

Public Health Goal for 1,2-Dichloroethane In Drinking Water

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PREFACE

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

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

1. PHGs for acutely toxic substances shall be set at levels at which no known or anticipated adverse effects on health will occur, with an adequate margin of safety.
2. PHGs for carcinogens or other substances which can cause chronic disease shall be based solely on health effects without regard to cost impacts and shall be set at levels which OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of insufficient data to determine a level of no anticipated risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.
9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.
10. PHGs adopted by OEHHA shall be reviewed every five years and revised as necessary based on the availability of new scientific data.

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

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

Additional information on PHGs can be obtained at the OEHHA web site at www.oehha.ca.gov.

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PUBLIC HEALTH GOAL FOR 1,2 –DICHLOROETHANE IN DRINKING WATER

SUMMARY

A Public Health Goal (PHG) of 0.0004 mg/L (0.4 ppb) is developed for 1,2-dichloroethane (1,2-DCA, also known as ethylene dichloride) in drinking water. The existing California Maximum Contaminant Level (MCL) is 0.5 ppb and the U.S. Environmental Protection Agency's (U.S. EPA) MCL is 5 ppb. The PHG is based on an evaluation of the carcinogenic potential of the chemical. 1,2-DCA has been identified by U.S. EPA as a probable human carcinogen (B2) and it is listed under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65) as a chemical known to the state to cause cancer. The National Cancer Institute (NCI, 1978) reported that in two long-term gavage studies, 1,2-DCA was carcinogenic to both rats and mice. However, Maltoni et al. (1980) exposed rats and mice to 1,2-DCA via inhalation for 78 weeks and did not observe any increase in tumor rates at the end of 148 weeks. Cheever et al. (1990) also exposed rats to 1,2-DCA via inhalation for two years and did not observe any increase in tumor rates. Klaunig et al. (1986) exposed male mice to 1,2-DCA in drinking water for one year and reported no increase in tumor incidences.

In 1988, the Office of Environmental Health Hazard Assessment (OEHHA) developed cancer potency values with a range of 0.014 to 0.088 (mg/kg-day)⁻¹ for 1,2-DCA, using the NCI (1978) carcinogenicity study results. Since that time, studies published by Baertsch et al. (1991) and the National Toxicology Program (NTP, 1991) showed that 1,2-DCA administered over a short duration but at a high concentration produced more DNA-adducts and greater toxicity than when the compound was administered over a long period of time but at a lower concentration. In an inhalation study, Cheever et al. (1990) showed that inhalation exposure of rats to 50 ppm of 1,2-DCA did not induce tumors at any site. However, when the rats were exposed to both 50 ppm 1,2-DCA and disulfiram (an inhibitor of cytochrome P-450 enzymes), elevated cancer rates were observed in the liver, skin, testes, bile ducts, and mammary glands. It is possible that when 1,2-DCA was administered by injection or by gavage at high doses, the normal detoxifying pathway mediated through the cytochrome P-450 enzymes became saturated and consequently enhanced the carcinogenic potency of 1,2-DCA.

Based on the recently available toxicity information and the pharmacokinetic, metabolic and toxicity studies of 1,2-DCA published earlier, there are reasons to believe that the high doses and the gavage administration used in the NCI studies (1978) might have augmented the carcinogenic potential of 1,2-DCA. For this reason, cancer potency values were also derived from the Maltoni et al. (1980) and Cheever et al. (1990) studies. However, the cancer potency values of 1,2-DCA derived from the two negative studies are within the range of values based on the NCI (1978) studies. We conclude that the values derived from the Maltoni et al. (1980) and Cheever et al. (1990) studies support the use of cancer potency values derived from the NCI (1978) studies. Therefore, cancer potency value of 0.047 (mg/kg-day)⁻¹ was developed based on the incidence data of hemangiosarcomas in male rats. The PHG of 0.0004 mg/L (0.4 ppb) was calculated assuming a de minimis theoretical excess individual cancer risk level of 10⁻⁶ from exposure to 1,2-DCA in drinking water.

Based on the NTP sub-chronic drinking water study (1991) in which renal lesions were observed in female rats, a NOAEL of 45.3 mg/kg-day was identified. Applying an uncertainty factor of 1,000 to account for inter-species extrapolation, subchronic exposure to chronic exposure extrapolation, and sensitive human subpopulations, a health protective concentration of 0.48 mg/L or 480 ppb was developed for 1,2-DCA based on noncarcinogenic effects.

INTRODUCTION

The purpose of this document is to develop a PHG for 1,2-DCA. A Maximum Contaminant Level (MCL) of 0.0005 mg/L (0.5 ppb) was established by the California Department of Health Services (DHS) [California Code of Regulations (CCR) Title 22 for organic chemicals Section 64444]. This level is higher (less stringent) than the federal Maximum Contaminant Level Goal (MCLG) of 0 mg/L, but lower (more stringent) than the federal Maximum Contaminant Level (MCL) of 0.005 mg/L (5 ppb) for 1,2-DCA (U.S. EPA, 1998). U.S. EPA reported that this level is “the lowest level to which water systems can reasonably be required to remove this contaminant (1,2-DCA) should it occur in drinking water” (U.S. EPA, 1998).

Under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65), 1,2-DCA is listed as a chemical known to the state to cause cancer (Cal/EPA, 1997). The International Agency for Research on Cancer (IARC) has classified 1,2-DCA as a Group 2B carcinogen, i.e., possibly carcinogenic to humans (IARC, 1979). U.S. EPA (1997) has classified 1,2-DCA as a probable human carcinogen (B2).

In this document, we evaluate the available data on the toxicity of 1,2-DCA, primarily by the oral and inhalation routes. To determine a public health-protective level of 1,2-DCA in drinking water, sensitive groups are identified and considered, and relevant studies were identified, reviewed and evaluated.

CHEMICAL PROFILE

Chemical Identity

1,2-DCA is a short-chain chlorinated hydrocarbon. The chemical formula, structure, synonyms and identification numbers are listed in Table 1 and are adapted from an ATSDR document (1994).

Table 1. Chemical Identity of 1,2-DCA (adapted from ATSDR, 1994).

Chemical name	1,2-Dichloroethane
Synonyms	1,2-Ethylene dichloride, ethylene dichloride, dichloroethylene
Trade name	Borer sol, Brocide, Dutch liquid, Dutch oil ⁽¹⁾

Table 1. Chemical Identity of 1,2-DCA (adapted from ATSDR, 1994). (Continued)

Chemical formula	C ₂ H ₄ Cl ₂
Chemical structure	$\begin{array}{c} \text{H} \quad \text{H} \\ \quad \\ \text{Cl} - \text{C} - \text{C} - \text{Cl} \\ \quad \\ \text{H} \quad \text{H} \end{array}$
Identification numbers	
Chemical Abstracts Service (CAS) Registry number:	107-06-2
NIOSH Registry of Toxic Effects of Chemical Substances (RTECS) [®] number:	KI0525000
U.S. EPA Hazardous Waste number:	U077
Oil and Hazardous Materials/Technical Assistance Data System (OHM/TADS) number:	7216717
Hazardous Substances Data Bank (HSDB) number:	65
National Cancer Institute (NCI) number:	C00511

(1) RTECS (1998)

Physical and Chemical Properties

Important physical and chemical properties of 1,2-DCA are given in Table 2.

Production and Uses

There are no known natural sources of 1,2-DCA (CARB, 1985; ATSDR, 1994). 1,2-DCA is produced commercially by either the catalytic vapor- or liquid-phase chlorination of ethylene or by oxychlorination of ethylene (Archer, 1979). In 1993, 18 billion pounds of 1,2-DCA was produced (U.S. EPA, 1998). 1,2-DCA is primarily used in the production of vinyl chloride, 1,1,1-trichloroethane, trichloroethylene, perchloroethylene, aziridines, and ethylene diamines. It is also used as a solvent in cleaning and degreasing industries, a grain fumigant, and is a constituent in varnish removers and scouring compounds.

Table 2. Physical and Chemical Properties of 1,2-DCA (adapted from ATSDR, 1994).

Property	Value
Molecular weight	98.96
Color	Colorless
Physical state	Heavy liquid
Melting point	-35.3° C
Boiling point	83-84° C
Density at 20° C	1.25 g/mL
Odor	Pleasant odor
Odor threshold:	
Water	20 mg/L
Air	6-100 ppm
Solubility	
Water at 20° C	0.869 g/100 mL
Organic solvents	Miscible with alcohol, chloroform, ether, and chlorinated solvents. Soluble in common organic solvents
Octanol-water partition coefficients (K_{ow})	
Log K_{ow}	1.45 to 1.48
Soil-organic carbon-water partition coefficients (K_{oc})	
Log K_{oc}	1.14 to 1.28
Vapor pressure	105 mmHg at 30° C, 61 mmHg at 20° C
Henry's law constant at 25° C	1.1×10^{-3} atm-m ³ /mol
Conversion factors ¹	1 ppm = 4.05 mg/m ³ ⁽¹⁾ (at 20° C) = 4 mg/m ³ ⁽²⁾ = 4.96 mg/m ³ ⁽³⁾

(1) Calculated based on the ideal gas law, ppm = mg/m³ x 24.45/molecular weight

(2) From IARC (1979)

(3) ATSDR (1994)

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Air

Due to the high volatility of 1,2-DCA, atmosphere is the environmental sink of 1,2-DCA. Once in the atmosphere, it may be transported or removed by photo-oxidation with a half-life of approximately one month (U.S. EPA, 1998). In a review of papers on volatile organic compounds in air published from 1970 to 1987, U.S. EPA (1988) found that the median daily atmospheric concentration of 1,2-DCA at urban sites was 0.012 ppb (1,214 samples), and 0.26 ppb (182 samples) for source-dominated samples. 1,2-DCA was not detected in 648 samples from suburban, rural, or remote sites. The California Air Resources Board has monitored ambient 1,2-DCA at four sites in the South Coast Air Basin. Among the 566 air samples collected between January 1983 and August 1984, only 13% of them were over the detection limit of 100 ppt(v). The highest 24-hour 1,2-DCA concentration measured at each site ranged from 200 to 390 ppt (CARB, 1985).

Relatively low levels of 1,2-DCA, with average concentrations ranging from 0.006 ppb to 0.044 ppb, were also measured in indoor air samples collected from a number of homes in Los Angeles and Antioch/Pittsburg, California (ATSDR, 1994). Possible sources of indoor air pollution are consumer products, building materials, and volatilization from contaminated potable water in domestic shower and bath systems.

Soil

There is no information on the ambient concentrations of 1,2-DCA in soil. Releases on land generally resulted in volatilization to air or percolation into groundwater where it is likely to persist for a very long time.

Water

In a survey of 14 heavily industrialized river basins in the United States, 1,2-DCA was detected at a frequency of 53% in 204 surface water samples collected; reported concentrations in domestic surface waters used as drinking water sources ranged from trace amounts to 4.8 $\mu\text{g/L}$ (ppb) (ATSDR, 1994). 1,2-DCA has also been detected in California drinking water sources. California monitoring data obtained between 1984 and 1996 indicate that 1,2-DCA was detected in 72 out of 13,417 drinking water sources. Among the 783 water samples with detectable amount of 1,2-DCA, the highest concentration measured was 24 $\mu\text{g/L}$, and the lowest was 0.5 $\mu\text{g/L}$ (near the detection limit), and the average and median concentrations of these samples were 2.8 $\mu\text{g/L}$ and 1.8 $\mu\text{g/L}$, respectively (DHS, 1998).

Food

Since 1,2-DCA is relatively volatile and has a low octanol/water partition function, bioconcentration in fish is not expected to be important. U.S. EPA (1998) reported that the measured log bioconcentration factor of 1,2-DCA in bluegill sunfish is 0.3. Its presence in some

food products is probably due to its use as an extractant. In a Total Diet Study conducted by the U.S. Food and Drug Administration, 1,2-DCA was not detected in 11 decaffeinated instant coffees or in 14 decaffeinated ground coffees. 1,2-DCA was detected only in one ready-to-eat cereal (mean value was 0.31 $\mu\text{g}/\text{kg}$) out of 19 table-ready food items (Heikes, 1987). 1,2-DCA was not detected in four other composite market basket surveys of dairy products, meats, oils and fats, and beverage products in the U.S. (Entz et al., 1982). It was detected in wheat and bleached flour samples at concentrations of 110 and 180 $\mu\text{g}/\text{kg}$ and 6.1 and 6.5 $\mu\text{g}/\text{kg}$, respectively (Heikes and Hopper, 1986). 1,2-DCA is currently not registered for use in agricultural products in the U.S.

METABOLISM AND PHARMACOKINETICS

Absorption

1,2-DCA is readily absorbed into the body following inhalation, ingestion, or dermal exposure. There is little information on the extent of absorption of 1,2-DCA in humans. Absorption of 1,2-DCA in laboratory animals through various exposure routes has been extensively studied. Spreafico et al. (1980) reported that when 1,2-DCA was administered to rats by gavage in corn oil, peak blood levels were reached within 10 to 20 minutes. When rats were exposed to uniform concentrations of 1,2-DCA through inhalation, plateau blood concentrations were observed within 1 to 2 hours (Spreafico et al., 1980; Reitz et al., 1982).

Reitz et al. (1980) administered ^{14}C -labelled 1,2-dichloroethane by gavage (150 mg/kg) in corn oil to male Osborne-Mendel rats and recovered almost all of the orally administered dose in exhaled air, urine, and carcass, thereby demonstrating that absorption of 1,2-DCA from the gastrointestinal tract is virtually complete. Spreafico et al. (1980) reported that the area under the blood concentration curve (AUC) after intravenous injection of 25 mg/kg was about 30% higher than the AUC after gavage treatment at the same dosage. Assuming complete absorption, the first-pass effect in liver (metabolism) and lung (elimination) after oral administration of 1,2-DCA is estimated to be approximately 30%. The vehicle used in oral administration appears to affect the rate of absorption. Withey et al. (1983) showed that 1,2-DCA is absorbed more readily by the oral route when administered in water than in corn oil. Peak blood concentration and AUC (85 $\mu\text{g}/\text{mL}$, 4864 $\mu\text{g} \times \text{min} \times \text{mL}^{-1}$) in male Wistar rats following an oral administration of 1,2-DCA, 100 mg/kg, in water were about 4-5 times higher than the peak blood concentration and AUC (16 $\mu\text{g}/\text{mL}$, 1299 $\mu\text{g} \times \text{min} \times \text{mL}^{-1}$) in rats exposed to the same dose by gavage in corn oil.

The amount of 1,2-DCA absorbed via the lung is dependent on a number of factors: (1) the concentration in the inspired air; (2) the duration of exposure; (3) the blood/air partition coefficient; (4) the solubility in various body tissues; and (5) physical activity which increases pulmonary ventilation rate and cardiac output (U.S. EPA, 1985). Several studies have provided information on the relationship between exposure concentration and blood level in laboratory animals; they are discussed in the section on distribution. Reitz et al. (1982) exposed male Osborne-Mendel rats to 150 ppm 1,2-DCA for 6 hr and estimated the dose of 1,2-DCA received was approximately 113 mg/kg, or about 75% of the gavage dose of 150 mg/kg.

Studies in animals demonstrated that 1,2-DCA is relatively well absorbed through the skin. Male rats exposed to 2 mL of 1,2-DCA under cover on a shaved area of the back had blood 1,2-DCA levels of 25 µg/mL after 30 minutes (Morgan et al., 1991). When the experiment was repeated using solutions of 1,2-DCA in water, blood levels peaked after 1-2 hours (at concentrations of 0.35-1.4 µg/mL, depending on degree of saturation of the applied solution).

Distribution

After pulmonary or oral exposure, 1,2-DCA is distributed into all body tissues. It can pass through the blood-brain barrier and the placental barrier. 1,2-DCA has been detected in fetuses as well as in breast milk of workers exposed to the chemical (Vozovaya, 1977 and Urusova, 1953 cited in U.S. EPA, 1985). There is little information on the distribution of 1,2-DCA in humans after exposure. A number of researchers have studied the distribution of 1,2-DCA in laboratory animals and the characteristics of dose-dependent tissue concentrations.

Spreafico et al. (1980) detected levels of 1,2-DCA in blood, liver, lung, and epididymal adipose tissue after single oral administration (in corn oil) to Sprague-Dawley rats at three doses, 25, 50, and 150 mg/kg (Table 3). Though they also determined the levels of 1,2-DCA in brain, kidney, and spleen tissues, the data were not reported separately as the data were superimposable with those observed in the blood. Spreafico et al. (1980) suggested that there is a linear relationship between the observed peak blood levels and doses administered up to 50 mg/kg. At the higher dose (150 mg/kg), they observed a downward inflection in the dose-peak blood level curve that may indicate the saturation of the gastrointestinal absorption of the chemical. They noted that when the oral dose was increased 6-fold from 25 to 150 mg/kg, an approximately 16-fold increase in the blood concentrations as measured by AUC was observed. This result indicates that the main elimination or metabolic pathway was saturated in the dose range tested.

Table 3. Blood and tissue levels after single oral administration (in corn oil) of 1,2-DCA in Sprague-Dawley rats. (Adapted from Spreafico et al., 1980).

Dose (mg/kg)	Parameter	Blood	Adipose tissue	Lung	Liver
25	AUC * peak level **	446 (1) 13.29	5119 (1) 110.67	136 (1) 2.92	679 (1) 30.02
50	AUC peak level	1700 (3.8) 31.94	12543 (2.5) 148.92	538 (4.0) 7.2	1897 (2.8) 55
150	AUC peak level	7297 (16.4) 66.78	29468 (5.7) 259.88	648 (4.8) 8.31	5384 (7.9) 92.1

Values in parenthesis = $\frac{\text{AUC of a tissue at a given dose}}{\text{AUC of the same tissue at 25 mg/kg}}$

*AUC (area under the blood concentration curve) in µg x min x mL⁻¹

** Peak blood level in µg/mL

Reitz et al. (1982) investigated the peak blood concentration and AUC of 1,2-DCA by administering the chemical in corn oil by gavage to male Osborne-Mendel rats. Their results obtained from the gavage study were lower than those obtained by Spreafico et al. (1980). Following oral dosing at 150 mg/kg, Reitz et al. (1982) found that peak blood levels and AUC were 30-44 $\mu\text{g/mL}$ and 4500 $\mu\text{g} \times \text{min} \times \text{mL}^{-1}$, respectively. Withey et al. (1983) administered 1,2-DCA to male Wistar rats by gavage in corn oil (100 mg/kg) and measured average peak blood concentration and AUC of 16 $\mu\text{g/mL}$ and 1299 $\mu\text{g} \times \text{min} \times \text{mL}^{-1}$, respectively. The observed differences in blood concentrations of 1,2-DCA in Osborne-Mendel rats, Sprague Dawley rats, and Wistar rats given similar gavage doses may be explained by the difference in the distribution, metabolism, and excretion of 1,2-DCA in the three strains of rats.

Spreafico et al. (1980) also reported 1,2-DCA levels in blood, liver, lung, and epididymal adipose tissue after inhalation exposure (50 ppm and 250 ppm, 6-hour exposure period) in Sprague-Dawley rats (Table 4). Similar to what was observed in the oral experiment, Spreafico et al. (1980) noted that when the inhalation concentration was increased 5-fold from 50 to 250 ppm, approximately 40-fold increases in the concentration of 1,2-DCA (as measured by AUC) in blood, adipose tissue, lung, and liver were observed.

