 402, 1,311 or 3,114 mg/kg-day for males and 0, 353, 1,257 or 2,809 mg/kg-day for females. At the end of the exposure, seven internal organs including brain, liver, spleen, lungs, thymus, kidneys, and ovaries were weighed, histological sections from livers, kidneys, and gonads were examined microscopically, and hematological, blood chemistry, and urinalysis parameters were measured. The authors found no compound-related effects on fluid consumption, body weights, hematology, serum chemistry or urinalyses. The authors noted a significant dose-related decrease in kidney weight at the 1,257 and 2,809 mg/kg-day doses in female rats.
A recent National Toxicology Program (NTP) study was conducted to determine the toxicological effect of ingested microencapsulated trans-1,2-DCE. This 14-week feed study was conducted on groups of 10 male and 10 female Fisher 344 rats and B6C3F1 mice per exposure level. Animals were fed diets containing microcapsules with a chemical load of 45 percent trans-1,2-DCE. Dietary concentrations of 3,125, 6,250, 12,500, 25,000, and 50,000 ppm microencapsulated trans-1,2-DCE resulted in average daily doses of 190, 380, 770, 1,540, and 3,210 mg/kg for male rats; 190, 395, 780, 1,580, and 3,245 mg/kg for female rats; 480, 920, 1,900, 3,850, and 8,065 mg/kg for male mice; and 450, 915, 1,830, 3,760, and 7,925 mg/kg for female mice. Additional groups of 10 male and 10 female rats and mice served as untreated and vehicle controls. There were no exposure-related deaths of rats or mice. Animals were evaluated for clinical pathology, reproductive system effects, and histopathology.

Liver weights of female rats exposed to 6,250 ppm or greater were significantly greater than those of the vehicle controls. The absolute kidney weights of male rats exposed to 25,000 or 50,000 ppm were significantly decreased. Mean body weights of male rats and male and female mice in the 50,000 ppm groups were significantly less than those of the vehicle controls. The mean body weight gains of female mice in the 12,500 and 25,000 ppm groups were also significantly less than that of the vehicle controls. On day 21 and at week 14, there were mild decreases in hematocrit values, hemoglobin concentrations, and erythrocyte counts in groups of male and female rats in the 25,000 and 50,000-ppm groups. At week 14, these effects were seen in male rats exposed to 6,250 and 12,500 ppm. There were no exposure-related alterations in clinical chemistry parameters in rats or mice, and no gross or microscopic lesions were observed in rats or mice that could be attributed to trans-1,2-DCE exposure.

NTP concluded that “very little toxicity was associated with ingestion of microencapsulated trans-1,2-dichloroethylene” and that “histopathology and clinical chemistry data, combined with body and organ weight data, revealed that the maximum tolerated dose was not reached in these studies” (NTP, 2002).

Mixture

No subchronic studies on animals exposed to a mixture of cis- and trans-1,2-DCE were found.

Genetic Toxicity

Cis

Several studies have investigated the genotoxic effects of cis-1,2-DCE. These tests include bacterial, fungal and mammalian cells with various endpoints. The question of whether cis-1,2-DCE is genotoxic is unclear based on mixed results from many studies.

The mutagenic activity of cis-1,2-DCE in Salmonella typhimurium was evaluated in vitro with and without S9 activation. The study also investigate the mutagenic effects of cis-1,2-DCE in a host-mediated assay in mouse bone marrow cells. Female ICR mice were used in the in vivo experiments along with the TA 1950, TA 1951, TA 1952, TA 1535, TA 1538, TA 100 and TA 98 strains of S. typhimurium (Cerna and Kypenova, 1977). DCE was dissolved in DMSO to achieve 1 and 10 percent dilutions; a volume of 0.05 ml
of the dilution or full-strength solvent was added per plate of bacterium, with and without S9 activation. The results were negative for all combinations studied.

Bronzetti et al. (1984) tested for possible mutagenic effects of cis-1,2-DCE for its ability to induce point mutations, mitotic gene conversions and mitotic recombinations in a diploid strain of the yeast *Saccharomyces cerevisiae* in suspension with and without mammalian microsomal activation. Concentrations of 40, 80 and 100 mmol cis-1,2-DCE were used for this in vitro assay. In the host-mediated assay, a single 1,300 mg/kg dose was used for an acute study and a cumulative dose of 3,000 mg/kg was given over 9 days for a subchronic study. Statistically significant increases in revertants were observed only at 100 mmol with S9 activation. Significant increases in convertants were also observed in yeast cells isolated from the liver, and an increase in revertants from the kidney after acute exposure to 1,300 mg/kg cis-1,2-DCE. The subchronic test had significant increases in convertants isolated from the lung, and increases in revertants from lung and kidney.

