

**PUBLIC HEALTH GOALS FOR
CHEMICALS IN DRINKING WATER**

1,1,1-TRICHLOROETHANE

March 2006

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**Public Health Goal for
1,1,1-TRICHLOROETHANE
in Drinking Water**

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PREFACE

**Drinking Water Public Health Goal
Pesticide and Environmental Toxicology Branch
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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 (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 that may cause chronic disease shall be based solely on health effects 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 potential adverse effects on members of subgroups that comprise a meaningful proportion of the population, including but not limited to infants, children, pregnant women, the elderly, and individuals with a history of serious illness.
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. OEHHA shall consider additive effects of exposure to contaminants in media other than drinking water, including food and air, and the resulting body burden.
7. In risk assessments that involve infants and children, OEHHA shall specifically assess exposure patterns, special susceptibility, multiple contaminants with toxic mechanisms in common, and the interactions of such contaminants.

8. In cases of insufficient data for OEHHA to determine a level that creates no significant risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.
9. 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.
10. The PHG may be set at zero if necessary to satisfy the requirements listed above in items seven and eight.
11. PHGs adopted by OEHHA shall be reviewed at least once 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 or technical feasibility, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. Each primary drinking water standard adopted by DHS 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 state and 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.

TABLE OF CONTENTS

LIST OF CONTRIBUTORS	II
PREFACE	III
TABLE OF CONTENTS	V
PUBLIC HEALTH GOAL FOR 1,1,1-TRICHLOROETHANE IN DRINKING WATER	1
SUMMARY	1
INTRODUCTION	1
CHEMICAL PROFILE	2
Chemical Identity.....	2
Physical and Chemical Properties	2
Production and Uses	3
ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE	4
Air	4
Soil.....	4
Water.....	5
Food	5
METABOLISM AND PHARMACOKINETICS	5
Absorption	5
Distribution	6
Metabolism	6
Excretion.....	7
TOXICOLOGY	8
Toxicological Effects in Animals	8
Acute Toxicity	8
Subchronic Toxicity.....	10
Genetic Toxicity	13
Developmental and Reproductive Toxicity	14

Immunotoxicity.....	15
Neurotoxicity	15
Chronic Toxicity	16
Carcinogenicity.....	17
Toxicological Effects in Humans	17
Acute and Short Term Toxicity	18
Developmental and Reproductive Toxicity	19
Immunotoxicity.....	19
Neurotoxicity	19
Chronic Toxicity	21
Carcinogenicity.....	21
DOSE-RESPONSE ASSESSMENT.....	22
Noncarcinogenic Effects.....	22
Carcinogenic Effects.....	23
CALCULATION OF PHG	23
Exposure Considerations	24
Noncancer Effects.....	24
Carcinogenic Effects.....	25
RISK CHARACTERIZATION	25
OTHER REGULATORY STANDARDS.....	25
REFERENCES	27

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

SUMMARY

The Office of Environmental Health Hazard Assessment (OEHHA) hereby establishes a Public Health Goal (PHG) of 1.0 mg/L or 1.0 parts per million (ppm) for 1,1,1-trichloroethane (1,1,1-TCA), or methyl chloroform (CASRN 71-55-6) in drinking water. The PHG is based on the non-cancer toxic effects in a subchronic inhalation study performed by Rosengren *et al.* (1985). The authors reported astrogliosis in the cerebral cortex of gerbils after 3-month inhalation exposures to 70, 210, or 1,000 ppm of 1,1,1-TCA, with the lowest concentration being the no observed adverse effect level (NOAEL) for the study (Rosengren *et al.*, 1985).

A lowest observed adverse effect level (LOAEL) of 230 mg/kg-d and a NOAEL of 76 mg/kg-d based on neurological effects were estimated for the Rosengren *et al.* (1985) study. A combined uncertainty factor of 1,000 was applied to this endpoint, comprised of 10 each for extrapolation from a subchronic study, 10 for interspecies extrapolation, and 10 for human variability. A relative source contribution value of 0.8 was used, because discontinuance of use of 1,1,1-TCA under the Montreal Protocol has greatly decreased its presence in the environment, so significant exposure from other sources is unlikely. The calculation also utilized an adult body weight of 70 kg and a combined-route estimate of exposure to the 1,1,1-TCA contained in 4 L of drinking water per day. The resulting value is judged to be health protective for sensitive subpopulations, including infants, pregnant women, and the elderly.

Although there have been three chronic studies on the carcinogenicity of 1,1,1-TCA, none of them are judged adequate for evaluating the potential carcinogenicity of this chemical. The U.S. Environmental Protection Agency (U.S. EPA) has classified 1,1,1-TCA as a group D chemical (not classifiable as to human carcinogenicity) based on the lack of reported human data and the inadequacy of the available animal studies (U.S. EPA, 2002a; IRIS, 2004). The current maximum contaminant level (MCL) drinking water standard set by U.S. EPA and the California Department of Health Services (DHS) for 1,1,1-TCA is 0.2 mg/L (U.S. EPA, 2001; CDHS, 2003).

INTRODUCTION

The purpose of this document is to develop a PHG for the chlorinated hydrocarbon solvent 1,1,1-trichloroethane 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 1,1,1-TCA in drinking water than was used in the prior risk assessment used to compute the existing California MCL. This document is not intended to provide an exhaustive review of all aspects of the use and toxicology of 1,1,1-TCA, but to focus on the lowest doses causing critical toxic effects

that may contribute to public health concerns from exposure to the solvent in drinking water.

CHEMICAL PROFILE

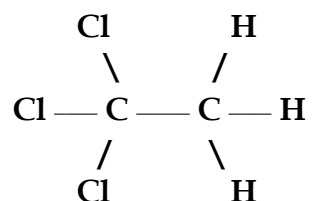
Chemical Identity

Table 1. Chemical Identity of 1,1,1-Trichloroethane

Parameter	Property or Value
Chemical name	1,1,1-Trichloroethane
Synonyms	Methylchloroform, Methyltrichloromethane, Trichloromethylmethane, alpha- Trichloromethane, Solvent 1,1,1, Chlorten, Inhibisol
Registered trade name	Chlorothene NU, Aerothene TT
Chemical formula	C ₂ H ₃ Cl ₃
NIOSH RETCS	KJ2975000
CAS Registry Number	71-55-6

Sources: (ATSDR, 1995; U.S. EPA, 2001)

Figure 1. Chemical structure of 1,1,1-trichloroethane



Physical and Chemical Properties

1,1,1-Trichloroethane is a colorless, volatile chemical, liquid at room temperature. It is sparingly soluble in water, and although combustible, burns with difficulty (NIOSH, 1994). 1,1,1-TCA has a sweet yet sharp chloroform-like odor (U.S. EPA, 2002a). The physical and chemical properties relevant to assessing human exposure to 1,1,1-TCA are provided in Table 2.

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

Property	Value or Information	References
Molecular weight	133	Pearson, 1983
Color	Colorless	U.S. EPA, 2002a
Physical state	Liquid	U.S. EPA, 2002a
Odor	Chloroform-like, sweet	U.S. EPA, 2002a
Melting point	-30.4 °C	U.S. EPA, 2001
Boiling point	74.1 °C	Pearson, 1983
Flash point	N/A	U.S. EPA, 2001
LEL / UEL	7.5% / 12.5%	NIOSH, 1994
Solubility, water	0.48 g/L at 20 °C	Pearson, 1983
Specific gravity, density	1.34 g/mL at 20 °C	U.S. EPA, 2001
Octanol/water partition coefficient log K _{ow}	2.49	U.S. EPA, 2001
Water/air partition coefficient	0.71 at 20°C	Pearson, 1983
Vapor pressure	127 mm Hg at 25 °C	U.S. EPA, 2001
Conversion factor	1 ppm = 5.55 mg/m ³	NIOSH, 1994

Production and Uses

Several methods are used for industrial preparation of 1,1,1-TCA. Commercial grades of 1,1,1-TCA usually contain inhibitors to retard reaction with metals that also may be found as contaminants. These inhibitors, which function as preservatives, include nitromethane, methyl ethyl ketone, toluene, 1,4-dioxane, butylene oxide, 1,3-dioxolane, and secondary butyl alcohols (U.S. EPA, 1984; ATSDR, 1995). Other potential impurities are 1,2- and 1,1-dichloroethane, chloroform, carbon tetrachloride, trichloroethylene, 1,1,2-TCE, and vinylidene chloride (HSDB, 2005). Although several of these are rodent carcinogens (e.g., 1,4-dioxane, chloroform, carbon tetrachloride, trichloroethylene, dichloroethanes, epichlorohydrin, and 1,1,2-TCE) and others have other known toxicities, it is considered beyond the scope of this evaluation to review the toxicology of these additives and impurities.

1,1,1-Trichloroethane was “developed initially as a safer solvent to replace other chlorinated and flammable solvents” (ATSDR, 1995). 1,1,1-Trichloroethane was used principally as a solvent and a degreasing agent in industry. The compound was used as a vapor degreasing agent for metal products, a solvent and carrier for ingredients used in aerosols, household cleaners, glues, inks, drain cleaners and as a postharvest fumigant

and solvent for various insecticides (U.S. EPA, 2001; U.S. EPA, 2002a; ATSDR, 1995). A “shopping basket” survey revealed in 1992 that 1,1,1-TCA was found in 216 of 1,159 common household products selected as likely to contain solvents (ATSDR, 1995).