Table 4. Blood and tissue levels after inhalation exposure (6 hours) to 1,2-DCA in Sprague-Dawley rats. (This table is adapted from Spreafico et al., 1980).

Concentration (ppm)	Parameter	Blood	Adipose tissue	Lung	Liver
50	AUC *	26 (1)	391 (1)	6 (1)	17 (1)
	plateau level **	1.42	10.24	0.39	1.02
250	AUC	1023 (39)	13558 (35)	279 (47)	694 (41)
	plateau level	30.92	265.47	13.88	22.06

Values in parenthesis = $\frac{\text{AUC of a particular tissue at 250 ppm}}{\text{AUC of the same tissue at 50 ppm}}$

*AUC (area under the blood concentration curve) in $\mu\text{g} \times \text{min} \times \text{mL}^{-1}$

** Plateau level in $\mu\text{g/mL}$

Reitz et al. (1982) also investigated the peak blood concentration and decay kinetics of 1,2-DCA in male Osborne-Mendel rats by exposing the test animals to 150 ppm 1,2-DCA for 6 hours. They found a plateau blood concentration of 8-10 $\mu\text{g/mL}$ that is consistent with those reported by Spreafico et al. (1980). However, the AUC of 1,2-DCA concentration in blood calculated by Reitz et al. (1982) is much higher (2910 $\mu\text{g} \times \text{min} \times \text{mL}^{-1}$) than the AUC (1023 $\mu\text{g} \times \text{min} \times \text{mL}^{-1}$) reported by Spreafico et al. (1980) after exposing the rats to 250 ppm 1,2-DCA for 6 hr. The observed discrepancy in blood concentrations of 1,2-DCA in Osborne-Mendel rats and Sprague Dawley rats exposed to 1,2-DCA via inhalation may be explained by the difference in the distribution, metabolism, and excretion of 1,2-DCA in the two strains of rats.

Metabolism

There have been extensive studies on the metabolism of 1,2-DCA in rats and mice both in vivo and in vitro. Davidson et al. (1982) reviewed the metabolism of 1,2-DCA and provided a list of metabolites which have been identified either in vivo in mice and rats or in liver and kidney tissue crude enzyme systems (Table 5).

Table 5. Identified metabolites of 1,2-DCA. (Adapted from Davidson et al., 1982).

Metabolite	Tissue
Inorganic halide	Rat liver cytosol
Carbon dioxide	Exhaled air of mouse and rat
2-Chloroethanol	Urine and blood of mouse and rat
2-Chloroacetic acid	Mouse urine
Bromoacetaldehyde	Rat liver microsomes
Thiodiglycolic acid	Urine of mouse and rat
Ethene	Rat liver cytosol
S-(2-Hydroxyethyl)-cysteine	Rat liver cytosol, rat urine
N-Acetyl-S-(2-hydroxyethyl)-cysteine	Urine and blood of rat
N-Acetyl-S-(2-hydroxyethyl)-cysteine oxide	Urine and blood of rat
S-Carboxymethyl cysteine	Mouse urine
S-(2-Hydroxyethyl)-glutathione	Rat liver cytosol, tissue
S-(2-Hydroxyethyl)-glutathione-S-oxide	Rat liver cytosol, tissue
S,S'-Ethene-bis-glutathione	Rat liver cytosol

Figure 1 depicts the major metabolic pathways and metabolites of 1,2-DCA. Metabolism appears to occur via two principal pathways: (1) microsomal oxidative metabolism that includes cytochrome P-450 enzymes, and (2) glutathione conjugation mediated by glutathione-S-transferase. These two metabolic pathways can account for all the identified sulfur-containing metabolites in the urine of 1,2-DCA exposed animals (Table 5). Van Bladeren et al. (1981) showed that the ratio of the oxidative pathway to the glutathione conjugation pathway in the metabolism of 1,2-dibromoethane in rats is about 4:1.

Guengerich et al. (1991) reported that cytochrome P-450 II E1 and cytochrome P-450 II B1 are mainly responsible for the oxidative metabolism of 1,2-DCA. Reactive intermediates such as gem-chlorohydrin and 1-chloroso-2-chloroethane can either lose a hydrogen chloride or react with water to form 2-chloroacetaldehyde and 2-chloroethanol. Alcohol dehydrogenase catalyzes the inter-conversion of 2-chloroacetaldehyde and 2-chloroethanol; the direction of the reaction is determined by enzyme, substrate and cofactor concentrations. 2-chloroacetaldehyde is an electrophile and can alkylate macromolecules such as proteins and DNA. Alternatively, 2-chloroacetaldehyde can be oxidized to 2-chloroacetic acid or react with glutathione and ultimately excreted in the urine (WHO, 1995).

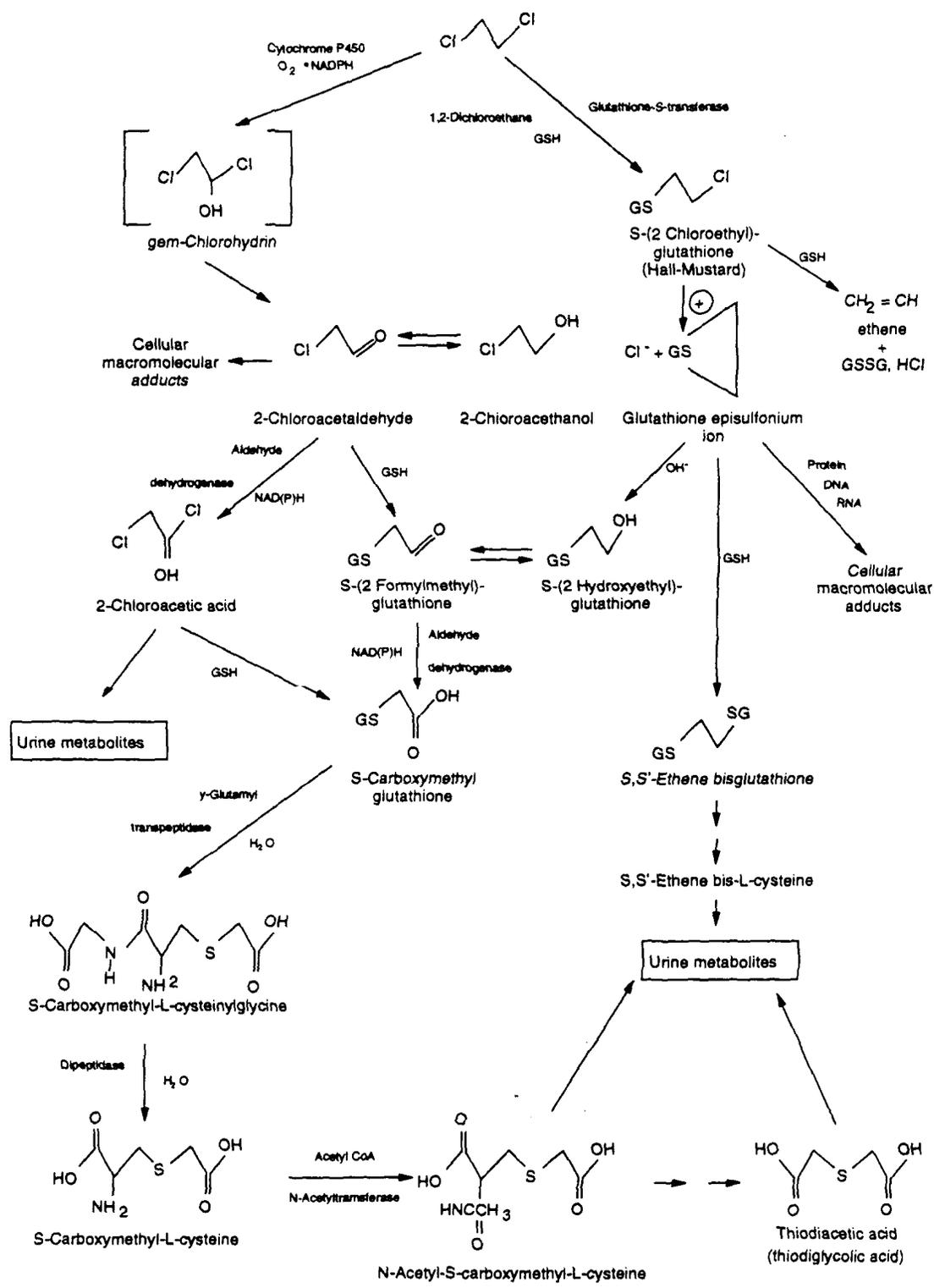


Figure 1. Proposed pathways for 1,2-DCA metabolism (from ATSDR, 1994).

The second pathway is catalyzed by glutathione-S-transferase and involves direct conjugation of 1,2-DCA with glutathione to form S-(2-chloroethyl)-glutathione, a half sulfur mustard. There is indication that S-(2-chloroethyl)-L-cysteine, an analog of S-(2-chloroethyl)-glutathione, has a relatively long half-life (7 -15 minutes at 37 ° C between pH 4 and 8) and has the potential of migrating from liver to other organs (Schasteen et al., 1983). The half sulfur mustard can react with another molecule of glutathione to form ethene, which is eliminated through exhaled air. S-(2-chloroethyl)-glutathione can also be converted to the corresponding episulfonium ion non-enzymatically. The episulfonium ion is an alkylating agent and can react with water to form S-(2-hydroxyethyl)glutathione, with thiols such as glutathione to form S,S'-ethene-bis-glutathione, or with DNA to form adducts (Davidson et al., 1982; WHO, 1995).

As glutathione is involved in both metabolic pathways (Figure 1), Reitz et al. (1982) studied the degree of glutathione depletion after administration of 1,2-DCA. They measured hepatic non-protein sulfhydryl concentrations in three groups of rats: one group was exposed by gavage at 150 mg/kg, a second group was exposed by inhalation at 150 ppm for 6 hours, and the third group served as controls. Four hours after the gavage treatment, they found levels of non-protein sulfhydryl in the exposed rats (average 0.35 mg-equivalent of glutathione/g liver) were significantly lower than levels measured in the controls (average 1.35 mg-equivalent of glutathione/g liver). Levels measured immediately after 6 hours of inhalation exposure (average 0.31 mg-equivalent of glutathione/g liver) were also significantly lower than the controls.

Using ¹⁴C-labelled 1,2-DCA, Reitz et al. (1982) investigated the metabolism of 1,2-DCA in rats after inhalation or gavage exposure. They found approximately 69% of the administered dose was metabolized in the test animals following oral exposure (150 mg/kg). The remaining dose (29%) was eliminated in exhaled air¹. For either exposure route, approximately 85% of the total metabolites were found in the urine, with the remainder eliminated as carbon dioxide (approximately 7%) in exhaled air and in feces (approximately 2%). They also reported that while it is not possible to determine the percent recovery after inhalation exposure, the body burden at the end of the 6-hour inhalation exposure at 150 ppm was about one-third that seen after oral dosing.

Yllner (1971) performed a similar study in mice and found the extent of 1,2-DCA metabolism was dose dependent. After injecting intraperitoneally 50 to 170 mg/kg of ¹⁴C-labelled 1,2-DCA to female albino mice of the Naval Medical Research Institute strain, the researcher recovered 92 to 96% of radioactivity in exhaled air and urine within 24 hours. At low doses (50 and 100 mg/kg) about 80% the administered dose was metabolized and excreted as carbon dioxide in breath or as non-volatile metabolites in urine. Only a small fraction (11 to 22%) was eliminated unchanged through exhaled air. As the administered doses were increased to 140 and 170 mg/kg, a smaller fraction (51%) was metabolized and a larger fraction (about 43%) was eliminated unchanged through exhaled air (Table 6). Yllner's data suggest mice have a limited capacity in metabolizing 1,2-DCA. Saturation of 1,2-DCA metabolism to carbon dioxide and urinary metabolites occurred at a dose level between 100 and 140 mg/kg; this also raised the concentration of 1,2-DCA in blood and increased the fraction of absorbed dose eliminated unchanged in breath.

¹ Charcoal trap was used to trap the unchanged 1,2-DCA and other metabolites such as ethene in exhaled air. The percentage of administered dose metabolized by the test animal should be slightly greater than 69%.

Table 6. Distribution of the radioactivity excreted by mice receiving ¹⁴C-labelled 1,2-DCA (in percentage) (from Yllner, 1971).

Dose (mg/kg)	Trap 1+2 ⁽¹⁾	Carbon dioxide	Urine	Total
50	10.7	10.6	71.3	92.3
100	20	7.1	69.1	96.2
140	43.5	3.8	46.4	93.7
170	42	4.2	48	94.2

(1) Trap 1+2 contained unchanged 1,2-DCA only.

Yllner (1971) analyzed the composition of 1,2-DCA metabolites in the urine of the dosed mice. The researcher reported that S-carboxymethylcysteine (together with its derivatives), thiodiacetic acid, and chloroacetic acid accounted for 48, 33, and 16% of urinary radioactivity, respectively. As radiochromatograms of the urinary metabolites of mice dosed with 1,2-DCA were found to be remarkably similar to those obtained from mice dosed with chloroacetic acid, Yllner (1971) suggested that the metabolism of 1,2-DCA occurs mainly via chloroacetic acid. It is interesting to note that S,S'-ethene-bis-cysteine, a metabolite of the glutathione mediated pathway, constituted only 0.9% of the total urinary activity (Yllner 1971). Mitoma et al. (1985) reported that urinary metabolite patterns of 1,2-DCA in mice were qualitatively similar to those of rats, and S-carboxymethylcysteine, thiodiacetic acid, and chloroacetic acid were found to be the main urinary metabolites.

Cheever et al. (1990) also analyzed the composition of 1,2-DCA metabolites in the urine of dosed rats and got results slightly different from those of Yllner (1971). They administered ¹⁴C-labelled 1,2-DCA to 24-month-old rats and found that thiodiacetic acid was the principal metabolite which accounted for 54 to 71% of the radioactivity in the urine. Another glutathione conjugate, thiodiglycolic acid sulfoxide, accounted for an additional 19 to 33%, and only 0.3 to 4% of the urinary radioactivity was present as chloroacetic acid.

Several researchers (Igwe et al., 1986a; Cheever et al., 1990) showed that the metabolism of 1,2-DCA can be altered by drugs that have inhibitory effects on microsomal mixed function oxidation enzymes. Disulfiram has been shown to be a potent inhibitor of the hepatic microsomal mixed function oxygenases in both experimental animals and humans (Freundt, 1978; Zemaitis et al., 1976). Igwe et al. (1986a) pretreated half of the rats with 68 mg/kg of disulfiram in diet for 10 days. Twenty-four hours after applying an intraperitoneal dose of 150 mg/kg of ¹⁴C-labelled 1,2-DCA, they found significantly lower levels of radioactivity in the urine of rats treated with disulfiram (53.9%) than the controls (75.4%). In addition, the total recovery (65.1%; including body tissues, urine, and feces) of radioactivity from rats exposed to both disulfiram and 1,2-DCA was also lower than those exposed to 1,2-DCA alone (83.4%). Since 1,2-DCA in exhaled air was not collected, it can not be confirmed that a greater fraction of the administered dose was eliminated through breath in animals exposed to both chemicals than those to 1,2-DCA only.

Cheever et al. (1990) also investigated the effect of disulfiram on the elimination of a single ¹⁴C-labelled gavage dose (150 mg/kg) of 1,2-DCA from male and female rats. They found urinary excretion of ¹⁴C from control rats was 47 to 55% of the administered dose with 28 to 30% detected as unchanged 1,2-DCA in the breath. Among the rats exposed to disulfiram (0.05% in diet for 2 years) 35 to 36% of the administered ¹⁴C was eliminated in the urine with 41 to 55% as unchanged 1,2-DCA in the breath. They suggested that the results might be explained by the

inhibitory effect of disulfiram on the metabolism of 1,2-DCA via the microsomal mixed function oxidase pathway, which in turn produced higher levels of unchanged 1,2-DCA in blood and increased excretion through exhaled air. This explanation is supported by their study of 1,2-DCA concentrations in blood of rats exposed to both disulfiram and 1,2-DCA and to 1,2-DCA only (Table 7). The higher levels of 1,2-DCA in blood measured in rats treated with disulfiram compared with those in rats exposed to 1,2-DCA alone confirms the primary role of microsomal mixed function oxidases in the metabolism and elimination of 1,2-DCA.

Table 7. Blood 1,2-DCA levels measured at 0.25 hour after a 7-hour exposure (adapted from Cheever et al., 1990).

Exposure group	Sex	Levels measured ($\mu\text{g/mL}$) ⁽¹⁾
1,2-DCA ⁽²⁾	male	0.28±0.13
1,2-DCA/disulfiram ⁽³⁾	male	1.46±0.48*
1,2-DCA	female	0.26±0.08
1,2-DCA/disulfiram	female	1.54±0.49*

(1) Blood levels were measured 0.25 hours after inhalation exposure.

(2) Animals were exposed to 50 ppm 1,2-DCA 7 hr/day, 5 days/week for 2 years.

(3) Animals were exposed to 50 ppm 1,2-DCA 7 hr/day, 5 days/week for 2 years plus 0.05% disulfiram in diet.

* Significantly different from the groups exposed to 1,2-DCA alone ($p < 0.05$)

In summary, 1,2-DCA is extensively metabolized in mice and rats. Within 24 hours of dosing, up to 70 to 90% of the administered dose is metabolized and excreted in breath and urine. The remaining fraction is eliminated unchanged via the exhaled air. Based on animal studies, there is evidence indicating that at low doses a majority of the administered dose is metabolized through the microsomal mixed function oxidative pathway. This pathway can be saturated by high doses of 1,2-DCA or blocked by chemicals such as disulfiram that have inhibitory effects on cytochrome P-450 enzymes. When this happens, there is a reduction in the fraction of dose excreted as urinary metabolites and a corresponding increase of 1,2-DCA levels in blood as well as the fraction of dose eliminated through exhaled air.

Excretion

Elimination of 1,2-DCA from the body is the sum of metabolism and excretion of unchanged 1,2-DCA via pulmonary and other routes. As discussed in the previous section, Yllner (1971) reported that when 50 mg/kg of 1,2-DCA was administered to mice, about 92% of the dose was metabolized; 71.3% of the dose was excreted as nonvolatile metabolites in urine and 10.3% excreted as carbon dioxide in exhaled air. Reitz et al. (1982) reported that after administering 150 mg/kg of 1,2-DCA to rats by gavage, urinary metabolites accounted for 60% of the administered dose, unchanged 1,2-DCA in the breath accounted for 29%, unchanged fecal 1,2-DCA accounted for 2%, and carbon dioxide accounted for 5% of the total dose.

Spreafico et al. (1980) studied the pharmacokinetics and excretion kinetics of 1,2-DCA in male Sprague-Dawley rats following intravenous administration of the compound. They showed that at 1, 5, and 25 mg/kg, the whole blood concentration decreased drastically with time (Figure 2). A biphasic decline of 1,2-DCA concentration in blood was evident for all doses, indicative of a two-compartment system, with a distributive phase and an excretion phase. They also noted that

the steepness of the second phase decreased with the increase in dose applied, indicating that the elimination process may be a saturable one (Spreafico et al., 1980).

