DRAFT

Public Health Goal for 1,1-Dichloroethane in Drinking Water

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NOT A REGULATORY STANDARD

LIST OF CONTRIBUTORS

PREFACE

Drinking Water Public Health Goals

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California Environmental Protection Agency

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

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365), 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 which can cause chronic disease shall be based upon currently available data and shall be set at levels which OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of insufficient data to determine a level of no anticipated risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.

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

10. PHGs 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 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-DICHLOROETHANE 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 **3**

Air 3

Soil 4

Water 4

Food 4

Other Sources 4

METABOLISM AND PHARMACOKINETICS **4**

Absorption 4

Distribution 4

Metabolism 5

Excretion 6

TOXICOLOGY **7**

Toxicological Effects in Animals and Plants 7

Acute Toxicity 7

Subchronic Toxicity 7

Genetic Toxicity 8
Developmental and Reproductive Toxicity 10
Immunotoxicity 10
Neurotoxicity 10
Chronic Toxicity 10
Carcinogenicity 13
Hepatocellular Carcinoma 13
Hemangiosarcoma 13
Mammary Adenocarcinoma 14
Endometrial Stromal Polyps 14
Bioassay Summary 14
Toxicological Effects in Humans 15
Acute Toxicity 15
Subchronic Toxicity 15
Genetic Toxicity 15
Developmental and Reproductive Toxicity 15
Immunotoxicity 15
Neurotoxicity 15
Chronic Toxicity 15
Carcinogenicity 15
DOSE-RESPONSE ASSESSMENT 16
Noncarcinogenic Effects 16
Carcinogenic Effects 16
CALCULATION OF THE PHG 16
Exposure Considerations 16
Noncarcinogenic Effects 17
Carcinogenic Effects 17
RISK CHARACTERIZATION 18
OTHER REGULATORY STANDARDS OR GUIDELINES 19
REFERENCES 20

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

SUMMARY

The Office of Environmental Health Hazard Assessment (OEHHA) has developed a proposed public health goal (PHG) of 3 ppb for 1,1-dichloroethane (1,1-DCA) in drinking water. This proposed PHG uses an existing OEHHA cancer potency value based on tumors in a study in rats, supported by data in mice. Uncommon tumors appeared in both species and there was decreased survival in the animals treated with 1,1-DCA in both species.

1,1-DCA is an organic solvent but is apparently not widely used. Its primary use is as an intermediate in the synthesis of vinyl chloride and 1,1,1-trichloroethane. There are fewer toxicological studies available than for many simple chlorinated organic solvents, but also less environmental and occupational exposure.

The current California MCL of 5 ppb (5 µg/L) is based on decreased survival of male rats in the same study on which the proposed PHG is based. At the time the MCL was developed, 1,1-DCA was not listed as a chemical known to the State of California to cause cancer and there was no cancer potency published. There were concerns about the adequacy of the only study of cancer available and the federal EPA had no cancer potency or MCL for this chemical. Therefore, the decreased survival was used as the basis of the MCL with a very large uncertainty factor.

INTRODUCTION

The purpose of this document is to propose a PHG for the chlorinated solvent 1,1-DCA in drinking water. 1,1-DCA is a volatile compound with a moderately low solubility in water, so it is expected to partition into the air in environmental situations. It has been detected in a small fraction of the groundwater samples (ca. 0.5 percent) in the California water screening program, but not in the surface water samples (DHS, 1999).

U.S. EPA has not set a federal Maximum Contaminant Level (MCL) or Maximum Contaminant Level Goal (MCLG) for 1,1-DCA. The California Department of Health Services (DHS) established an MCL of 0.005 mg/L or 5 parts per billion (ppb) in 1988 (DHS, 1988). The California MCL was computed using the lowest dose level to which male rats were exposed in a National Cancer Institute bioassay of 1,1-DCA (NCI, 1978).

The primary objective in producing this document is to reevaluate the toxicological literature, and determine if there is a more appropriate toxicological study or a better method for determining safe levels of 1,1-DCA in drinking water than were used in the earlier risk assessments supporting the development of the California MCL.

CHEMICAL PROFILE

Chemical Identity

The structure and CAS registry number are given below as well as the chemical formula and various names.

Table 1. Chemical Identity of 1,1-DCA

Chemical Name	1,1-Dichloroethane
Synonyms	Ethylidene chloride, Ethylidene dichloride, 1,1-Ethylidene dichloride, alpha alpha-Dichloroethane, asymmetric Dichloroethane, Dutch Oil
Chemical Formula	$C_2H_4Cl_2$
CAS Registry Number	75-34-3

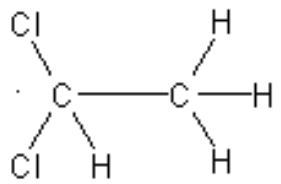

Figure 1. Structure of 1,1-dichloroethane.

Physical and Chemical Properties

1,1-DCA is called a volatile chemical, as opposed to a non-volatile or semi-volatile chemical, based on its physical properties and the method used to measure its concentration in water. 1,1-DCA can be detected by a variety of instruments including mass spectrometry or electron capture. No matter what detection instrument is used, the first step of most analyses is to separate 1,1-DCA from the water and non-volatile chemicals in the water. This is accomplished by purging the volatile chemicals from the water with an inert gas and trapping the volatile chemicals on a solid absorbing material (Cleseri *et al.*, 1989). Physical and chemical properties are given in Table 2. While there is theoretically no variability in physical and chemical properties, there is error in the estimation of those constants. Different values appear in the literature for these properties. MacKay *et al.* (1993) has surveyed the literature for physical/chemical properties of a variety of chemicals and published those values along with the literature

references. The values in the table represent a mean and standard deviation of the values found in MacKay *et al.* (1993) for 1,1-DCA.