Cantelli-Forti and Bronzetti (1988) tested for possible mutagenic effects of cis-1,2-DCE for its ability to induce point mutations, mitotic gene conversions and mitotic recombinations in a diploid strain of the yeast *S. cerevisiae* in suspension with and without mammalian microsomal activation. In vitro concentrations were not given; however, the results were negative for these tests. The authors reported that in a host-mediated assay using mice, positive results were obtained. Doses were not given.

Human lymphocytes from healthy male and female volunteers were used to conduct the comet and micronucleus assays (Tafazoli and Kirsch-Volders, 1996). Concentrations of 0, 2, 4, 6, 8, 20 and 40 mmol were used in the micronucleus test, and concentrations of 0 and 2–20 mmol were used in the comet assay. At 20 mmol, significant increases in the number of binucleated cells were reported in the micronucleus assay. In the comet assay, positive responses for tail length were observed at 4, 6 and 8 mmol with S9 activation. A LOAEL of 20 mmol was obtained in the micronucleus assay. A LOAEL of 2 mmol was obtained in the comet test.

Costa and Ivanetich (1984) studied the metabolism of cis-1,2-DCE and its ability to induce unscheduled DNA synthesis in rat hepatocytes. Male Long-Evans rats were used to obtain the hepatocytes and the cells were exposed in vitro to 4.3 mmol for 120 minutes. This concentration induced unscheduled DNA synthesis. However, the authors noted that this result should be viewed as tentative until confirmed by other experiments.

Several other in vitro tests provided negative results for chromosomal aberrations or sister chromatid exchanges in Chinese hamster cells (Sawada et al., 1987), point mutation, gene conversion or recombination in *S. cerevisiae* (Galli et al., 1982) at similar or higher concentrations than discussed above.

**Trans**

A review of the genetic testing reports on trans-1,2-DCE shows that not one positive result can be found in over twenty tests. These tests include bacterial, fungal and mammalian cells with various endpoints reported in six different publications (ATSDR, 1996). No mutagenic activity was seen when trans-1,2-DCE was tested on *Escherichia coli*, *S. cerevisia*, or *S. typhimurium* (Greim et al., 1975, Bronzetti et al., 1984, Cantelli-
Forti and Bronzetti, 1988, Galli et al., 1982) or in Chinese hamster cells or rat hepatocytes (Sawada et al., 1987, Costa and Ivanetich, 1984) at levels discussed above.

**Mixture**

An *in vivo* mouse bone marrow micronucleus assay using a mixture of 1,2-DCE was negative (Crebelli et al., 1996). Male and female CD-1 mice were given an i.p. dose of 70-80 percent of the respective LD$_{50}$ of cis- and trans-1,2-DCE 24 and 48 hours before sacrifice. Distinct toxicity was observed (piloerection, hypoactivity, and hunched posture), but there was no marked depression of bone marrow proliferation. This raises the question as to whether this test is a sensitive indicator for this compound.

**Developmental and Reproductive Toxicity**

**Cis**

No studies were found on the developmental or reproductive toxic effect of cis-1,2-DCE.

**Trans**

Inhalation exposure to trans-1,2-DCE has been shown to affect fetal weight in Sprague-Dawley rats. Hurtt et al. (1993) exposed groups of 24 pregnant rats to 0, 2,000, 6,000 or 12,000 ppm of trans-1,2-DCE in air for 6 hours per day during days 7-16 of gestation. These doses correspond to 0, 1,300, 3,900 or 7,800 mg/kg-day, calculated assuming a 0.33 m$^3$/day breathing volume times 6/24 hours, for rats assumed to average about 0.25 kg during the exposure period, with a net systemic retention assumed to be 50 percent. Maternal toxicity was evidenced by significant decreases in body weight and food consumption at 7,800 mg/kg-day and by a significant decrease in food consumption at 3,900 and 1,300 mg/kg-day. Exposure to the two highest levels had a narcotizing effect on the dams. At the highest dose level, dams were salivating during exposure.

As a comparison, the Permissible Exposure Limit (PEL) for occupational exposures to 1,2-DCE is 200 ppm, and an Immediately Dangerous to Life and Health (IDLH) limit is 1,000 ppm (NIOSH, 1994). The concentrations tested in this study were ten to sixty times greater than those allowed in an occupational setting, and two to twelve times higher than concentrations that would mandate an immediate evacuation of premises.