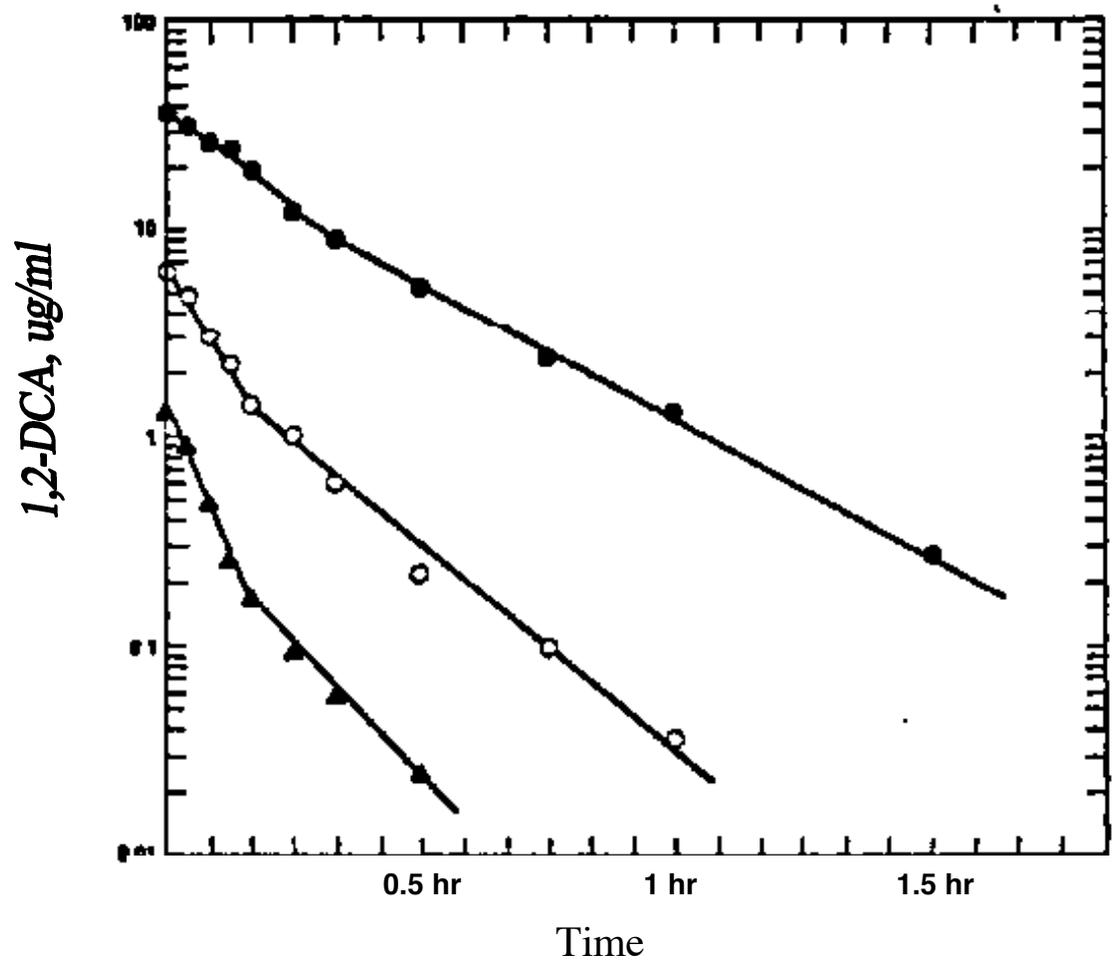


Figure 2. Blood levels of 1,2-DCA in rats after i.v. administration. (●) 25 mg/kg i.v.; (○) 5 mg/kg i.v.; (▲) 1 mg/kg i.v. Source: Spreafico et al. (1978, 1979, 1980) (from US EPA, 1985).

They found their data seemed to fit a two-compartment open model; some of the pharmacokinetic parameters of the model are shown in Table 8. It is suggested that the kinetic parameters are not independent of the dose (U.S. EPA, 1985). For example, the half-time of body elimination from the central (or blood) compartment increases with the dose, while whole-body clearance and the volume of distribution decrease with an increase of the dose.

Table 8. Excretion kinetics of 1,2-DCA after intravenous injection. (Adapted from U.S. EPA, 1985)

Parameter	Dose (mg/kg)		
	1	5	25
Initial conc., $\mu\text{g/mL}$	1.5	8.0	38.1
Half-time (second phase), min	7.3	9.5	14.1
Clearance, mL/min	22	17.5	8
Volume of distribution, mL	231	239	162

Spreafico et al. (1980) also investigated the excretion kinetics of 1,2-DCA in male Sprague-Dawley rats after oral and inhalation exposures. Figure 3 shows semilog plots of blood and tissue concentrations during distribution and excretion phases following single oral doses of 25, 50, and 150 mg/kg given in corn oil. They found rapid disappearance of 1,2-DCA from blood, liver, lung, and epididymal adipose tissue, with most of the administered dose excreted after 10 hr. The data for blood were computer-fitted to the kinetic equations for a two-compartment open model; the results are given in Table 9. Like the kinetics observed for intravenous dosing, the values for the parameters, half-time of body elimination and whole-body clearance, are dose-dependent. Spreafico et al. (1980) also reported that repeated oral treatments (50 mg/kg) did not significantly modify the excretion kinetics of 1,2-DCA in the rat; nor were significant differences seen between male and female rats.

Table 9. Excretion kinetics of 1,2-DCA after oral exposure. (Adapted from U.S. EPA, 1985)

Parameter	Dose (mg/kg)		
	25	50	150
Peak conc., $\mu\text{g/mL}$	13.3	31.9	66.8
Half-time (second phase), min	24.6	44.1	56.7
Clearance, mL/min	10.6	5.6	3.9
Volume of distribution, mL	367	328	390

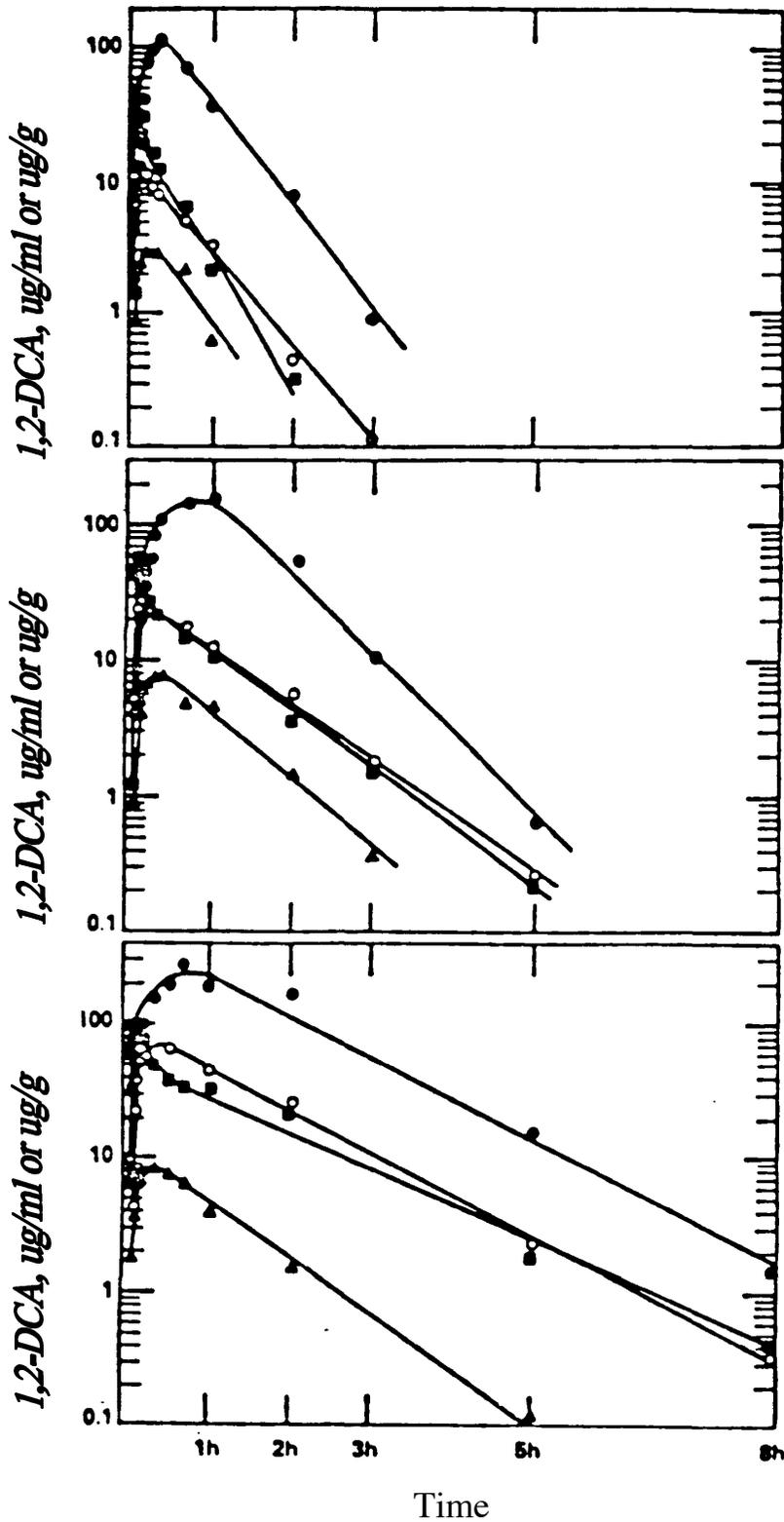


Figure 3. 1,2-DCA levels after single oral administration in rats: Top panel, 25 mg/kg; middle, 50 mg/kg; bottom, 150 mg/kg dose. Adipose tissue (•), blood (o), liver (□), lung (▲) (from US EPA, 1985).

A similar excretion kinetic study was performed by Spreafico et al. (1980) using rats exposed to 50 ppm and 250 ppm of 1,2-DCA. Exposure was stopped after 6 hours, when a steady state was reached, and the decay of 1,2-DCA levels in blood and other tissues was followed over time. The blood and tissue levels after the end of exposure showed an exponential decay over time; the results were fitted to a single compartment open model with some of the pharmacokinetic parameters presented in Table 10. A comparison of the areas under the blood decay curves, a reflection of body burden, suggests that the body burden after 250 ppm exposure was 40 times that of the 50 ppm exposure, rather than the 5-fold increase expected. These data indicate that the half-life of 1,2-DCA is dose-dependent (U.S. EPA, 1985). These results from inhalation exposure are in accord with the dose-dependent pharmacokinetics exhibited after intravenous and oral exposure. Results from these three studies indicate that the rate of whole-body excretion of 1,2-DCA is largely determined by the metabolism of 1,2-DCA, a saturable process and a major route of elimination (Spreafico et al., 1980; U.S. EPA, 1985).

Table 10. Excretion kinetics of 1,2-DCA after inhalation exposure. (Adapted from U.S. EPA, 1985)

Parameter	Exposure concentration (ppm)	
	50	250
Plateau conc., $\mu\text{g/mL}$	1.4	30.9
Half-time, min	12.7	22.1
AUC, $\mu\text{g} \times \text{min} \times \text{mL}^{-1}$	26	1023

Reitz et al. (1980, 1982) studied distribution and excretion kinetics of 1,2-DCA in male Osborne-Mendel rats exposed via inhalation and gavage. Their findings are in general agreement with those reported by Spreafico et al. (1980). However, Reitz et al. (1982) found a biphasic elimination of 1,2-DCA after inhalation exposure with an initial rapid alpha phase and a slower beta phase, and this observation is in contrast to the monophasic elimination reported by Spreafico et al. (1980). From the gavage experiment (with an oral dose of 150 mg/kg), Reitz et al. (1982) observed a biphasic elimination and estimated apparent half-times of 90 and 25 minutes for the first and second parts, respectively. These values are also different from those reported by Spreafico et al. (1980), who estimated elimination half-times of 44 and 57 minutes at gavage doses of 50 and 150 mg/kg, respectively. U.S. EPA (1985) suggested the explanation for these differences might lie in the different kinetic models, species differences and inability of linear kinetics to accurately describe the excretion kinetics of 1,2-DCA.

TOXICOLOGY

Toxicological Effects in Animals

Acute Toxicity

Acute exposure to 1,2-DCA generally produced liver and kidney injury in laboratory animals. It can cause death via both the inhalation and oral route if the concentration is sufficiently high.

Heppel et al. (1945, 1946) and Spencer et al. (1951) studied the acute (less than or equal to 14 days) toxic effect of inhaled 1,2-DCA in a number of species. They reported increased mortality in rats and guinea pigs at 400 ppm and in mice, rabbits, and dogs at 1,500 ppm. These were the lowest exposure concentrations that produced death in animals (ATSDR, 1994). Daniel et al. (1994) administered 1,2-DCA in corn oil to groups of 10 male and 10 female Sprague-Dawley rats by gavage for 10 consecutive days. The study doses were 10, 30, 100, and 300 mg/kg-day. In the high dose group, all female animals died and only 2 of 10 males survived. The main histopathological lesion exhibited was inflammation of the mucosal and submucosal layers of the forestomach of male and female rats in the 100 mg/kg dose group. Animals in the 300 mg/kg dose group were not histopathologically examined due to protocol limitations.

Francovitch et al. (1986) treated mice with either the cytochrome P-450 inducers phenobarbital or 3-methylcholanthrene prior to exposure to 1000, 1250, or 1500 ppm 1,2-DCA and found an increased mortality compared with animals exposed to 1,2-DCA alone. Alternatively, pretreatment with SKF-525A, an inhibitor of hepatic mixed function oxidases, protected mice from the pathologic effects in liver and kidney produced by exposure to 1,2-DCA. They suggested that chloroacetaldehyde, chloroethanol, and chloroacetic acid formed from the oxidative metabolism of 1,2-DCA could be responsible for the observed acute toxicity. The acute oral LD₅₀ for 1,2-DCA in rats was reported to be 680 mg/kg. Muson et al. (1982) used log probability analysis to derive an LD₅₀ for male mice of 489 mg/kg and for female mice of 413 mg/kg.

Subchronic Toxicity

Lower LC₅₀ values were obtained among test animals when exposure durations were extended from acute periods to 6-25 weeks. ATSDR (1994) reported that increased mortality was observed in rats and guinea pigs exposed to 200 ppm, rabbits exposed to 400 ppm, and dogs, cats, and monkeys exposed to 1,000 ppm. Similar to observations following acute exposure, necropsy of these animals revealed effects on the liver, kidney, heart, and lung. Daniel et al. (1994) administered 1,2-DCA in corn oil to groups of 10 male and 10 female Sprague-Dawley rats by gavage for 90 consecutive days. The study doses were 37.5, 75, and 150 mg/kg-day. There were no treatment-related effects pertaining to clinical observations. Body weight gain and total food consumption were significantly decreased in high dose males. Significant increases of organ weights and changes in hematology were reported in the high dose groups. The 75 mg/kg dose was better tolerated by the animals. However, relative kidney weights were significantly increased in females at this dose level while brain and liver weight ratios were significantly increased in males. Daniel et al. (1994) suggested a NOAEL of 37.5 mg/kg-day, based on the results of this study.

In a NTP study (1991), male and female B6C3F₁ mice were exposed to 1,2-DCA in drinking water at 0, 500, 1000, 2000, 4000 or 8000 ppm for 13 weeks. Nine of 10 female mice exposed to 8000 ppm 1,2-DCA in drinking water died before the end of the study. No early mortality was observed in the other dose groups. Kidney weights were significantly increased for dosed males and females. Minimal renal tubular cell regeneration was observed in males at 4000 ppm; more severe conditions were seen at 8000 ppm.

NTP (1991) administered 1,2-DCA to male and female F344/N rats, Sprague-Dawley rats, and Osborne-Mendel rats through drinking water at 0, 500, 1000, 2000, 4000 or 8000 ppm for 13 weeks. No excess mortality was observed in any dose group. Renal tubular regeneration was observed in all dosed and control male F344/N rats. The incidence of renal tubular regeneration in females, however, was dose related and was observed in 9/10 at 8,000 ppm, 3/10 at 4,000 ppm, 2/10 at 2,000 ppm, 1/10 at 1,000 ppm, 0/10 at 500 ppm, and 0/10 controls. This lesion was of minimal severity in all affected rats. The researchers did not notice any clinical signs or lesions in the liver that could be related to the compound. Water consumption at the higher concentrations was significantly reduced compared with the controls. It was estimated that rats administered drinking water containing 8000 ppm 1,2-DCA received a daily intake of about 500-725 mg/kg. This dosage is close to the reported oral LD₅₀ for 1,2-DCA administration by gavage (680-850 mg/kg); however, intake of this dose over 24 hours rather than as a bolus resulted in little toxicity. The authors reported that they did not observe any difference in susceptibility to 1,2-DCA toxicity by the three strains of rats tested.

It appears that subchronic toxicity of 1,2-DCA through the oral route is dependent on the method of administration. In the same study described above, NTP (1991) also administered 1,2-DCA to male and female F344/N rats by gavage in corn oil for 13 weeks. The gavage doses were selected to be within the range of doses ingested by rats exposed to formulated drinking water. They found that F344/N rats were more sensitive to 1,2-DCA administered by gavage than in drinking water, as evidenced by the fact that all males (10/10) receiving 480 mg/kg-day died in week 1, and 5/10 of males receiving 240 mg/kg-day died before week 7. Similarly, 7/10 females receiving 300 mg/kg-day died before week 6. Necrosis of the cerebellum observed in the brains of three males receiving 240 mg/kg and three females receiving 300 mg/kg, appeared to be related to 1,2-DCA administration. The authors also reported a significant increase of hyperplasia and inflammation of the forestomach in the male and female rats exposed to high doses of 1,2-DCA. This finding may be of significance, since long-term administration of 1,2-DCA by gavage has been shown to cause neoplasms of the forestomach in Osborne-Mendel rats (NCI, 1978).

To explain the greater toxicity observed in F344/N rats administered by gavage compared with that after drinking water exposure, NTP (1991) postulated that administration of bolus doses of 1,2-DCA by gavage might have resulted in the saturation of the elimination mechanism and increased levels of 1,2-DCA in the blood. Exposure at lower concentrations of 1,2-DCA over the course of a day (in drinking water) would result in lower peak blood levels and a lower AUC and the chemical could be rapidly eliminated, even when the total daily dose was equal to the amount administered by gavage.

Genetic Toxicity

In this section, the genotoxicity data of 1,2-DCA and its metabolites are discussed. There are evidences to indicate that 1,2-DCA and its metabolites bind to DNA and proteins both in vitro and in vivo. Of the two major metabolic pathways of 1,2-dihaloethanes (Figure 1), experimental results reported by Guengerich et al. (1980), Storer et al. (1985), White et al. (1983), Inskeep et al. (1986), Sundheimer et al. (1982), and Igwe et al. (1986a) showed that the pathway mediated by the glutathione-S-transferase may be more important than the microsomal oxidative pathway in explaining the DNA-damaging potential of 1,2-DCA and 1,2-dibromoethane.

Reitz et al. (1982), Baertsch et al. (1991), and Storer et al. (1984) reported that the genotoxicity of 1,2-DCA was affected by the way the chemical was administered to the test animals. When 1,2-DCA was administered over a short period of time and at high concentrations, it produced more DNA damage in the liver than when it was administered over a long period of time and at lower concentrations. It is postulated that when 1,2-DCA was administered over a long period of time, such as by inhalation exposure, most of the dose was detoxified through the microsomal oxidative metabolism. However, when the same dose was administered over a short period of time, by gavage or by injections, the administered dose might have overwhelmed the detoxifying mechanism and caused a greater portion of the dose to be bio-transformed through the glutathione-S-transferase pathway.