United States industrial demand was estimated at 700 million pounds in 1988, and was projected to grow from there to 735 million pounds in five years (U.S. EPA, 2001). However, as a result of the Montreal Protocol on Substances that Deplete the Ozone Layer (an international agreement which controls the production and trade of ozone depleting chemicals among over 120 countries) 1,1,1-TCA was to be fully phased out of production and importation as of January, 1996 (HSIA, 1994; U.S. EPA, 1993). This was later amended for a U.S. production phase-out in 2002 (LII, 2005). The substantial emissions into California air reported in 2003 (CARB, 2003) indicate that the phase-out has been prolonged, perhaps due to use of remaining stocks of the solvent.

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Air

Most of the 1,1,1-TCA in the environment will partition into the air medium. Neely (1982) estimated that under environmental conditions, more than 99 percent of 1,1,1-TCA would distribute into the air compartment, while 0.08 percent would be in the water and zero in benthic sediments or soil. The World Health Organization (WHO) as well as the Halogenated Solvents Industry Alliance (HSIA) reported that 1,1,1-TCA has a tropospheric residence time of about six years (WHO, 1992; HSIA, 1994). 1,1,1-Trichloroethane is considered a stratospheric ozone-depleting chemical, although its ozone depleting potential is ten-fold lower than the chlorofluorocarbon CFC-11, and the global warming potential is about 40-fold lower. Generally, 1,1,1-TCA reacts with hydroxyl radicals in the troposphere and photodegrades in the stratosphere (WHO, 1992). Of all the chloroethanes, 1,1,1-TCA is the least photoreactive (Spence and Hanst, 1978).

Emissions of 1,1,1-TCA into the air in California have been decreasing for several years, in accordance with its scheduled phase-out under the Montreal Protocol. Statewide monitored median and mean concentrations of 1,1,1-TCA, as monitored by the California Air Resources Board, have been generally declining; decreasing from 0.8 or 1.71 parts per billion (ppb) in 1990 to 0.12 or 0.30 ppb in 1996 (OEHHA, 2000). However, total emissions of 1,1,1-TCA into California air were reported as 846,000 pounds (as methyl chloroform) in the California Air Resources Board’s 2003 summary (CARB, 2003).

Soil

1,1,1-Trichloroethane is generally not strongly adsorbed to most soils, especially soils beneath the upper surface. The chemical is strongly adsorbed to soils with high organic carbon content, such as peat moss. The chemical is less strongly attached to clay and even less strongly adsorbed to sand. 1,1,1-Trichloroethane has the capability to pass right through soil banks, and into groundwater (U.S. EPA, 2001). Degradation of the chemical is typically slow or non-existent in soil. Slow degradation has been observed in loamy

soil in both aerobic and anaerobic conditions. Such degradation can take weeks or longer (U.S. EPA, 2001). Under anaerobic conditions, biodegradation to 1,1-dichloroethane and chloroethane has been observed (WHO, 1992). The principal removal mechanism of this chemical from soil is evaporation to the atmosphere (U.S. EPA, 2001).

Water

When 1,1,1-TCA was in heavy industrial use, it could enter the groundwater as a residual contaminant from industrial processes such as degreasing and cleaning. An additional route was leaching from landfills (U.S. EPA, 2001). As the production of 1,1,1-TCA has now virtually ceased and these uses have now been curtailed (HSIA, 1994; U.S. EPA, 1993), the contamination of water has correspondingly diminished.

1,1,1-Trichloroethane evaporates from water surfaces, with evaporation half-time ranges of a few hours (laboratory), 3-29 hours (rivers), and about 4-12 days for ponds, and a biodegradation half-life in aquifers of 321 days. The chemical is slightly soluble in water with a solubility of 0.48 g/L at 20 °C (Pearson, 1982). 1,1,1-Trichloroethane is slowly degraded in water to 1,1-dichloroethene (especially under alkaline conditions) and hydrolyzed to ethanoic acid (WHO, 1992).

Food

1,1,1-Trichloroethane is not thought to bioconcentrate in aquatic organisms and accordingly, is not believed to biomagnify within the food web (ATSDR, 1995).

Since the chemical is no longer used in equipment cleaning and food packaging, human exposure via the food route is not expected to be significant.

METABOLISM AND PHARMACOKINETICS

Absorption

1,1,1-Trichloroethane is absorbed by inhalation, ingestion, and, to a lesser extent, dermally. As 1,1,1-trichloroethane enters the environment principally via evaporation into the atmosphere (WHO, 1992) inhalation is the more likely route of exposure. Rate of absorption through the respiratory tract depends on ventilation rate during short-term exposures. As the duration of exposure increases, the percent absorbed decreases as steady-state levels are reached in the blood and tissues (ATSDR, 1995). Absorption through the skin, especially under occluded conditions, and through the gastrointestinal tract also occurs, but these are less important routes than inhalation. Absorption from the gastrointestinal tract is more rapid when given in water than when administered in oil-based vehicles. Percutaneous absorption of 1,1,1-TCA from aqueous solutions or soil is judged to be insignificant from non-occluded exposures (Poet *et al.*, 2000).

1,1,1-Trichloroethane is rapidly absorbed via the lungs (IPCS, 2002; Dallas *et al.*, 1989). In humans, about 25 to 40 percent of the inhaled dose is absorbed over exposures of six

to eight hours (WHO, 1992; Dallas *et al.*, 1989). Dallas *et al.* (1989) examined 1,1,1-TCA uptake and elimination for SP rats by direct measurement of inhaled and exhaled compound. The authors found that during a 2-hour test at 50 or 500 ppm, that the percentage of uptake decreased 30-35 percent during the first hour and diminished to about 45 percent by the end of the 2-hour exposure (Dallas *et al.*, 1989). As steady state is approached, absorption is expected to be lower, because 1,1,1-TCA is poorly metabolized (WHO, 1992). WHO (2002) assumed an inhalation absorption factor of 30 percent in their analysis of a subchronic mouse inhalation study.

Nolan and colleagues (1984) used human subjects for an exposure to 1,1,1-TCA. Six male Caucasians, ranging in age from 26 to 54 years, weighing between 77 and 106 kg were exposed as a group for 6 hours to 35 ppm 1,1,1-TCA. Three weeks later, the same group was exposed to 350 ppm. Blood, expired air, and urine samples were taken; the authors calculated that about 25 percent of the inhaled 1,1,1-TCA was absorbed (Nolan *et al.*, 1984).

Tsurata *et al.* (1975) compared the percutaneous absorption of 1,1,1-TCA to seven other chlorinated solvents by quantitating their absorption *in vivo* through mouse skin. 1,1,1-Trichloroethane was among the chemicals with the lowest rates of percutaneous absorption, at 45.7 nmoles/mm/cm² of skin. The author established a direct correlation between water solubility and percutaneous absorption for eight chlorinated solvents in the study, with 1,1,1-TCA's limited water solubility corresponding with its relatively poor skin absorption (Tsurata, 1975).

Animal data suggest that uptake of 1,1,1-trichloroethane via the oral route is nearly complete. In its review of the pharmacokinetic data from Reitz *et al.* (1988), WHO (1992) concluded that the chemical is readily taken up from the G.I. tract. Similarly, ATSDR (1995) inferred from the Reitz *et al.* (1988) PBPK data that rats absorbed approximately 95 percent of the orally administered dose.

Distribution

1,1,1-Trichloroethane is widely distributed within body tissues, with higher concentrations found in tissues with higher lipid content such as adipose tissue and brain. The chemical crosses blood-brain and blood-placental barriers (WHO, 1992).

Metabolism

In a study with human volunteers, Nolan and coworkers (1984) found that only 5-6 percent of inhaled 1,1,1-TCA was metabolized, and subsequently excreted as either trichloroethanol or trichloroacetic acid. The metabolites were measured in both the urine and the blood (Nolan *et al.*, 1984).

Mitoma *et al.* (1985) performed a metabolic disposition study of several chlorinated hydrocarbon solvents, including 1,1,1-TCA, on rats and mice. Male Osborne-Mendel rats and B6C3F₁ mice were orally dosed at the NCI-determined maximum tolerated dose and also at one-quarter of that MTD. For rats, the daily MTD of 1,1,1-TCA in corn oil was 3,000 mg/kg-day; and, for mice, the dose was 4,000 mg/kg-day for 5 days/week for 4

weeks, followed by a single dose of radiolabeled compound. The rodents were then kept in metabolism cages for 48 hours. The authors observed that 1,1,1-TCA was largely eliminated (70-93 percent) unchanged in expired air (Mitoma *et al.*, 1985). Table 3 summarizes the metabolic disposition results of Mitoma *et al.* for 1,1,1-TCA in rats and mice.

Table 3. Metabolic Disposition of 1,1,1-Trichloroethane in Rats and Mice, Expressed as Average Percentage of Administered Dose

	Expired Air	CO ₂	Excreta	Carcass	Recovery	Percent Metabolized
Rats	85.13	0.87	2.05	1.20	89	4.12
Mice	92.94	2.01	3.36	0.72	99	6.09

Table adapted from Mitoma *et al.* (1985) Table 1.