Mean fetal weights were slightly but significantly reduced (4 percent) in the litters of the dams exposed at the highest level. However, as the authors of the paper stated, the reduced mean fetal weights most probably were a result of decreased food consumption and reduced weight gain in the dams at the highest dose (33 percent) and not an indication of chemically-induced developmental effects. The authors concluded that the NOAEL for maternal toxicity was less than 1,300 mg/kg-day for the dam, and that the NOAEL was 3,900 mg/kg-day for the conceptus.

**Mixture**

No studies were found on the developmental or reproductive toxicity in animals exposed to a mixture of cis- and trans-1,2-DCE.
Immunotoxicity

*Cis*

There were no effects observed on the spleens of Sprague-Dawley rats gavaged with cis-1,2-DCE for 90 days at 32, 97, 290 or 870 mg/kg-day (McCauley *et al.*, 1990).

*Trans*

The effect of orally administered trans-1,2-DCE on the immune system has been studied in mice and rats. No effects were observed in the spleens of Wistar rats exposed to air containing 200 ppm (198 mg/kg-day) for 8 hours/day, 5 days/week for 1, 2, 8 or 16 weeks (Fruendt *et al.*, 1977). Leukocyte counts were unchanged in mice gavaged with 2,200 to 2,400 mg/kg-day of trans-1,2-DCE in an acute study (Munson *et al.*, 1982).

However, Barnes *et al.* (1985) reported an increased leukocyte count and decreased relative thymus weight in female mice exposed to 224 mg/kg-day in drinking water for 90 days. These effects were not observed in male rats at any dose.

Shopp *et al.* (1985) assessed the immunotoxicity of trans-1,2-DCE in mice during a 90-day drinking water study. This study examined immunological parameters in the same mice as the study published by Barnes *et al.* (1985). The cell-mediated and humoral immune status of these mice was assessed and no changes were observed in either sex or in the humoral immune status of female mice. Spleen cells of male mice displayed a reduced ability to form IGM antibodies to sheep erythrocytes at all three doses. The LOAEL for this effect was set at 17 mg/kg-day. The conclusion of the authors was that “…the immune system of the CD-1 mouse did not appear to be overly sensitive to the effects of DCE.”

Inhalation of trans-1,2-DCE at 200 ppm or greater caused slight to severe fatty degeneration of Kupffer cells in rats. Kupffer cells are highly phagocytic macrophages that protect the systemic circulation from gastrointestinal bacteria. Decreased leukocyte counts were also observed after an 8-hour exposure to 200 ppm and 1000 ppm (Freundt *et al.*, 1977). The mechanism of change in leucocytes after the single exposure is not clear; the authors stated that the origin of this decrease is “unresolved.”

*Mixture*

No effects were seen in leukocyte counts as reported in a 30-day oral gavage study on rats at 480 mg/kg-day of a mixture of cis- and trans-1,2-DCE (McMillan *et al.*, 1986).

Neurotoxicity

*Cis*

Signs of central nervous system depression have been observed in animals at the terminal stages after receiving lethal doses of cis-1,2-DCE (McCauley *et al.*, 1990), consistent with expected depressant effects of the volatile halogenated hydrocarbons.

*Trans*

Symptoms indicative of neurological effects were reported following a single oral dose administered to rats (Barnes *et al.*, 1985). The symptoms included decreased activity,
ataxia, suppressed or total loss of righting reflex, and depressed respiration. These symptoms were observed with increasing severity at doses ranging from 800 to 3,500 mg/kg.

Inhalation of 12,000 ppm of trans-1,2-DCE for six hours by pregnant rats was shown to cause increases in lethargy and salivation. This exposure corresponds to 7,800 mg/kg. Narcoisis in pregnant rats at 2,000 ppm (1,300 mg/kg) was also reported (Hurtt et al., 1993). In the terminal stages after receiving lethal oral doses of trans-1,2-DCE, animals exhibited central nervous system depression (Barnes et al., 1985, Hayes et al., 1987).

Mixture

No data were located on neurotoxic effects of exposure to a mixture of 1,2-DCE on animals.

Chronic Toxicity

Cis

No studies were found on animals exposed chronically to cis-1,2-DCE.

Trans

No studies were found on animals exposed chronically to trans-1,2-DCE.

Mixture

No chronic toxicity studies were found on animals exposed to a mixture of cis- and trans-1,2-DCE.

