DRAFT

For Review Only

Public Health Goal for
1,1,2-Trichloroethane
in Drinking Water

Prepared by

Pesticide and Environmental Toxicology Section
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

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PREFACE

Drinking Water Public Health Goal of the
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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 publish 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 that can cause chronic disease shall be based upon currently available data and shall be set at levels that 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 published 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 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.

LIST OF CONTRIBUTORS

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PUBLIC HEALTH GOAL FOR 1,1,2-TRICHLOROETHANE IN DRINKING WATER

SUMMARY

1,1,2-Trichloroethane (1,1,2-TCA) is a halogenated aliphatic hydrocarbon. It is a nonflammable liquid with a pleasant odor, insoluble in water, and miscible with alcohol, ether, and many other organic liquids. 1,1,2-Trichloroethane is used in manufacturing 1,1-dichloroethene; as a solvent for fats, waxes, natural resins, and alkaloids; and in other organic syntheses. Small amounts of 1,1,2-TCA are formed during chlorination of drinking water.

Limited human data are available on the toxicity of 1,1,2-TCA. It is rapidly absorbed by inhalation, and can exert a narcotic effect. 1,1,2-Trichloroethane is irritating to the eyes, nose, and respiratory tract. When the liquid solvent comes in contact with skin, it may cause cracking and erythema. Animal studies showed nervous system effects such as excitation and sleepiness, and at high levels, toxicity to the liver and kidneys.

No epidemiologic studies are available to address adequately the potential for carcinogenicity of 1,1,2-TCA in humans. In a rodent bioassay of 1,1,2-TCA by gavage, no effects on tumor development were noted in rats, while treated mice had significantly increased incidences of hepatocellular carcinomas and adrenal pheochromocytomas. 1,1,2-Trichloroethane is negative in genotoxicity studies. The carcinogenic potential of 1,1,2-TCA is a concern, and the data are adequate to use for estimating a human health-protective level of 1,1,2-TCA in drinking water. 1,1,2-TCA is listed as "known to the state to cause cancer" by its synonym, vinyl trichloride, under California's Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65). The U.S. EPA classifies 1,1,2-TCA as a possible human carcinogen (group C), and provides a cancer potency factor based upon the mouse tumor data (U.S. EPA, 2004). The International Agency for Research on Cancer has classified 1,1,2-TCA as "not classifiable as to its carcinogenicity to humans" (Group 3) based upon limited evidence in experimental animals and the absence of epidemiological evidence (IARC, 1999).

The proposed Public Health Goal (PHG) for 1,1,2-TCA is 0.0002 mg/L, based on the 95 percent upper confidence bound of the slope of the fit by the linearized multistage model to the carcinogenicity dose-response data, calculated for a one in one million cancer risk with a lifetime of exposure. This value is considerably lower than the current California and federal Maximum Contaminant Level (MCL) of 0.005 mg/L, based on non-cancer toxic effects and considerations of analytical feasibility. The basis of the proposed PHG is positive evidence of carcinogenicity in oral cancer bioassays in mice performed by the National Cancer Institute (NCI, 1978). NCI examined the effects of technical grade 1,1,2-TCA administered orally in corn oil to mice and rats. Groups of 50 male and female $B6C3F_1$ mice were treated via gavage five days/week for 78 weeks, with time-weighted average doses of 195 and 390 mg/kg-d, respectively, for the low and high dose groups for both sexes over the course of the dosing. In the high dose males, 37/49 (76 percent), and in the high dose females, 40/45 (89 percent), developed hepatocellular

carcinoma. The results in rats were negative. Both OEHHA and U.S. EPA have judged these data in mice adequate for estimating a cancer potency value (OEHHA, 1999; U.S. EPA, 2004). A positive association between administration of 1,1,2-TCA and the incidence of pheochromocytoma of the adrenal gland was also observed in the high dose female mice (NCI, 1978).

INTRODUCTION

The purpose of this document is to propose a Public Health Goal (PHG) for the chlorinated hydrocarbon solvent 1,1,2-trichloroethane (1,1,2-TCA) in drinking water. This task involves performing an updated literature review and a detailed risk assessment. A primary objective was to determine if there is a more appropriate toxicological study or a better method of calculating a public-health protective level for 1,1,2-TCA in drinking water than was used in the prior risk assessment used to develop the existing California MCL. This document is not intended to provide an exhaustive review of all aspects of the use and toxicology of 1,1,2-TCA, but to concentrate on the lowest-dose for the critical toxic effects that may contribute to public health concern from exposure to the solvent in drinking water.

U.S. EPA proposed a federal Maximum Contaminant Level Goal (MCLG) of 0.003 mg/L for 1,1,2-TCA on the basis of liver, kidney or immune system toxicity in 1990 (U.S. EPA, 1990, 2001a). An MCL of 0.005 mg/L was set based on analytical feasibility at that time, and the two criteria were finalized in 1992 (U.S. EPA, 1992, 2002). The California MCL was subsequently revised to match the federal MCL (see DHS, 2002).

CHEMICAL PROFILE

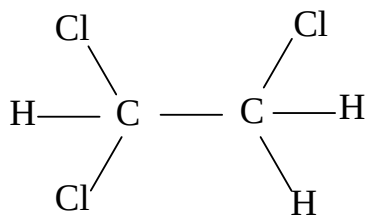
Chemical Identity

The structure, CAS registry number, and chemical formula are given below, as well as various names used to identify this solvent.