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

Property	**Value** (mean ± std. dev.)
Molecular weight	98.96 gm/mole
Octanol-water partition coefficient (K_{ow})	62 ± 1 (unitless)
Water solubility	5,170 ± 313 mg/liter
Vapor pressure	0.3 ± 0.0054 atm
Henry's law constant	0.0054 ± 0.0009 atm-m^3/mol
Melting point	-97 ± 0.3 ^oC
Boiling point	57.3 ± 0.2 ^oC
Conversion factor	1 ppm = 4.12 mg/m^3

Production and Uses

1,1-DCA is a chemical intermediate in the synthesis of vinyl chloride and 1,1,1-trichloroethane (ATSDR, 1995). Vinyl chloride is used in the production of vinyl plastics and 1,1,1- trichloroethane is used extensively as a solvent and degreaser. U.S. EPA's Toxic Release Inventory (U.S. EPA, 1999) for data extracted on May 4, 1999 showed no reported releases in California.

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Air

Because 1,1-DCA is listed as a federal hazardous air pollutant, the California Air Resources Board (CARB) identified it as a Toxic Air Contaminant in 1993 under AB 2728 (CARB, 1996). 1,1-DCA is not one of the 75 Toxic Air Contaminants for which CARB reports monitoring data (CARB, 1998). Therefore, ambient outdoor air concentrations could not be identified for California. A review of reports of ambient air concentrations of 1,1-DCA, either monitored or estimated, at places throughout the United States largely from locations outside California, summarizes ambient air concentrations (ATSDR, 1990). Since many of the samples appear to be from regions manufacturing 1,1-DCA, the relevance of these reported concentrations to exposures experienced by Californians is unclear because 1,1-DCA is not produced in California.

Soil

A review of the literature on soil concentrations found no data and concluded, "…the lack of available soil monitoring data is at least in part due to rapid repartitioning of 1,1-dichloroethane released to soils into ambient air and groundwater" (ATSDR, 1990). Therefore, soil is unlikely to be a direct source of 1,1-DCA exposure for people because it is rapidly repartitioned to air and groundwater.

Water

Analyses of 13,347 California groundwater sources of drinking water found 1,1-DCA in 68 samples, ranging from 0.51 ppb to 30 ppb. No 1,1-DCA was found in any of the 754 surface water sources of drinking water sampled (DHS, 1999).

Food

No information could be found on 1,1-DCA levels in food. The high volatility of 1,1-DCA makes its presence in foods very unlikely.

Other Sources

Populations experiencing the highest exposures would likely be workers in occupations where 1,1-DCA is present at high concentrations in workplace air (ATSDR, 1990).

METABOLISM AND PHARMACOKINETICS

Absorption

1,1-DCA is well absorbed by the oral and inhalation routes, as expected for a small lipophilic solvent. Oral administration of 1,1-DCA to rats and mice resulted in most of the solvent found in chamber air, which should largely result from exhalation of the absorbed solvent (Mitoma *et al.*, 1985). No direct measurements of absorption in humans following inhalation exposure were found. However, the fact that 1,1-DCA was used as an anesthetic indicates adequate lung/blood partitioning to induce anesthesia (Miller *et al.*, 1965). The extensive physiologically-based pharmacokinetic modeling of the chlorinated solvents could be used to evaluate inhalation and oral toxicokinetics (Gargas *et al.*, 1989, 1990). Dermal absorption from water could be significant, but because of the rapid partitioning of 1,1-DCA into air, exposure to this chemical in bathing and showering would be dominated by the inhalation route.

Distribution

1,1-DCA will be rapidly distributed throughout the body similar to other small chlorinated hydrocarbons (Gargas *et al.*, 1989, 1990; Barton *et al.*, 1995). Radioactivity

was detected in liver, kidney, lung and stomach of rats and mice injected intraperitoneally with ^{14}C-1,1-DCA (Colacci *et al.*, 1985). Most of the radioactivity was found in chamber air after oral administration of ^{14}C-1,1-DCA, indicating efficient distribution and exhalation (Mitoma *et al.*, 1985). The fact that anesthesia occurs following inhalation administration to humans indicates that 1,1-DCA is well distributed to the central nervous system in humans.

Metabolism

The most comprehensive report of metabolism is in rat tissue (McCall *et al.*, 1983). Microsomes were prepared from the livers of rats treated with the cytochrome P450 inducer, phenobarbital. ^{14}C-Labelled 1,1-DCA was incubated with the microsomes and the radioactive components of the mixture were identified.

Figure 2 shows a predicted metabolic pattern for 1,1-DCA, with inferred intermediates in parentheses. Varying amounts of the other structures shown in this diagram were detected in the incubation mixture (McCall *et al.*, 1983). The diagram can most easily be understood by recognizing the similarity of the production of the three acetic acid derivatives with the steps in the metabolism of ethanol. The steps are shown in four columns to highlight the similarities of the reactions. The first step is the hydroxylation of 1,1-DCA to one of two ethanol analogs shown in the second column. The second step is dehydrogenation of the ethanol analogs to chloroaldehyde or one of two acetyl chlorides shown in the third column. The third and final step is conversion of the aldehyde/acetyl chloride to the corresponding acetic acid analog. The production rate of acetic acid was far greater than production of either of the two chloroacetic acids. Production of acetic acid was over 800 times greater than the monochloroacetic acid and over 2000 times greater than dichloroacetic acid.