1,2-DCA has been reported to test positive in many *Salmonella*/microsome plate incorporation assays. It is not necessary to have an exogenous metabolic system, but increased mutagenic activity was observed in tests with a metabolic activation system supplemented with glutathione. 1,2-DCA has not produced consistent responses in mutation assays with *E. coli* and was negative in a mouse peritoneal host-mediated assay with *E. coli* (Davidson et al., 1982; WHO, 1995). It has been shown to cause sex-linked recessive lethal mutations in *Drosophila melanogaster* as well as induction of somatic cell mutations. 1,2-DCA has been shown to cause gene mutation and unscheduled DNA synthesis in rodent cells as well as human cells. However, several negative results in the micronucleus tests may indicate 1,2-DCA does not cause chromosomal damage in mice (ATSDR, 1994; U.S. EPA, 1985; WHO, 1995).

Rannug et al. (1978) reported that 1,2-DCA produced a two-fold increase of revertants in *Salmonella* strain TA 1535 without activation. When S-9 fraction is used in the mutagenicity test, a 10-fold increase of revertants was observed. However, addition of cytosol and glutathione increased the revertant rate by almost 20-fold. These findings have been confirmed by Guengerich et al. (1980) and Reitz et al. (1982). Guengerich (1980) found the mutagenic activity of 1,2-DCA was questionable when it was tested without any activating enzyme systems. Addition of microsomes alone or in combination with a NADPH-generating system and glutathione did not enhance the mutagenic activity. However, the use of cytosol containing glutathione transferases markedly increased the mutagenicity of 1,2-DCA. Reitz et al. (1982) compared the ability of cytosol and purified microsomes to induce mutation upon incubation with 1,2-DCA and bacteria. They reported that the cytosol incubation increased the reversion of the TA1535 approximately 84-fold while the microsomal fractions of rat liver failed to increase the reversion rate in TA1535.

As shown in Figure 1, both the microsomal mixed function oxidative pathway and the glutathione mediated metabolic pathway generate reactive metabolites that can covalently bind to proteins and DNA. The production of these metabolites, 1-chloro-2-chloroethane, 2-chloroacetaldehyde, 2-chloroethanol, the half sulfur mustard, and glutathione episulfonium ion, may be responsible for the DNA damage, mutagenicity, and carcinogenicity related to 1,2-DCA (U.S. EPA, 1985). Inskeep et al. (1986) administered a single dose of ¹⁴C-labelled 1,2-DCA to Sprague-Dawley rats at 150 mg/kg and found N⁷-guanyl adducts account for approximately 75% and 57% of the DNA isolated from liver and kidney, respectively. When the N⁷-guanyl adducts were further analyzed by high performance liquid chromatography, they found two to five major fractions and two of them appeared to be S-[2-(N⁷-guanyl)ethyl]glutathione and S-[2-(N⁷-guanyl)ethyl]cysteinylglycine. These adducts are formed as a result of the reaction between the putative episulfonium ion and guanine. Inskeep et al. (1986) reported that though N⁷-(2-oxoethyl)guanine was identified by Svensson et al. (1986) as a major hepatic DNA adduct formed from 1,2-DCA, they failed to detect it in their investigation.

There is evidence indicating that 2-chloroacetaldehyde alkylates DNA, causes errors during in vitro DNA synthesis and is mutagenic in bacterial viruses. It has been shown to be weakly mutagenic and recombinogenic in yeast, and mutagenic in the fungus *Aspergillus nidulans* as well as in mammalian cell cultures (NTP, 1985). In a 104 week bioassay, male B6C3F₁ mice exposed to 17 mg/kg-day 2-chloroacetaldehyde via drinking water exhibited a significant increase in the prevalence of liver tumors (Daniel et al., 1992). However, Chang et al. (1992) showed that chloroacetic acid and 2-chloroacetaldehyde did not produce DNA strand breaks in intact rodent liver or in primary cultures of rat and mouse hepatocytes.

2-Chloroethanol has been shown to be mutagenic in bacteria but negative in a variety of eukaryotic systems, including *Drosophila*, mammalian cells, and rodents (NTP, 1985). In a 2-year skin painting experiment, 2-chloroethanol was not shown to be carcinogenic to F344/N rats and Swiss CD-1 mice (NTP, 1985).

Guengerich et al. (1980) demonstrated that liver microsomes and cytosolic fractions catalyzed the metabolism of 1,2-DCA to metabolites irreversibly bound to calf thymus DNA in vitro. However, there is evidence showing that metabolites of 1,2-DCA catalyzed by the cytosolic fraction are more effective in binding to DNA than those catalyzed by microsomes (Table 11). Guengerich et al. (1980) demonstrated that cytosolic fractions and glutathione affect the rate and nature of DNA binding in vitro. When synthetic homopolyribonucleotides were incubated with microsomes in the presence of NADPH, metabolites of 1,2-DCA were found to bind to all four ribonucleotides. When glutathione was added to such incubations, uridine became the preferred target and relative binding to other ribonucleotides was markedly decreased. When the synthetic homopolyribonucleotides were incubated with cytosol and glutathione, guanidine became the preferred target. It is interesting to note that when Inskeep et al. (1986) administered ¹⁴C-labelled 1,2-DCA to Sprague-Dawley rats, they found N⁷-guanyl adducts account for approximately 75% and 57% of the DNA adducts isolated from liver and kidney, respectively. These data showed that glutathione can both deactivate the reactive metabolites generated by microsomal mixed function oxidases and biotransform 1,2-DCA into DNA binding metabolites through the enzymatic action of glutathione-S-transferase in the cytosol.

Table 11. Irreversible binding of 1,2-DCA to calf thymus DNA catalyzed by microsomal and cytosolic fractions (adapted from Guengerich et al., 1980).

System	Total nonvolatile metabolites (nmol mg ⁻¹ protein)	Irreversible bound metabolites (pmol mg ⁻¹ protein)
Microsomes + GSH	1.0	73 ± 36
Microsomes + NADPH	11.0	60 ± 34
Microsomes + NADPH + GSH	18.3	409 ± 67
Cytosol + GSH	2.2	2340 ± 421
Cytosol + NADPH	0	0 ± 19
Cytosol + GSH + NADPH	9.8	1507 ± 143
Microsomes + cytosol + GSH	3.7	1104 ± 197 ⁽¹⁾
Microsomes + cytosol + NADPH	18.6	44 ± 17 ⁽¹⁾
Microsomes + cytosol + GSH + NADPH	18.4	1152 ± 152 ⁽¹⁾

(1) Expressed as mg⁻¹ total protein. When expressed on the basis of only microsomal or cytosolic protein, the values are twice as high.

Relative importance of the two metabolic pathways of 1,2-DCA in causing genotoxicity

There are several in vitro and in vivo studies demonstrating that metabolites of microsomal mixed function oxidases are more active in binding proteins than DNA. Guengerich et al. (1980) in an in vitro experiment showed that pretreatment of rats with a cytochrome P-450 inducer, phenobarbital, increased microsomal rates of nonvolatile metabolite formation twofold and irreversible binding to protein fourfold. Interestingly, this treatment did not significantly affect covalent binding to DNA.

Storer et al. (1985) administered a single, 200 mg/kg, intraperitoneal dose of 1,2-DCA to two groups of male B6C3F₁ mice. One group was pretreated with piperonyl butoxide, an inhibitor of microsomal oxidative enzymes, and another group was used as the control. Four hours after administration, they found significantly higher hepatic DNA damage in the mice treated with piperonyl butoxide and 1,2-DCA (-30.6% change) than those treated with 1,2-DCA only (-23.8% change). If the microsomal oxidative pathway were the major route leading to genotoxicity, one would expect a sharp decrease of DNA damage in the mice treated with piperonyl butoxide and 1,2-DCA.

In a follow-up study, Storer et al. (1985) investigated the potential of 2-chloroethanol, an oxidative metabolite of 1,2-DCA, to produce single-strand breaks and/or alkali labile lesions in hepatic DNA from mice treated in vivo.² The researchers reported that 4 hours after intraperitoneal injection of 2-chloroethanol at 72 mg/kg, 84 mg/kg, and 96 mg/kg to male B6C3F₁ mice, there was no evidence of DNA damage. Hepatotoxicity was observed only at the highest dose level tested, 96 mg/kg. Based on the results of these two studies, Storer et al. (1985) suggested that 2-chloroethanol and 2-chloroacetaldehyde are not responsible for the type of hepatic DNA damage induced by 1,2-DCA.

White et al. (1983) used tetradeutero-1,2-dibromoethane to study the metabolism of 1,2-dibromoethane in male Swiss-Webster mice. Since 1,2-dibromoethane is a bromine analog of 1,2-DCA and the metabolism of these two chemicals is similar (U.S. EPA, 1985), metabolic information on 1,2-dibromoethane may provide additional information about the metabolism and mechanism of genotoxicity of 1,2-DCA. White et al. (1983) showed that in vitro studies, the hepatic microsomal metabolism of 1,2-dibromoethane was significantly reduced (decreased 77%) by deuterium substitution, while metabolism by hepatic cytosol (glutathione S-transferases) was unaffected. The molecular basis for this phenomenon is the greater strength of the carbon-deuterium bond compared to the carbon-hydrogen bond, and thus decreases microsomal metabolism. There was no isotope effect on the biotransformation catalyzed by glutathione S-transferases as the reaction does not require the breakage of carbon-hydrogen bonds.

In an in vivo study, White et al. (1983) showed that intraperitoneal injection of tetradeutero-1,2-dibromoethane (50 mg/kg) caused significantly greater (about 60-100% at 24 hr and 72 hr after treatment) hepatic DNA damage (as measured by alkaline elution) than 1,2-dibromoethane

² 2-Chloroethanol instead of 2-chloroacetaldehyde was used in the study because of the acute toxicity of 2-chloroacetaldehyde and evidence of its reactivity at the site of administration. 2-Chloroethanol is metabolized by alcohol dehydrogenases to 2-chloroacetaldehyde and was employed in the study as a means of generating 2-chloroacetaldehyde intracellularly in vivo.

(50 mg/kg) in mice. They also found that concentrations of tetradeutero-1,2-dibromoethane in hepatic tissues were significantly higher (up to 10 times) than concentrations of 1,2-dibromoethane in hepatic tissues at 1, 3, and 8 hours after administration. Since the administration of tetradeutero-1,2-dibromoethane reduces the rate of microsomal oxidation and increases the availability of the compound to react with glutathione, these data suggest that while microsomal oxidative pathway is the main elimination pathway, the metabolic pathway mediated by glutathione S-transferases may be responsible for the majority of the genotoxic effects of 1,2-dibromoethane.

Inskeep et al. (1986) demonstrated that treatment of isolated rat hepatocytes with diethylmaleate (i.e., glutathione depletion) decreased covalent binding of 1,2-dibromoethane to DNA, but treatment with the relatively nonspecific cytochrome P-450 inhibitor 1-phenylimidazole did not. This finding is consistent with the report of Sundheimer et al. (1982), who found that diethylmaleate inhibited DNA binding by 1,2-dibromoethane in vivo, but SKF-525A did not.

Genotoxicity of 1,2-DCA is affected by dose regimen and route of administration

There are experimental data to indicate that the extent of DNA damage produced by 1,2-DCA in the liver and the lung is dependent on the dose rate and route of exposure. Baertsch et al. (1991) exposed Fischer-344 rats either to 80 ppm of ¹⁴C-labelled 1,2-DCA for 4 hours (“constant” exposure) or a peak concentration of up to 4400 ppm for a few minutes followed by exponential decay (“peak” exposure). They found significantly higher radioactivity in lung and liver DNA in the exposed animals compared with the unexposed controls. Furthermore, the total amount of 1,2-DCA administered in the “peak” exposure was about 7 to 8 fold higher than that used in the “constant” exposure, but the level of DNA covalent binding was approximately 35 times higher after “peak” exposure. Baertsch et al. (1991) suggested that under these experimental conditions, genotoxicity of 1,2-DCA was dependent upon the dosing regimen.

Reitz et al. (1982) determined total macromolecular binding and DNA binding in male Osborne-Mendel rats exposed to ¹⁴C-labelled 1,2-DCA by gavage (150 mg/kg) and inhalation (150 ppm, 6 hour) routes. Test animals were killed 4 hour after gavage or immediately following inhalation exposure. Reitz et al. (1982) found that there were no marked differences between the group of tissues where increased incidence of tumors were observed in the gavage bioassay (NCI, 1978) and those tissue where increased incidence were not observed. Except for the forestomach, slightly higher levels of macromolecular binding were observed in the tissues examined after inhalation compared to gavage exposure (Table 12). However, when Reitz et al. (1982) determined DNA binding, the results were opposite to total macromolecular binding data. The levels of DNA binding among the various organ tissues examined were generally higher (three to five times) after gavage versus inhalation exposure (Table 12).

Storer et al. (1984) reported that peak concentration of 1,2-DCA in the liver may be critical in determining the extent of bioactivation and genotoxicity of the compound in vivo. They administered 1,2-DCA to male B6C3F₁ mice by single intraperitoneal injection, gavage in corn oil, or inhalation. Single-strand breaks and/or alkali-labile lesions were observed in hepatic DNA at 4 hours after intraperitoneal injection or gavage administration of nonnecrogenic doses (100 mg/kg by gavage; 150 mg/kg by intraperitoneal injection). No evidence of hepatic DNA damage was found following 4-hour inhalation exposure of mice to a nonnecrogenic (150 ppm) or necrogenic (500 ppm) concentration of 1,2-DCA. Evidence of hepatic DNA damage was observed only after 4-hour inhalation exposures of mice to concentrations of 1,2-DCA causing

high mortality within 24 hr (1000 to 2000 ppm). Reitz et al. (1982) and Spreafico et al. (1980) demonstrated that blood levels in rats after gavage treatment (150 mg/kg) were generally higher than those obtained during inhalation exposure (150 to 250 ppm)(Tables 3 and 4). Storer et al. (1984) suggested that normal detoxification pathways of 1,2-DCA might have been saturated at the dose levels used in the gavage (100 and 200 mg/kg) experiments.

Table 12. Total macromolecular binding and DNA binding in selected tissues of rats after exposure to ¹⁴C 1,2-DCA by gavage or inhalation exposure routes (from Reitz et al. (1982).

Total macromolecular binding (n=4)	Nanomole equivalents 1,2-DCA/g tissue	
	gavage (150 mg/kg)	inhalation (150 ppm, 6 hr)
Liver ^a	175 ± 24	268 ± 45
Kidney	183 ± 25	263 ± 48
Spleen ^a	65 ± 21	130 ± 22
Lung	106 ± 34	147 ± 16
Forestomach ^a	160 ± 19	71 ± 19
Stomach	90 ± 2	156 ± 29
Experiment 1 (n=3)		
Liver ^a	21.3 ± 7.4	8.2 ± 3.3
Spleen ^a	5.8 ± 0.7	1.8 ± 0.3
Kidney	17.4 ± 2.3	5.2 ± 3.7
Stomach	14.9 ^b	2.8 ^b
Experiment 2 (n=3)		
Liver ^a	13.9 ± 2.1	3.3 ± 1.2
Spleen ^a	2.5 ± 0.3	1.8 ± 0.5
Kidney	14.5 ± 6.2	2.0 ± 0.3
Stomach	6.7 ^b	1.9 ^b

Animals were sacrificed 4 hr after oral dosing or immediately following a 6-hr inhalation exposure.

^a Site where malignant tumors were observed in the NCI study (1978) after 1,2-DCA was given by gavage.

^b Tissue from all three animals was pooled for DNA isolation.

Genotoxicity of 1,2-DCA is dose dependent

The amount of covalent binding, and hence genotoxicity, is related to the concentration of 1,2-DCA or its metabolites at the target organ. It may be possible that at low doses, a majority of electrophilic metabolites are detoxified; but at high doses, a larger fraction of the administered dose escapes the detoxifying mechanisms and reacts with proteins and DNA. This hypothesis is supported by a study result reported by Kitchin et al. (1994). 1,2-DCA was administered to female Sprague-Dawley rats by gavage in corn oil at 0 mg/kg, 1.3 mg/kg, 13.4 mg/kg, or 134 mg/kg. The first dose was given 12 hours before killing and the second dose was given 4 hours before killing. While they observed a statistically significant increase in rat hepatic DNA damage in the highest dose group (134 mg/kg), the DNA damage observed in the other two low-dose groups (13.4 mg/kg and 1.3 mg/kg) was not statistically different from that observed in the controls.

DNA and protein binding of 1,2-DCA is affected by disulfiram treatment

Igwe et al. (1986a) reported that disulfiram can modulate 1,2-DCA binding to protein and DNA in vivo. They investigated the distribution and level of macromolecular binding of 1,2-DCA by injecting intraperitoneally 150 mg/kg of ¹⁴C-labelled 1,2-DCA into four groups of male Sprague-Dawley rats. Group 1 animals were the controls; they were exposed to filtered air and fed on a regular diet. Group 2 animals were exposed to filtered air and fed a diet containing 0.15% disulfiram for 10 days before the injection. Groups 3 and 4 animals were exposed to 150 ppm 1,2-DCA for 35 days, 7 hr/day, 5 days/week. Group 3 animals were fed a regular diet, but group 4 animals were fed a diet containing 0.15% disulfiram for 10 days before the injection. Igwe et al. (1986a) observed that exposure to both 1,2-DCA and disulfiram (groups 2 and 4) caused higher levels of DNA binding than exposure to 1,2-DCA alone (groups 1 and 3) in all tissues except kidney. They also noted that while there were significant decreases between the 4- and 24-hr time points in DNA binding in all of the tissues derived from the air controls and 1,2-DCA controls (groups 1 and 3), no such changes were observed in disulfiram treated animals (groups 2 and 4)(Table 13). These data indicate DNA adducts produced by 1,2-DCA in the presence of disulfiram may be more persistent than those produced by 1,2-DCA in the absence of disulfiram.

As shown in Table 14, the radioactivity bound to protein was higher in groups 1 and 3 than in groups 2 and 4 for liver and spleen at 4 hr and for liver, kidney, and spleen at 24 hr. These data show that in the presence of disulfiram, the metabolites of 1,2-DCA showed a higher tendency to bind to DNA; in the absence of disulfiram, they showed a higher tendency to bind to proteins.

Table 13. DNA binding of ¹⁴C-labelled 1,2-DCA in selected tissues of male Sprague-Dawley rats at 4 hr and 24 hr following an intraperitoneal dose of 150 mg/kg (from Igwe et al., 1986a) ⁽¹⁾

Tissue	Air control (group 1)	Disulfiram control (group 2)	1,2-DCA, 150 ppm (group 3)	Disulfiram and 1,2-DCA, 150 ppm (group 4)
Liver	0.105±0.105 ⁽²⁾ (0.067±0.003) ⁽²⁾	0.260±0.05 (0.240±0.05)	0.113±0.019 ⁽²⁾ (0.084±0.008) ⁽²⁾	0.29±0.026 (0.270±0.036)
Kidney	0.043±0.009 ⁽²⁾ (0.018±0.003) ⁽²⁾	0.055±0.010 (0.045±0.004)	0.090±0.026 ⁽³⁾ (0.024±0.009) ⁽²⁾	0.062±0.012 (0.048±0.006)
Spleen	0.071±0.011 ⁽²⁾ (0.033±0.006) ⁽²⁾	0.118±0.014 (0.114±0.023)	0.083±0.012 ⁽²⁾ (0.039±0.01) ⁽²⁾	0.136±0.020 (0.131±0.019)
Testis	0.056±0.014 ⁽²⁾ (0.044±0.007) ⁽²⁾	0.090±0.018 (0.088±0.011)	0.068±0.024 ⁽²⁾ (0.040±0.007) ⁽²⁾	0.113±0.032 (0.143±0.042) ⁽⁴⁾

Each value represents the mean±SD of duplicate determinations on three animals per group.