Carcinogenicity

Cis

No literature was found on the carcinogenicity of cis-1,2-DCE in animals.

Trans

No literature was found on the carcinogenicity of trans-1,2-DCE in animals.

Mixture

No literature was found on the carcinogenicity of exposure to a mixture of cis- and trans-1,2-DCE in animals.

Toxicological Effects in Humans

Acute Toxicity

In a report from 1936, two human subjects experienced burning in their eyes after a 30-minute exposure to between 830 and 2,220 ppm of trans-1,2-DCE. At concentrations of 1,200 to 2,200 ppm for five to ten minutes, both subjects reported neurological
symptoms. These symptoms included nausea, drowsiness, fatigue, vertigo, and a feeling of intracranial pressure (Lehmann and Schmidt-Kehl, 1936).

**Subchronic Toxicity**

No studies on subchronic exposure of humans to cis or trans-1,2-DCE or the mixture were identified.

**Genetic Toxicity**

No human studies of genotoxic effects of cis or trans-1,2-DCE or the mixture were identified.

**Developmental and Reproductive Toxicity**

No human studies of developmental or reproductive toxicity of cis or trans-1,2-DCE or the mixture were identified.

**Immunotoxicity**

No reports of immunotoxicity to humans were identified for cis or trans-1,2-DCE or the mixture.

**Neurotoxicity**

In a report from 1936, inhalation of trans-1,2-DCE at concentrations of 1,200 to 2,200 ppm for five to ten minutes caused neurological symptoms in two subjects. These symptoms included nausea, drowsiness, fatigue, vertigo and a feeling of intracranial pressure (Lehmann and Schmidt-Kehl, 1936). These effects are consistent with the effects on animals, and consistent with the depressant effects of similar halogenated hydrocarbons.

**Chronic Toxicity**

No studies were identified on chronic exposure to cis or trans-1,2-DCE or the mixture on humans.

**Carcinogenicity**

There are no studies on the carcinogenicity of cis- or trans-1,2-DCE or its mixture in humans. U.S. EPA has rated cis-1,2-DCE as a Class D carcinogen, indicating that it is not classifiable as to its human carcinogenicity (IRIS, 2004a). This determination is based on the paucity of data in humans and animals, in conjunction with the generally nonpositive results in mutagenicity assays. U.S. EPA has not rated trans-1,2-DCE (IRIS, 2004b) or the mixture for carcinogenicity.
DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

Cis

McCauley et al. (1990) conducted two separate experiments in male and female Sprague-Dawley rats. Cis-1,2-DCE was administered by gavage in corn oil for either 14 or 90 days. The dosing regimen for the 14-day study was set at 0, 97, 290, 970 and 1,900 mg/kg-day. The 14-day study showed a statistically significant, dose-related increase in relative liver weight at and above the LOAEL dose of 97 mg/kg-day in both males and females. Females had statistically significant, dose-related increases in absolute liver weight at and above the LOAEL, while males had statistically significant increases in absolute liver weight at and above 970 mg/kg-day. BUN levels were significantly decreased in females at the highest dose. Females also had statistically significant increases in absolute and relative kidney weights at 970 mg/kg-day and above, and statistically significant decreases in hematocrit values and erythrocyte counts at and above 290 mg/kg-day.

For the 90-day study, the dosing regimen was 0, 32, 97, 290, and 870 mg/kg-day. A statistically significant dose-related increase in liver-to-body weight ratios was observed for both sexes at 97 mg/kg-day and above. Absolute liver weights were significantly increased in females and BUN levels were significantly decreased in males at the highest dose. Males were observed to have significantly increased kidney-to-body weight ratios at all test levels. Significant decreases in hematocrit values were reported in males at and above 97 mg/kg-day, and in females at the two highest doses.

A thorough evaluation of the kidney and the liver data indicates that the liver effects are the most scientifically sound, credible endpoint given the substantial weight-of-evidence that cis-1, 2-DCE exposure is associated with adverse effects on the liver. The kidney data are more equivocal and less suitable for dose-response extrapolation. Therefore OEHHA concludes that the LOAEL of 97 mg/kg-day and NOAEL of 32 mg/kg-day based on adverse liver effects are the more meaningful for risk assessment, and will represent the preferred basis of our PHG calculation. However, a risk assessment calculation based on the kidney effects is provided for additional perspective and discussion.

U.S. EPA based its MCL and MCLG values on this study and also set the LOAEL at 97 mg/kg-day based on the adverse liver effects.