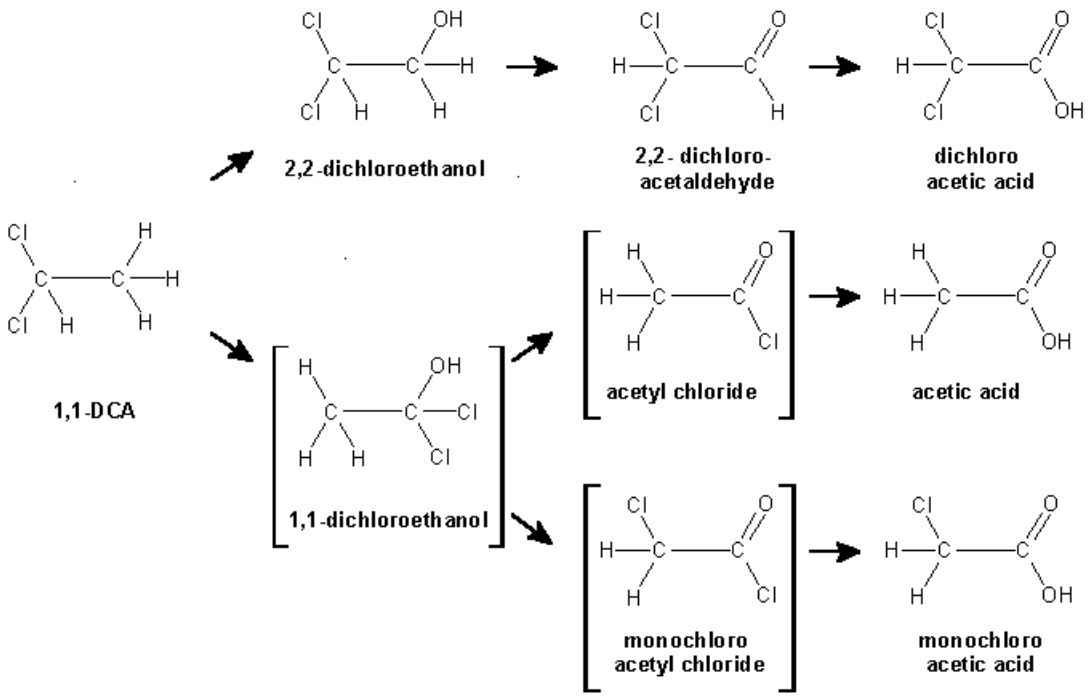

Figure 2. Proposed Metabolism of 1,1 DCA

Excretion

Mitoma *et al.* (1985) collected urine, feces and the chamber air of mice and rats for 48 hours after oral administration of ^{14}C-1,1-DCA. Radioactivity was measured in the urine and feces that together were called excreta. Volatile metabolites in the chamber air were pulled through three sequential traps: methylcellulose, toluene and a CO_2 trap. The animals were killed at 48 hours after dosing. The livers and kidneys were removed for analysis of protein binding and the radioactivity remaining in the carcass was measured. The following table shows the dose and the percent of administered dose recovered in air, excreta and the carcass.

Table 3. Excretion of 1,1-DCA

Dose (mmol/kg)	Recovery	Expired Air*	CO_2	Excreta	Carcass
			(assumed to be metabolized)		
RAT					
7.1	93%	86%	5.1%	0.92%	1.5%
MOUSE					
18	99.7%	70%	25%	1.6%	2.4%

*Radioactivity sequentially trapped in methylcellulose and toluene

Metabolism appears to be greater in the mouse than in the rat. This was also found after chronic administration of 1,1-DCA in a companion study from the same laboratory (Mitoma *et al.*, 1985).

TOXICOLOGY

Toxicological Effects in Animals and Plants

Acute Toxicity

No primary studies were found with detailed information on the effects of acute exposure. However, like other chlorinated aliphatic solvents, 1,1-DCA is anticipated to be acutely sedative, and anesthetic at a high dose. Secondary sources report an inhalation LC_{50} of 17,300 ppm for two hours in mice (Verschueren, 1983) and 16,000 ppm for eight hours in rats (Verschueren, 1983), and an oral LD_{50} in rats of 14,100 mg/kg (Kirk-Othmer, 1978).

Subchronic Toxicity

The dose selection study for the cancer bioassay (NCI, 1978) was a six-week subchronic exposure followed by a two week observation period. Rats and mice of both sexes were gavaged with corn oil or one of five concentrations of 1,1-DCA in corn oil. The doses were 562, 1000, 1780, 3160, and 5620 mg/kg-d in rats and 1000, 1780, 3160, 5620, and 10,000 mg/kg-d in mice. The following table shows the doses at which decreased body weight and death were observed in this range-finding study.

Table 4. Subchronic Toxicity in Rats and Mice

Species, sex	Dose (mg/kg)	Decreased body weight (percent)	Death (incidence)
Rats			
male	562	16	0/5
	1000	29	0/5
female	1780	20	0/5
	3160	20	2/5
Mice			
male	5620	NA	2/5
female	5620	NA	3/5

NA: Not applicable.

At the higher doses in both these studies, presumably more severe body weight decreases and an increased incidence of lethality occurred, although this is not stated in the brief description in the NCI report. Very few observations or measurements were conducted

on the exposed animals because this was a dose finding study for the two-year study (NCI, 1978).

The initial high doses estimated for the chronic studies from these subchronic studies were 700 and 1500 mg/kg-d for the rat males and females, respectively, and 1800 mg/kg-d for mice of both sexes, based on the 5 day/week gavage schedule. The high doses for the chronic studies are nominally set at the maximum tolerated dose determined in the subchronic study. The derivation of the maximum exposure levels for the chronic studies is therefore understandable in rats, but not in mice. That is, it is not clear from these data that 1800 mg/kg-day (5 days/week) would represent an MTD for mice, and the mouse doses were in fact increased during the chronic study because the high dose animals were exhibiting no toxic effects.

A no-observed-adverse-effect level (NOAEL) cannot be determined for male rats from this subchronic study; the lowest dose of 562 mg/kg-day represents a lowest-observed-adverse-effect level (LOAEL). The lowest dose (562 mg/kg-day) is apparently a NOAEL for female rats. The 3160 mg/kg-day dose from the mouse study probably represents a NOAEL for body weight changes or death, but it is not clear whether it represents a true subchronic NOAEL for mice, since it was above the dose chosen as the maximum dose for the chronic study.

Genetic Toxicity

The results from genetic toxicity testing are somewhat contradictory. Table 5 summarizes the reports from the literature. The table has four sections for *in vitro* exposure tests (bacteria, yeast, fungi and mammalian cells) and a single section for *in vivo* exposures. 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 media concentration are 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 reactive intermediates capable of mutating DNA. Therefore, mammalian activating enzymes can be added to the media during the exposure. The third and fourth columns show results with and without such activating enzymes.