- (1) The values in parentheses are the 24-hr values; others are the 4-hr values. All values are in nmol eq/mg DNA.
- (2) Significantly different from groups 2 and 4, p is equal to or less than 0.05.
- (3) Significantly different from groups 1, 2 and 4, p is equal to or less than 0.05.
- (4) Significantly different from groups 1, 2 and 3, p is equal to or less than 0.05.

Table 14. Protein binding (soluble and particulate fraction) of ¹⁴C-labelled 1,2-DCA in selected tissues of male Sprague-Dawley rats at 4 hr and 24 hr following an intraperitoneal dose of 150 mg/kg (from Igwe et al., 1986a) ⁽¹⁾

Tissue	Air control (group 1)	Disulfiram control (group 2)	1,2-DCA, 150 ppm (group 3)	Disulfiram and 1,2-DCA, 150 ppm (group 4)
Liver	1.54±0.16 ⁽²⁾ (0.89±0.14) ⁽²⁾	0.82±0.18 (0.60±0.03)	1.23±0.19 ⁽²⁾ (0.84±0.07) ⁽²⁾	0.81±0.12 (0.65±0.09)
Kidney	1.51±0.21 (0.58±0.10) ⁽²⁾	1.14±0.16 (0.41±0.06)	1.20±0.03 (0.72±0.02) ⁽²⁾ ⁽³⁾	1.07±0.23 (0.44±0.07)
Spleen	3.65±0.42 ⁽²⁾ (2.61±0.06) ⁽²⁾	2.11±0.41 (1.21±0.42)	2.91±0.08 ⁽²⁾ (2.74±0.32) ⁽²⁾	2.22±0.36 (1.80±0.22)
Testis	0.36±0.05 ⁽⁴⁾ (0.25±0.04)	0.24±0.07 (0.20±0.02)	0.21±0.03 (0.16±0.02)	0.17±0.04 (0.18±0.03)

Each value represents the mean±SD of duplicate determinations on three animals per group.

- (1) The values in parentheses are the 24-hr values; others are the 4-hr values. All values are in nmol eq/mg protein.
- (2) Significantly different from groups 2 and 4, p is equal to or less than 0.05.
- (3) Significantly different from groups 1, 2 and 4, p is equal to or less than 0.05.
- (4) Significantly different from groups 2, 3 and 4, p is equal to or less than 0.05.

Developmental and Reproductive Toxicity

Rao et al. (1980) exposed Sprague-Dawley rats to 0, 25, 75, or 150 ppm 1,2-DCA 6 hr/day, for 60 days prior to mating and 116 days after mating. The treatment had no effects on the fertility, gestation, sex ratios, or survival indices. Rao et al. (1980) also exposed pregnant Sprague-Dawley rats to 0, 100, or 300 ppm 1,2-DCA 7 hr/day, during gestation. While high maternal mortality was observed at the highest concentration, no fetotoxic or teratogenic effects were observed at 100 ppm. ATSDR (1994) reported that inhalation exposure of pregnant rabbits to 100 or 300 ppm of 1,2-DCA during days 6-18 of gestation also did not change the incidence of pregnancy, mean litter size, incidence of resorption, or fetal body measurements.

Lane et al. (1982) exposed mice to doses of 0, 5, 15, or 50 mg/kg-day in drinking water for 24-49 weeks and did not observe any dose-dependent effects on fertility, gestation, litter size, viability, or lactation indices. Alumot et al. (1976) exposed rats through diets containing 12.5 or 25 mg/kg-day 1,2-DCA for two years. They found no changes in fertility and gestation indices. Furthermore, no fetotoxic or teratogenic effects were noted in either generation of offspring of F_{1C} and F_{2B} litters sacrificed on day 18.

There are several Russian studies describing a variety of adverse reproductive effects associated with exposure to 1,2-DCA. However, due to inadequate study design or inadequate reporting, the implications of the observed effects cannot be determined (Vozovaya, 1974 and 1977 cited in ATSDR, 1994). Although administration of 1,2-DCA alone did not cause male reproductive toxicity, inhalation exposure of 300 ppm 1,2-DCA, 7 hr/day, 5 days/week for 30 days, in the presence of disulfiram (0.15% of diet) caused testicular atrophy and abnormal histopathology in the testes of Sprague-Dawley rats (Igwe et al., 1986b). Cheever et al. (1990) reported a significant increase in interstitial cell tumors of the testes in male rats exposed to 50 ppm 1,2-DCA, 7 hr/day, 5 days/week for 2 years with 0.05% disulfiram in the diet.

Immunotoxicity

There is evidence from animal studies indicating that the immune system is a target of 1,2-DCA exposure. Female CD-1 mice exposed to 5-10 ppm of 1,2-DCA for 3 hours exhibited significantly increased mortality from streptococcal challenge, whereas a single 3-hr exposure or five consecutive daily 3-hr exposures to 2.3 ppm 1,2-DCA had no significant effect (Sherwood et al., 1987). Male Sprague-Dawley rats exposed to 200 ppm for 5 hours or 100 ppm 5 hours/day for 12 days did not exhibit any increased susceptibility to infection from these microbes (Sherwood et al., 1987). The reason for this difference in sensitivity between mice and rats is unclear.

Munson et al. (1982) administered 1,2-DCA to mice by gavage, in water, at 4.9 and 49 mg/kg-day for 14 days. They found a significant reduction in humoral immunity (measured by immunoglobulin M response to sheep erythrocytes) and cell-mediated immunity (measured by delayed-type hypersensitivity response to sheep erythrocytes). However, when mice were administered 1,2-DCA in drinking water at 189 mg/kg-day for 90 days, no treatment-related effects were observed on either the antibody-forming cell response or the delayed-type hypersensitivity response after immunization with sheep erythrocyte antigens. The author suggested that the conflicting results in mice treated by gavage and by drinking water may be explained by the difference in routes of compound administration.

Neurotoxicity

A number of studies showed that acute exposure to high concentrations of 1,2-DCA causes central nervous system depression. Tremors, uncertain gait, and narcosis were seen in rats, guinea pigs, and rabbits exposed to 3,000 ppm for 7 hours (ATSDR, 1994). Similarly, tremors, salivation, emaciation, abnormal posture, ruffled fur, and dyspnea were observed in rats exposed to 240 mg/kg-day by gavage for 13 weeks. Necrotic lesions were reported in the cerebellum of rats dosed with 240 or 300 mg/kg-day. However, no neurological effects or lesions in nervous system tissues were reported in rats (500 to 725 mg/kg-day) or mice (4200 mg/kg-day in males and 4900 mg/kg-day in females) exposed to 1,2-DCA in drinking water for 13 weeks (NTP, 1991). No abnormal histopathological changes were found in nervous tissues from rats exposed to 50 ppm of 1,2-DCA via inhalation for 2 years (Cheever et al., 1990).

Chronic Toxicity

Small numbers of rats, guinea pigs, rabbits and monkeys were exposed to 1,2-DCA at 100 and 400 ppm for 7 hr/day, 5 days/week for 6 months. Repeated exposure at 100 ppm did not produce adverse effects in any of the four species as determined by general appearance and behavior, mortality, growth, body and organ weights, and gross and microscopic examination of tissues (Spencer et al., 1951). Severe toxic effects were found in the rats, guinea pigs, and monkeys that were exposed to 400 ppm 1,2-DCA. Heppel et al. (1946) exposed rats and guinea pigs to 200 ppm 1,2-DCA through inhalation. About 50% of the exposed rats died after 44 exposures (7 hr/day). Among the 5 rats killed after 86 exposures, fatty degeneration of the kidney was found in one rat; no other changes were noted in the liver, heart, lungs, kidneys, adrenals, or spleen. Four out of 14 guinea pigs died after 88 exposures. Among the 9 guinea pigs killed after 124 exposures, pulmonary congestion was found in four, liver necrosis in one, and necrosis of the adrenal cortex in one (Heppel et al., 1946). Cheever et al. (1990) exposed rats to 50 ppm 1,2-DCA for 2 years and failed to find any adverse effects in the respiratory system, the cardiovascular system, the gastrointestinal system, the musculoskeletal system, the hepatic system, or the renal system.

Carcinogenicity

Evaluations of carcinogenicity studies in animals have been published by U.S. EPA (1985) in the "Health Assessment Document for 1,2-Dichloroethane" and summarized in U.S. EPA's IRIS on-line file (U.S. EPA, 1997).

The National Cancer Institute (NCI, 1978) conducted a chronic toxicity and oncogenicity oral bioassay of technical grade 1,2-DCA in male and female Osborne-Mendel rats and B6C3F₁ mice. There were four groups for each sex of both species, including an untreated control, a vehicle (corn oil) control, a low dose group and a high dose (the maximum tolerated dose) group. Time-weighted average low and high dose levels were 47 and 95 mg/kg for both male and female rats, 97 and 195 mg/kg for male mice, and 149 and 299 mg/kg for female mice, respectively. The animals were dosed by gavage five days per week for 78 weeks and observed for an additional 12-32 weeks.

Signs of toxicity in the animals early in the study led to changes of the dosage several times (Tables 15 and 16). Weight depression was observed in both groups of rats exposed to 1,2-DCA and in the high-dose female mice. Mortality was early and severe in dosed animals. The mean survival was approximately 56 weeks on test for high-dose male and female rats. The early deaths were usually not due to cancer; rather, the toxic effects of 1,2-DCA appeared to be responsible for these deaths. Rats dying prematurely had a variety of lesions, including bronchopneumonia and endocardial thrombosis (U.S. EPA, 1985). Survival of female mice was rather good until week 60. Among the high-dose females, 72% (36/50) of the animals died between weeks 60 and 80. These deaths may have been tumor-related, since 69% (25/36) had one or more tumors (U.S. EPA, 1985). Among the high-dosed male mice, 50% (25/50) were alive at 84 weeks and 42% (21/50) survived until the end of the study. By week 70, about 45% of the low-dose males and 55% of the untreated males had died.

Table 15. Design summary for 1,2-DCA gavage experiment in Osborne-Mendel rats (NCI, 1978). (Adapted from U.S. EPA, 1985)

Group	1,2-DCA dosage (mg/kg body weight)	Observation period		Time-weighted average dosage over a 78-week period ⁽¹⁾ (mg/kg body weight)
		Treated (weeks)	Untreated (weeks)	
Untreated control, male and female rats	--	--	106	--
Vehicle control, male and female rats	0	78	32	0
Low-dose, male and female rats	50	7	--	47
	75	10	--	--
	50	18	--	--
	50 ⁽²⁾	34	9	--
	0	--	32	--
High-dose, male and female rats	100	7	--	95
	150	10	--	--
	100	18	--	--
	100 ⁽²⁾	34	9	--
	0	--	23 (male) 15 (female) ⁽³⁾	--

(1) Time-weighted average dosage = \sum (dosage x weeks received)/78 weeks.

(2) These dosages were cyclically administrated with a pattern of one dosage-free week followed by 4 weeks (5 days/week) of dosage at the level indicated.

(3) All animals in this group died before the bioassay was terminated.

Table 16. Design summary for 1,2-DCA gavage experiment in B6C3F₁ mice (NCI, 1978) (Adapted from U.S. EPA, 1985).

Group	1,2-DCA dosage (mg/kg body weight)	Observation period		Time-weighted average dosage over a 78-week period ⁽¹⁾ (mg/kg body weight)
		Treated (weeks)	Untreated (weeks)	
Untreated control, male and female mice	--	--	90 (males) 91 (females)	--
Vehicle control, male and female mice	0	78	12 (males) 32 (females)	0
Low-dose, male mice	75	8	--	97
	100	70	--	--
	0	--	12	--
High-dose, male mice	150	8	--	195
	200	70	--	--
	0	--	13	--
Low-dose, female mice	125	8	--	149
	200	3	--	--
	150	67	--	--
	0	--	13	--
High-dose, female mice	250	8	--	299
	400	3	--	--
	300	67	--	--
	0	--	13	--

(1) Time-weighted average dosage = \sum (dosage x weeks received)/78 weeks.

A variety of tumors was observed in both low and high dose male and female rats (Table 17 A, B)³. A statistically significant increase in the incidence of squamous cell carcinomas of the forestomach, hemangiosarcomas of the circulatory system, and fibromas of the subcutaneous tissue occurred in male rats. Female rats exhibited a statistically significant increase in the incidence of adenocarcinomas of the mammary gland and hemangiosarcomas of the circulatory system. Male B6C3F₁ mice demonstrated a statistically significant increase in incidence of hepatocellular carcinomas and alveolar/bronchiolar adenomas, while female mice exhibited an increased incidence of alveolar/bronchiolar adenomas, mammary gland adenocarcinomas and endometrial stromal sarcomas (Table 17 C, D)³.

³ The purpose of this table is to compare tumor sites reported by different studies. Different types of tumor belonging to the same organ are combined. Information presented in this table should not be used for dose-response evaluation.

Table 17 A. Comparison of tumor sites in male rats exposed to 1,2-DCA.

(Different tissues and tumor types, benign and malignant, of a single target organ are combined for comparison purposes)

Study	NCI (1978)	Maltoni et al. (1980)	Cheever et al. (1990)
Treatment and observation periods	gavage; treated for 78 wk and observed for another 23-32 wk	inhalation; 78 wk exposure; observed for another 70 wk	inhalation; 2 years exposure; no observation period
Animal strain	Osborne-Mendel rats	Sprague-Dawley rats	Sprague-Dawley rats
Adjusted dose on a weekly basis	0 (vehicle control); 34; 68 mg/kg-day	0 (chamber control); 3.5; 7; 36; 107-178 ppm (7 hr/day)	0; 36 ppm (7 hr/day); 36 ppm + disulfiram; 36 ppm + ethanol
Toxicity	toxicity observed in the high dose group	toxicity observed in the high dose group	no toxicity was observed
Liver	1/20; 0/50; 2/50	0 in all groups	1/50; 3/50; 6/49; 4/50
Lung	0/20; 0/50; 0/50	not reported separately	0/50; 0/50; 1/50; 0/49
Stomach	0/20; 3/50; 10/50*	2/90; 1/90; 0/89; 1/90; 0/89	0/48; 0/49; 0/50; 0/50
Nasal cavity (combined)	not reported separately	not reported separately	not reported separately
Mammary gland	1/20; 2/50; 0/50	8/90; 11/90; 5/89; 10/90; 11/89	1/44; 1/40; 1/38; 2/44
Leukemia	0/20; 0/50; 0/50	1/90; 2/90; 4/90; 1/90; 0/89	not reported separately
Kidneys	0/20; 1/50; 6/50	0/90; 1/90; 0/90; 0/90; 0/89	0/50; 1/50; 0/50; 0/50
Skin (combined)	0/20; 6/50; 6/50	0/90; 1/90; 1/90; 1/90; 0/89	3/50; 1/50; 13/50* ; 2/50
Others (brain, reproductive organs)	0 in all dosed groups	8/90; 16/90; 4/90; 14/90; 9/89	see specific organs
Testes	see others	not reported separately	2/50; 3/50; 13/50* ; 5/50
Pituitary	2/20; 1/50; 4/49	not reported separately	31/48; 18/48; 31/49; 23/44
Bile duct	not reported separately	not reported separately	1/50; 0/50; 21/49* ; 0/50
Hemangiosarcomas	0/20; 11/50* ; 7/50	not reported separately	not reported separately
Tunica vaginalis, mesotheliomas	not reported separately	not reported separately	not reported separately

* Statistically significant when compared with the controls, $p \leq 0.05$, one-sided Fisher exact test.

Table 17 B. Comparison of tumor sites in female rats exposed to 1,2-DCA.

(Different tissues and tumor types, benign and malignant, of a single target organ are combined for comparison purposes)

Study	NCI (1978)	Maltoni et al. (1980)	Cheever et al. (1990)
Treatment and observation periods	gavage; treated for 78 wk and observed for another 15-32 wk	inhalation; 78 wk exposure; observed for another 70 wk	inhalation; 2 years exposure; no observation period
Animal strain	Osborne-Mendel rats	Sprague-Dawley rats	Sprague-Dawley rats
Adjusted dose on a weekly basis	0 (vehicle control); 34; 68 mg/kg-day	0 (chamber control); 3.5; 7; 36; 107-178 ppm (7 hr/day)	0; 36 ppm (7 hr/day); 36 ppm + disulfiram; 36 ppm + ethanol
Toxicity	toxicity observed in the high dose group	toxicity observed in the high dose group	no toxicity was observed
Liver	0/20; 2/50; 0/50	0 in all groups	1/50; 2/50; 3/50; 1/50
Lung	0/20; 0/50; 0/50	not reported separately	0/50; 0/50; 0/50; 0/49
Stomach	0/20; 1/49; 0/50	1/90; 0/90; 1/90; 0/90; 0/90	0/48; 0/49; 0/50; 0/50
Nasal cavity (combined)	not reported separately	not reported separately	not reported separately
Mammary gland	0/20; 15/50* ; 26/50*	38/90; 65/90* ; 43/90; 58/90* ; 52/90*	21/50; 30/50; 34/48* ; 21/47 ⁽¹⁾
Leukemia	not reported separately	3/90; 6/90; 0/90; 2/90; 0/90	not reported separately
Kidneys	0/20; 0/50; 4/50	0 in all groups	0/50; 1/50; 0/50; 0/50
Skin (combined)	1/20; 3/50; 5/50	1/90; 0/90; 0/90; 0/90; 0/90	0/49; 3/50; 6/49* ; 1/50
Others (brain, reproductive organs)	0 in all dosed groups	4/90; 9/90; 4/90; 6/90; 11/90	see specific organs
Pituitary	7/20; 7/50; 5/49	not reported separately	41/50; 25/43; 38/49; 41/47
Bile duct	not reported separately	not reported separately	1/50; 0/50; 41/49* ; 0/50
Hemangiosarcomas	0/20; 5/50; 4/50	not reported separately	not reported separately

* Statistically significant when compared with the controls, $p \leq 0.05$, one-sided Fisher exact test.

(1) Incidence rates of mammary gland adenocarcinomas for rats exposed to 0; 36 ppm (7 hr/day); 36 ppm + disulfiram; 36 ppm + ethanol were 4/50, 5/50, 12/48, and 2/47, respectively.

Incidence rates of mammary gland adenomas for rats exposed to 0; 36 ppm (7 hr/day); 36 ppm + disulfiram; 36 ppm + ethanol were 2/50, 4/50, 3/48, and 4/47, respectively.

Incidence rates of mammary gland fibroadenomas for rats exposed to 0; 36 ppm (7 hr/day); 36 ppm + disulfiram; 36 ppm + ethanol were 15/50, 21/50, 19/48, and 15/47, respectively.

Table 17 C. Comparison of tumor sites in male mice exposed to 1,2-DCA.