Table 1. Chemical Identity of 1,1,2-TCA

Parameter	Property or Value
Chemical name	1,1,2-trichloroethane
Synonyms	Ethane trichloride, β-trichloroethane, vinyl trichloride, 1,2,2-trichloroethane
Registered trade name	β-T, Cement T-339
Chemical formula	$C_2H_3Cl_3$
CAS Registry Number	79-00-5

Figure 1. Chemical structure of 1,1,2-TCA



Physical and Chemical Properties

1,1,2-TCA is a volatile, lipophilic chlorinated solvent. 1,1,2-TCA can be detected by a variety of instruments including mass spectrometry and an electron capture detector. No matter which detection instrument is used, the first step of most analyses is to separate 1,1,2-TCA from the water and non-volatile chemicals in the water by purging the volatile chemicals from the water with an inert gas and trapping them on a solid absorbent (Cleseri *et al*., 1989). Physical and chemical properties relevant to assessing human exposure to 1,1,2-TCA are provided in Table 2.

Table 2. Physical and Chemical Properties of 1,1,2-TCA

Property	Value or Information	References
Molecular weight	133.4	NIOSH, 1994
Color	Colorless	NIOSH, 1994
Physical state	Liquid	NIOSH, 1994
Odor	Chloroform-like, sweet	NIOSH, 1994
Melting point	-36 ^{o}C	U.S. EPA, 2001b
Boiling point	113.8 ^{o}C	U.S. EPA, 2001b
Flash point	N/A	NIOSH, 1994
Flammability limits	UEL 15.5%, LEL 6%	NIOSH, 1994
Solubility, Water	4.4 g/L at 20 ^{o}C	U.S. EPA, 2001b
Specific gravity, density	1.4 at 20 ^{o}C	U.S. EPA, 2001b
Octanol/water log K_{ow}	2.17	U.S. EPA, 2001b
Vapor pressure	23 mm Hg at 25 ^{o}C	U.S. EPA, 2001b
Conversion factor	1 ppm = 5.5 mg/m^3	NIOSH, 1994

Production and Uses

1,1,2-Trichloroethane is produced in the U.S., although not in California, by serial chlorination of ethylene. 1,1,2-TCA is a chemical intermediate in the synthesis of 1,1-

dichloroethene, also known as vinylidene chloride (ATSDR, 1989). 1,1-Dichloroethene is used in the production of polyvinylidene chloride copolymers. These copolymers are used extensively in consumer products including flexible food film wraps, and carpet backing. U.S. EPA's Toxic Release Inventory showed no reported releases of 1,1,2-TCA in California (U.S. EPA, 1999; data extracted May 4, 1999).

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Air

Because 1,1,2-TCA is listed as a federal hazardous air pollutant, the California Air Resources Board (ARB) identified it as a Toxic Air Contaminant in 1993 under AB2728 (ARB, 1996). 1,1,2-TCA is not one of the 75 Toxic Air Contaminants for which ARB reports monitoring data (ARB, 1998). The principal mechanism for removal of airborne 1,1,2-TCA is via reaction with the hydroxyl radical. In the atmosphere, 1,1,2-TCA is relatively reactive compared to other chlorinated ethanes. The most abundant products are hydrochloric acid, formyl chloride, phosgene, and chloroacetyl chloride (Spence and Hanst, 1978). The half-life of 1,1,2-TCA ranges from 24-50 days in unpolluted atmospheres to only a few days in polluted air (HSDB, 2001).

Soil

Published information on soil levels of 1,1,2-TCA in California is not available. 1,1,2-Trichloroethane was detected at 25 of 418 hazardous wastes sites on U.S. EPA's nationwide National Priority List (ATSDR, 1989). With soil sorption coefficient value estimates ranging from 83 to 209, 1,1,2-TCA is moderately to highly mobile in soils. When released to soil, 1,1,2-TCA is partially volatilized into air and partially leached into groundwater. Biodegradation proceeds very slowly, if at all (U.S. EPA, 2001b).

Water

Only 13 of 13,328 groundwater sources of public drinking water tested in California had measurable levels of 1,1,2-TCA. The highest of the 13 concentrations was 40 ppb and the lowest was 0.6 ppb. No 1,1,2-TCA was detected in any of the 755 surface water samples (DHS, 1999). Of 1,069 sites sampled in New Jersey, 8.7 percent had detectable 1,1,2-TCA (ATSDR, 1989). 1,1,2-TCA has been detected in surface water up to 0.6 ppb, tap water at 0.1 to 31 ppb, and in subsurface water up to 350,000 ppb (ATSDR, 1989). When released into surface water, 1,1,2-TCA primarily evaporates. Chemical losses by adsorption to sediment, aquatic hydrolysis, or biodegradation are not likely to be significant (U.S. EPA, 2001b).

METABOLISM AND PHARMACOKINETICS

Absorption

Due to its lipophilic, or fat-soluble, nature, 1,1,2-TCA is readily absorbed via inhalation and dermal routes (CPHF, 1987). There is evidence that 1,1,2-TCA is rapidly absorbed following inhalation by humans. Rats and mice were found to absorb more than half the respective oral doses of 70 mg/kg and 300 mg/kg (Mitoma *et al*., 1985). Human retention of inhaled 1,1,2-TCA vapors would also be expected to be about 50 percent, based on these findings in rats and mice and on the inhalation uptake of similar solvents, including trichloroethylene, in beagle dogs and humans (Raabe, 1986,1988). 1,1,2-TCA is also absorbed through the skin of guinea pigs and mice (Jacobson *et al*., 1977). Tsurata *et al.* (1975) measured the dermal absorption of 1,1,2-TCA after a 15-minute application of 0.5 mL to male ICR mice, producing an estimated absorption rate of about 130 nmole/min-cm^2 of skin. Based on the results, these authors calculated that humans could retain 13.9 mg/minute of 1,1,2-TCA in contact with both hands (Tsurata *et al.*, 1975).