Several studies found *Salmonella typhimurium* not to be mutated by 1,1-DCA. However, Riccio *et al.* (1983) report a positive result in some of the same strains previously tested with and without activation. This chemical caused chromosome abnormalities in *Aspergillus nidulans,* but did not mutate yeast. 1,1-DCA was negative in the mouse 3T3 cell transformation assay, but induced unscheduled DNA synthesis in both rats and mice and induced viral transformation in hamster embryo cells. Radioactivity was found in DNA, RNA and protein of liver, kidney, lung, and stomach following an intraperitoneal (ip) injection of radioactive 1,1-DCA into mice and rats. However, an ip injection failed to induce single strand breaks in the liver DNA of mice. The results of the tests for genotoxicity do not enable us to categorize this chemical as genotoxic or epigenetic.

Table 5. Genotoxicity of 1,1-DCA*

Test Species/ Strains	Exposure Conditions	Activation With	Activation Without	Reference
Bacteria Reverse Mutation (Ames assay)				
S. typhimurium TA98, TA100, TA1535	Desiccator Assay: Vapor Exposure	+	+	Mitoma *et al.*, 1984
S. typhimurium TA97,TA98, TA100, TA102	unknown	-	-	Nohmi *et al.*, 1986
S. typhimurium TA98, TA100, TA1535	Desiccator Assay: Vapor Exposure	+	+	Riccio *et al.*, 1983
S. typhimurium TA1537	Desiccator Assay: Vapor Exposure	-	-	Riccio *et al.*, 1983
S. typhimurium TA98, TA100, TA1535, TA1537,1538	Desiccator Assay: Vapor Exposure	-	Not tested	Simon *et al.*, 1977
S. typhimurium TA97,TA98, TA100, TA1535	Desiccator Assay: Vapor Exposure	-	-	Zeiger, *et al.*, 1992
Yeast Mutation Assay				
S. cerevisiae D3	Suspension assay	-	-	Simon *et al.*, 1977
S. cerevisiae D7	No enclosure but other chemicals positive	-	Not tested	Bronzetti *et al.*, 1987
Fungi Chromosomal Effects				
Aspergillus nidulans	Sealed capped glass tube	+	Not tested	Crebelli *et al.*, 1995
Mammalian Cells				
Syrian hamster embryo cells - cell transformation	Chamber withVapor Exposure	Not tested	+	Hatch *et al.*, 1983
BALB/C-3T3 – viral transformation	Sealed Chamber: Vapor Exposure	Not tested	-	Tu *et al.*, 1985
Rat/mouse - DNA repair	No enclosure	Not tested	+	Williams, 1983; Williams *et al.*, 1989
***In Vivo* Rodent Exposures**				
Rat/mouse organ - macromolecular binding	Not applicable	+**		Colacci *et al.*, 1985
Balb/c (single strand breaks in DNA)	Not applicable	-		Taninger *et al.*, 1991

* This table is a modification of a table found in OEHHA 1999b
** Binding indices in liver, kidney, lung and stomach were similar to other weak carcinogens

There were few endpoints and a limited range of organisms in which measurements were made. The existing data includes only a few *in vitro* mammalian cell assays and 1,1-DCA has not been tested in many of the standard assays (e.g., sister chromatid exchange (SCE), chromosomal aberrations, mutations in mouse lymphoma cells). Nor has the chemical been tested in many of the standard *in vivo* mammalian assays (e.g., rodent bone marrow micronucleus, or SCE, micronucleus, chromosomal aberrations in peripheral blood cells). There are no reports of data in humans (*in vivo* or *in vitro*). Given these facts and the ambiguity of the existing data, it is difficult to assess the genotoxic potential of 1,1-DCA.

Developmental and Reproductive Toxicity

Schwetz *et al.* (1974) evaluated the developmental toxicity of three chlorinated hydrocarbons including 1,1-DCA. Pregnant rats were exposed by inhalation to 1,1-DCA for 7 hours/day on days 6 through 15 of gestation at 3,800 and 6,000 ppm (2,300 and 3,600 mg/kg-d, respectively, assuming 50 percent pulmonary absorption). The 6,000 ppm exposure to 1,1-DCA caused delayed ossification of the sternebrae; this concentration was not considered to be maternally toxic. No adverse effects were observed at the lower concentration of 3,800 ppm, so the NOAEL is 2,300 mg/kg-day for developmental effects.

Immunotoxicity

No studies were identified.

Neurotoxicity

No studies were identified.

Chronic Toxicity

One comprehensive toxicity study involving chronic exposure of animals to 1,1-DCA was found (NCI, 1978). This study followed the typical NCI protocol of gavaging Osborne-Mendel rats and B6C3F$_1$ mice of both sexes with 1,1-DCA in corn oil. Fifty animals per sex of both species were treated 5 days per week for 78 weeks. While it is not typical of NCI studies, the dose levels for both sexes of rats and mice changed during the exposure. The following tables show how doses were changed throughout the course of the study for each species. The week of the study is shown in the first column and dose level associated with that week is shown for each of the four different groups across the row. Values in the table are doses in mg/kg-d.

Table 6. Dose Level Changes for Osborne-Mendel Rats

Week	Female		Male	
	Low Dose	High Dose	Low Dose	High Dose
0	750	1500	350	700
9	900	1800	450	900
18	450	900		
32	One week with no gavage followed by four weeks of exposure at the week 18 dose levels. This five-week cycle repeated until study end.			
78	Surviving animals observed 33 weeks more, then killed and necropsied.			

Table 7. Dose Level Changes for B6C3F$_1$ Mice

	Female		Male	
Week	**Low Dose**	**High Dose**	**Low Dose**	**High Dose**
0	900	1800	900	1800
7	1200	2400	1200	2400
10	1500	3000	1500	3000
21	1800	3600		
78	Surviving animals killed and necropsied after 12 or 13 more weeks.			

The study author's estimates of the chronic daily doses from this complicated exposure regimen is shown in the second column of Table 8. The third column includes an adjustment to daily doses, based on the fact that these animals were dosed five rather than seven days per week. The doses in the third column are those used in the OEHHA calculations.