(Different tissues and tumor types, benign and malignant, of a single target organ are combined for comparison purposes)

Study	NCI (1978)	Maltoni et al. (1980)	Klaunig et al. (1986)
Treatment and observation periods	gavage; treated for 78 wk and observed for another 12-13 wk	inhalation; 78 wk exposure; observed for another 41 wk	drinking water; 52 wk exposure; no observation period
Animal strain	B6C3F ₁ mice	Swiss mice	B6C3F ₁ mice
Adjusted dose on a weekly basis	0 (vehicle control); 69; 139 mg/kg-day	0; 3.5; 7; 36; 107-178 ppm (7 hr/day)	0; 160; 500 mg/kg-day
Toxicity	toxicity observed	toxicity observed in the high dose group	no toxicity was observed
Liver	1/19; 6/47; 12/48*	0 in all dosed groups	5/25; 4/25; 3/25
Lung	0/19; 1/47; 15/48*	4/111; 1/69; 4/89; 3/87; 0/81	2/25; 1/25; 3/25
Stomach	1/19; 1/46; 2/46	0 in all dosed groups	not examined
Mammary gland	not reported	0/111; 0/69; 1/89; 0/87; 0/81	not examined
Oesophagus	not reported separately	not reported separately	not examined
Kidneys	0 in all dosed groups	0 in all dosed groups	not examined
Skin (combined)	0/19; 1/47; 4/48	2/111; 0/69; 1/89; 0/87; 0/81	not examined
Others (e.g., brain, reproductive organs)	not reported separately	1/111; 1/69; 1/89; 1/87; 0/81	not examined

* Statistically significant when compared with the controls, $p \leq 0.05$, one-sided Fisher exact test.

Table 17 D. Comparison of tumor sites in female mice exposed to 1,2-DCA.

(Different tissues and tumor types, benign and malignant, of a single target organ are combined for comparison purposes)

Study	NCI (1978)	Maltoni et al. (1980)
Treatment and observation periods	gavage; treated for 78 wk and observed for another 12-13 wk	inhalation; 78 wk exposure; observed for another 41 wk
Animal strain	B6C3F ₁ mice	Swiss mice
Adjusted dose on a weekly basis	0 (vehicle control); 106; 213 mg/kg-day	0; 3.5; 7; 36; 107-178 ppm (7 hr/day)
Toxicity	toxicity observed in the high dose group	toxicity observed in the high dose group
Liver	1/20; 0/50; 1/47	0 in all dosed groups
Lung	1/20; 7/50; 16/48*	4/133; 4/89; 2/88; 2/87; 3/84
Stomach	1/20; 2/50; 5/44	0 in all dosed groups
Oesophagus	1/20; 1/50; 0/46	not reported separately
Mammary gland	0/20; 9/50* ; 7/48	7/133; 5/89; 6/88; 3/87; 5/84
Kidneys	1/20; 0/50; 1/47	0/133; 0/89; 1/88; 0/87; 0/84
Skin (combined)	0/20; 3/50; 1/48	1/133; 1/89; 1/88; 1/87; 0/84
Others (brain, reproductive organs)	see specific organs	4/133; 4/89; 2/88; 4/87; 2/84
Ovary	0/20; 1/49; 1/46	see others
Uterus	0/20; 8/49; 9/47*	see others
Subcutaneous tissue or rib	not reported separately	not reported separately
Nasal cavity	not reported separately	not reported separately
Hemangiosarcomas and hemangiomas	not significantly elevated	not reported separately

* Statistically significant when compared with the controls, $p \leq 0.05$, one-sided Fisher exact test.

Maltoni et al. (1980) conducted inhalation studies in Sprague-Dawley rats and Swiss mice. Four groups, each consisting of 90 rats or mice of both sexes, were exposed to 1,2-DCA concentrations of 5, 10, 50, or 150 - 250 ppm. All animals were exposed to the chemical seven hours a day, five days a week, for 78 weeks. After several days of exposure⁴, the concentration of the highest dose group was reduced from 250 ppm to 150 ppm because of severe toxic effects seen in both rats and mice. Two groups of 180 rats per sex, or one group of 249 mice, served as controls. Although all animals were allowed to live until spontaneous death, and extensive histopathology was performed on each animal, no exposure related increase in the incidence of tumor development was seen in either species (Table 17 A, B, C, and D). The apparent increase in mammary tumors in some of the treated female Sprague-Dawley rats when compared to controls in the exposure chamber, was not due to malignant tumors, but to fibromas and fibroadenomas. The increased incidence of mammary fibromas and fibroadenomas is statistically significant in groups exposed to 1,2-DCA at 107-178 ppm, 36 ppm, and 3.5 ppm, when compared to controls in the chamber, but not significant when compared to controls outside of the chamber (US EPA, 1985). U.S. EPA (1985) suggested that the observed difference in the incidences of these tumors in the various groups were probably due to the differences in survival rates within the groups. The highest difference in incidence was found between the control groups in the chamber, which had low survival rates, and the groups treated with 1,2-DCA at 3.5 ppm, which had high survival rates.

Cheever et al. (1990) exposed male and female Sprague-Dawley rats to 50 ppm 1,2-DCA for seven hours a day, five days a week, for two years by inhalation. Additional rats were exposed to 50 ppm 1,2-DCA either with 0.05% disulfiram in the diet or with 5% ethanol in the drinking water. A relatively high percentage of the animals survived the 24-month study, with 46 to 72% of the male and 48 to 70% of the female rats euthanized at termination. Combined exposure to 1,2-DCA and disulfiram resulted in a significant increase in the incidence of intrahepatic bile duct cholangiomas in both male and female rats. Male rats exposed to both chemicals also had an increased incidence of subcutaneous fibromas, neoplastic nodules, and interstitial cell tumors of the testes. The female rats exposed to both chemicals also had a higher incidence of mammary adenocarcinomas (Table 17 A, B). It is important to note that subcutaneous fibromas and mammary adenocarcinomas have also been observed in Osborne-Mendel rats exposed to 1,2-DCA alone, by gavage (NCI, 1978).

However, no significant increase in the number of any tumor type was observed in rats exposed to only 1,2-DCA, disulfiram, or ethanol. Similarly, no significant increase in the number of tumors was observed in rats exposed to inhaled 1,2-DCA and ethanol in water (Table 17 A, B). Cheever et al. (1990) noted that as disulfiram has an inhibitory effect on aldehyde dehydrogenase and mixed-function oxidases, rats exposed to both disulfiram and 1,2-DCA would have a reduced rate of elimination for 1,2-DCA. As discussed in the section on metabolism, Cheever et al. (1990) also demonstrated that rats chronically exposed to both disulfiram and 1,2-DCA had higher sustained blood levels of the unchanged compound than those exposed to 1,2-DCA alone (Table 7). Igwe et al. (1986c) suggested that exposure to both disulfiram and 1,2-DCA may increase the activity of glutathione S-transferases and tissue levels of reduced glutathione, in

⁴ There is a discrepancy between the text and the figures in the report. The text suggested that the high-dose group was exposed to 250 ppm 1,2-DCA for several days. However the figure describes the group as being exposed to 250 ppm for a few weeks.

addition to inhibiting microsomal mixed-function oxidases. The increased level of 1,2-DCA in blood and the induction of glutathione S-transferases could be related to the carcinogenic effects observed in the group of rats exposed to both disulfiram and 1,2-DCA.

It is interesting to note that disulfiram has also been reported to increase the carcinogenic potential of 1,2-dibromoethane (Plotnick et al., 1980). Sprague-Dawley rats of both sexes exposed to 0.05% disulfiram in diet and 20 ppm 1,2-dibromoethane for 18 months showed significantly higher incidences of hepatocellular carcinoma and hemangiosarcoma of the spleen than rats exposed to 20 ppm 1,2-dibromoethane alone. Plotnick et al. also performed studies to investigate whether disulfiram modifies the tissue distribution and excretion of orally administered 1,2-dibromoethane (15 mg/kg). At both 24 and 48 hours after administration of ¹⁴C 1,2-dibromoethane, tissue concentrations of ¹⁴C in the liver, kidneys, spleen, testes, and brain were significantly higher in the rats receiving the disulfiram diet than in those receiving the control diet. Urinary excretion of radioactivity during the first 24 hours was also significantly depressed in the disulfiram diet group.

Klaunig et al. (1986) studied the carcinogenicity of 1,2-DCA by administering the chemical to male B6C3F₁ mice in drinking water. Three groups, each consisting of 35 mice, were exposed to 1,2-DCA concentrations of 0, 835 mg/L or 2500 mg/L, for 52 weeks. Mice were sampled after 24 weeks (10 mice) and 52 weeks (25 mice). All treated mice displayed mean body weight gains that paralleled those of the control mice but were lower, and all treated and untreated mice survived until the 52-week sampling time. At sampling, liver and lung tumors were detected. The average weekly dose received by the high-dose mice was estimated to be 500 mg/kg-day, a level higher than that used in the NCI gavage study (1978). Klaunig et al. reported that incidence rates of liver and lung tumors in the exposed mice were not statistically different from those of the controls (Table 17 C). The bioassay is limited in the small number of animals per dose group, the limited histopathological examination (see Table 17 C), and the short study duration. In the NCI study (1987), all tumors in male mice were identified after 52 weeks of exposure.

Theiss et al. (1977) conducted a pulmonary tumor bioassay with 1,2-DCA in mice. Groups of 20 mice received intraperitoneal injections of either 0, 20, 40, or 100 mg/kg 1,2-DCA three times weekly for a total of 24 injections per mouse. The lungs were examined for surface adenomas. Although the incidence of lung tumors increased with dose, none of the groups had a significantly greater number of pulmonary adenomas than did vehicle-treated control mice.

Van Duuren et al. (1979) conducted a bioassay of 1,2-DCA and of a suspected metabolite, chloroacetaldehyde, as potential initiators, promoters and complete carcinogens using the two-stage mouse skin test. Female Swiss mice were administered one or the other of the test compounds three times weekly to their shaved dorsal skin, with certain groups having previously received applications of the classic tumor-promoting agent, phorbol myristate acetate. The results of the van Duuren et al. (1979) study indicated that neither 1,2-DCA nor chloroacetaldehyde induced a statistically significant increase of papillomas or carcinomas of the skin, although dermal application of 1,2-DCA was associated with a significant increase in the number of mice afflicted with benign lung papillomas.

Among the three long-term bioassays reported, Maltoni et al. (1980) and Cheever et al. (1990) did not observe any statistically significant increases of tumor that were related to inhalation exposure of 1,2-DCA. NCI (1978) administered 1,2-DCA to rats and mice by gavage and observed a statistically significant increase of tumor in a number of organ tissues. In male rats, the incidence rates of squamous cell carcinomas of the forestomach, hemangiosarcomas of the circulatory system, and fibromas of the subcutaneous tissue were significantly increased. In female rats, a statistically significant increase in the incidence of adenocarcinomas of the mammary gland and hemangiosarcomas of the circulatory system was observed. In male

B6C3F₁ mice, a statistically significant increase in incidence of hepatocellular carcinomas and alveolar/bronchiolar adenomas was reported, and in female mice increased incidence of alveolar/bronchiolar adenomas, mammary gland adenocarcinomas and endometrial stromal sarcomas was also observed.

Toxicological Effects in Humans

Acute Toxicity

Ingestion or inhalation of large quantities of 1,2-DCA is lethal to humans. ATSDR (1994) reported that when adults ingested 30 to 60 mL (37 to 75 g) of 1,2-DCA, death generally occurred within one to two days. However, in two cases of 1,2-DCA poisoning, the patients drank 15 to 20 mL Marament (equivalent to approximately 15 to 20 g of 1,2-DCA); they suffered gastrointestinal disorders and were discharged from the hospital in a few days. Death was usually ascribed to circulatory and respiratory failure. Autopsies revealed tissue congestion, cellular degeneration, necrosis and hemorrhagic lesions of the gastrointestinal tract, liver, kidneys, spleen, lung, respiratory tract and brain (U.S. EPA, 1985).

Many cases of acute occupational exposure to 1,2-DCA or a vapor mixture that contains 1,2-DCA have been published (U.S. EPA, 1985). Death from acute inhalation exposure was generally attributed to respiratory and circulatory failure. Autopsies of the victims revealed organ and tissue damages similar to those observed exposed through the oral route.

Subchronic Toxicity

There are reports that workers exposed to 70-100 ppm of 1,2-DCA experienced a number of toxic effects including anorexia, nausea, vomiting, weakness and fatigue, epigastric discomfort and irritation of the respiratory tract and eyes (U.S. EPA, 1985). A Russian health survey of workers routinely exposed to 1,2-DCA found excess rates of gastrointestinal diseases, liver and gall bladder diseases, and diseases of the muscle, tendons and ganglion. Based on the air monitoring data available, the time weighted average concentration was estimated to be 10-15 ppm (U.S. EPA, 1985).

Genetic Toxicity

No studies were located regarding genotoxic effects of 1,2-DCA in humans (ATSDR, 1994; Cal/EPA, 1998).

Developmental and Reproductive Toxicity

Only one human study was located regarding cardiac effects in newborns after oral exposure of the mother to 1,2-DCA via contaminated water (NJDH, 1992 reference in ATSDR, 1994). However, this is an ecological study and its findings are only suggestive and therefore, should be interpreted with caution.

Immunotoxicity

No studies were located regarding immunological effects in humans after inhalation or oral exposure to 1,2-DCA (ATSDR, 1994, Cal/EPA, 1998).

Neurotoxicity

1,2-DCA has an anesthetic narcotic effect in humans. In two Russian studies, adverse nervous system effects were reported by workers exposed to 25 to 50 ppm of 1,2-DCA (ACGIH, 1996). A Polish paper reported symptoms such as nausea, vomiting, and dizziness from exposures of 10 to 37 ppm of 1,2-DCA in 1 of 6 workers (ACGIH, 1996).

Chronic Toxicity

No studies were located regarding chronic toxicity in humans resulting from exposure to 1,2-DCA (Cal/EPA, 1998).

Carcinogenicity

The potential carcinogenicity of 1,2-DCA in the human population has not been extensively studied. In a retrospective epidemiological study, Benson and Teta (1993) found increased mortality due to pancreatic and lymphopietic cancers in chlorohydrin production workers. The data were insufficient to identify conclusively the causative agent. Based on probable exposure and the known toxicity of the chemicals the workers were exposed to, the researchers suggested that exposure to 1,2-DCA, perhaps in combination with other chlorinated hydrocarbons, was the most likely cause.

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

The most sensitive noncarcinogenic adverse effects of 1,2-DCA exposure appear to be on the immune system of mice reported by Sherwood et al. (1987). They found that female CD-1 mice exposed to 5-10 ppm of 1,2-DCA for 3 hours exhibited significantly increased mortality from streptococcal challenge, whereas a single 3-hr exposure or five consecutive daily 3-hr exposures to 2.3 ppm 1,2-DCA had no significant effect. Sherwood et al. (1987) noted there could be significant differences in response by different species. Male Sprague-Dawley rats exposed to 200 ppm for 5 hours or 100 ppm 5 hours/day for 12 days did not exhibit any increased susceptibility to infection from these microbes. Whether human susceptibility is closer to mice or rats is unknown. Also, this toxic endpoint may be specific to inhalation exposure; it may not be applicable to exposure by the oral route. Using the data reported by Sherwood et al. (1987), a NOAEL of 2.3 ppm for 3 hours for inhalation exposure is identified.

Daniel et al. (1994) administered 1,2-DCA in corn oil to groups of 10 male and 10 female Sprague-Dawley rats by gavage for 90 consecutive days. The study doses were 37.5, 75, and 150 mg/kg-day. Significant increases in organ weights and changes in hematology were reported in the high dose groups. The 75 mg/kg dose was better tolerated by the animals. However, relative kidney weights were significantly increased in females at this dose level while brain and liver weight ratios were significantly increased in males. Daniel et al. (1994) suggested a NOAEL of 37.5 mg/kg-day, based on the results of this study. NTP (1991) reported 1,2-DCA caused more severe toxic effects in rats exposed by gavage than by drinking water. Sprague-Dawley rats, F344/N rats, and Osborne-Mendel rats exposed to high levels (1,000 ppm) of 1,2-DCA in drinking water for 13 weeks showed little or no compound-related clinical signs with the exception of increases in kidney and liver weights. Female F344/N rats exposed to 1,000 ppm

1,2-DCA in drinking water showed renal lesions and regeneration of renal tubules. This toxic effect was not observed in female rats exposed to 500 ppm. NTP (1991) estimated that for rats exposed to 8,000 ppm 1,2-DCA in the drinking water, the estimated daily intake is about 500-725 mg/kg-day. Using the higher estimate provided, the daily intake of rats exposed to 500 ppm is about 45.3 mg/kg-day. Based on the NTP study (1991), a NOAEL of 45.3 mg/kg-day for the oral route is identified.

Carcinogenic Effects

In 1988, OEHHA developed a cancer potency value of $0.07 \text{ (mg/kg-day)}^{-1}$ for 1,2-DCA, using the NCI (1978) carcinogenicity study results. This cancer potency value is used in both the Toxic Air Contaminant and the Proposition 65 programs. Since that time, studies published by Baertsch et al. (1991) and NTP (1991) showed that 1,2-DCA administered over a short duration but at a high concentration produced more DNA-adducts and greater toxicity than when the compound was administered over a long period of time but at a lower concentration. It was hypothesized that when 1,2-DCA was administered by injection or by gavage at high doses, the normal detoxifying pathway mediated through the cytochrome P-450 enzymes became saturated and some of the administered 1,2-DCA conjugated with glutathione to form metabolites that bind to DNA. In an inhalation study, Cheever et al. (1990) showed that inhalation exposure of rats to 50 ppm of 1,2-DCA did not induce tumors at any site. However, when the rats were exposed to both 50 ppm 1,2-DCA and disulfiram (an inhibitor of cytochrome P-450 enzymes), elevated cancer rates were observed in the liver, skin, testes, bile ducts, and mammary glands. Because of the availability of these new toxicity and carcinogenicity data of 1,2-DCA, OEHHA decided to re-evaluate the carcinogenic potency of 1,2-DCA.

There are three carcinogenicity studies of 1,2-DCA in the literature, they are the gavage study reported by NCI (1978), and the two inhalation studies conducted by Maltoni et al. (1980) and Cheever et al. (1990). The designs and results of the studies have been summarized in the section on the carcinogenicity of 1,2-DCA in animals. Of the three studies, only the NCI study (1978) demonstrated statistically significant dose-related increases of tumor incidence in the exposed animals. The other two long-term bioassays did not show an association between the applied dose and the observed tumor rates. For comparison purposes, the carcinogenic potency of 1,2-DCA was estimated based on each of the three sets of data. This section describes the approaches and methods used in making these estimates. Factors that have to be considered in deciding which set of data is the most appropriate for dose-response evaluation are also discussed.

The gavage study reported by NCI (1978)

As described earlier, the NCI study (1978) is the only long-term bioassay that showed 1,2-DCA induced tumors in rats and mice of both sexes. In addition, for a number of tumor sites, there is a statistically significant positive trend between the observed tumor rates and the applied doses. For the purpose of this dose-response evaluation, cancer potency of 1,2-DCA was estimated based on the most sensitive sites (Table 18). Only one alveolar/bronchiolar carcinoma was reported among the 30 male and female mice in the high-dose group that had alveolar-bronchiolar adenomas. For this reason, data on alveolar-bronchiolar adenomas were not used for dose-response evaluation as they were considered benign tumors.

In the NCI study, the time-weighted average doses were 95 and 47 mg/kg-day for male and female rats, 195 and 97 mg/kg-day for male mice, and 299 and 149 mg/kg-day for female mice.

Doses in this range given in corn oil have been found to be completely absorbed by rats (Reitz et al., 1982). Assuming this is also the case for mice, continuous lifetime average daily dose for rats and mice can be calculated by the following equation:

$$\text{CLADD} = \text{TWAD} \times 5 \text{ days}/7 \text{ days} \times \text{DP}/\text{LS}$$

Where:

CLADD = continuous lifetime average daily dose, mg/kg-day;

TWAD = time-weighted average dose, mg/kg-day;

DP = dosing period, 78 weeks in the NCI study;

LS = estimated life span of the test animal, 104 weeks for rats and 90 weeks for mice.