Trans

Barnes et al. (1985) exposed CD-1 male and female mice to trans-1,2-DCE in drinking water for 90 days and reported changes in biochemical measurements in serum and liver indicative of liver toxicity. These measurements include serum alkaline phosphatase (SAP) increases and liver glutathione depletion in male mice. Additionally, a statistically significant increase in relative liver weight was observed in male mice exposed to the LOAEL of 175 mg/kg-day, but no such effect was noted in the females. The authors concluded that the NOAEL in this study was 17 mg/kg-day.
CALCULATION OF PHG

Noncarcinogenic Effects

The following equation is used for calculating a public health protective level (C) based on non-carcinogenic endpoints of chemical contaminants in drinking water.

\[
C = \frac{(NOAEL \text{ or } LOAEL) \times BW \times RSC}{UF \times L/day} = \text{mg/L}
\]

where:

- **NOAEL/LOAEL** = no-observed-adverse-effect level or lowest-observed-adverse-effect level, in mg/kg-day;
- **BW** = adult body weight in kilograms (70 kg default);
- **RSC** = relative source contribution of the chemical from drinking water (usually values 0.2 to 0.8, based on estimated exposure to a chemical from all sources);
- **UF** = uncertainty factor (typically, defaults of 10 to account for extrapolation from a LOAEL to a NOAEL, interspecies extrapolation, intraspecies extrapolation (including sensitive human subpopulations), or extrapolation from a subchronic study to chronic exposures);
- **L/day** = daily water consumption rate, a default of 2 liters/day for adults, or higher values of \(L_{\text{equiv}}/\text{day}\) to account for inhalation and dermal exposure resulting from other household water uses.

**Cis**

The current California MCL for cis-1,2-DCE is based upon an acute inhalation study conducted by Freundt and Macholz (1978). They reported that a single 8-hour exposure to 200 ppm (198 mg/kg) of cis-1,2-DCE increased hexobarbital sleeping time and zoxazolamine paralysis in rats, which illustrates an inhibition of the liver mixed function oxidase system. Acute, generally reversible effects of this nature are less useful for risk assessment than longer-term studies showing frank effects.

The proposed PHG for cis-1,2-DCE is based upon the no observed effect level (NOAEL) of 32 mg/kg-day for adverse effects on the liver determined from the 90-day oral gavage study on rats by McCauley et al., 1990. OEHHA concludes that the McCauley study is superior to the Freundt and Macholz as a basis for deriving a health protective drinking water exposure level. The McCauley study uses a more appropriate exposure route, is of
longer duration, and is far more comprehensive in the analysis and investigation of toxicological endpoints.

McCauley reported that significant dose-related increases in liver to body weight ratios were observed in both sexes at all doses above the NOAEL of 32 mg/kg-day. To this NOAEL, an uncertainty factor of 3,000 is applied to account for multiple sources of uncertainty. A factor of ten is used because the NOAEL is based on a non-human species. A default uncertainty factor of ten is used to account for sensitive subpopulations of people. For the exposure of less than a lifetime, a factor of ten is used to account for the possibility of more severe effects in a chronic exposure. An additional uncertainty factor of three is applied in this case to account for the incompleteness of the toxicological database, including the lack of any chronic or developmental studies. (Three represents one-half log unit, or one-half of 10.)

Since cis-1,2-DCE is a small volatile organic compound, inhalation and dermal exposures resulting from other household water use is anticipated. A value of 4 Leq/day is used to account for these exposures. An RSC of 60 percent is used here because drinking water sources are anticipated to be the primary source contributor of exposure to cis-1,2-DCE.

Using these values, a public health protective level for cis-1,2-DCE is calculated as:

\[
C = \frac{32 \text{ mg/kg-day} \times 70 \text{ kg} \times 0.6}{3000 \times 4 \text{ Leq/day}}
\]

\[
C = 0.112 \text{ mg/L}, \text{ rounded to } 0.100 \text{ mg/L} = 100 \mu\text{g/L} = 100 \text{ ppb}
\]