Rats administered the chemical in drinking water exhaled greater than 90 percent of the unchanged compound. The authors recovered about 3 percent of the absorbed 1,1,1-TCA as CO₂ and in the urine as metabolized compound (Reitz *et al.*, 1988).

Wang *et al.* (1996) examined the comparative effects of exposure to four organic solvents on selected cytochrome P450 isoenzymes in male Wistar rats. Groups of five rats were exposed to 4,000 ppm of benzene, toluene, trichloroethylene, or 1,1,1-TCA for six hours in a dynamic inhalation exposure chamber. Following termination, liver microsomes were prepared and tested for enzyme activity. Toluene, benzene, and trichloroethylene each resulted in increases in the activities of nitrosodimethylamine demethylase and 7-pentoxoresorufin o-depentylase; however 1,1,1-TCA exposure resulted in little difference from controls for these enzyme activities. Similarly, 1,1,1-TCA exposure resulted in no significant induction of CYP2E1 and CYP2B1/2 (Wang *et al.*, 1996), although this is a relatively short exposure duration for enzyme induction. Other workers have described a stimulation of hepatic drug-metabolizing enzymes by 1,1,1-TCA in mice (Shah and Lal, 1976; Lal and Shaw, 1970) and rats (Fuller *et al.*, 1970, Bruckner *et al.*, 2001).

Excretion

Excretion of unchanged 1,1,1-TCA via exhalation from the lungs accounts for greater than 90 percent of the absorbed dose, regardless of the route of exposure (Nolan *et al.*, 1984; Mitoma *et al.*, 1985; Reitz *et al.*, 1988; WHO, 1992; U.S. EPA, 1984). 1,1,1-Trichloroethane metabolites, principally trichloroethanol and trichloroacetic acid, are excreted in the urine (Nolan *et al.*, 1984; U.S. EPA, 1984)

Nolan *et al.* 1984 observed the kinetics and metabolism of 1,1,1-TCA in six male humans following the inhalation of either 35 or 350 ppm for a single dose over six hours. Approximately 25 percent of the inhaled dose was absorbed; and, then eliminated in three phases with half-lives of 44 minutes, 5.7 hours, and 53 hours. Less than one percent remained after nine days (Nolan *et al.*, 1984).

TOXICOLOGY

Toxicological Effects in Animals

Acute Toxicity

Numerous studies of animal lethality of 1,1,1-TCA exposure were reviewed by ATSDR (1995), WHO (1992), and U.S. EPA (1984). Acute lethal toxicities reported for oral and inhalation exposures and intraperitoneal injection are generally quite low (WHO, 1992). Table 4 summarizes some of the more germane acute lethality study results across several species and routes of administration. Death from acute exposure to 1,1,1-TCA results from central nervous system depression and respiratory arrest (WHO, 1992; Pise *et al.*, 1998). At sublethal levels, some key acute effects observed in animals are acute sedation, psychomotor changes, blood pressure depression, cardiac dysrhythmia, and mild hepatic effects (WHO, 1992; Pise *et al.*, 1998; Xia and Yu, 1992; Warren *et al.*, 2000; Bruckner *et al.*, 2001; U.S. EPA, 2002a).

Table 4. Acute Lethal Toxicity Values for 1,1,1-Trichloroethane

Species	Sex	Route	LD ₅₀ mg/kg	LC ₅₀ ppm	Ref	Comment
Rat	M	Oral	14,300		1	
Rat	F	Oral	11,000		1	
Mouse	F	Oral	9,700		1	
Guinea pig	Both	Oral	8,600		1	
Rat	Both	Inhalation		18,000	2	3 hr exposure
Rat	M	Inhalation		10,300	3	6 hr exposure
Mouse	M	Inhalation		3,910	4	2 hr exposure
Rat	M	i.p.	5,054		5	
Mouse	M	i.p.	16,000		6	

References: (1) Torkelson *et al.*, 1958; (2) Adams *et al.*, 1950; (3) Bonnet *et al.*, 1981; (4) Horiguchi and Horiguchi, 1971; (5) Klaassen and Plaa, 1966; and (6) Plaa *et al.*, 1958.

Table adapted from U.S. EPA, 1984; WHO, 1992; and ATSDR, 1995.

Bruckner and colleagues (2001) performed acute, short term, and subchronic oral hepatotoxicity studies of 1,1,1-TCA in rats. For the acute study, male Sprague-Dawley rats were given a single dose of 0, 0.5, 1, 2, or 4 g/kg of 1,1,1-TCA, and killed after 24 hours. The authors found no treatment-related mortality as well as little evidence of toxicity at any dose level. Histopathological examination, serum enzymes, hepatic nonprotein sulfhydryl, and glucose-6-phosphatase activity analyses did not reveal hepatic

damage at any dosage level. Liver:body weight ratios were normal after the acute exposure.

The potential for human substance abuse of 1,1,1-TCA has been documented, and has been the focus of acute as well as longer term animal research (Balster *et al.*, 1997, Evans and Balster, 1993; Pise *et al.*, 1998).

Pise and coworkers (1998) evaluated the acute effects of 1,1,1-TCA on the activity of the hypothalamo-pituitary-adrenal axis. Following inhalation exposure of male Sprague-Dawley rats to 3,500 or 5,000 ppm of 1,1,1-TCA for 10 or 30 minutes, the authors determined plasma levels of adrenocorticotrophic hormone (ACTH), corticosterone, and corticotrophin-releasing factor (CRF) in three brain regions - hypothalamus, hippocampus, and frontal cortex, all via selective radioimmunoassays. Stable brain concentrations were achieved within 10 minutes and maintained for 30 minutes. During the course of time, the authors observed a significant decrease only in ACTH at 30 minutes exposure time, at the low dose. At the higher dose, ACTH, and corticosterone were both reduced at the 10-minute exposure. Hypothalamic CRF was increased at the low dose for the 10-minute exposure only. The authors interpreted this complex relationship as “strikingly similar” to those of benzodiazepines (Pise *et al.*, 1998).

Warren *et al.* (98) examined the effect of 1,1,1-TCA via acute inhalation on operant behavior in rats, and related those effects to blood and brain concentrations of the chemical. Male Sprague-Dawley rats that were trained to press a lever for food (operant behavior) were exposed to 500, 1,000, 2,000, 3,500, or 5,000 ppm 1,1,1-TCA for 100 minutes. The authors observed that exposure to 1,000 ppm slightly increased operant response rates, whereas concentrations of 2,000 and above decreased response rates in a concentration- and time-dependent manner. Thus, acute inhalation of 1,1,1-TCA led to an observed biphasic neurotoxicological effect (Warren *et al.*, 1998), in a pattern similar to that of other CNS depressants.

Kobayoshi *et al.* (1987) studied the effects of acute inhalation of 1,1,1-TCA on heart rate in the dog. Twenty-four male and female dogs of undocumented lineage were anesthetized with 25 – 30 mg/kg sodium pentobarbital i.v. Each dog was connected to a positive pressure, volume-type respirator, with a respiration rate of 20 cycles per minute while heart rate and arterial blood pressure were monitored. 1,1,1-Trichloroethane was introduced via the ventilator over 2-minute periods. Concentrations in inspired air of 1.32 ± 0.14 percent increased heart rate. Increases in heart rate were accompanied by corresponding decreases in blood pressure to 70-80 mm Hg. The researchers observed tachycardia at relatively lower 1,1,1-TCA concentrations, beginning about 0.6 percent; and observed bradycardia beginning at inhaled concentrations of about 1.4 percent 1,1,1-TCA. These dysrhythmias were blocked by pre-administration of an adrenergic beta-blocking drug, but were only slightly affected by severing the vagus nerve – all of which suggested to the authors that the observed 1,1,1-TCA-induced dysrhythmias were controlled by the sympathetic nervous system (Kobayoshi *et al.* 1987). The results of Kobayoshi *et al.* (1987) serve to emphasize the potential for neurologic effects in animals from 1,1,1-TCA administration.

Herd *et al.* (1974) demonstrated a dose-dependent, biphasic depression of blood pressure due to 1,1,1-TCA inhalation in mongrel dogs. Nine dogs were anesthetized with sodium

pentobarbital or chloralose plus pentobarbital. Blood pressure and cardiac parameters were monitored as 1,1,1-TCA was administered via inhalation. 1,1,1-Trichloroethane exposures were given sequentially at 0.8, 1.5, 2.0, and 2.5 percent of inspired air, and lasted approximately 5 minutes. A decline in blood pressure was observed to begin within 10-15 seconds after exposures began, with the magnitude and pattern dependent upon dosage. The authors observed that the initial phase of response is characterized by a parallel decline in both systolic and diastolic pressures. The second phase is characterized by a greater decline in systole versus diastole, and a reduction in cardiac output (Herd *et al.*, 1974).