Table 18. Summary of tumor incidence data of the NCI carcinogenicity study on 1,2-DCA (1978).

Species	Tumor type and location	Continuous lifetime average daily dose (mg/kg-day)	Number of animals alive at the time when the first tumor was identified ⁽¹⁾	Number of animals with tumor
Male rats	Squamous cell carcinoma of forestomach	0	36 ⁽²⁾	0
		25	47 ⁽²⁾	3
		51	28 ⁽²⁾	9
Male rats	Hemangiosarcoma	0	31 ⁽³⁾	0
		25	41 ⁽³⁾	9
		51	21 ⁽³⁾	7
Female rats	Adenocarcinoma of mammary glands	0	40 ⁽⁴⁾	2
		25	46 ⁽⁴⁾	1
		51	42 ⁽⁴⁾	18
Male mice	Hepatocellular carcinoma	0	32 ⁽⁵⁾	3
		60	41 ⁽⁵⁾	6
		121	41 ⁽⁵⁾	12
Female mice	Adenocarcinoma of mammary glands	0	37 ⁽⁶⁾	0
		92	48 ⁽⁶⁾	9
		185	34 ⁽⁶⁾	7

- (1) There were 20 animals in the untreated control group and 20 animals in the vehicle control group. Tumor incidence data of these two groups were combined in this evaluation. At the beginning of the study, there were 50 animals each in the low-dose and high-dose groups.
- (2) Number of male rats alive at week 51, the week when the first stomach tumor was identified.
- (3) Number of male rats alive at week 60, the week when the first hemangiosarcoma was identified.
- (4) Number of female rats alive at week 20, the week when the first adenocarcinoma of the mammary gland was identified.
- (5) Number of male mice alive at week 58, the week when the first hepatocellular carcinoma was identified.
- (6) Number of female mice alive at week 64, the week when the first adenocarcinoma of the mammary gland was identified.

For the purposes of this evaluation, both the benchmark dose approach and the linearized multistage model (LMS) are used for dose extrapolation. Cancer potency estimates of 1,2-DCA derived from the NCI study using these two approaches are summarized in Table 19.

In applying the benchmark dose approach, the 95% lower confidence limit on the dose that gives a 10% excess lifetime individual risk of cancer (the LED₁₀) is used as the end-point. In the LMS modeling, the 95% upper confidence limit on the slope (q₁^{*}) is used as the end-point. Potency values based on the LED₁₀, or the LMS were calculated by using TOX_RISK (Version 3) software (K. S. Crump Division, Clement International Corp., Ruston, LA). All procedures are for estimates of extra risk. For determination of goodness of fit a criterion of p > 0.05 was adopted for the LMS modeling.

One numerical adjustment must be made to convert the q₁^{*} calculated from the animal data to a q₁^{*} relevant to humans. Cross-species scaling of doses by the 3/4 power of body weight proposed by the U.S. EPA (1992), instead of the previous 2/3 (OEHHA, 1994), has been employed here. A surface area scaling factor, the human to animal body weight ratio raised to the 1/4 power, is applied to relate the experimental animal doses to equivalent human doses (U.S. EPA, 1996a, b) instead of the 1/3 power used in our previous calculations (OEHHA, 1993; 1994). That is, (human body weight/animal body weight)^{1/4}, or (70 kg/0.03 kg)^{1/4} for mice and (70 kg/0.35 kg)^{1/4} for rats. Therefore:

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

Table 19. Summary of estimated cancer potency values of 1,2-DCA derived from the NCI (1978) data.

	CSF ⁽¹⁾ (mg/kg-day) ⁻¹	q ₁ [*] (human) (mg/kg-day) ⁻¹	P-value
Male rats, forestomach tumor	2.12E-2	2.15E-2	0.6
Male rats, hemangiosarcoma	4.71E-2	4.96E-2	0.66
Female rats, adenocarcinoma of mammary gland	1.83E-2	1.04E-2	0.02 ⁽²⁾
Male mice, hepatocellular carcinoma	2.06E-2	2.17E-2	0.99
Female mice, adenocarcinoma of mammary gland	1.62E-2	1.70E-2	0.23

(1) CSF, cancer slope factor = 0.1/LED₁₀

(2) Tumor incidence data for the control, low-, and high-dose groups were 2/40, 1/46, and 18/42, respectively.

According to the U.S. EPA's proposed 1996 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996) the preferred approach in dose response assessment is one based on a relevant biologically based model or a case specific model for tumor responses in both the observed range and in the extrapolated range. The default procedure, in the absence of specific models, is to fit the data in the observed range with a curve-fitting model. The choice between a nonlinear

extrapolation, a linear extrapolation, or a combination of linear and nonlinear is based on the information available on the mode of action (MOA) of the agent. When the MOA information is insufficient to support a nonlinear approach, a linear approach is recommended, as the default, method of analysis. A nonlinear approach is used when adequate data on the MOA show that linearity is not the most reasonable judgment and there is sufficient evidence to support a nonlinear MOA, e.g., a clearly nonlinear overall dose response or a sharp reduction in tumor incidence with decreasing dose. In this case the default approach would employ either a margin of exposure (MOE) analysis using an LED₁₀ from tumor data or related biological response data as the point of departure, or, if a specific numerical value is required, the LED₁₀ could be used as a benchmark dose or LOAEL. Factors to be considered in determining the margin for the analysis include: the dose response slope at the LED₁₀; the severity of the effect chosen; extent of human variability; the persistence in the body following exposure; interspecies differences in sensitivity; and distinguishing pharmacodynamic differences from pharmacokinetic factors which may already be included in a human equivalent LED.

It is possible that the high doses and route of administration used in the NCI study might have impacted the metabolism and genotoxicity of 1,2-DCA. At low doses, there is a delicate balance between the generation of reactive metabolites and deactivation of these chemicals. When the oxidative pathway is blocked by drugs such as disulfiram or saturated by high doses of 1,2-DCA, this balance is altered and allowed a larger fraction of the absorbed dose to remain in the systemic circulation and be converted into genotoxic metabolites.

As discussed in the section on genotoxicity, Storer et al. (1985) and White et al. (1983) showed that the glutathione-S-transferase mediated metabolic pathway is probably more important than the microsomal mixed function oxidative pathway in inducing hepatic DNA damage in mice. Cheever et al. (1990) exposed Sprague-Dawley rats to either 50 ppm 1,2-DCA via inhalation or 0.05% disulfiram in diet for two years and reported no significant increase of tumors in both groups. However, when rats were exposed to both 1,2-DCA and disulfiram, a drug that inhibits microsomal mixed function oxidases, they found a significant increase in tumors in both sexes. Furthermore, Cheever et al. showed that blood concentrations of 1,2-DCA in male and female rats exposed to both 1,2-DCA (50 ppm) and disulfiram were about 4 to 5 fold higher than those in rats exposed to 1,2-DCA (50 ppm) only (Table 7). It was postulated that the observed carcinogenicity of 1,2-DCA in Sprague-Dawley rats that were also exposed to disulfiram was related to the inhibitory effect of disulfiram on microsomal mixed function oxidative metabolism. Since microsomal mixed function oxidative metabolism is the main metabolic pathway by which absorbed 1,2-DCA is biotransformed into urinary metabolites, blocking this pathway by disulfiram increases the concentration of 1,2-DCA in blood. This might cause an increased production of reactive metabolites, such as the half-mustard and the episulfonium ion that does not involve the oxidative enzymes. The potential of disulfiram to induce glutathione-S-transferase activities may have also contributed to the observed carcinogenicity.

Baertsch et al. (1991) and Storer et al. (1984) demonstrated that the peak concentration of 1,2-DCA in blood may be critical in determining the extent of bioactivation and genotoxicity of the compound in vivo. Baertsch et al. (1991) demonstrated that a short peak exposure to 1,2-DCA produced much higher DNA binding in liver and lungs than a constant low exposure. Storer et al. (1984) reported that hepatic DNA damage occurred at non-necrogenic doses when 1,2-DCA was administered to B6C3F₁ mice by intraperitoneal injection or by gavage. When exposure to 1,2-DCA was spread out over a period of time, such as by inhalation, no evidence of hepatic

DNA damage was found following 4-hour inhalation exposure of mice to a non-necrogenic (150 ppm) or necrogenic (500 ppm) concentration. Evidence of hepatic DNA damage was observed only when mice were exposed to concentrations of 1,2-DCA causing high mortality within 24 hr (1000 to 2000 ppm). Similarly, NTP (1991) showed that 1,2-DCA is more toxic to F344/N rats when the chemical was administered by gavage compared with that after drinking water exposure.

There is evidence indicating that the microsomal mixed function oxidative pathway is likely to be the major elimination pathway at low doses. Yllner (1971) reported that when mice were injected intraperitoneally with 50 to 100 mg/kg of 1,2-DCA, over 75% of the dose could be recovered from urine within 24 hours. Cheever et al. (1990) demonstrated that when the microsomal mixed function oxidative pathway is blocked by disulfiram, there was a 4 to 5-fold increase in the concentration of 1,2-DCA in the blood. Similar results were reported by White et al. (1983) in their comparative genotoxicity study of tetradeutero-1,2-dibromoethane and 1,2-dibromoethane.

As discussed in the section on excretion, Spreafico et al. (1980) showed that the main metabolic (also the main elimination) pathway of 1,2-DCA can be saturated at high doses. They studied the disappearance of 1,2-DCA in blood and major organs in Sprague-Dawley rats following intravenous injection, gavage treatment, or inhalation exposure (Tables 8, 9, and 10). For all cases, they found that the rate of whole-body excretion of 1,2-DCA was largely determined by the metabolism of 1,2-DCA, a saturable process and a major route of elimination. Based on the data provided in Table 9, it can be estimated that for rats exposed to 1,2-DCA by gavage, saturation of the elimination process occurred at about 25-50 mg/kg. Similarly, based on the information presented in Table 6 (Yllner, 1971) a saturation dose of about 50-100 mg/kg is estimated for mice exposed to 1,2-DCA by intraperitoneal injection.

Table 20 compares the highest actual doses used in the NCI study with the estimated saturation dose for rats and mice. It is believed that the gavage doses used in the NCI study (1978) are either over or very near the respective estimated saturation doses of elimination.

Table 20. Comparison of the highest doses of 1,2-DCA used in the NCI studies (1978) with the estimated saturation doses for rats and mice.

Exposure group	Time-weighted average dosage ⁽¹⁾	Highest actual dose used (mg/kg-day)	Duration of treatment at the highest dose (weeks)	Estimated saturation dose (mg/kg)
Male and female rats, low dose	47	75	10	25-50
Male and female rats, high dose	95	150	10	25-50
Male mice, low dose	97	100	70	50-100
Male mice, high dose	195	150 ⁽²⁾	70	50-100
Female mice, low dose	149	150	67	50-100
Female mice, high dose	299	300 ⁽³⁾	67	50-100

(1) Time-weighted average dosage = $\sum (\text{dosage} \times \text{weeks received}) / 78 \text{ weeks}$.

(2) The highest dose used was 200, but it was applied for only 3 weeks.

(3) The highest dose used was 400, but it was applied for only 3 weeks.

Human exposure to 1,2-DCA in drinking water is expected to be much lower than the levels administered in the NCI study. As discussed in the environmental occurrence and human exposure section, levels of 1,2-DCA as high as 24 µg/L have been detected in samples taken from drinking water sources in California (DHS, 1998). This level of contamination is associated with an estimated daily dose of 0.7 µg/kg or 0.0007 mg/kg, assuming a drinking water consumption rate of 2 L/day and an adult body weight of 70 kg. The estimated daily dose is more than four orders of magnitude lower than the lowest dose (50 mg/kg-day) actually administered in the NCI study (Table 15).

Based on the reasons discussed above, there is a concern that the high doses and gavage administration used in the NCI study (1978) might have altered the metabolism of 1,2-DCA and enhanced its carcinogenic potential.

The inhalation study reported by Maltoni et al. (1980)

Maltoni et al. exposed groups of 90 rats and mice of both sexes to different levels of 1,2-DCA for two years and did not find any increase in tumor rates that was related to the exposure. Maltoni et al. (1980) noted that there was a non-dose-dependent increase in mammary fibromas and fibroadenomas in exposed female rats, when compared with the exposure chamber controls. They suggested that the observed difference in mammary tumor incidence rates may be explained by the relatively low survival of the controls in the exposure chamber.

The survival rate was rather poor among the highly exposed rats. Among the rats exposed to 150 ppm only 11/90 of the males and 21/90 of the females survived until the end of the study (104 weeks). The initial concentration applied to this group was 250 ppm. The inhalation concentration was reduced to 150 ppm after a short period due to the severe toxic effect observed among the test animals. The mortality in rats differed in the different dose groups, but did not show a direct relationship with treatment. More than 50% of the males and females exposed to 5 ppm 1,2-DCA survived until the end of the study. In contrast, only 13.3% and 24.4% of the male and female controls in exposure chambers survived at week 104. Survival among the mice was better; 28.9% of the male and 48.9% of the female mice exposed to 150 ppm of 1,2-DCA survived at week 78. Reporting of histopathological findings in the Maltoni et al. (1980) study is limited by today's standards and further increases the difficulty in the interpretation of the bioassay results.

U.S. EPA (1985) in the "Health Assessment Document for 1,2-Dichloroethane" provided an upper-bound cancer risk estimate of 1,2-DCA based on the Maltoni et al. (1980) data. U.S. EPA selected the male rat data because it was found the most sensitive in the NCI study (1978). The smallest upper-bound estimate was calculated by using the information from the high-dose group (150 ppm) in which 79 male rats survived at 52 weeks. U.S. EPA (1985) calculated that the lifetime average exposure concentration for these rats was 23.44 ppm, equivalent to 96,596 µg/m³. Assuming no "tumor" was observed among the 79 animals, the 95% upper limit of the tumor probability was $R=0.037$, calculated by solving the equation $(1-R)^{79} = 0.05$. By using the one-hit model, $R=1-\exp(-b \times d)$, the slope, b , was calculated as:

$$\begin{aligned} b &= [-\ln(1-R)]/d \\ &= 3.9 \times 10^{-7} / (\mu\text{g}/\text{m}^3) \end{aligned}$$

U.S. EPA (1985) estimated that for male rats, the upper bound estimate of cancer risk due to 1 $\mu\text{g}/\text{m}^3$ of 1,2-DCA in air is 3.9×10^{-7} .

Based on the U.S. EPA (1985) estimate, it is possible to calculate the upper bound cancer potency value of 1,2-DCA. Assuming that the breathing rate of the rat is $0.0108 \text{ m}^3/\text{hr}$, the body weight of the rat is 0.35 kg (Clement, 1991), and 50% of the inhaled 1,2-DCA is absorbed, an upper bound cancer risk of 3.9×10^{-7} is associated with a lifetime average daily dose of 0.00037 mg/kg-day. The cancer potency of 1,2-DCA in the rat can be determined by dividing the cancer risk by the estimated lifetime average daily dose. The upper bound animal cancer potency, q_1^* (animal), is estimated to be $0.00105 \text{ (mg/kg-day)}^{-1}$. Using the equation described previously, q_1^* (human) can be calculated:

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

The upper bound cancer potency of 1,2-DCA for humans, q_1^* (human), is estimated to be $0.0039 \text{ (mg/kg-day)}^{-1}$.

As cancer risk is known to increase exponentially with age and most of the tumors identified in the NCI study (1978) were late occurring, it may be prudent to calculate upper-bound estimates of risk based on the number of survivors at the end of the study. For the purpose of this evaluation, the end of the study is defined as 104 weeks for rats and 90 weeks for mice. Using data provided in the Maltoni et al. study (1980), it is determined that 10 male and 21 female rats exposed to 150 ppm were still alive at week 104. Similarly, the number of male and female mice exposed to 150 ppm that survived week 90 are estimated to be 10 and 15, respectively. Using the same approach as described above, upper-bound estimates of cancer risk for human (q_1^*) based on the rat and mouse data in the Maltoni et al. study (1980) are calculated (Table 21). These estimates are about four to eight times higher than the one calculated by U.S. EPA (1985) based on the Maltoni et al. study (1980).

Table 21. Upper-bound estimates of cancer risk for human (q_1^*) based on the rat and mouse data in the Maltoni et al. study (1980).

Exposure group	Calculated tumor probability, R ⁽¹⁾	Calculated risk due to 1 $\mu\text{g}/\text{m}^3$ of 1,2-DCA, b ⁽²⁾	q_1^* (animal) (mg/kg-day) ⁻¹ ⁽³⁾	q_1^* (human) (mg/kg-day) ⁻¹ ⁽⁴⁾
Male rats exposed to 150 ppm 1,2-DCA	0.2589	3.156E-06	0.00852	0.0321
Female rats exposed to 150 ppm 1,2-DCA	0.1329	1.502E-06	0.00406	0.0153
Male mice exposed to 150 ppm 1,2-DCA	0.2589	2.732E-06	0.00328	0.0228
Female mice exposed to 150 ppm 1,2-DCA	0.181	1.821E-06	0.00219	0.0152

(1) $(1-R)^m = 0.05$; where R is the upper 95% limit of tumor probability, and m is the number of animals alive at the end of the study.

(2) $b = [-\ln(1-R)]/d$; d is the continuous lifetime average exposure concentration. The equation used to calculate d is provided in this section. For rats exposed to 150 ppm 1,2-DCA, 7 hr/day, 5 days/week for 78 weeks, $d = 94,932 \mu\text{g}/\text{m}^3$. For mice exposed to 150 ppm 1,2-DCA, 7 hr/day, 5 days/week for 78 weeks, $d = 109,674 \mu\text{g}/\text{m}^3$.

(3) Absorbed dose = inhalation rate x 24 hr x absorption efficiency (50%) / body weight

(4) q_1^* (human) = q_1^* (animal) x (human body weight/animal body weight)^{1/4}

The NCI study (1978) showed that 1,2-DCA was carcinogenic to mice and rats of both sexes when administered by gavage for two years. By contrast, Maltoni et al. (1980) exposed mice and rats of both sexes to 1,2-DCA by inhalation and did not observe any increase in tumor incidence related to the chemical exposure. Hooper et al. (1980) and U.S. EPA (1985) suggested that there are at least five factors alone or in combination that can explain the discrepancy between the bioassay results reported by Maltoni et al. (1980) and NCI (1978):

- Test animals in the NCI study may have been exposed to other carcinogens
- Dose levels
- Routes of exposure
- Early mortality of test animals in the Maltoni et al. study
- Differences in sensitivity in the strains of rats and mice used

Test animals in the NCI study were exposed to other carcinogens

Some of the test animals in the NCI study (1978) were housed in the same rooms as other mice and rats intubated with other chlorinated hydrocarbons such as dibromochloropropane, trichloroethylene, 1,2-dibromoethane, tetrachloroethylene, carbon disulfide, and carbon

tetrachloride. However, based on the estimated release rate of these contaminants into the air and the air change rate of the room housing the test animals, Hooper et al. (1980) determined that contamination in air is not likely to contribute appreciably to the observed tumor incidence.

Dose levels and routes of exposure used

The pharmacokinetic study results reported by Reitz et al. (1982) and Spreafico et al. (1980) can be used for comparing the dosage employed in the two studies. As shown in Table 22, in terms of AUC the dose received by rats in the high-dose group in the Maltoni et al. study (1980) was about 46-75 % of that used in the high-dose group of the NCI study (1978).