In addition, effects on the kidneys in the McCauley et al. (1990) study are worth further consideration. The small but significant effect on relative kidney to body weight ratio at 32 mg/kg-day in males represents a LOAEL without a NOAEL, which commonly would be used in risk assessment with a 10-fold uncertainty factor for LOAEL to NOAEL extrapolation. In this case, since the effect appears equivocal (weak dose-response, no effect on absolute kidney weight, no effect in females, no discernable kidney pathology), a factor of three seems more relevant. A default factor of ten is added for extrapolation from rats to humans, another factor of ten for potential human variability, and another factor of ten for subchronic to chronic exposure. We could add another factor of three for database uncertainty as described above. However, multiplying this list of uncertainty factors together (3x10x10x10x3) equals 10,000, which exceeds the standard maximum combined uncertainty factor of 3,000 (U.S. EPA, 2002). (Note also that the two half-log units, represented here as 3, when multiplied together equal ten.) Therefore the calculation we would use for the kidney is identical to the calculation shown above, with a combined uncertainty factor of 3,000. The public-health-protective value derived from the use of the kidney endpoint would be the same as that from use of the more robust adverse effect on the liver in the same study.
OEHHA therefore proposes a PHG of 100 ppb for cis-1,2-DCE based upon significant
dose-related increases in liver to body weight ratios seen in both sexes as reported in the
90-day oral gavage study on Sprague-Dawley rats conducted by McCauley et al., 1990.

Trans

The current California MCL for trans-1,2-DCE is based upon a 90-day drinking water
study on mice conducted by Barnes et al., 1985. The MCL is based upon a LOAEL of 17
mg/kg-day for significant increases in serum glucose levels.

However, a review of the Barnes et al. (1985) data calls into question the biological and
toxicological significance of these small increases in serum glucose levels. Specifically,
as presented in Table 7, the data show that even with a 20-fold low- to high-dose range,
there are no significant differences in the serum glucose levels among the treated groups.
Additionally, the glucose concentrations, while significantly increased compared with
control levels, are all well within the range of measured values in control mice because
the normal range is so large (Charles River, 2000). For these reasons, OEHHA does not
consider the increases in serum glucose levels to represent a clear and demonstrated
adverse effect suitable for risk assessment, in this case.

The proposed PHG for trans-1,2-DCE is based upon a NOAEL of 17 mg/kg-day from the
Barnes et al., 1985 drinking water study on mice. A significant increase in relative liver
weight and an increase in serum alkaline phosphatase levels in males were reported
above the NOAEL. To this NOAEL, an uncertainty factor of 3,000 is applied to account
for various sources of uncertainty. A factor of ten is used when the NOAEL is based on a
non-human species. A default uncertainty factor of ten is used to account for sensitive
subpopulations of people. Also, because the exposure in the critical study was less than a
lifetime, a factor of ten is used to account for the possibility of more severe effects in a
chronic exposure. An additional uncertainty factor of three is used to account for the
incompleteness of the toxicological database, including the lack of any chronic studies.

Since trans-1,2-DCE is a small volatile organic compound, inhalation and dermal
exposures resulting from other household water use is anticipated. A value of 4 L\text{eq}/day
is used to account for these exposures. An RSC of 60 percent is used here because
drinking water sources are anticipated to be the primary source contributor of exposure to
trans-1,2-DCE.

Using these values, a public health protective level for trans-1,2-DCE is calculated as
follows:

\[
C = \frac{17 \text{ mg/kg-day} \times 70 \text{ kg} \times 0.6}{3000 \times 4 \text{ L}_{eq}/\text{day}}
\]

\[
= 0.0595 \text{ mg/L}, \text{ rounded to } 0.060 \text{ mg/L} = 60 \mu\text{g/L} = 60 \text{ ppb}
\]

OEHHA therefore proposes a PHG of 60 ppb for trans-1,2-DCE based upon significant
increases in relative liver weight and serum alkaline phosphatase levels in male CD-1
mice reported from the 90-day drinking water study conducted by Barnes et al., 1985.
RISK CHARACTERIZATION

Cis

The primary sources of uncertainty in the development of the PHG for cis-1,2-DCE in drinking water are also the general issues of uncertainty in most risk assessments, particularly the mode of action, inter- and intra-species extrapolation, relative source contribution (RSC), and limitations in available data.

The proposed PHG of 100 ppb was calculated based on the adverse noncancer effect of cis-1,2-DCE on the liver. Vinyl chloride, a closely related chemical, is a known human carcinogen and other halogenated ethylenes have been found to induce tumors in experimental animals. These facts coupled with the presumption that a reactive epoxide can be formed in the metabolism of cis-1,2-DCE can lead one to suspect that cis-1,2-DCE may be carcinogenic. The positive mutagenicity results in the in vivo experiments provide a further reason for concern. However, far too little data are available to resolve this question. No chronic studies have been conducted on this compound.