Distribution

Following inhalation by mice of 1000 ppm 1,1,2-TCA for one hour, the highest levels of the compound were detected in the fat. 1,1,2-TCA was also found in kidney, liver, blood, brain and heart in decreasing order of concentration. A single oral administration to rats and mice of 70 and 300 mg 1,1,2-TCA/kg, respectively, resulted in detectable levels in the livers of both species (Mitoma *et al*., 1985). Based on the lipophilic nature of the chemical, the lack of an ionizable functional group, and the results of the dermal absorption studies, it can be concluded that 1,1,2-TCA will readily diffuse into the bloodstream and subsequently distribute to tissues of organs with high fat content (CPHF, 1987).

Metabolism

1,1,2-Trichloroethane is metabolized chiefly in the liver by the cytochrome P-450 system in the endoplasmic reticulum (CPHF, 1987). Mitoma *et al.* (1985) investigated the metabolic disposition of 1,1,2-TCA administered orally to rats and mice at 30 and 70 mg/kg-day, respectively, 5 days/week for 4 weeks, followed by a single dose of ^{14}C-labeled 1,1,2-TCA. The authors determined that 81 percent of the total radiolabeled dose was metabolized in each species. They observed that 1,1,2-TCA undergoes glutathione-dependent metabolism yielding S-carboxy-methylcysteine, thiodiacetic acid and chloroacetic acid (Mitoma *et al.*, 1985). Mazzullo *et al.* (1986) suggested that 1,1,2-TCA undergoes a cytochrome P-450-mediated oxidation process yielding a highly reactive free radical which could react directly with DNA or be oxidized to an electrophile (Mazzullo *et al.*, 1986; CPHF, 1987).

Excretion

Morgan *et al.* (1970) noted that 2.9 percent of the single-breath inhalation dose of 1,1,2-TCA was recovered via the exhaled air of a human volunteer during the first hour following exposure. Compared with 12 other common C_1 and C_2 chlorinated hydrocarbons, 1,1,2-TCA had the lowest excretion rate via exhalation.

Mitoma *et al.* (1985) collected urine, feces and the chamber air of mice and rats for 48 hours after a single oral dose of ^{14}C-1,1,2-TCA. Radioactivity was measured in the urine and feces combined, identified as excreta. CO_2 and volatile metabolites in the chamber air were trapped separately and quantified. The animals were killed at 48 hours after dosing. The livers and kidneys were removed for analysis of ^{14}C-protein binding and the radioactivity remaining in the carcass was measured. The authors observed that rats and mice excreted respectively 72 and 76 percent of an oral dose of 1,1,2-TCA via the urine. Table 2 shows the dose and percent of administered dose recovered in air, excreta and carcass as well as the total recovery.

Table 2. Excretion of 1,1,2-TCA (Mitoma *et al*., 1985)

Species	Dose (mg/kg)	Recovery	Expired Air	CO_2	Excreta	Carcass	Metabolized
		Percent of administered dose					
Rat	70	91	9.5	5.1	72	3.9	81
Mouse	300	88	6.8	3.1	76	2.3	81

TOXICOLOGY

Toxicological Effects in Animals and Plants

Acute Toxicity

White *et al.* (1985) administered 1,1,2-TCA via gavage to male and female CD-1 mice to evaluate acute lethal effects of the chemical. The authors administered one of seven doses ranging from 200 to 600 mg/kg to groups of eight mice of each sex. All mice receiving doses equal to or greater than 450 mg/kg became sedated within an hour. Most deaths occurred within 24 hours, and no deaths occurred after 48 hours. Necropsies revealed a dose-dependant irritation of the upper gastrointestinal tract. Fifty to 75 percent of the animals in each group had pale livers and up to 25 percent demonstrated lung damage of reddened or hemorrhagic areas. The LD_{50} values were 378 mg/kg and 491 mg/kg respectively in male and female mice (White *et al.*, 1985).

The median lethal inhalation concentrations (LC_{50}s) for 6-hour exposures were 1654 ppm in rats (Bonnet, 1980, as cited in ATSDR, 1996) and 416 ppm in mice (Gradiski *et al*.,

1978, as cited in ATSDR, 1989) (both studies in French). These concentrations correspond to approximate dose levels of 1137 mg/kg and 458 mg/kg, respectively. For the rat dose level, we assumed 0.25 m^3/d breathing rate, 0.25 kg body weight, and 50 percent retention. For the mouse dose, we assumed 0.04 m^3/d breathing rate, 0.025 kg body weight, and 50 percent retention. The rodent strains were not stated.

In a study examining the effect of phenobarbital or 3-methylcholanthrene pretreatment on hepatotoxicity of trichloroethanes, Carlson (1973) observed deaths in 3 of 5 rats exposed to 2080 ppm 1,1,2-TCA for 2 hours (approximately 379 mg/kg) and no deaths among 5 rats exposed to 890 ppm for 2 hours (approximately 204 mg/kg). For the rat dose level, we assumed 0.25 m^3/d breathing rate, 0.25 kg body weight, and 50 percent retention. Interestingly, 3-methylcholanthrene potentiated liver toxicity, but only at the higher 1,1,2-TCA concentration. At this higher exposure level, the author observed greater relative liver weights, decreased glucose-6-phosphatase, and increased SGPT and SGOT levels. The group treated with 1,1,2-TCA-only and the 1,1,2-TCA group pretreated with phenobarbital had no hepatic changes at either 1,1,2-TCA dose level.

A lethal dermal dose (LD_{50}) determined in rabbits was 3.73 mL/kg (Smyth *et al*., 1969). Irritation and skin damage were identified in rabbits and guinea pigs, respectively.