Table 8. Time-weighted Average Doses

	Time weighted average low dose/high dose (mg/kg-d)	**Five/seven day adjustment** low dose/high dose (mg/kg-d)
Male rats	382/764	273/546
Female rats	475/950	339/679
Male mice	1442/2885	1030/2061
Female mice	1665/3331	1189/2379

The control groups for these studies are somewhat complicated due to the fact that the 1,1-DCA study occurred at a facility with animals being exposed to many other chemicals, concurrently. Both the rat and mouse studies included two different control groups. There were 20 vehicle- and 20 untreated-control animal of each sex and species assigned to each chemical under study. An untreated group was not necessarily housed with the vehicle control and 1,1-DCA exposed animals.

The rats in the vehicle control group for trichloroethylene were combined with those from those in the 1,1-DCA study in the analysis of the data. This resulted in 40 male and 40 female rats for statistical analysis. The mice in the vehicle control groups of 1,1,2-trichloroethane, trichloroethylene and allyl chloride were combined with the mice of those in 1,1-DCA to increase the number of vehicle control animals. This resulted in 80 male and 80 female vehicle control mice for statistical analysis.

This study poses serious problems because few of the rats survived the entire study period and significant early deaths were observed in the male mice. Female mice were the only animals to survive in good numbers to the end of the study. Both dose levels for male and female rats appeared to exhibit lower survival than their corresponding controls. The decreased survival was significantly lower for male rats ($p = 0.006$) but was not significant by the Tarone test for the females. Male mice in both treatment groups exhibited a significant decrease in survival, while the female mice had significantly decreased survival only at the highest dose. The percentages of animals alive at the end of the study (week 111 for rats and week 91 for mice) are shown in the following table. The rats had very high incidences of pneumonia. The values in parentheses indicate the percentage of rats diagnosed with chronic pneumonia.

Table 9. Survival to Study End and (Incidence of Pneumonia) for Rats and Mice

	Untreated Control	Corn Oil Control	Low Dose Group	High Dose Group
Male rats	30% (70%)	5% (95%)	4% (80%)	8% (84%)
Female rats	40% (85%)	20% (89%)	16% (68%)	18% (64%)
Male mice	35%	55%	62%	32%
Female mice	80%	80%	80%	50%

The NCI protocol is designed to test the carcinogenic potential of a chemical. A pathologist examined histological sections of about 27 tissues from each animal in the study using a light microscope. In addition to the pneumonia, a number of other disease processes were detected at levels above 10 percent in most of the groups including controls. The lesions not related to treatment included testicular atrophy in male rats, chronic inflammation of the kidney in female rats and male mice, and hydrometra of the uterus in female mice. There were no treatment-related lesions reported in either sex of rats or mice.

Body weights were lower in all treated groups compared to the untreated controls, but corn oil controls did not differ from the treated animals. The survival curves of animals in the four treatment groups over time (graphs not shown) indicated differences for male and female rats as well as female mice. In male rats, for example, survival at 78 weeks was about 90 percent in controls versus 40 percent in both 1,1-DCA-dosed groups. Of these three species-sex combinations, male rats were exposed to the lowest dose level, 273 mg/kg-d. This is a chronic LOAEL for a noncancer endpoint of decreased survival.

Carcinogenicity

One report of 1,1-DCA-induced cancer in animals was found (NCI, 1978). The experiment and its exposure protocol for mice and rats is described above under chronic toxicity. Male B6C3F$_1$ mice exhibited hepatocellular carcinomas in control and treatment groups. Female Osborne-Mendel rats had evidence of two types of neoplasms, circulatory system hemangiosarcomas and mammary adenocarcinomas.

Hepatocellular Carcinoma

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 F$_1$ (first generation offspring) 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-DCA because the F$_1$ generation was thought to balance the sensitivity to carcinogens with a moderate background level of hepatocellular carcinoma. The incidence in the pooled corn oil control, low and high dose groups were 6/72, 8/48 and 8/32, respectively.

In males, the incidence of tumors at both the high and low doses was not significantly different ($p>0.05$) from the corn oil controls using either a Fisher's exact or Cochran-Armitage test (NCI, 1979).

Hemangiosarcoma

Hemangiosarcoma is a malignant neoplasm of vascular origin characterized by masses of endothelial cells displaying atypical morphology of malignant cells. Microscopically, these sarcomas may be similar in their cytological detail to fibrosarcomas and leiomyosarcomas. Therefore, it can be difficult to determine the exact cell or tissue of origin and careful scrutiny of the better-differentiated areas is required to identify the endothelial and vascular origin (Robbins, 1967).

Hemangiosarcomas were not observed in either control group, or in the low dose group. At the high dose level, they appear in subcutaneous tissue (2/50), lung (1/50) and spleen (1/49). A pair-wise comparison does not show statistical significance, but there is a positive trend test (OEHHA, 1999b).

Mammary Adenocarcinoma

Mammary adenocarcinomas arise from the epithelial cells of the breast. The incidence of mammary tumors at both the high and low doses was not significantly different ($p>0.05$) from the corn oil controls using either a Fisher exact or Cochran-Armitage test (NCI, 1978).

Endometrial Stromal Polyps

The Fisher exact test was positive for endometrial polyps in the high-dose group ($p=0.017$) relative to the pooled vehicle controls. None of the 18 laboratory historical vehicle control $B6C3F_1$ mice used in studies by the NCI Bioassay Program had ever exhibited an endometrial stromal polyp.

Bioassay Summary

The NCI evaluation concludes that, "There were dose-related marginal increases in mammary adenocarcinomas and in hemangiosarcomas among female rats and there was a statistically significant increase in the incidence of endometrial stromal polyps among dosed female mice as compared to controls. These findings are indicative of the possible carcinogenic potential of the test compound. However, it must be recognized that under the conditions of this bioassay there was no conclusive evidence for the carcinogenicity of 1,1-dichloroethane in Osborne-Mendel rats or $B6C3F_1$ mice." The NCI review committee (a subcommittee of the Clearinghouse on Environmental Carcinogens) concluded that "there was no conclusive evidence as to the carcinogenicity of 1,1-dichloroethane in the treated mice and that the rat study was inadequate to draw any conclusion." The committee also recommended a retest (NCI, 1978).