Subchronic Toxicity

Along with the acute test described earlier, Bruckner *et al.* (2000) performed short-term and subchronic oral hepatotoxicity testing. For the short-term study, 10-15 male SD rats per group were given 0, 0.5, 5, or 10 g/kg of 1,1,1-TCA via gavage once daily for five consecutive days, rested two days, then dosed for an additional four days. The animals were terminated at one, five, and 12 days following initiation of the experiment, and examined for hepatotoxic effects. The authors observed numerous fatalities at the 5 and 10 g/kg-day doses, but saw no increases in serum enzymes or histopathological changes in the liver.

For the subchronic portion of this study, male SD rats were gavaged with 0, 0.5, 2.5, or 5.0 g/kg of 1,1,1-TCA for 50 days, with the control and low-dose group continuing dosage for a total of 13 weeks. The authors describe several deaths among the 2.5 and 5.0 g/kg-day dose groups, and ascribed these to the apparent effects of repeated, protracted CNS depression. Slight evidence of hepatotoxicity was observed at two and four weeks at the high dosage level as serum ornithine carbamoyl-transferase and alanine amino-transferase levels were slightly but significantly elevated above control levels. No histopathological changes were seen in livers of the high dose group, and absolute and relative liver weights did not differ between treatment and control groups (Bruckner *et al.*, 2001).

As part of the above study, the authors performed an additional P450 induction experiment, which determined that 0.5-5.0 g/kg induced cytochrome CYP2E1 and CYP2B1/2 on a dose-dependent basis, with the lowest dosage to significantly induce CYP2E1 and CYP2B1/2 being 2.5 g/kg (Bruckner *et al.*, 2001).

McNutt *et al.* (1975) exposed male CF-1 mice to either 250 ppm or 1,000 ppm 1,1,1-TCA in air continuously for 14 weeks. These doses equate to 680 and 2,720 mg/kg-day, respectively, assuming an 0.053 m³/day inhalation rate by .0316 kg male mice, with an inhalation retention of 30 percent. The authors observed significant changes in the centrilobular hepatocytes of the high dose group as well as moderate liver triglyceride accumulation, peaking after seven weeks of exposure. Cytoplasmic alterations included vesiculation of the rough endoplasmic reticulum, microbodies, and triglyceride droplets. Necrosis of individual hepatocytes occurred in 40 percent of the high-dose mice, and was associated with hypertrophy of the Kupffer cells. Effects were mild to minimal in the low-dose group. Since the low dose group produced significant relative liver weight gains and cytoplasmic alterations such as vesiculated rough

endoplasmic reticulum containing small liquid droplets as well as an increase in smooth endoplasmic reticulum and an increase in the number of microbodies, this 250 ppm concentration represents the LOAEL (McNutt et al., 1975).

Rosengren *et al.* (1985) exposed Mongolian gerbils to 1,1,1-TCA at concentrations of 70, 210, or 1,000 ppm continuously for three months, followed by a four-month post-exposure solvent-free period. Four male and four female animals were used at each exposure level, with 24 sex-matched littermates as controls. Following termination of the test animals, the authors determined two astroglial proteins, S-100 and glial fibrillary acidic (GFA) protein. Astroglia fibers form following damage to the brain and can be characterized by the presence of the protein GFA (Bogen and Hall, 1989). As with GFA, S-100 can be a useful marker for astroglial cell increase in response to brain damage (Rosengren *et al.*, 1985).

In the above study, the authors observed no differences in body weights between active and control groups. A small, but significant, decrease in brain weight was noted between the high-dose group and the control rodents. GFA protein was significantly elevated in two of the three brain regions tested, the sensorimotor cerebral cortex and the occipital cerebral cortex, with the effect observed at both the medium and high doses for both brain regions. No GFA elevation was noted in the frontal cerebral cortex region. S-100 protein was elevated at the middle dose only and in the occipital cerebral cortex brain region only. For this study, 70 ppm is the NOAEL and 210 ppm is the LOAEL for brain changes to gerbils exposed to 1,1,1-TCA for 30 days (Rosengren *et al.*, 1985). Assuming a breathing rate of 0.032 m³/d, a body weight of 0.048 kg (U.S. EPA, 1988), and an absorption rate of 30 percent (WHO, 2002), the daily doses were approximately 75.6 mg/kg-d and 226.8 mg/kg-d.

Evans and Balster (1993) investigated the ability of 1,1,1-TCA to produce a physical dependence in mice. Noting that 1,1,1-TCA was among the solvents that "...lead many to deliberately inhale...to achieve intoxication," the author tested the compound's ability to produce withdrawal symptoms in exposed mice. Male Charles River Swiss mice were exposed to 1,1,1-TCA at concentrations of 500, 1,000, 2,000, or 4,000 ppm continuously for four days, at which time the exposure was abruptly terminated. To measure withdrawal reaction, mice were lifted by the tail and observed for tonic and tonic-clonic convulsions, and scored for severity of reaction as functions of dose and time following cessation of exposure. The authors observed that severity of reaction was dose-related, and generally occurred from two to four hours post exposure stoppage. The LOAEL for this experiment was 500 ppm. Further experiments showed that ethanol, pentobarbital, benzodiazepine, and re-exposure to 1,1,1-TCA all suppressed withdrawal convulsions in exposed mice (Evans and Balster, 1993).

Prendergast and coworkers (1967) evaluated the health effects of 1,1,1-TCA and four other chemicals by inhalation in Sprague-Dawley or Long Evans rats, Hartley guinea pigs, squirrel monkeys, New Zealand albino rabbits, and beagle dogs. 1,1,1-TCA exposures were either at 2,200 ppm, 8 hours/day, 5 days/week, for 30 exposures, or 380 or 140 ppm for 90 days. The study parameters included mortality, visible signs of toxicity, and hematologic, biochemical, pathologic, and body weight changes. In the 30-day exposure study, gross histopathological examinations of the brain, heart, lung, spleen, liver, kidney, and spleen revealed no exposure-related abnormalities. Rabbits and dogs

showed a weight loss. For the 90-day exposures at 380 ppm, the authors observed no deaths or visible toxic signs in any of the species. One rat had gray nodules on the lung and one rabbit had encapsulated collections of clear fluid within the abdominal wall. The authors found non-specific inflammatory changes in the lungs of all species. Varying degrees of lung congestion and pneumonitis were observed in several species in treated animals at the 140 ppm level and in controls. Unlike the higher dose level, there were some animal deaths (2 rats and 1 rabbit) at the lower dose. The authors could draw no conclusion as to whether the effects were associated with exposure. The 1,1,1-TCA used in the study contained 8 percent stabilizers (Prendergast *et al.*, 1967).

NTP (1996) studied 1,1,1-TCA along with several other halogenated ethanes for renal toxicity. F334/N male rats were dosed at 0.62 and 1.24 mmole/kg (70 and 141 mg/kg) in groups of five rodents per dose, via gavage in corn oil once daily for 21 consecutive days. The experimental evaluations were survival, mean body weight gains, clinical signs, organ weight changes, urinalyses, and renal and hepatic histopathology. The kidney histopathology focused on a difference of renal cell protein droplet accumulation compared with vehicle controls. The researchers observed slightly higher liver weights as well as greater urinary protein output and aspartate aminotransferase (AST) activity in the higher dose group than in the controls. The authors concluded that the positioning of all three chlorine atoms on one of the ethane carbons prevented the induction of hyaline droplet nephropathy; and while there was no microscopic evidence of kidney injury, the observation of elevated urinary protein and AST activity suggested mild kidney injury. Assuming an oral absorption rate of 95 percent (Reitz *et al.*, 1988), the NOAEL for this study is 66.8 mg/kg-d based on the absence of elevated urinary protein and AST activity versus control animals at the lower dose level (NTP, 1996).

NTP (2000) performed a longer duration, 91-day study using microencapsulated 1,1,1-TCA in animal feed. Male and female F344/N rats and B6C3F1 mice (all at 10 rodents per group) were given concentrations of 5,000, 10,000, 20,000, 40,000, and 80,000 ppm of 1,1,1-TCA in their feed. This resulted in doses of 300, 600, 1,200, 2,400, and 4,800 mg/kg, and 300, 650, 1,250, 2,500 and 5,000 mg/kg, respectively for male and female rats. The doses were 850, 1,770, 3,500, 7,370, and 15,000 mg/kg, and 1,340, 2,820, 5,600, 11,125, and 23,000 mg/kg, respectively, for male and female mice. The experimental objectives were to evaluate clinical pathology (rats only), histopathology, and reproductive system effects. The researchers also performed genetic toxicity tests with Ames assays, L5178Y mouse lymphoma cells, and Chinese hamster ovary cells. Peripheral blood slides from the mice were analyzed for frequency of micronucleated erythrocytes. The researchers observed that liver weights for female rats treated at the 4,800 mg/kg level were significantly lower than those of untreated and vehicle controls. Additionally, nonneoplastic lesions in male rats exposed to 1,200 mg/kg and greater included nephropathy represented by hyaline degeneration characterized by accumulation of hyaline droplets within the lining of the proximal convoluted tubules. The authors estimate the NOAEL as 10,000 ppm for male and female rats and mice (NTP, 2000). Thus the highest NOAEL is 2,820 mg/kg-d for the female mouse.