Subchronic Toxicity

In a study to determine the potential of selected aliphatic hydrocarbon chemicals to initiate or promote neoplastic progression, Story *et al.* (1986) observed that rats gavaged with 69 mg/kg-d of 1,1,2-TCA 5 days per week for 7 weeks increased body weight at a rate 60 percent less than that of control animals. Male Osborne-Mendel rats, at 10 rats per group, were given partial hepatectomies and examined for initiation or promotion propensities. 1,1,2-Trichloroethane significantly increased the putative neoplastic promotion effect as measured via γ-glutamyltranspeptidase activity (Story *et al*., 1986).

Male and female mice were exposed to plain water or 20, 200, or 2000 ppm of 1,1,2-TCA in water for 90 days (White *et al*., 1985). Control groups for both sexes each had 48 mice and there were 32 mice in each of the exposed groups. The authors calculated time-weighted doses delivered based on fluid consumption and body weights (Table 3). There was a 30 percent decrease in water consumption in male mice at the highest dose level, with no corresponding decrease in females at the high dose level (White *et al*., 1985).

Table 3. Ninety-day Oral Doses of 1,1,2-TCA in Mice (White *et al*., 1986)

1,1,2-TCA Concentration (ppm)	Male Dose (mg/kg-d)	Female Dose (mg/kg-d)
20	4.4	3.9
200	46	44
2000	305	384

Over forty endpoints were monitored in these mice: organ weights, serum chemistry, hematological, and liver microsome parameters including glutathione levels and enzyme activities. For males, both liver and kidney weights were significantly decreased at the mid and upper dosage levels. For females, liver, spleen, and kidney weights increased significantly at the highest dose while brain weights decreased at the highest level and thymus weights decreased at the middle level only. Serum alkaline phosphatase in male mice was significantly elevated only at the highest dose level. In addition, liver glutathione levels in males were significantly decreased at the middle and highest dose level, but not the lowest dose level. Finally, hepatic cytochrome P-450 and aniline hydroxylase activity levels were decreased at the middle and highest, but not the lowest dose in females. While these observations indicate 1,1,2-TCA affects the liver, none of the measured liver parameters represents a serious toxicological effect. In addition, frank liver toxicity was not observed at higher dose levels in either sex of the study. The following table summarizes the subchronic NOAEL and LOAEL for the selected effects.

Table 4. Significant Effect Levels in 90-day Mouse Study (White *et al*., 1986)

Effect Observed (sex)	**LOAEL (mg/kg-d)**	**NOAEL (mg/kg-d)**
Decreased liver and kidney weights (male)	46	4.4
Liver glutathione decrease (male)	46	4.4
Cytochrome P-450 decrease (female)	44	3.9
Aniline hydroxylase decrease (female)	44	3.9

Genetic Toxicity

The results from genetic toxicity testing are not conclusive. Table 5 summarizes the reports from the literature and includes *in vitro* exposure tests (bacteria, yeast, fungi and mammalian cells) and *in vivo* tests. It is important to note that conducting tests *in vitro* with volatile chemicals requires some care to ensure that tests do not yield false negative results. If the chemical volatilizes so that the media concentration is very low, a negative result may occur with a genotoxic chemical. Therefore, the second column of the table indicates if the exposures were conducted in a sealed container such as a desiccator. Many of the non-mammalian species used in these tests lack the enzymes to convert chemicals to potentially reactive intermediates capable of mutating DNA, and mammalian activating enzymes can be added to the media during the exposure, as indicated in the third and fourth columns.

Table 5. Genotoxicity of 1,1,2-TCA

Test Species, Strains	Exposure Conditions	Activation With	Activation Without	Reference
Bacteria Reverse Mutation (Ames assay)				
S. typhimurium TA 1535	Unknown	-	-	Rannug *et al*., 1978
S. typhimurium TA 98, 100, 1535	Desiccator assay, vapor exposure	-	-	Barber and Donish, 1982
S. typhimurium TA 98, 100, 1535, 1537, 1538	Desiccator assay, vapor exposure	-	No data	Simmon *et al.*, 1977
S. typhimurium TA 97, 98, 100, 1535	Desiccator assay, vapor exposure	-	No data	Zeiger *et al*., 1992
Yeast Mutation Assay				
S. cerevisiae D3	Suspension assay	-	-	Simmon *et al.*, 1977
S. cerevisiae D7	Unknown, but other chemicals positive	+	No data	Bronzetti *et al*., 1987
Fungi Chromosomal Effects				
Aspergillus nidulans	Sealed capped glass tube	+	No data	Crebelli *et al*., 1995
Mammalian Cells				
BALB/C-3T3 – viral transformation	Sealed chamber, vapor exposure	No data	+/-	Tu *et al*., 1985
Rat - DNA repair	None	No data	+	Williams, 1983
Mouse - DNA repair	None	No data	-	Williams, 1983
In Vivo Rodent Exposures				
Balb/c (single strand breaks in DNA)	IP injection	-	NA	Taninger *et al*., 1991

Four publications reported 1,1,2-TCA to be negative in *Salmonella typhimurium*, and one paper reported it to be positive in *Saccharomyces*. Surprisingly, 1,1,2-TCA induced DNA repair in hepatocytes isolated from rats but not from mice. The reverse might have been expected because hepatic tumors were observed in mice but not rats (see Carcinogenicity). Additionally, IARC (1999) summarized genetic test results showing that the chemical binds to DNA, RNA and caused strong S-phase induction but not unscheduled DNA synthesis in rodents tested *in vivo*. IARC noted that in vitro testing showed induction of DNA damage and micronuclei in human lymphocytes (IARC, 1999). The overall evidence regarding the genotoxic potential of 1,1,2-TCA is mixed, with some positive evidence for cytogenetic damage in mammalian cells and fungus, and mixed evidence for mutagenic activity in bacteria and yeast.