The current California MCL for cis-1,2-DCE is derived from a previous assessment of the toxicological data and utilized an acute inhalation study (Freundt and Macholz, 1978). From the LOAEL of this study, an applied dose was derived and combined with a 10,000-fold uncertainty factor to yield an MCL of 0.006 mg/l. The endpoint identified from this study was significant but presumably reversible changes in the liver mixed function oxidases.

OEHHA selected a subchronic oral gavage study (McCauley et al., 1990) as the basis for the proposed PHG. The rationale for this decision is as follows. The McCauley study provides a better basis for establishing an ingestion-basis value than the study utilized earlier by this office. The study is route specific and therefore more applicable to the exposure pathway under analysis. Exposures to the chemical were of longer duration (90 days) and more relevant to lifetime exposure effects. Further, pronounced increases of liver to body weight ratios observed in both males and females provide a more accurate indication of the type, magnitude, and potential for biologically significant, long-term effects resulting from continual exposures. Effects on the kidney (increased kidney to body weight ratio in male rats) in the same study provide an alternative risk assessment endpoint. Estimation of a public health-protective dose from the kidney effect results in the same proposed value, using common risk assessment assumptions. Finally, the McCauley study includes a comprehensive analysis and investigation of toxicological endpoints, thus providing further toxicological evidence for a proposed PHG.

The federal MCL for cis-1,2-DCE is derived from the LOAEL for hepatotoxicity in the McCauley study cited above. U.S. EPA utilized an uncertainty factor of 10,000; a relative source contribution of 20 percent; and a default consumption value of 2 L/day (U.S. EPA, 1989).

In its evaluation of the data, OEHHA determined that an uncertainty factor of 3,000, a relative source contribution of 60 percent and a consumption value of 4 L_{eq}/day are more in line with the available data. Our uncertainty factor of 3,000 includes values of ten for each of the three major areas of uncertainty (inter- and intraspecies extrapolations and less-than-lifetime exposure), and a factor of three for uncertainties associated with the
lack of important data, including chronic and developmental toxicology studies. Current U.S. EPA policy is to use a maximum uncertainty factor of 3,000 (U.S. EPA, 2002); OEHHA concurs with this approach.

The use of a relatively high value (60 percent) for the RSC is supported by the expectation that drinking water should be the primary source of exposure to cis-1,2-DCE (ATSDR, 1996). Finally, a drinking water equivalent value of 4 L eq/day is anticipated to be representative of potential combined exposures from consumption, plus inhalation and dermal exposures that may result from other household water use of this volatile organic chemical.

The NOAEL for liver effects from the McCauley study was chosen since it represents the lowest NOAEL from the most robust and biologically significant endpoint from the available toxicological literature.

**Trans**

The primary sources of uncertainty in the development of the PHG for trans-1,2-DCE in drinking water are also the general issues of uncertainty in most risk assessments, particularly the mode of action, inter- and intra-species extrapolation, relative source contribution (RSC), and limitations in available data.

The proposed PHG of 60 ppb was calculated based on the adverse noncancer effect of trans-1,2-DCE on the liver. Vinyl chloride, a closely related chemical, is a known human carcinogen and other halogenated ethylenes have been found to induce tumors in experimental animals. These facts coupled with the presumption that a reactive epoxide can be formed in the metabolism of trans-1,2-DCE could lead one to suspect that it may be carcinogenic. On the other hand, negative mutagenicity results for this compound provide no indication of genotoxic effect, and there is reason to believe that symmetrical halogenated ethylenes are more stable and less apt to cause mutagenic events (Henschler, 1977) than their unsymmetrical congeners. However, far too little data are available to resolve the question of potential carcinogenesis, since no chronic studies have been conducted.

The current California MCL for trans-1,2-DCE is derived from a previous assessment of the toxicological data, which utilized a subchronic drinking water study in mice (Barnes et al., 1985) as the basis for the MCL. The previous assessment identified significant increases in serum glucose levels as the most sensitive endpoint and established the lowest level tested as the LOAEL. To that LOAEL, a 10,000-fold uncertainty factor was applied along with the default values for relative source contribution and daily water consumption of 20 percent and two L/day, respectively. The existing California MCL for trans-1,2-DCE is 0.010 mg/L.

However, our current review of the data indicates that the biological and toxicological significance of these increases in serum glucose levels is questionable. Specifically, although the range among the low-to high-dose levels administered to the mice is 20 fold, there are no differences in the serum glucose levels among the doses. Additionally, the glucose concentrations, while significantly increased compared with control levels, are all well within the range of measured values in control mice (Charles River, 2000). Finally, in their discussion, the study authors did not note the blood glucose changes as a
presumed compound-related toxic effect. For all these reasons, OEHHA does not consider the increases in serum glucose levels to be a suitable endpoint for risk assessment in this case.