Genetic Toxicity

The potential for genetic toxicity of 1,1,1-TCA has been extensively tested in short-term *in vitro* studies. Numerous of these studies were reviewed by U.S. EPA, WHO, and ATSDR, with the most pertinent studies summarized below. Most of the studies reviewed were clearly negative, and the few positives, while possibly correct, may have been the result of stabilizer chemicals or other mutagenic impurities of the tested product (U.S. EPA, 1984; WHO, 1992). The U.S. EPA (1984), however, makes the case that when the investigators used protocols to prevent excessive evaporation of the solvent, some positive results have been observed in *Salmonella typhimurium* strains TA 100 and/or TA 1535 (U.S. EPA, 1984). The U.S. EPA also mentioned chemical impurities as possible causes for the mutagenic activity.

Simmon and colleagues (1977) tested 1,1,1-TCA for mutagenic activity using *S. typhimurium* strains TA 98, TA 100, TA 1535, TA 15367, and TA 1538, each test being run with and without S9 metabolic activation. A weak positive was observed in TA 100 both with and without S9. After purifying the chemical, the authors observed the same weak positive with TA 100 (Simmon *et al.*, 1977). Approximately 2 percent of the purified solvent was still unidentified impurities, however (U.S. EPA, 1984).

Snow and coworkers (1979) also reported weak, dose-related positives using TA 100 and two different samples of 1,1,1-TCA. The first sample also contained about 3 percent contaminants, which included 1,1- and 1,2-dichloroethane, nitromethane, trichloroethylene, methylisobutyl ketone, 1,1,2-trichloroethane, and toluene. The second sample also contained about 3 percent contaminants, including acetone, nitromethane, methyl ethyl ketone, toluene, trichloroethylene, vinylidene chloride, and possibly dimethyl formamide (Snow *et al.*, 1979). U.S. EPA concluded that the metabolic responses obtained by Snow *et al.* (1979) "...must have been due to 1,1,1-TCA *per se* or to a mutagenic stabilizer..." that might have degraded before analysis (U.S. EPA, 1984).

More recently, Brennan and Schiestl (1998) examined 1,1,1-TCA (along with chloroform and carbon tetrachloride) for potential to induce intrachromosomal recombination and oxidative free radicals in the yeast *Saccharomyces cerevisiae*. Since previous genotoxicity data for 1,1,1-TCA may have been compromised by the presence of stabilizing additives such as 1,2 epoxybutane and 1,4 dioxane, the authors obtained a specially purified sample of 1,1,1-TCA for the assay. The authors observed that the deletion (DEL) of intervening sequences was induced "very weakly" by 1,1,1-TCA, to that of just slightly over the recombination frequency required to consider it a positive response. Interestingly, and importantly for the analysis of previous work, adding low alkyl epoxide stabilizers (at 0.05 percent of the 1,1,1-TCA) increased the DEL recombination frequency 3.1-fold. Unlike the other two chemicals tested, 1,1,1-TCA did not induce oxidative free radical species in this yeast strain. From their investigation, the authors concluded that the weak response to 1,1,1-TCA in the DEL assay, coupled with the lack of generation of free radicals, is in accordance with the lack of clear evidence for carcinogenicity for this compound (Brennan and Schiestl, 1998).

Developmental and Reproductive Toxicity

Lane *et al.* (1971) studied potential effects of 1,1,1-TCA (as well as 1,1,2-trichloroethane) in drinking water on reproduction and development in mice. The authors performed a multigeneration reproduction study concentrating on dominant lethal and teratogenic effects at 1,1,1-TCA drinking water concentrations of 0, 0.58, 1.75, or 5.83 mg/mL, which yielded 0, 100, 300, or 1,000 mg/kg-day doses in male and female ICR Swiss mice. Exposures began 35 days prior to F/0 mating and were maintained through the second generation. The authors observed that 1,1,1-TCA exposures had no dose-dependent effects on fertility, gestation, viability, or lactation indices. Similarly, there were no adverse effects on pup survival and weight gain. The authors concluded that the 1,1,1-TCA exposures produced no significant dominant lethal mutations or teratogenicity in either of the two generations tested (Lane *et al.*, 1982).

George and colleagues (1989) evaluated 1,1,1-TCA for pre- and postnatal developmental effects in Sprague-Dawley rats. For this study, 1,1,1-TCA was administered in drinking water at concentrations of 3, 10, or 30 ppm using 0.05 percent Tween 80 as an emulsifying agent. Male and female rats (>30 per group) were exposed to study compound or the control solution for 14 days prior to cohabitation and for up to 13 days during the cohabitation phase. Authors maintained chemical exposure to females throughout pregnancy and lactation to 21 days post-parturition. Doses as calculated by the authors are presented in Table 5.

Table 5. Average Doses of 1,1,1-Trichloroethane in the Drinking Water Developmental Toxicity Study of George *et al.* (1989), in mg/kg-day.

Sex	Comment	1,1,1-TCA concentration		
		3 ppm	10 ppm	30 ppm
Male	Pre-mating	0.3	0.9	2.6
Female	Pre-mating	0.3	1.3	3.3
Female	Maternal	0.3	1.2	3.5
Female	Post-parturition	0.6	2.0	5.9

The authors observed no deaths or morbidity in either male or female breeder rats during pre-mating or cohabitation periods. No significant effects on body weight, weight gain, or food consumption were observed. For both sexes, there was a decreasing trend of water consumption with increasing dose. During the gestational period, no effects of treatment were observed, such as maternal deaths or clinical signs. The authors observed no effects on the number of implantation sites per dam, length of gestation, number of live pups per litter, or average pup weight. Likewise, there were no significant increases in malformations. In one treatment litter, the authors observed a slight but significant increase in post-implantation mortality. Although the authors stated that the significance of the pup mortality was unclear, the fact that the fetal deaths were confined to one litter

(thus potentially artifactual) led to the authors' conclusion that 1,1,1-TCA is not a reproductive toxicant (George *et al.*, 1989).

In 1993, Maurissen *et al.* (1993) performed a rat study to investigate potential neurological effects from maternal exposure to 1,1,1-TCA. The offspring were tested both as pups and as adults. The authors orally dosed dams with 0, 75, 250, or 750 mg/kg-day from gestation day 6 through lactation day 10. The pups (4 male and 4 female per dose) were examined for physical maturation signs: pinna detachment, incisor eruption, eye opening, testes descent, and vaginal opening. At specific periods, the authors evaluated motor activity, auditory brainstem response, brain measurements, and neuropathology. At 2-3 months of age, learning, task performance, and short-term memory were tested. The authors observed no treatment effects on rat pup maturation landmarks. Small decreases in pup weight were noted, but not considered biologically significant. Motor activity was not affected in either pup or young adult stages. There were no neurological lesions or brain dimension changes. Similarly, there were no effects on short-term memory, learning, or performance.

Immunotoxicity

In 1986, Aranyi and colleagues investigated potential immunological effects of several volatile chemicals, including 1,1,1-TCA, in a mouse respiratory infection test. The effects of single and multiple 3-hour inhalation exposures were evaluated in mice at the threshold limit value of 350 ppm (NIOSH, 1994). The authors monitored the rodents' susceptibility to artificially introduced aerosolized *Streptococcus zooepidemicus* and *in vivo* bactericidal activity of alveolar macrophages against *Klebsiella pneumoniae*. Mortality was not different from controls from exposure to the first pathogen; and bactericidal activity was not decreased by exposure to the second pathogen. The data indicate that in short term inhalation exposure of mice to 350 ppm, 1,1,1-TCA had no effect on the immunological parameters evaluated by the authors (Aranyi *et al.*, 1986). The limited existing data do not indicate that 1,1,1-TCA is a significant immunotoxicant.

Neurotoxicity

1,1,1-Trichloroethane produces central nervous system depression demonstrated by impaired performances on behavioral tests, ataxia, and unconsciousness in laboratory animals. The effects are similar to those observed in human cases (ATSDR, 1995). At higher levels, the chemical is an anesthetic (U.S. EPA, 1984). These central effects are similar to those of many other halogenated hydrocarbon compounds. The potential for human abuse of 1,1,1-TCA as an inhalant has been documented, and has been the focus of considerable animal research (Balster *et al.*, 1997, Evans and Balster, 1993; Pise *et al.*, 1998).

Warren *et al.* (98) examined the effect of 1,1,1-TCA via acute inhalation on operant behavior in rats, and related those effects to blood and brain concentrations of the chemical. Male Sprague-Dawley rats that were trained to press a lever for food were exposed to 500, 1,000, 2,000, 3,500, or 5,000 ppm 1,1,1-TCA for 100 minutes. The authors observed that exposure to 1,000 ppm slightly increased operant response rates,

whereas concentrations of 2,000 and above decreased response rates in a concentration- and time-dependent manner. This biphasic pattern of neurotoxicological effects is similar to that of other CNS depressants, which is often considered to represent disinhibition at low doses followed by sedation at higher doses.

As discussed earlier, Rosengren *et al.* (1985) observed protein changes indicating damage to astrocytes in the brains of Mongolian gerbils from inhalation exposure to 210 and 1,000 ppm, but not to 70 ppm of 1,1,1-TCA continuously for three months. A small, but significant, decrease in brain weight was noted between the high-dose group and the control rodents. GFA protein was significantly elevated in the sensorimotor cerebral cortex and the occipital cerebral cortex at both the medium and high doses, but not in the frontal cerebral cortex. S-100 protein was elevated at the middle dose only and in the occipital cerebral cortex only. For this study, 70 ppm is the NOAEL and 210 ppm is the LOAEL for brain changes in gerbils, corresponding to doses of approximately 75.6 mg/kg-d and 226.8 mg/kg-d.