Developmental and Reproductive Toxicity

In a large comparative study of developmental effects of 55 chemicals in ICR/SIM mice, Seidenberg and coworkers administered a maternal dose of 350 mg/kg-d of 1,1,2-TCA by gavage in corn oil on gestation days 8 through 12. Dams were allowed to deliver normally, but those that had not delivered by GD 21 or 22 were killed and their uteri were examined. Several growth and viability parameters were measured in the offspring as part of an evaluation of the Chernoff/Kavlock developmental toxicity screen. No significant developmental toxic effects of 1,1,2-TCA were observed (Seidenberg *et al*., 1986).

Immunotoxicity

Sanders and coworkers assessed the immunological effect of 1,1,2-TCA on CD-1 mice following oral exposure for 14 or 90 days. For the 14-day range-finding study, male rodents were exposed to 3.8 or 38 mg/kg. The authors observed no alterations in either humoral or cell-mediated immune status. For the 90-day drinking water exposure, males received 4.4, 46, or 305 mg/kg-d and females received 3.9, 44, and 384 mg/kg-d. Cell mediated immunity was unchanged for both sexes. Humoral immune status, determined by hemagglutination titers, was significantly depressed at 46 mg/kg-d, but not at 4.4 mg/kg-d. Therefore, these values were selected as the LOAEL and NOAEL for this study, respectively (Sanders *et al*., 1985).

Neurotoxicity

Kallman and associates (1983) evaluated five halogenated hydrocarbons including 1,1,2-TCA to determine their thresholds for induction of conditioned taste aversion in male CD-1 mice (a sensitive test for adverse neurological effects). The authors administered 3, 10, 30, 100, or 300 mg/kg 1,1,2-TCA to mice once via gavage in acute trials, and once daily for seven consecutive days, with seven mice per dose. When paired with saccharin ingestion, a dose-related aversion to saccharin in drinking water was observed at the two highest levels. Accordingly, the LOAEL for 1,1,2-TCA in this study is 100 mg/kg-d and the NOAEL is 30 mg/kg-d (Kallman *et al.*, 1983). Note that although this is a behavioral test that can be sensitive to neurological (aversive) effects, any adverse effect including gastrointestinal discomfort is capable of inducing conditioned aversion. Therefore this test response is more generally classified as acute toxicity rather than neurotoxicity.

Chronic Toxicity

NCI (1978) studied the effects of technical grade 1,1,2-TCA administered orally in corn oil on rats and mice. Groups of 50 male and female Osborne-Mendel rats were treated via gavage five days per week for 78 weeks. Rats of both sexes received 35 or 50 mg/kg-d of 1,1,2-TCA for 20 weeks. The respective doses were then increased to 50 or 100 mg/kg-d for the remaining 58 weeks. The time-weighted average doses were 46 and 92 mg/kg-d, respectively, for the low and high dose groups for both sexes. The rats were observed for 35 weeks post-treatment.

In the same study, groups of 50 male and female B6C3F$_1$ mice were treated via gavage five days per week for 78 weeks. Mice of both sexes received 150 or 300 mg/kg-d of 1,1,2-TCA for eight weeks. The respective doses were then increased to 200 or 400 mg/kg-d for the remaining 58 weeks. The time-weighted average doses were 195 and 390 mg/kg-d, respectively, for the low and high dose groups for both sexes. The mice were observed for 13 weeks post-treatment.

For both rats and mice, two control groups of 20 animals of each sex received either corn oil alone (vehicle control) or remained untreated. The NCI protocol was designed primarily to test the carcinogenic potential of a chemical, but non-neoplastic lesions were evaluated by a pathologist examining histological sections of the organs of animals by light microscopy. No significant increases in non-neoplastic lesions were reported in the organ systems examined, including liver, in either rats or mice. Therefore the highest doses, 92 mg/kg-d for rats and 390 mg/kg-day for mice, are determined to be chronic NOAELs for noncancer effects in these NCI studies.

Carcinogenicity

Oral Exposure

Only one report examining the carcinogenicity of 1,1,2-TCA in animals from long-term oral exposure was found (NCI, 1978). The details of dosing of rats and mice are described in the *Chronic Toxicity* subsection. Neither sex of Osborne-Mendel rats showed an increased incidence of any type of neoplasm at either of the two doses. In both sexes of B6C3F$_1$ mice in both treatment groups, the incidence of hepatocellular carcinomas was significantly increased above the incidence in control animals. The increases in liver tumor incidence were also dose-dependent, showing a monotonic increase in both sexes. Positive trends with increasing dose were observed for adrenal pheochromocytomas in both male and female mice, although a statistically significant increase over the incidence in control animals was only observed among female mice in the high dose group.

Hepatocellular carcinoma is a neoplasm arising from the most abundant cell in the liver, the hepatocyte. Some strains of mice such as the C57Bl/6 have very high spontaneous incidence rates of this particular tumor. In contrast, C3H mice have a much lower spontaneous rate of hepatocellular carcinoma. The B6C3H is the first generation (F_1) of a cross of the C57Bl/6 and C3H inbred mouse strains. B6C3H mice were selected for conducting carcinogenicity bioassays like that for 1,1,2-TCA because the use of an F_1 hybrid was thought to balance the sensitivity to carcinogens with a moderate background level of hepatocellular carcinoma.