The U.S. EPA concluded that this bioassay "provides limited evidence of the carcinogenicity of 1,1-DCA in Osborne-Mendel rats and $B6C3F_1$ mice...based on significant dose-related increases in the incidence of hemangiosarcomas at various sites and mammary carcinomas in female rats and statistically significant increases in the incidence of liver carcinoma in male mice and benign uterine polyps in female mice" (U.S. EPA, 1996). The U.S. EPA also noted that the statistical power of the study is limited by the low survival rates in many groups, which precluded the appearance of possible late-developing tumors.

"Survival analysis conducted by Gold and colleagues (Gold and Zeiger, 1997) reported a significant association with exposure and uterine endometrial polyps ($p<0.004$) compared to pooled controls in female mice. Additional positive findings included liver tumors ($p<0.05$) and lung tumors ($p<0.04$) in male mice compared to matched controls…

In female rats, they reported statistically significant associations of exposure and hemangiosarcomas of the circulatory system with matched controls ($p<0.05$) or pooled controls ($p<0.02$) and adenocarcinomas of the mammary gland ($p<0.04$) with matched controls" (OEHHA, 1999b)

Toxicological Effects in Humans

Acute Toxicity

No studies were identified. However, it was reported that 1,1-DCA can cause "salivation, sneezing, and coughing. In those few cases of intoxication...reported, the anticipated anesthetic effects have been observed with associated dizziness, nausea and vomiting. In severe & fatal cases hepatic & renal injury have been observed" (Hamilton and Hardy, 1974, as cited in HSDB, 2001).

Subchronic Toxicity

No studies were identified.

Genetic Toxicity

No studies were identified.

Developmental and Reproductive Toxicity

No studies were identified.

Immunotoxicity

No studies were identified.

Neurotoxicity

No studies were identified.

Chronic Toxicity

No studies were identified.

Carcinogenicity

No studies were identified.

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

NCI (1978) reported that subchronic exposure decreased body weight gain of male rats at 562 mg/kg-d, while chronic exposure of male rats to 1,1-DCA caused decreased survival at 273 mg/kg-d. The chronic exposure dose is lower so it was chosen as the LOAEL for 1,1-DCA noncancer risk assessment.

Carcinogenic Effects

A cancer potency for 1,1-DCA has been published by OEHHA. The current OEHHA potency was developed under the expedited cancer potency value method (OEHHA, 1992). "Cancer potency is based on mammary tumor adenocarcinoma observed in female rats, the most sensitive species/sex combinations tested. Because survival was poor for the study in female rats, the potency was derived using a time-to-tumor analysis" (OEHHA, 1992).

U.S. EPA downgraded the status of 1,1-DCA from B2 to C in 1990 based on professional judgment. The Proposition 65 Carcinogen Identification Committee considered delisting 1,1-DCA as a substance known to the State of California to cause cancer. The panel unanimously voted that "1,1-DCA has been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer and therefore should remain on the list" (Portale & Associates, 1999).

An OEHHA Air Toxics evaluation observed that "Cancer potency for 1, 1-dichloroethane is based on mammary gland adenocarcinomas observed in female rats, the most sensitive of the species/sex combinations tested. Because female rat survival was poor in this study, the potency was derived using a time-to-tumor analysis. Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor" (OEHHA, 1999a). The OEHHA estimated cancer potency is 0.0057 $(mg/kg\text{-}day)^{-1}$ (OEHHA, 1992).

CALCULATION OF THE PHG

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

Exposure Considerations

Tap water is used directly as drinking water and also is used for showering. The inhalation exposure while showering may contribute more to the daily dose than drinking, depending on the volatility of the chemical. 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. Application of this model to 1,1-DCA predicts that the inhalation dose will be approximately equal to the ingested dose. Therefore the equivalent volume of water (L_{eq}) is assumed to be 4 L/d; 2 L/d is ingested and a dose equal to 2 L/d is inhaled in the shower plus other household uses of water. The dose from dermal absorption is judged to be negligible.

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:

$$C = \frac{NOAEL \times BW \times RSC}{UF \times L_{eq}/d}$$

where,

NOAEL/LOAEL	=	no-observed-adverse-effect-level or lowest-observed-adverse-effect-level (a LOAEL of 273 mg/kg-d in this case);
BW	=	adult body weight (a default of 70 kg);
RSC	=	relative source contribution (a default of 20 percent);
UF	=	uncertainty factors (in this case, 10 each for intra- and inter-species extrapolations, and 10 to estimate a NOAEL from a LOAEL);
L_{eq}/d	=	daily water consumption rate (4 L_{eq}/d).

Therefore,

$$C = \frac{273\ mg/kg\text{-}d \times 70\ kg \times 0.2}{1000 \times 4\ L_{eq}/d} = 1\ mg/L = 1000\ ppb$$

A public-health protective concentration of 1,1-DCA in drinking water to protect against non-cancer effects is 1000 ppb, based on higher mortality in male rats (NCI, 1978).

Carcinogenic Effects

For carcinogens, the following general equation can be used to calculate the public health-protective concentration (C) for 1,1-DCA in drinking water (in mg/L):

$$C = \frac{BW \times R}{CSF \times L_{eq}/d} = mg/L$$

where,

BW	=	adult body weight (a default of 70 kg);
R	=	*de minimis* level for lifetime excess individual cancer risk (a default of 10^{-6});
CSF	=	cancer slope factor (0.0057 $(mg/kg\text{-}d)^{-1}$);
L_{eq}/d	=	daily volume of water consumed (4 L_{eq}/d).

Therefore,

$$C = \frac{70\ kg\ \times\ 10^{-6}}{0.0057\ (mg/kg\text{-}d)^{-1}\ \times\ 4\ L_{eq}/d} = 0.003\ mg/L = 3\ ppb$$

The PHG is proposed to be set at 0.003 mg/L (3 µg/L, or 3 ppb), based on mammary tumors in female Osborne-Mendel rats, because this level is much lower than the value derived for non-cancer effects, based on decreased survival.