The federal MCL for trans-1,2-DCE is derived from the NOAEL for hepatotoxicity in the Barnes study cited above. The NOAEL was set at the lowest dose tested of 17 mg/kg-day. U.S. EPA utilized an uncertainty factor of 1,000; a, relative source contribution of 20 percent; and a default consumption value of 2 L/day. The federal MCL for trans-1,2-DCE is 0.10 mg/L.

OEHHA selected a subchronic oral gavage study (Barnes et al., 1985) as the basis for the proposed PHG. In its evaluation of the data, OEHHA concluded that the hepatotoxic effect as evidenced by significant increases in relative liver weight and serum alkaline phosphatase in male mice is the most biologically relevant endpoint, and that the NOAEL for these effects was the lowest dose tested. An uncertainty factor of 3,000, a relative source contribution of 60 percent and an equivalent consumption value of 4 L eq/day were applied to the NOAEL. These factors are consistent with the available literature and properties of trans-1,2-DCE.

Our uncertainty factor of 3,000 includes values of ten for inter- and intraspecies extrapolations and less-than-lifetime exposure, and a factor of three to account for uncertainties associated with an incomplete scientific database, including the lack of chronic toxicology data. The use of 60 percent for the RSC appears justified because drinking water is anticipated to be the primary source of exposure to trans-1,2-DCE (ATSDR, 1996). Finally, an equivalent consumption value of 4 L eq/day is anticipated to be representative of combined consumption and inhalation and dermal exposures from other uses of household water.

The NOAEL from the Barnes et al. study was chosen since it represents the lowest NOAEL from the most sensitive biologically significant endpoint from the available toxicology literature.

**OTHER REGULATORY STANDARDS**

*Cis*

U.S. EPA proposed a federal Maximum Contaminant Level Goal (MCLG) and MCL of 0.07 mg/L for cis-1,2-DCE (U.S. EPA, 1989). U.S. EPA adopted these criteria as final in 1991 (U.S. EPA, 1991). The California Department of Health Services (DHS) set a ten-fold lower Maximum Contaminant Level (MCL) of 0.006 mg/L. The California MCL for cis-1,2-DCE, set prior to 1990, was based upon an acute inhalation study conducted by Freundt and Macholz (1978). The federal MCL was based on a 3-month oral gavage study conducted by McCauley et al., 1990.

The Agency for Toxic Substances and Disease Registry (ATSDR) has an acute and intermediate Minimum Risk Level (MRL) of one mg/kg-day and 0.3 mg/kg-day, respectively. The Integrated Risk Information System (IRIS) has no chronic oral RfD for cis-1,2-DCE (IRIS, 2004a).
Trans

U.S. EPA proposed a federal Maximum Contaminant Level Goal (MCLG) and MCL of 0.1 mg/L for trans-1,2-DCE (U.S. EPA, 1989). U.S. EPA adopted these criteria as final in 1991 (U.S. EPA, 1991). The California Department of Health Services (DHS) adopted a ten-fold lower Maximum Contaminant Level (MCL) of 0.01 mg/L in 1994 (DHS, 1994). The federal and California MCLs are based on the same dose level in the same study (Barnes et al., 1985). The ten-fold difference is because DHS determined that there was an adverse effect at the lowest dose tested, while EPA concluded that there was no effect at that dose. Wisconsin has adopted a level equal to U.S. EPA (0.1 mg/L), New Jersey set its level equal to California (0.01 mg/L), and twelve other states have an intermediate level of 0.07 mg/L (ATSDR, 1996).

ATSDR has an intermediate MRL of 0.2 mg/kg-day and IRIS has a chronic oral RfD of 0.02 mg/kg-day for trans-1,2-DCE based on an uncertainty factor of 1,000 from the NOAEL of 17 mg/kg-day in the Barnes et al. (1985) study (IRIS, 2004b).

Mixture

The National Institute for Occupational Safety and Health (NIOSH) has established a Recommended Exposure Level (REL) for occupational exposure to 1,2-DCE at 200 ppm. The Occupational Safety and Health Administration (OSHA) has set a Permissible Exposure Limit (PEL) for occupational exposures to 1,2-DCE at 200 ppm, and an Immediately Dangerous to Life and Health (IDLH) limit at 1,000 ppm (NIOSH, 1994).
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