Pheochromocytoma is a neoplasm stemming from a chromaffin cell in the medulla of the adrenal gland. These cells have vesicles that contain the catecholamines epinephrine and norepinephrine. The catecholamines can be oxidized and polymerized after reacting with potassium bichromate (chromaffin reaction). Chromaffin cells appear to be filled with fine brown granules after adrenal tissue sections are stained with potassium bichromate.

In the NCI mouse studies, the authors observed that 1,1,2-TCA produced significant increases in liver tumors, to a relatively high incidence, in a dose-dependent manner in chronic exposure to both male and female mice. Please see Table 6.

Table 6. Hepatocellular Carcinoma Incidence in Mice (NCI, 1978)

	Control (Untreated)	Control (Vehicle)	Low Dose	High Dose
Male	2/17 (12%)	2/20 (10%)	18/49 (37%)	37/49 (76%)
Female	2/20 (10%)	-	16/48 (33%)	40/45 (89%)

The interpretation of the NCI (1978) rat bioassays is limited by the relatively short treatment duration of 78 weeks. Short treatment duration is generally a limitation of negative studies. When less-than-lifetime studies show positive carcinogenicity findings – as this one does in mice – concern is enhanced.

An uncertainty in the NCI studies is the potential presence of toxic impurities in the technical grade 1,1,2-TCA used as the test substance. Three purity tests were performed by gas-liquid chromatography and infrared spectroscopy on the batch of chemical used in these studies, with a determination of 99.2 percent purity at the beginning of the study, and two further determinations of 90.8 percent and 95.4 percent, seven and 13 months into the studies, respectively. The major impurities were not identified in the report (NCI, 1978). The NCI studies were conducted before the implementation of current Good Laboratory Practices (GLP), although no specific evidence casts doubt on the findings (ATSDR, 1989).

Subcutaneous Exposure

Norpoth *et al*. (1988) investigated carcinogenicity in male and female Sprague-Dawley rats subcutaneously injected with 15.4 or 46.8 μmole of 1,1,2-TCA in DMSO once a week for two years. The authors observed an increased incidence of sarcomas, mostly localized on the extremities. The incidence was not significant when compared with vehicle controls, but was significant when compared with untreated controls. No sarcomas were reported in the untreated controls.

Transgenic Mouse Studies

Lifetime rodent bioassays are expensive and time-consuming. There have been a number of efforts to find alternatives that could be used to identify carcinogens more rapidly. Yamamoto *et al*. (1998) developed a transgenic strain of C57BL/6J mice having 5 or 6 copies of the human c-Ha-*ras* gene integrated into its genome. The F_1 generation from a cross of males of this transgenic genotype with normal female BALB/cByJ were exposed to a variety of chemicals of known carcinogenic potential for 26 weeks or less and examined for tumors. Validation studies have been conducted to determine if these mice

will predict the carcinogenic human potential of a chemical such as animal bioassays using $B6C3F_1$ mice and Fischer rats. 1,1,2-TCA was selected as a chemical that, according to the authors, was carcinogenic but not mutagenic. In this study, 1,1,2-TCA induced no tumors, despite doses of chemical that were high enough to induce evidence of liver toxicity (Yamamoto *et al.*, 1998).

Toxicological Effects in Humans

Acute Toxicity

The human data available to evaluate the toxicity of 1,1,2-TCA are "very limited" (RAIS, 2002). The chemical is rapidly absorbed by the body and has a narcotic effect at "low" concentrations. Exposure to 1,1,2-TCA is irritating to eyes and the mucous membranes of the respiratory tract (RAIS, 2002).

Wahlberg *et al.* (1984) observed that a five-minute exposure of 698 mg 1,1,2-TCA/cm^2 to the forearm skin of a healthy male subject resulted in erythema as assessed by laser Doppler flowmetry. The subject reported a stinging or burning sensation (Wahlberg, 1984).

Subchronic Toxicity

No human studies were found.

Genetic Toxicity

IARC (1999) reports that 1,1,2-trichloroethane induced DNA damage and micronuclei in *in vitro* testing of human lymphocytes.

Developmental and Reproductive Toxicity

No human studies were found.

Immunotoxicity

No human studies were found.

Neurotoxicity

No human studies were found.

Chronic Toxicity

No human studies were found.

Carcinogenicity

Dosemeci *et al.* (1999) examined potential risk of renal cell carcinoma from occupational exposures to chlorinated aliphatic hydrocarbons, with an emphasis on gender differences. Among women, significantly elevated relative risks of renal cell carcinoma were associated with exposure to "all organic solvents" (odds ratio [OR] = 2.3, confidence interval [CI] = 1.3-4.2), "all chlorinated aliphatic hydrocarbons combined" (OR = 2.1, CI = 1.1-3.9), and to trichloroethylene alone (OR = 2.0, CI = 1.0-4.0), but not to 1,1,2-TCA alone. None of the comparisons were significant for men. Exposure levels were low for individual solvents, so statistical power was limited

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

In humans, exposure to 1,1,2-TCA can cause irritation to skin and mucous membranes and has a narcotic effect. In experimental animals, there were no non-neoplastic adverse effects reported in the only chronic oral exposure study identified (NCI, 1978). The 90-day drinking water study in mice (White *et al*., 1985) described in the Subchronic Toxicity subsection provides the best study on which to estimate a health-protective concentration for drinking water for non-cancer effects because the nature of the exposure is the closest to the human drinking water exposure conditions. In addition, the effect level identified for this study is the lowest of the available studies. The liver was clearly affected by 1,1,2-TCA in both male and female mice at the middle and highest but not the lowest dose. A LOAEL of 44 mg/kg-d and NOAEL of 3.9 mg/kg-d were selected based on liver effects in female mice. For comparison, the chronic time-weighted average doses in the NCI (1978) mouse study were 195 and 390 mg/kg-d, respectively, for the low and high dose groups, for both sexes.