RISK CHARACTERIZATION

The existing OEHHA cancer potency was used to develop the proposed PHG for 1,1-DCA. The value based on the non-cancer endpoint, increased death rates in male rats, is over 300 times greater. The only observed adverse developmental endpoint was delayed ossification of the sternebrae, indicative of retarded fetal development. No specific teratogenic effects were observed. However, no multi-generation reproductive studies have been conducted for 1,1-DCA.

The proposed PHG of 3 ppb was calculated based on the carcinogenic potency of 1,1-DCA. In calculating the PHG, a *de minimis* theoretical excess individual cancer risk level of 10^{-6} was assumed. The corresponding levels for cancer risk levels of 10^{-5} or 10^{-4} are 30 and 300 ppb, respectively. These calculations assume lifetime (70 year) consumption of 2 L/d of 1,1-DCA in drinking water, plus daily exposure to an equal amount via inhalation from other household uses of the water.

Sensitive subpopulations have been considered. Although toxicological data are extremely limited, we have identified no sensitive subpopulations, and see no reason to suspect special sensitivity in such groups as infants, pregnant women, and the elderly. Potentially sensitive populations cited in HSDB (2001) include persons with existing skin disorders or impaired pulmonary function (for occupational exposures involving high concentrations). Neither of these potentially sensitive populations is considered to be at special risk of toxic effects of 1,1-DCA at the concentrations that have been reported in California ground water (up to 30 ppb; DHS, 1999).

OTHER REGULATORY STANDARDS OR GUIDELINES

There is no federal MCL for 1,1-DCA. The California Department of Health Services established an MCL of 0.005 mg/L (5 ppb) for 1,1-DCA in 1988 (DHS, 1988). The California MCL was based on noncancer effects at the lowest dose level to which male rats were exposed in the National Cancer Institute bioassay of 1,1-DCA (NCI, 1978), with a very large uncertainty factor.

Table 13 lists enforceable standards and recommended guidelines for other states taken from the Hazardous Substance Database (HSDB, 2001).

Table 13. Other State Drinking Water Standards or Guidelines for 1,1-TCA

STATE	CONCENTRATION µg/L	STATUS
New Jersey	50	Standard
Maine	5	Guideline
Massachusetts	70	Guideline
Minnesota	70	Guideline
New Hampshire	81	Guideline
Florida	700	Guideline
Michigan	840	Guideline
Wisconsin	850	Guideline

HSDB, 2001

REFERENCES

ATSDR (1995). Toxicological Profile for 1,1,1-Trichloroethane. Prepared by Research Triangle Institute under Contract No. 205-93-0606 for Agency for Toxic Substances and Disease Registry (ATSDR), U.S. Department of Health and Human Services, Public Health Service, in collaboration with U.S. EPA. Atlanta, Georgia.

ATSDR (1990). Toxicological Profile for 1,1-Dichloroethane. ATSDR/TP-90-12. Prepared by Clement Associates under Contract No. 205-88-0608 for Agency for Toxic Substances and Disease Registry (ATSDR), U.S. Department of Health and Human Services, Public Health Service, in collaboration with U.S. EPA. Atlanta, Georgia.

Barton HA, Creech JR, Godin CS, Randall GM, Seckel CS (1995). Chloroethylene mixtures: pharmacokinetic modeling and *in vitro* metabolism of vinyl chloride, trichloroethylene, and trans-1,2-dichloroethylene in rat. Toxicol Appl Pharmacol 130:237-247.

Bronzetti G, Galli A, Vellosi R, Rossi F, Morichetti E, Del Carratore R (1987). Genetic activity of chlorinated ethanes. IXth meeting of the European Association for Cancer Research, Helsinki, Finland. Cancer Clin Oncol 23:1737-1738.

CARB (1996). Toxic Air Contaminant Identification List - June 1996. California Air Resources Board Website, http://www.arb.ca.gov/toxics/tac/taclist.htm. Sacramento, California.

CARB (1998). California Ambient Air Quality Data 1980-1997. California Air Resources Board (CARB). Sacramento, California.

Colacci A, Arfellini G, Mazzullo M, Prodi G, Grilli S (1985). Genotoxicity of 1,1-Dichloroethane. Res Commun Chem Pathol Pharmacol 49:243-254.

Cleseri LS, Greenberg AE, Trussel AR, eds. (1989). Volatile Organics. In: Standard Methods for the Examination of Water and Wastewater. American Public Health Association, Washington, DC.

Crebelli R, Andreoli C, Carere A, Conti L, Crochi B, Cotta-Ramusino M, Benigni R (1995). Toxicology of halogenated aliphatic hydrocarbons: Structural and molecular determinants for the disturbance of chromosome segregation and the induction of lipid peroxidation. Chem-Biol Interact 98:113-129.

DHS (1988). Proposed Maximum Contaminant Level for 1,1-dichloroethane. California Department of Health Services (DHS), Health and Welfare Agency, Sacramento, California.

DHS (1999). Drinking Water Monitoring Data 1984-1998. Annual Status Report. California Department of Health Services, Sacramento, California.

Gargas ML, Andersen ME (1989). Determining kinetic constants of chlorinated ethane metabolism in the rat from rates of exhalation. Toxicol Appl Pharmacol 99:344-353.

Gargas ML, Clewell HJ III, Andersen ME (1990). Gas uptake inhalation techniques and the rates of metabolism of chloromethanes, chloroethanes, and chloroethylenes in the rat. Inhal Toxicol 2:295-319.

Gold LS, Zeiger E (eds.) (1997). Handbook of carcinogenic potency and genotoxicity database. CRC Press, Boca Raton.

Hamilton A, Hardy HL (1974). Industrial Toxicology, 3rd Ed. Publishing Sciences Group, Inc., Acton, Massachusetts (as cited in HSDB, 2001).