Chronic Toxicity

Oral exposure

NCI (1977) cancer bioassay report was obtained to determine whether any incidental findings might suggest more subtle noncancer effects not detected by histopathology and found that no vehicle-treated control groups were used in these studies. Reduced weight gain was seen in both rats and mice during the oral gavage exposure period for all dose levels. Bloody discharge around the eyes of some rats was found during the second year of this carcinogenesis study. Whereas the omission of an appropriate control group did not preclude the conclusion of no carcinogenic effect because tumor incidence in treated animals did not exceed untreated control incidence, the absence of a vehicle-treated control makes it impossible to attribute any incidental toxicological findings in this chronic gavage study to exposure to 1,1,1-TCA alone (NCI, 1977).

Inhalation exposure

Quast *et al.* (1988) performed a chronic inhalation toxicity and oncogenicity study of 1,1,1-TCA on F334 and B6C3F₁ mice. The authors exposed groups of male and female rats and mice to vapor concentrations of 0, 150, or 1,500 ppm 1,1,1-TCA for 6 hours/day, 5 days/week for 2 years. Initially, there were 80 rodents per group, with 10 from each group terminated and examined at intervals of 6, 12, and 18 months, and the remainder terminated at 24 months. The study parameters included mortality, clinical signs of toxicity, hematology, urinalysis (rats only), clinical chemistry, body and organ weights, gross pathology and histopathology. No toxic effects were observed in male or female mice at any dosage level or any exposure period. Female rats had a significant decrease in body weight at 2 years at the high dose of 1,500 ppm (458 mg/kg-day, with the assumptions of 0.229 kg bw, 0.24 m³/d breathing rate, and 30 percent absorption). Also, at 1,500 ppm, very slight microscopic hepatic effects were seen in male (410 mg/kg-day, assuming 0.38 kg bw, 0.36 m³/d breathing rate, and 30 percent absorption) and female (458 mg/kg-day) rats necropsied at 6, 12, and 18 months. In rats exposed to lower doses, there were no exposure-related changes (Quast *et al.*, 1988).

Carcinogenicity

Oral exposure

Three oral exposure studies are described, two in rats and one in mice. The NCI (1977) performed gavage carcinogenesis bioassays of technical grade 1,1,1-TCA using Osborne-Mendel rats and B6C3F₁ mice. Rats were dosed with 750 and 1,500 mg/kg-day in corn oil and mice at 2,807 and 5,615 mg/kg-day for 78 weeks. There were 50 animals per sex in each treated group and 20 per sex in control groups. Both studies showed no increased incidence of tumors in the exposed animals as compared to untreated controls. Vehicle controls were not used. Survival was very poor in both treated and in control animals. Only six of the total of 240 animals in the rat studies survived to 110 weeks. In the mouse studies, all were sacrificed after 90 weeks. Three percent 1,4-dioxane was known to be present in the technical grade 1,1,1-TCA used. Survival was low but better than in the rat study. Both studies were considered inadequate to assess the carcinogenicity of 1,1,1-TCA. The U.S. EPA classified 1,1,1-TCA as Class D, not applicable to assess human carcinogenicity (U.S. EPA, 2002).

Maltoni (1986) reported an apparent increased incidence of leukemias in rats exposed to 500 mg/kg-day of 1,1,1-TCA in olive oil by gavage for 4-5 days/week for 104 weeks compared with historical data on vehicle controls. 1,4-Dioxane (4 percent) and other impurities (1 percent) were known to be present in the 1,1,1-TCA. This was considered to be a screening study and not a standard cancer bioassay. No statistical analysis was done. This study also used only a single dose and a smaller sample size than customary (n=40 per sex per group). Assessment of carcinogenic potential via the oral route based on this study is difficult because of several irregularities in the study design and methods.

Inhalation exposure

Dow Chemical performed 2-year inhalation studies on 1,1,1-TCA (Quast *et al.*, 1988). Male and female Fischer 344 rats and B6C3F₁ mice were exposed to 0, 820, 2,730, and 8,190 mg/m³ of 1,1,1-TCA vapors for 6 hours/day, 5 days/week for 2 years, again with several known impurities administered along with the 1,1,1-TCA. These concentrations correspond to 0, 150, 500 and 1,500 ppm, with 1,500 ppm approaching the MTD. No statistically significant increase in tumor incidence was observed in the treated animals when compared to controls. The conclusion was no evidence of carcinogenicity by the inhalation route at exposure levels almost at the MTD (Quast *et al.*, 1988).

Toxicological Effects in Humans

Local and systemic effects reported after exposures to high doses of 1,1,1-TCA are skin, eye, throat and respiratory tract irritation; gastrointestinal distress; dizziness, headaches, lightheadedness and CNS depression; mild hepatic toxicity, and cardiac arrhythmias. Effects are considered to be reversible. Symptoms of CNS depression include headache, weakness, dizziness, nausea, and loss of coordination and judgment, with coma and death observed at very high doses (HSDB, 2002). Controlled experimental human studies of effects of 1,1,1-TCA have used either the inhalation or dermal routes of exposure (no oral), usually employing technical grade 1,1,1-TCA containing stabilizers, since this is the typical exposure scenario.

The lowest exposure documented to show an adverse effect (neurological) is 175 ppm for 3.5 hr, described in Mackay *et al.* (1987). When liver and renal function tests were conducted after controlled or accidental exposures, effects were observed sometimes but not consistently (Mackay *et al.*, 1987). Cardiotoxicity has been reported after very high exposures (U.S. EPA, 1984; WHO, 1992; ATSDR, 1995). Studies of developmental, immunological or neurological effects are discussed later in the corresponding sections.

In 1977, the FDA observed that 1,1,1-TCA was potentially toxic to the cardiovascular system by sensitizing the heart to adrenaline (WHO, 1992). Ventricular arrhythmias have persisted after long-term exposures to very high vapor concentrations associated with solvent abuse or occupational exposure (ATSDR, 1995; WHO, 1992).

Acute and Short Term Toxicity

Oral exposure

ATSDR (1995) summarized the clinical symptoms associated with human exposure to significant quantities of 1,1,1-trichloroethane as including CNS depression, hypotension, cardiac dysrhythmia, GI distress, mild hepatic effects, and skin and eye irritation. The main tissues affected by large amounts of ingested 1,1,1-TCA are the gastrointestinal tract, nervous system (from behavioral observations and psychomotor testing), and liver. The effects seen in these areas are considered to be reversible. A medical case report described an accidental ingestion of 600 mg/kg 1,1,1-TCA which was not only not fatal, but also did not alter blood urea nitrogen or hepatic serum transaminase levels, and only slightly elevated serum bilirubin (Stewart and Andrews, 1966; ATSDR, 1995). This exposure caused severe vomiting and diarrhea (ATSDR, 1995).

Dermal exposure

Dermally applied 1,1,1-TCA can be detected in the systemic circulation (see Absorption). There have been no reports of human deaths involving dermal exposures (ATSDR, 1995), and apparently few attempts to thoroughly characterize more subtle adverse systemic effects after dermal exposures. Dermal exposure to the pure compound can result in mild, reversible skin irritation and fine scaling. Case reports cite a variety of local effects including defatting action when the solvent was applied repeatedly to the skin, erythema, and vesication (Stewart and Dodd, 1964; Jones and Winter, 1983); and other effects considered to be minor, including allergic contact dermatitis. Exposure levels are not always clear. The scarcity of data following repeated dermal exposures to 1,1,1-TCA in humans does not allow a quantitative assessment of systemic toxicity in any major organ system resulting from this type of exposure. Inability to clearly establish causality in the few existing studies that suggest a potential effect make these case reports and epidemiologic surveys inappropriate for setting a PHG (ATSDR, 1995).

Inhalation exposure

Deaths have occurred following inhalation of high concentrations of 1,1,1-TCA (e.g., occupationally related accidents or intentional “solvent sniffing”), but actual exposure concentrations were not well documented in these cases. Simulations suggest that 6,000 ppm may be a lethal concentration for humans (ATSDR, 1995). Death in humans is

attributable to respiratory failure secondary to CNS depression and in some cases to cardiac arrhythmias (ATSDR, 1995).

Developmental and Reproductive Toxicity

Epidemiological studies of effects of ingesting water contaminated with 1,1,1-TCA on reproductive and developmental endpoints, and also exposures at workplaces, are often confounded due to the effects of concurrent exposure to other chemical and physical agents. A number of environmental and occupational exposure studies involve mixed exposures. Prominent among these are the epidemiologic studies of communities within the Santa Clara Valley, California in which the drinking water was contaminated with up to 1,700-8,000 ppb of 1,1,1-TCA (Deane *et al.*, 1989; Swan *et al.*, 1989; Wrensch *et al.*, 1990; Epstein *et al.*, 1991).