Carcinogenic Effects

Based upon the increased incidence of liver tumors observed in both male and female mice treated with two doses of 1,1,2-TCA, and on the development of pheochromocytomas in both sexes of mice, this compound should be treated as a potential human carcinogen. The mechanism by which these tumors are induced in mice is not presently understood. Although not all tests for genotoxicity were positive, some evidence for genetic damage (*e.g.*, cytogenetic damage) may point to the involvement of this mechanism in the tumors induced by 1,1,2-TCA.

1,1,2-TCA appears on the Proposition 65 list of chemicals known to cause cancer (as vinyl trichloride). A Proposition 65 No Significant Risk Level of 10 micrograms/day has been promulgated based upon the liver tumor findings in female mice, which appear to be slightly more sensitive than male mice to the carcinogenic effects of 1,1,2-TCA, resulting in a calculated human oral cancer potency estimate of 0.072 $(mg/kg\text{-}d)^{-1}$ (OEHHA, 1992,

1999). U.S. EPA (2004) has estimated a carcinogenic potency of 0.057 $(mg/kg\text{-}d)^{-1}$ for 1,1,2-TCA based on the male mouse hepatocellular carcinoma data from NCI (1978).

CALCULATION OF PHG

Calculations of concentrations of chemical contaminants in drinking water associated with negligible risks for carcinogens or noncarcinogens must take into account the toxicity of the chemical and the potential exposure of individuals using the water.

Exposure Considerations

Tap water is used directly as drinking water and also is used for showering and other household uses. The inhalation exposure while showering may contribute more to the daily dose than drinking, depending on the volatility of the chemical, while exposure resulting from the other household uses of drinking water is often much smaller. McKone (1987) has developed a mathematical model for predicting volatile organic chemical concentrations in shower air based on water concentration, water flow rates and ventilation. This model was developed largely using the chemical trichloroethylene.

$$Dose = \frac{BR_{hr} \times ET}{BW} \times Cw \times 3000000 \left[\frac{2.5}{Dw} + \frac{298\ R \times Zw}{\left(Da / 86400 \right)^{2/3}} \right]^{-1} \times 0.6 \frac{W}{VR}$$

Dose	=	daily dose from inhalation while showering (mg/kg-d);
BR_{hr}	=	breathing rate (0.833 m^3/hr);
BW	=	body weight (70 kg);
ET	=	exposure time in shower (0.27 hr/d);
Cw	=	concentration in water (1.0 mg/L);
Dw	=	diffusion coefficient in water (0.0001 m^2/d);
R	=	gas constant (8.31 Pa-m^3/mol-K);
Zw	=	fugacity capacity of pure water (0.001 mol/Pa-m^3);
Da	=	diffusion coefficient in air (0.61 m^2/d);
W	=	water use in the shower (8.0 L/min);
VR	=	bathroom ventilation rate (1.0 m^3/min).

1,1,2-Trichloroethane has physical and chemical properties very similar to trichloroethylene. Therefore, this equation was used to determine the human daily exposure dose to 1,1,2-TCA from showering. The daily dose computed by the equation above is 0.029 mg/kg-d. Assuming that a 70-kg person consumed 2 liters of water per day with the concentration assumed in the shower water of 1.0 mg/L, that person would

get an additional dose of 0.029 mg/kg-d. Therefore, a person would receive the sum of the drinking water and shower inhalation doses of 0.058 mg/kg-d. This corresponds to an equivalent drinking water exposure (or L_{eq}) of 4 L/day. This value will be used in the calculation of a health-protective level for 1,1,2-TCA.

Noncarcinogenic Effects

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

$$C = \frac{NOAEL \times BW \times RSC}{UF \times WC} = \text{mg/L}$$

where,

NOAEL	=	no-observed-adverse-effect-level (3.9 mg/kg-d);
BW	=	adult body weight (70 kg);
RSC	=	relative source contribution (80 percent);
UF	=	uncertainty factor of 10,000, which includes factors of 10 for inter-species extrapolation, 10 for subchronic to chronic extrapolation, 10 for potentially sensitive human subpopulations, and 10 for potential carcinogenicity;
WC	=	equivalent daily water consumption/contact rate (4 L_{eq}/d).

The 90-day drinking water study in mice (White *et al*., 1985) was used to determine a LOAEL of 44 mg/kg-d and a NOAEL of 3.9 mg/kg-d based on liver effects in female mice. Using these parameter values, a health-protective value (C) is calculated as follows:

$$C = \frac{3.9 \text{ mg/kg-d} \times 70 \text{ kg} \times 0.8}{10{,}000 \times 4\ L_{eq}/d} = 0.005 \text{ mg/L} = 5 \text{ ppb}$$

Based on this calculation, the noncancer health-protective value for 1,1,2-TCA in drinking water is 5 ppb.

Carcinogenic Effects

Calculation of carcinogenic potency utilizes the following equation:

$$C = \frac{R \times BW}{CPF \times L/day} = \text{mg/L}$$

where,

R	=	*de minimis* level for lifetime excess individual cancer risk (a default of 10^{-6});
BW	=	body weight for an adult male (70 kg);
CPF	=	the cancer potency factor or the oral potency slope; the CPF for 1,1,2-TCA is 0.072 $(mg/kg\text{-}day)^{-1}$;
L/day	=	volume of drinking water consumed by an adult; the default is 2 L/d, but multiroute exposures should be considered as discussed above.