Haseman JK, Hailey JR, Morris RW (1998). Spontaneous neoplasm incidences in Fischer 344 rats and $B6C3F_1$ mice in two-year carcinogenicity studies: a National Toxicology Program update. Toxicol Pathol 26:428-41.

Hatch GG, Mamay PD, Ayer ML, Casto BC, Nesnow S (1983). Chemical enhancement of viral transformation in Syrian hamster embryo cells gaseous and volatile chlorinated methanes and ethanes. Cancer Res 43:1945-50.

HSDB (2001). Hazardous Substance Database. Available: http://toxnet.nlm.nih.gov/cgi-bin/sis/search.

Kirk-Othmer (1978). Kirk-Othmer Encyclopedia of Chemical Technology, 3rd Ed., Volumes 1-26. John Wiley and Sons, New York, NY, 1978-1984. p. 5(78) 724.

Mackay D, Shiu WY, Ma KC (1993). Illustrated Handbook of Physical-Chemical Properties and Environmental Fate for Organic Chemicals: Vol. 1. Lewis Publishers, Boca Raton, Florida.

McCall SN, Jurgens P, Ivanetich KM (1983). Hepatic microsomal metabolism of the dichloroethanes. Biochem Pharmacol 32:207-13.

McKone TE (1987). Human exposure to volatile organic compounds in household tap water - the indoor inhalation pathway. Environ Sci Technol 21:1194-1201.

Miller KW, Patton WDM, Smith EB (1965). Site of action of general anesthetics. Nature 206:575-577.

Mitoma C, Tyson CA, Riccio ES (1984). Investigation of the species sensitivity and mechanism of carcinogenicity of halogenated hydrocarbons. Prepared for U.S. EPA by SRI International. EPA/OTS, Document #40-842-8424225. (As cited in OEHHA, 1999b)

Mitoma C, Steeger T, Jackson SE, Wheeler KP, Rogers JH, Milman HA (1985). Metabolic disposition study of chlorinated hydrocarbons in rats and mice. Drug Chem Toxicol 8:183-194.

Nohmi T, Miyata R, Yoshikawa K, *et al.* (1986). Mutagenicity tests on organic chemical contaminants in city water and related compounds: I. Bacterial mutagenicity tests. Bull Natl Hyg Sci 103:60-64.

NCI (1978). Bioassay of 1,1-dichloroethane for possible carcinogenicity. National Cancer Institute Carcinogenesis Technical Report Series 66. NCI-CG-TR-66, PB-283 345.

OEHHA (1992). Expedited Cancer Potency Values and Proposed Regulatory Levels for Certain Proposition 65 Carcinogens. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, California.

OEHHA (1999a). Air Toxics Hot Spots Program. Risk Assessment Guidelines. Part II. Technical Support Document for Describing Available Cancer Potency Factors. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, California.

OEHHA (1999b). Notice to Interested Parties. October 7, 1999 Meeting of the Science Advisory Board's Carcinogen Identification Committee (CIC). Consideration for delisting of Allyl Chloride, Chlorodibromomethane, 1-1-Dichloroethane, p-Toluidine, and Zineb. [09/03/99]

OEHHA (2001). Toxicity Criteria Database. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, California. http://www.oehha.ca.gov/risk/chemicalDB/start.asp.

Portale & Associates (1999). Transcript of the October 4, 1999 Meeting of the Scientific Advisory Panel, pp. 159-173. Available from the Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, California.

Riccio E, Griffin A, Mortelmans K, Milman HA (1983). A comparative mutagenicity study of volatile halogenated hydrocarbons using different metabolic activation systems. Env Mut 5:472.

Robbins SL (1967). Pathology. W.B. Saunders Co., Philadelphia, Pennsylvania.

Schwetz BA, Leong BK, Gehring PJ (1974). Embryo- and fetotoxicity of inhaled carbon tetrachloride, 1,1-dichloroethane and methyl ethyl ketone in rats. Toxicol Appl Pharmacol 28:452-464.

Simmon VF, Kauhanen K, Tardiff RG (1977). Mutagenic activity of chemicals identified in drinking water. Dev Toxicol Environ Sci 2:249-258.

Taningher M, Parodi S, Grilli S, Colacci A, Mazzullo M, Bordone R, Santi L (1991). Lack of correlation between alkaline DNA fragmentation and DNA covalent binding induced by polychloroethanes after *in vivo* administration: Problems related to the assessment of a carcinogenic hazard. Cancer Detect Prev 15:35-40.

Tu AS, Murray TA, Hatch KM, Sivak A, Milman HA (1985). *In vitro* transformation of BALB/c-3T3 cells by chlorinated ethanes and ethylenes. Cancer Letters 28:85-92.

U.S. EPA (1990). National Primary Drinking Water Regulations, Synthetic Organic Chemicals and Inorganic Chemicals, Proposed Rule. Federal Register July 25, 1990, p. 30406.

U.S. EPA (1992). National Primary Drinking Water Regulations, Synthetic Organic Chemicals and Inorganic Chemicals, Final Rule. Federal Register July 17, 1992, p. 31795.

U.S. EPA (1999). Toxic Release Inventory. [Online, accessed June 30, 2000]. U.S. Environmental Protection Agency, Washington, DC. Available: http://www.epa.gov/triinter/index.htm.

U.S. EPA (1996). 1,1-Dichloroethane (last revised 12/01/1996). Integrated Risk Information System (IRIS). U.S. Environmental Protection Agency, Cincinnati, Ohio. Online, accessed May 5, 2001 at: http://www.epa.gov/iris/subst/index.html.

Verschueren K (1983). Handbook of Environmental Data of Organic Chemicals, 2nd Ed. Van Nostrand Reinhold Co. New York, New York.

Williams GM (1983). DNA repair tests of 11 chlorinated hydrocarbon analogs. Final Report U.S. EPA contract. NTIS/OTS 0509403.

Zeiger E (1992). Carcinogenicity of mutagens: Predictive capability of the Salmonella mutagenesis assay for rodent carcinogenicity. Carcinogenesis 47:1287-1296.