No relationship was established between exposure to 1,1,1-TCA and an increased incidence of spontaneous abortions or major cardiac anomalies. Other studies of inhalation exposures to solvents which included 1,1,1-TCA were unable to establish a relationship between solvent exposure and spontaneous abortions, congenital malformations (either with maternal or paternal exposure), or decreased male fertility (Taskinen *et al.*, 1989; Lindbohm *et al.*, 1990; Windham *et al.*, 1991; Sallmen *et al.*, 1998; Hewitt and Tellier, 1998). Based on reviews of these studies reported in U.S. EPA (1984, 1985), ATSDR (1995), and HSDB (2005), it is evident that no epidemiology investigation has yet provided well substantiated evidence of adverse effects on reproduction and development that could be attributed to 1,1,1-TCA exposure.

Immunotoxicity

Little immunotoxicity data exist for human 1,1,1-TCA exposures. ATSDR (1995) describes one case report of a worker with allergic contact dermatitis from 1,1,1-TCA (Ingber, 1991). His job involved cleaning metal plates with 1,1,1-TCA. He developed severe acute hand eczema soon after starting the job, which disappeared after a few weeks when contact with 1,1,1-TCA was stopped. The possibility that the reaction might have been caused by a 1,1,1-TCA stabilizer was not discussed in the case report.

Neurotoxicity

Central nervous system toxicity is a principal effect of inhaled 1,1,1-TCA in humans (WHO, 1992). Effects range from slight behavioral changes accompanied by mild eye irritation at low exposures to unconsciousness and respiratory arrest at higher levels (WHO, 1992). Symptoms of CNS depression following 1,1,1-TCA inhalation include headache, weakness, dizziness, nausea, and loss of coordination and judgment. Very high doses lead to coma and death (HSDB, 1999). Several studies of human volunteers under controlled conditions have investigated the effects of 1,1,1-TCA on performance in sensitive behavioral and neurophysiologic tests.

A thorough examination found no neurological abnormalities in a man 4 hours after an accidental ingestion of 600 mg/kg of 1,1,1-TCA (Stewart and Andrews, 1966; ATSDR,

1995). Information regarding neurological effects in humans following oral exposure is quite limited.

The vast majority of nonlethal acute and subchronic human neurological effects studies profiled by the ATSDR involve inhalation exposures. The 1998 RTECS database lists the lowest toxic concentrations (TC_{LO}) in humans exposed by inhalation as 920 ppm for 70 minutes (Torkelson *et al.*, 1958) or 200 ppm for 4 hour (RTECS, 1998).

Published reports have often involved at least one exposure level of the same order of magnitude as, although often exceeding, permissible occupational exposure concentrations. For example, the NIOSH Recommended Exposure Level and the OSHA Permissible Exposure Level are both 350 ppm. Investigations made within a factor of 3 of these exposure levels examined such endpoints as behavioral changes. Two such studies showed a measurable neurological adverse effect of 1,1,1-TCA, one with an exposure of 920 ppm for just over an hour (Torkelson *et al.*, 1958) and the other following a 3.5 hr exposure at 175 ppm (Mackay *et al.*, 1987). Torkelson *et al.* (1958) exposed four volunteers to 920 ppm for 70-75 minutes in an inhalation chamber. Symptoms of slight CNS disturbances (changes in coordination and equilibrium) were observed in three of the four subjects. Slight eye irritation was noted by one individual. Recovery was rapid, within 5-10 minutes.

Mackay *et al.* (1987) noted reduced performance in psychomotor tests of human volunteers exposed to 175 ppm for 3.5 hr. In 1995, the ATSDR selected this study as one of two for derivation of an MRL (Minimum Risk Level). The MRL derived from this study was 2 ppm based on a LOAEL of 175 ppm for reduced performance on psychomotor tests. More recently, Laine *et al.* (1996) also studied effects of exposure to 200 ppm in 21- to 24-year old male volunteers who were exercising while being exposed for almost 3.75 hr/day for 3 days. Measurements made were EEG, visual evoked potentials, and body sway. Although some changes were observed in all parameters measured, their conclusion was that no deleterious effects of exposure persisted under these circumstances. Therefore, the human study by Mackay *et al.* (1987) shows effects at the lowest exposure levels; importantly, however, these effects are reversible. We also note that this exposure level of 175 ppm is higher than the 100 ppm human odor threshold.

Short-term exposure to airborne concentrations of 250 to 500 ppm increased reaction time, impaired manual dexterity, and induced anesthesia (Clayton and Clayton, 1993).

Lack of significant findings by Maroni *et al.* (1977) at levels ranging from 110 to 990 ppm is complicated by incomplete exposure information. The authors found no significant difference between exposed and unexposed female workers with respect to neuron conduction velocity, conduction velocity of slow fibers and psychometric data (Maroni *et al.*, 1977). Similarly, exposure of humans to 500 ppm for up to 78-186 minutes (Stewart *et al.*, 1961) was reported as not producing CNS toxicity or any other toxic effects.

Chronic Toxicity

Epidemiologic and case reports of chronic inhalation exposures to 1,1,1-TCA thus far do not provide adequately quantified dose-response information in the absence of confounding exposures to other substances. Epidemiological studies relating 1,1,1-TCA exposures to potential cancer causation are discussed in the following section.

Carcinogenicity

Among the major problem areas in studies relating long term exposure of 1,1,1-TCA to humans are concurrent exposure to other agents and small population cohort sizes. The studies summarized here do not provide compelling evidence of an effect.

Isacson *et al.* (1985) investigated the relationship of organic chemicals in drinking water and cancer incidence in people over 55 years of age from different areas of Iowa. Using data from the Iowa Cancer Registry for the years 1969-1981, the authors found no differences in the incidence of bladder, colon, lung, rectum, breast, or prostate cancer in towns with small amounts of 1,1,1-TCA present in the water.

Lynge *et al.* (1997) reviewed epidemiological studies addressing the relationship between inhaled organic solvents and cancer. They note that little epidemiological research has been done on 1,1,1-TCA (only 3 studies). According to these authors, the three cancer risk studies (Siemiatycki, 1991; Spirtas *et al.*, 1991; Anttila *et al.*, 1995) found increased incidence of multiple myeloma. However, this observation is based on small numbers. Spirtas *et al.* (1991) conducted a retrospective cohort mortality study of workers at an aircraft maintenance facility and found increased multiple myeloma (with small numbers). Anttila *et al.* (1995) studied cancer incidence among Finnish workers exposed to halogenated hydrocarbons. Male and female workers were reported as potentially exposed to 1,1,1-TCA by inhalation for up to 18 years. This study reported that exposure of Finnish workers to 1,1,1-TCA may increase the incidence of nervous system cancer and myeloma. However, the statistical power of the study was extremely low, with a confidence interval of 1.93-57.7 for myeloma and 1.25-17.7 for cancer of the nervous system. These results were statistically significant when compared to other halogenated hydrocarbons, but there were only two cases of myeloma and three cases of CNS cancer with an N = 271. The authors also acknowledged that the workers were probably exposed to more than one compound during their careers. Overall, the evidence provided by these studies is weak. Exposure levels sometimes exceeded the 100 ppm workplace standard. Levels measured were between 1 and 444 ppm during the 8-hour workday.

Zarchy (1996) describes three men, aged 45 years or younger, who developed cholangio, ampullary, and pancreatic cancer after prolonged heavy exposure to trichlorinated hydrocarbon solvents. The authors reported that two of the workers had exposure to other carcinogenic chemicals and the third had a strong family history of cancer.

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

The main systems or organs affected by ingested 1,1,1-TCA are the nervous system and liver. In animals and humans, neurological effects seem to be the most sensitive endpoint. The 90-day inhalation study in Mongolian gerbils by Rosengren *et al.* (1985) described in the Subchronic Toxicity subsection provides the best study upon which to estimate a health protective concentration in drinking water. The study endpoints were increased glial fibrillary acidic (GFA) protein at the high dose, but not at the low dose. The daily doses were 76 and 230 mg/kg-d, assuming a breathing rate of 0.032 m³/d, a body weight of 0.048 kg (U.S. EPA, 1988) and an absorption rate of 30 percent (WHO, 2002). A LOAEL of 210 ppm (230 mg/kg-d) and a NOAEL of 70 ppm (76 mg/kg-d) are selected.

The most relevant non-cancer studies for estimation of a health-protective concentration of 1,1,1-TCA are summarized in Table 6.

Evaluation of the noncancer effects of 1,1,1-TCA focused mainly on identifying the highest adequately documented NOAELs and the lowest LOAELs in subchronic or chronic exposure studies, although acute effects were also considered. We identified no ideal study for conducting a dose-response assessment for the PHG. Most of the information on non-cancer toxicity in humans involves inhalation exposures. There are no human health studies that clearly link adverse effects to 1,1,1-TCA exposure through ingestion of contaminated water. Studies conducted in California's Santa Clara Valley investigating exposure to 1,1,1-TCA-contaminated well water used for drinking are the only human chronic oral exposure studies found. Results of these studies designed to evaluate developmental endpoints did not support an association between 1,1,1-TCA exposure and the endpoints studied.