Therefore,

$$C = \frac{(1x10^{-6}) \ x \ 70 \text{ kg}}{(0.072) \ x \ 4 \ L_{eq}/\text{day}} = 0.00024 \text{ mg/L or } 0.2 \text{ ppb (rounded)}$$

Based on the above considerations, the estimated health-protective concentration for carcinogenicity is much lower than for non-cancer effects. We propose a PHG value of 0.2 ppb for 1,1,2-TCA based on a cancer risk level of one cancer in a million people exposed for a lifetime to the chemical in their drinking water. The equivalent concentration in drinking water at a risk level of one in 10,000 would be 20 ppb, and at 1 in 100,000 would be 2 ppb.

RISK CHARACTERIZATION

The recommendation of the PHG value was based on carcinogenic, rather than non-cancer effects, for two reasons. First, the cancer-based PHG is lower than the non-cancer by a factor of over 20, and thus more health protective. Second, the non-cancer PHG calculation had a greater than typical amount of uncertainty associated with its derivation, to the point of an uncertainty divisor of 10,000 when a factor for uncertainty about carcinogenicity is added. Other sources of uncertainty in the development of the health-protective value for non-cancer endpoints for 1,1,2-TCA in drinking water are also the general issues of uncertainty in many risk assessments, particularly mode of action and inter- and intra-species extrapolations. The subchronic duration of the critical noncancer study provides additional uncertainty in this case. Uncertainty in the relative source contribution (RSC) is relatively minimal for this solvent, because there are few if any other common sources of 1,1,2-TCA.

The proposed carcinogenic effect-based PHG, however, also includes uncertainty. The frank carcinogenicity in animals was only found in one species, albeit both sexes and two tissues of origin. 1,1,2-Trichloroethane was shown to result in statistically significant increases in hepatocellular carcinoma at two doses and pheochromocytoma at the high dose in $B6C3F_1$ mice of both sexes. Concern for a carcinogenic endpoint is generally enhanced by a positive cancer data in more than one species, or from replicate positive studies in the same species. However, in the case of 1,1,2-TCA, concern is also increased by evidence of a dose-related increase in the carcinogenic response and by the magnitude of the response. The fact that 1,1,2-TCA was positive in only one species resulted in

U.S. EPA classifying it as a "possible" (group C), rather than "probable," human carcinogen. The International Agency for Research on Cancer has classified 1,1,2-TCA as "not classifiable as to its carcinogenicity to humans" (Group 3) based upon limited evidence in experimental animals and the absence of epidemiological evidence (IARC, 1999). However, IARC notes the ability of 1,1,2-TCA to bind to DNA, RNA and protein, cause strong S-phase induction in rodents *in vivo*, and induce DNA damage and micronuclei in human lymphocytes and cell transformation in BALB/c-3T3 cells *in vitro* (IARC, 1999). Such effects can indicate potential carcinogenicity.

1,1,2-TCA did not produce a tumor response following relatively short-term exposures when tested in a transgenic strain of C57BL/6J mice with 5 or 6 integrated copies of the human c-Ha-*ras* gene. Other hepatocarcinogens have caused liver tumors in these transgenic mice. Further complicating interpretation of the available data, 1,1,2-TCA increased putative preneoplastic lesions in rats in a study examining tumor promotion properties (Story *et al.*, 1986; see Subchronic Toxicity section).

Confirmatory studies, such as human epidemiological corroboration and *in vitro* genetic toxicity testing, were generally absent, negative or inconclusive, although the number of tests was relatively small. OEHHA considers it prudent to assume carcinogenicity of 1,1,2-TCA for this risk assessment purpose, which is to estimate a concentration of the solvent in drinking water that is unlikely to provide any toxic hazard after a lifetime of exposure. OEHHA considers that the proposed PHG value of 0.2 ppb is adequately health protective for potential sensitive subpopulations, including infants, children, and the elderly.

OTHER REGULATORY STANDARDS

U.S. EPA proposed a federal Maximum Contaminant Level Goal (MCLG) of 0.003 mg/L and an MCL of 0.005 mg/L for 1,1,2-TCA in 1990 (U.S. EPA, 1990) and finalized these two criteria in 1992 (U.S. EPA, 1992). The federal MCLG is computed using a NOAEL from a 90-day drinking water exposure study in mice (Sanders, 1985; White, 1985) and a safety factor of 10,000, whereas the MCL is set at the practical quantitation limit (U.S. EPA, 2002). California subsequently promulgated an MCL for 1,1,2-TCA of 0.005 mg/L (DHS, 2002), consistent with the U.S. EPA MCL. U.S. EPA recently reviewed their primary drinking water regulations and concluded that it might be possible to decrease the MCL from the present value of 0.005 mg/L based on methodological improvements since the original regulation was promulgated (U.S. EPA, 2002). However, the U.S. EPA concluded that a revision to the MCL is not warranted at this time, because 1,1,2-TCA is very rarely detected in drinking water at concentrations exceeding the MCLG.

The available regulatory standards and guidelines are summarized in Table 7, below.

Table 7. Selected Guidelines and Regulations for 1,1,2-Trichloroethane

Agency	Standard or Criterion	Level	Comment
ACGIH	TLV-TWA	10 ppm	8-hr work day
OSHA	PEL (permissible exposure limit)	10 ppm	8-hr work day
U.S. EPA	MCL (maximum contaminant level)	0.005 mg/L	
U.S. EPA	MCLG (maximum contaminant level goal)	0.003 mg/L	
U.S. EPA	Ten-day Health Advisory	0.40 mg/L	
CDHS	MCL (maximum contaminant level)	0.005 mg/L	Based on U.S. EPA MCL

Table adapted from ATSDR (1989), NIOSH (1994), U.S. EPA (2001), DHS (2003).

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