As with other chlorinated solvents, 1,1,1-TCA has the potential for adversely affecting the liver and the nervous system. Reversible CNS depression occurs with high concentrations. A number of acute oral and inhalation human studies were identified involving accidental or intentional (solvent abuse) high exposure concentrations. Only one human study was identified that addresses subchronic or chronic exposure effects of 1,1,1-TCA alone (by any route) with exposure levels adequately documented. A study by Mackay *et al.* (1987) was a well-controlled study using human volunteers that detected reduced performance on psychomotor tests at 175 ppm (LOAEL). This appears to be the lowest concentration for any well-documented neurological, albeit reversible, effect in humans. Data from this study were used by the ATSDR as recently as 1995 to recommend safe levels for humans.

Table 6. Dose-Response Summary Table

Study	Conditions	Toxicity endpoint and LOAEL or NOAEL	Comments
NTP 1988a; George <i>et al.</i> , 1989; male and female CD rats	Drinking water exposure to 3, 10 and 30 ppm from 14 days before mating through gestation and weaning at PND 21. Time-weighted average doses (mg/kg-day): Premating males 0.3, 0.9, 2.6; pre mating females 0.3, 1.3, 3.3; pregnant dams 0.3, 1.2, 3.5.	Developmental: Increased fetal mortality during period of implantation through PND 1 with 30 ppm exposure; mortality from implantation through PND 4 was unchanged. Results could be attributable to high mortality in one litter.	One of the studies used by California DHS to generate a proposed MCL. No maternal toxicity observed at these doses. The authors note that the fetal effect could have been due to high mortality in one litter; subsequent mortality from implantation through PND 4 was unchanged.
Mackay <i>et al.</i> , 1987; humans	Inhalation, 3.5 hr exposure.	CNS: Reduced performance on psychomotor tests. LOAEL = 170 ppm	Used by ATSDR to develop Minimum Risk Level (MRL). Effects were reversible
Rosengren <i>et al.</i> , 1985; Mongolian gerbil	Inhalation, 70, 210 or 1,000 ppm continuously for three months, corresponding to about 76, 230, or 1080 mg/kg-day.	CNS: Increased glial fibrillary acidic (GFA) protein, signifying astrocytic injury. NOAEL = 70 ppm	Gerbils among most sensitive animal models. Study used by ATSDR to develop MRL, and by OEHHA to calculate a health-protective concentration.
McNutt <i>et al.</i> , 1975; male CF-1 mice	Inhalation, 250 or 1,000 ppm for 14 weeks, corresponding to 680 or 2,720 mg/kg-day	Liver: Increased weight and triglyceride content; cytoplasmic changes in hepatocytes LOAEL = 250 ppm	Study used by U.S. EPA to determine MCL.

Carcinogenic Effects

As there are no reliable human and animal oncogenicity data, there is no justification at this time for conducting a dose-response assessment based on cancer as an endpoint. 1,1,1-TCA is designated as not classifiable as a human carcinogen (U.S. EPA, 1984; IARC, 1987, 1999; IRIS, 2004)

CALCULATION OF PHG

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

1,1,1-Trichloroethane in Drinking Water

Exposure Considerations

The value of 2 L/day for water consumption is a traditional default value for an adult, nominally representing all uses of water, including that added to food and used for coffee or tea. Inhalation of volatile organic chemicals released from water used in the household may result in additional human exposure. Calculations of equivalent exposures from other household uses of drinking water with the CalTOX multimedia exposure program yield an amount roughly equal to the drinking water contribution for small, volatile halogenated hydrocarbons such as 1,1,1-TCA. Thus, we have added an exposure equivalent to drinking two L/day to account for exposures from bathing or showering. This total exposure of four Leq/day accounts for exposures to a toxicant from all household uses of drinking water.

Noncancer 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:

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

where,

- NOAEL = no-observed-adverse-effect-level (76 mg/kg-d);
- BW = adult body weight (70 kg);
- RSC = relative source contribution (80 percent);
- UF = uncertainty factor of 1,000, which includes factors of 10 for inter-species extrapolation, 10 for subchronic to chronic extrapolation, and 10 for potentially sensitive human subpopulations;
- WC = equivalent daily water consumption/contact rate (4 L_{eq}/d).

The 90-day inhalation study in gerbils (Rosengren *et al.*, 1985) was used to determine a LOAEL of 230 mg/kg-d and a NOAEL of 76 mg/kg-d based on neurological effects (increased glial fibrillary acidic protein, representing damage to brain astrocytes). Because 1,1,1-trichloroethane is not typically present in the environment, no exposure sources other than drinking water are likely, so the maximum default value of 0.8 is used for the relative source contribution. Using these parameter values, a health-protective value (C) is calculated as follows:

$$C = \frac{76 \text{ mg/kg-d} \times 70 \text{ kg} \times 0.8}{1,000 \times 4 \text{ L}_{\text{eq}}/\text{d}} = 1.058 \text{ mg/L} = \mathbf{1.0 \text{ ppm}}$$

Based on this calculation, the noncancer PHG for 1,1,1-TCA in drinking water is 1.0 mg/L. This PHG value is judged to be protective of sensitive populations, including infants, children, and the elderly.

Carcinogenic Effects

1,1,1-Trichloroethane is not classifiable as to carcinogenicity on the basis of inadequate human and animal data (U.S. EPA, 1984; IARC, 1987, 1999; IRIS, 2004).

RISK CHARACTERIZATION

We selected the subchronic animal study from Rosengren *et al.* (1985) as best suited for calculation of the PHG value. The human study from Mackay *et al.* (1987) yielded a low LOAEL value of 175 ppm, however, the psychomotor effects were reversible, and not considered adequate on which to base a PHG. We also considered the McNutt *et al.* (1975) subchronic mouse LOAEL value of 250 ppm, based on small but significant liver weight and cytoplasmic changes. The minimal toxic effects at higher doses in the chronic rat and mouse studies of Quast *et al.* (1988) were also considered. However, since the LOAEL in the Rosengren *et al.* (1985) study of 210 ppm was lower than the values derived from the McNutt (1975) and Quast *et al.* (1988) studies, use of the Rosengren study was slightly more health-protective, and was judged to be more appropriate for our purpose.

The U.S. EPA (2004) offered some cautions in the use of Rosengren *et al.* (1985), most importantly, that non-pathological conditions such as intense stimulation can lead to detectable increases in GFAP. However, these are typically of smaller magnitude. U.S. EPA (2004) also made the point that the determination of GFAP in specific brain regions of test animals requires precise technique; and, that no replication studies of Rosengren *et al.* (1985) have been published. Thus, some uncertainty may exist over the toxicological relevance to humans.

Other than the above-mentioned weakness in both the human and animal cancer studies, one of the larger limitations in the health data on 1,1,1-TCA is the presence of contaminants and stabilizers in the product. Many of these compounds have toxic properties, with the potential to confound the data, especially from the earlier studies.

OTHER REGULATORY STANDARDS

The federal Maximum Contaminant Level Goal (MCLG) and Maximum Contaminant Level (MCL) for 1,1,1-TCA are both 0.2 mg/L (U.S. EPA, 2001). The federal MCLG is computed using a NOAEL from a 14-week inhalation study in which mice exposed to 1,1,1-TCA developed significant liver changes (McNutt *et al.*, 1975). The U.S. EPA calculation also uses a lower value for RSC (U.S. EPA, 1985; U.S. EPA, 2002b). It is relevant to note that U.S. EPA withdrew their discussion of an oral RfD from IRIS on 08/01/91, "pending further review by the RfD/RfC Work Group" (IRIS, 2004). The IRIS

file also states that “A screening level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for 1,1,1-trichloroethane conducted in November 2001 identified one or more significant new studies.” OEHHA agrees.

The present toxicity review and the previous OEHHA review of the chronic effects of 1,1,1-TCA (OEHHA, 2000) picked the study of Rosengren *et al.* (1985) as the critical study for risk assessment. In both cases, the 210 ppm exposure level is considered the study LOAEL, and the 70 ppm exposure level is considered a NOAEL.

In 1989, the California Department of Health Services adopted a Maximum Contaminant Level for 1,1,1-TCA of 0.2 mg/L, based upon the U.S. EPA MCL (CDHS, 1989), which is still applicable (CDHS, 2003). Table 7 summarizes available toxicity criteria values for 1,1,1-TCA.

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

Agency	Standard or Criterion	Level	Comment
ACGIH	TLV	350 ppm in air	8-hr work day (TWA)
OSHA	PEL (permissible exposure limit)	350 ppm in air	8-hr work day (TWA)
OEHHA	Acute REL (inhalation reference exposure level)	68 mg/m ³ 12 ppm in air	1-hr exposure
OEHHA	Chronic REL (inhalation reference exposure level)	1 mg/m ³ 0.2 ppm in air	combined UF = 300
U.S. EPA	MCL (maximum contaminant level)	0.2 mg/L	
U.S. EPA	MCLG (maximum contaminant level goal)	0.2 mg/L	
CDHS	RPHL (recommended public health level)	0.2 mg/L	Based on U.S. EPA MCL
CDHS	MCL (maximum contaminant level)	0.2 mg/L	Based on U.S. EPA MCL

Table adapted from ATSDR, 1995; NIOSH, 1994; OEHHA, 1999, 2000; U.S. EPA, 2001; CDHS, 1989, 2003.

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