Another way to estimate the relative amount of 1,2-DCA received by the high-dose groups in the Maltoni et al. (1980) and NCI studies (1978) is to make use of a radioactive labeling experiment reported by Reitz et al. (1982). Two groups of Osborne-Mendel rats were exposed to ¹⁴C-labelled 1,2-DCA either by gavage at 150 mg/kg or by inhalation at 150 ppm for 6 hours. Based on the amount of 1,2-DCA necessary to maintain a constant concentration of 1,2-DCA (150 ppm) in the exposure chamber, Reitz et al. (1982) estimated that the dose received by a rat exposed to 150 ppm for 6 hr was approximately 113 mg/kg, or about 75% of the gavage dose of 150 mg/kg. Two days after the exposure, Reitz et al. (1982) reported that the total radioactivity recovered from urine, carcass, and feces of rats in the inhalation group was about 33% of that seen after oral dosing. However, this is probably an underestimate since the daily exposure time in the Maltoni et al. study (1980) was 7 hr instead of 6 hr used by Reitz et al. (1982), and the total radioactivity recovered did not include the amount of 1,2-DCA eliminated unchanged in exhaled air.

Table 22. A summary of the pharmacokinetic study data on 1,2-DCA measured by Reitz et al. (1982) and Spreafico et al. (1980).

Exposure	Rat strain	Peak or plateau blood concentration ($\mu\text{g/L}$)	AUC ($\mu\text{g} \times \text{min} \times \text{mL}^{-1}$)
Inhalation exposure at 150 ppm for 6 hr	Osborne-Mendel rats	8-10	2910 (3395) ⁽¹⁾
Gavage at 150 mg/kg	Osborne-Mendel rats	30-44	4500
Gavage at 150 mg/kg	Sprague-Dawley rats	66.8	7297
Gavage at 50 mg/kg	Sprague-Dawley rats	31.9	1700
Inhalation exposure at 50 ppm for 6 hr	Sprague-Dawley rats	1.4	26 (30) ⁽¹⁾

(1) Assuming AUC is directly proportional to the duration of inhalation exposure, the AUC reported by Reitz et al. (1982) and Spreafico et al. (1980) is adjusted with a factor of 7/6 to account for the longer exposure time (7 hours) used in the Maltoni et al. (1980) and the Cheever et al. (1990) studies.

After exposing male Osborne-Mendel rats to 1,2-DCA either by inhalation (150 ppm for 6 hr) or by gavage at 150 mg/kg, Reitz et al. (1982) observed slightly higher levels of total macromolecular binding in the liver, kidney, spleen, lung, and stomach after inhalation compared to gavage exposure (Table 12). This finding showed that the internal dose received by the test animals after the inhalation exposure was about the same as that after the gavage exposure. However, Reitz et al. (1982) also noted that the levels of DNA bindings among the various organ tissues were significantly higher after gavage versus inhalation exposure (Table 12).

Dosage received by rats in the high-dose group of the Maltoni et al. study (1980) can also be estimated by the following equation:

$$\begin{aligned} \text{Absorbed dose (mg/kg-day)} &= \text{IR} \times \text{ED} \times \text{AE} \times \text{AC} / \text{BW} \\ \text{IR} &= \text{inhalation rate of rats, assumed to be } 0.0108 \text{ m}^3/\text{hr} \text{ (Clement, 1991);} \\ \text{ED} &= \text{daily exposure time, 7 hr/day;} \\ \text{AE} &= \text{absorption efficiency, assumed to be 50 \%;} \\ \text{[Stott et al. (1984) showed that the absorption efficiency of 1,2-dibromoethane in rats is approximately 58\%]} \\ \text{AC} &= \text{concentration of 1,2-DCA in air, 150 ppm or } 607.5 \text{ mg/m}^3\text{;} \\ \text{BW} &= \text{body weight of rats, 0.35 kg (Clement, 1991).} \end{aligned}$$

The inhalation dose received by rats exposed to 150 ppm 1,2-DCA for 7 hr/day is estimated to be approximately 66 mg/kg-day. Results of all four approaches described indicate the total 1,2-DCA dose received by rats in the high-dose group of the Maltoni et al. study (1980) is approximately 33-75% of that received by rats in the high-dose group of the NCI study (1978).

Thus it could be concluded that the 1,2-DCA doses administered to rats in the Maltoni et al. (1980) and NCI studies (1978) are roughly comparable. However, it is important to note that route of administration has a profound effect on the peak blood concentration (Table 22). While the total dose (AUC) received by an Osborne-Mendel rat resulting from exposure to 150 ppm of 1,2-DCA for 7 hr was about 75% of that resulting from a gavage treatment at 150 mg/kg, the steady-state or plateau blood concentration resulting from the inhalation exposure was 3-5.5 times lower than the peak blood levels measured after oral administration. The high blood and tissue concentrations of 1,2-DCA achieved by gavage administration of 150 mg/kg could either saturate the detoxifying mechanism or increase the fraction of dose biotransformed by the pathway mediated by glutathione-S-transferase.

Although detailed pharmacokinetic data of 1,2-DCA in mice are not available, the following equation can be used to calculate the amount of 1,2-DCA absorbed by mice in the high-dose group of the Maltoni et al. study (1980):

Absorbed dose (mg/kg-day)	=	IR x ED x AE x AC / BW
IR (Clement, 1991);	=	inhalation rate of mice, assumed to be 0.00208 m ³ /hr
ED	=	daily exposure time, 7 hr/day;
AE	=	absorption efficiency, assumed to be 50 %;
AC	=	concentration of 1,2-DCA in air, 150 ppm or 607.5 mg/m ³ ;
BW	=	body weight of mice, 0.03 kg (Clement, 1991).

The dose absorbed by mice exposed to 150 ppm 1,2-DCA for 7 hr/day is estimated to be approximately 147 mg/kg-day. This value is slightly lower than the gavage dose received by male mice (150 and 200 mg/kg-day) in the high-dose groups of the NCI study (1978) (Table 16).

Early mortality of test animals in the Maltoni et al. study

A major problem with the bioassay results reported by Maltoni et al. (1980) is the early and high mortality rates in the high-dosed rats and male mice. It could be argued that because of the early mortality, an insufficient number of animals survived long enough for tumors to develop. While early mortality was observed in both studies, it is possible to show that at least one group of test animals in the Maltoni et al. study (1980) should have survived long enough to manifest tumors. The survival and tumor rates of the high-dose group in the Maltoni et al. study (1980) were compared with those of the low-dose group in the NCI study as it is estimated that the daily doses of 1,2-DCA absorbed by the two groups were approximately the same. In the NCI study (1978), 37 male rats survived at week 72, the week when the first hemangiosarcoma was identified in the low-dose group. A total of eight male rats developed hemangiosarcomas between week 72 and week 104. From the survival curve of male rats in the Maltoni et al. study (1980), it was estimated that approximately 27 of the high-dose (150 ppm) male rats were alive at week 72. Ten male rats survived until the end of the study (104 weeks) and none of the 27 test animals developed hemangiosarcoma. Assuming the absorbed dose is the only factor that determines tumor response, the probability of not seeing any hemangiosarcomas in the high-dose males (150 ppm) of the Maltoni et al. study (1980) is very small $\{p = [(37-8)/37]^{27} = 0.0014\}$.

U.S. EPA (1985) performed a similar analysis comparing the bioassay results reported by NCI (1978) and Maltoni et al. (1980). They concluded that the high-dose group (150 ppm) in the Maltoni et al. study (1980) should be at least as responsive as the NCI low-dose group (47 mg/kg-day) of rats in which 19% (9/48) of the male rats developed hemangiosarcomas. Using slightly different assumptions, U.S. EPA (1985) estimated that the probability of seeing 19% incidence of hemangiosarcomas in one study and none in another was very small ($p < 0.0001$) if the total dose available to animals was the only factor that determined the tumor response.

Difference in sensitivity in the strains of rats and mice used

The discrepant results obtained in the NCI study (1978) and the Maltoni et al. study (1980) may be explained by the fact that different strains of test animals were used in the two studies. NCI (1978) used Osborne-Mendel rats and B6C3F₁ mice while Maltoni et al. (1980) used Sprague-Dawley rats and Swiss mice. Hooper et al. (1980) compared the responsiveness of the test animals used in the two studies to various halogenated hydrocarbons. They reported that the B6C3F₁ mouse is responsive to aldrin, chlordane, heptachlor, DDE, kepone, chloroform, carbon tetrachloride, hexachloroethane, tetrachloroethane, perchloroethylene, and trichloroethane by the oral route. The Swiss mouse is responsive to vinyl chloride and 1,1-dichloroethene by inhalation. The Osborne-Mendel rat is responsive to chloroform, chlordane, and kepone by the oral route but not to the other chlorinated compounds listed above. The Sprague-Dawley rat is responsive to vinyl chloride by inhalation but not to 1,1-dichloroethene.

Maltoni et al. (1980) did not observe any increase in tumor incidence following exposure of Sprague-Dawley rats to 1,2-DCA via inhalation. Cheever et al. (1990) exposed Sprague-Dawley rats to disulfiram in diet and 1,2-DCA via inhalation and found a significant increase in intrahepatic bile duct cholangiomas in both male and female rats. Male rats exposed to both chemicals had an increased incidence of subcutaneous fibromas, neoplastic nodules of the liver, and interstitial cell tumors of the testes. The female rats also had a higher incidence of mammary adenocarcinomas. Thus, Cheever et al. (1990) demonstrated that under certain conditions, 1,2-DCA could and did induce tumors in Sprague-Dawley rats of both sexes.

The section on excretion describes the pharmacokinetics and excretion kinetics of 1,2-DCA in Osborne-Mendel and Sprague-Dawley rats and showed that they are not the same. As shown in Table 22, peak blood levels and AUCs measured in the two strains of rats after gavage administration of 150 mg/kg were significantly different. The blood levels measured in the Sprague-Dawley rats were almost twice as large as those detected in Osborne-Mendel rats.

In conclusion, route of exposure and strain differences, either alone or in combination are the two most likely reasons that can explain the discrepant carcinogenicity results reported by NCI (1978) and Maltoni et al. (1980).

The inhalation study reported by Cheever et al. (1990)

Cheever et al. exposed groups of 50 Sprague-Dawley rats of both sexes to 50 ppm of 1,2-DCA, 7 hr/day, 5 days/week for two years and did not find any increase in tumor rates related to the exposure. Unlike the other two studies, the survival of the test animals in this study was relatively good. It was reported that 26 male rats (52%) and 27 female rats (54%) in the control groups survived 104 weeks. Similar survival rates were observed in the group exposed to 1,2-DCA; 26 male rats (52%) and 32 female rats (64%) were still alive at the end of the two-year inhalation experiment (MRI, 1985).

Using the approach⁵ described by U.S. EPA (1985) in analyzing the negative results of the Maltoni et al. study (1980), the upper 95% limits of tumor probability, R, for male and female rats were 0.109 and 0.0894, respectively. The test animals were exposed to 50 ppm 1,2-DCA. The lifetime continuous average exposure concentration (d) was calculated to be:

$$\begin{aligned} d &= 50 \text{ ppm} \times 7 \text{ hr}/24 \text{ hr} \times 5 \text{ days}/7 \text{ days} \times 104 \text{ weeks}/104 \text{ weeks} \\ &= 10.42 \text{ ppm} \times 4.05 \times 1000 \\ &= 42,201 \text{ } \mu\text{g}/\text{m}^3 \end{aligned}$$

By using the one-hit model, $R=1-\exp(-b \times d)$, the slope, b, was calculated. The upper bound estimates of risk due to $1 \text{ } \mu\text{g}/\text{m}^3$ (b) calculated for male and female rats are $2.729\text{E}-6$ and $2.219\text{E}-6$, respectively. The daily dose equivalent to a lifetime continuous average exposure of $1 \text{ } \mu\text{g}/\text{m}^3$ can be calculated by the following equation:

$$\begin{aligned} \text{Absorbed dose (mg/kg-day)} &= \text{IR} \times \text{ED} \times \text{AE} \times \text{AC} / \text{BW} \\ \text{IR} &= \text{inhalation rate of rats, assumed to be } 0.0108 \text{ m}^3/\text{hr} \text{ (Clement, 1991);} \\ \text{ED} &= \text{daily exposure time, 24 hr/day;} \\ \text{AE} &= \text{absorption efficiency, assumed to be 50\%;} \\ \text{AC} &= \text{concentration of 1,2-DCA in air, } 0.001 \text{ mg}/\text{m}^3; \\ \text{BW} &= \text{body weight of rats, 0.35 kg (Clement, 1991).} \end{aligned}$$

Using this method, a lifetime average daily dose of $0.00037 \text{ mg}/\text{kg-day}$ is estimated to be associated with upper bound estimates of risk of $2.729\text{E}-6$ and $2.219\text{E}-6$ for male and female rats, respectively. The cancer potency of 1,2-DCA in the rat can be determined by dividing the cancer risk by the estimated lifetime average daily dose. Upper bound animal cancer potencies, q_1^* (animal), estimated for male and female rats are 0.00737 and $0.00599 \text{ (mg}/\text{kg-day})^{-1}$, respectively. Using the equation described below, q_1^* (human) can be calculated:

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

The two upper bound cancer potency estimates of 1,2-DCA for humans, q_1^* (human), derived from the Cheever et al. (1990) study are 0.0277 and $0.0225 \text{ (mg}/\text{kg-day})^{-1}$.

⁵ $(1-R)^m = 0.05$, where m is the number of animals at risk.

m = 26 for male rats and 32 for female rats.

Blood levels measured in animals exposed to 50 ppm for 7 hr are significantly lower than those measured in animals exposed to 50 mg/kg-day via gavage administration. As listed in Table 22, the AUC and plateau concentrations resulting from inhalation exposure are about 57 and 23 fold lower, respectively, than those resulting from gavage treatment. Nevertheless, when the rats in the Cheever et al. study (1990) were exposed to both 1,2-DCA and disulfiram for two years, the combination proved to be carcinogenic to both male and female rats. Since the disulfiram treatment was shown to increase the concentration of 1,2-DCA levels in blood by a factor of five (Table 7), this effect alone may not be able to explain the observed carcinogenicity. It is postulated that disulfiram might have induced other enzymes, such as glutathione-S-transferase, that potentiated the carcinogenic effect of 1,2-DCA.

Cancer potency estimates developed in this analysis using the bioassay data published by NCI (1978), Maltoni et al. (1980) and Cheever et al. (1990) are summarized in Table 23.

Table 23. Estimates of the carcinogenicity potency of 1,2-DCA, expressed in units (mg/kg-day)⁻¹

Study	Tumor type	q ₁ * (human) multistage model	CSF ⁽¹⁾	q ₁ * (human) one-hit model
NCI (1978)	Male rats, forestomach tumor	2.2E-2	2.1E-2	--
	Male rats, hemangiosarcoma	5.0E-2	4.7E-2	--
	Female rats, adenocarcinoma of mammary gland	1.0E-2	1.8E-2	--
	Male mice, hepatocellular carcinoma	2.2E-2	2.1E-2	--
	Female mice, adenocarcinoma of mammary gland	1.7E-2	1.6E-2	--
Maltoni et al. (1980)	Negative study of male rats exposed to 150 ppm	--	--	3.2E-2
	Negative study of female rats exposed to 150 ppm	--	--	1.5E-2
	Negative study of male mice exposed to 150 ppm	--	--	2.3E-2
	Negative study of female mice exposed to 150 ppm	--	--	1.5E-2
Cheever et al. (1990)	Negative study of male rats exposed to 50 ppm	--	--	2.8E-2
	Negative study of female rats exposed to 50 ppm	--	--	2.3E-2

(1) CSF = 0.1/LED₁₀

While none of the three studies available is ideal for dose-response assessment of the carcinogenicity potential of 1,2-DCA, cancer potency estimates derived from these studies are not very different from each other. They range from 1.0E-2 to 5.0E-2 (mg/kg-day)⁻¹(Table 23). A potency value of 0.047 (mg/kg-day)⁻¹ was derived from the incidence rate of hemangiosarcomas in male rats reported by NCI (1978). This value was chosen because it is based on the most sensitive species and the most sensitive tumor site.

CALCULATION OF PHG

Calculations of concentrations of chemical contaminants in drinking water associated with negligible risks as carcinogens or noncarcinogens must take into account the toxicity of the chemical itself, as well as the potential exposure of individuals using the water. Tap water is used directly as drinking water, and for preparing foods and beverages. It is also used for bathing or showering, and in washing, flushing toilets and other household uses resulting in potential dermal and inhalation exposures.

Noncarcinogenic Effects

Based on the NTP sub-chronic drinking water study (1991) in which renal lesions were observed in female rats, a NOAEL of 45.3 mg/kg-day was selected for the calculation of a PHG for noncarcinogenic effects. Calculation of a public health-protective concentration (C, in mg/L) for 1,2-DCA in drinking water for noncarcinogenic endpoints follows the general equation:

$$\begin{aligned}
 C &= \frac{\text{NOAEL/LOAEL} \times \text{BW} \times \text{RSC}}{\text{UF} \times \text{Leqs/day}} \\
 &= \frac{45.3 \text{ mg/kg-day} \times 70 \text{ kg} \times 0.6}{1,000 \times 4 \text{ L/day}} \\
 &= 0.48 \text{ mg/L or } 480 \text{ } \mu\text{g/L (480 ppb)}
 \end{aligned}$$

where:

NOAEL	=	No-observed-adverse-effect-level, mg/kg-day;
BW	=	Adult body weight, a default of 70 kg for adults;
RSC	=	Relative source contribution (a default of 20% to 80%); 60% is used as 1,2-DCA is a volatile chemical and is not usually found in soil or food products;
UF	=	Uncertainty factor of 1,000 (defaults of a 10 to account for inter-species extrapolation, a 10 for uncertainty in extrapolating from a subchronic study, and a 10 for potentially sensitive human subpopulations);
Leqs/day	=	Adult daily water consumption rate, a default of 2 L/day. As 1,2-DCA is a volatile chemical and is likely to be volatilized into the air during bathing and showering, an addition exposure equivalent of 2 L/day is included to account for this route of exposure.

For PHGs, our use of the RSC has, with a few exceptions, followed U.S. EPA drinking water risk assessment methodology. U.S. EPA has treated carcinogens differently from noncarcinogens with respect to the use of RSCs. For noncarcinogens, RfDs (in mg/kg-day), drinking water equivalent levels (DWELs, in mg/L) and MCLGs (in mg/L) are calculated using uncertainty factors (UFs), body weights and water consumption rates (L/day) and the RSC, respectively. The RSC range is 20% to 80% (0.2 to 0.8) depending on the scientific evidence.

Thus the health protective concentration for 1,2-DCA based on noncarcinogenic effects would be 480 µg/L.

Carcinogenic Effects

The data sets and methods that can be used for estimating the carcinogenic potency of 1,2-DCA are described in the section on dose-response evaluation. The cancer potency estimate developed is 0.047 (mg/kg-day)⁻¹.

For carcinogens, the following general equation can be used to calculate the public health-protective concentration (C) for 1,2-DCA in drinking water (in mg/L):

$$\begin{aligned}
 C &= \frac{BW \times R}{q_1^* \text{ or CSF} \times L/\text{day}} \\
 &= \frac{70 \times 10^{-6}}{0.047 \times 4} \\
 &= 0.0004 \text{ mg/L or } 0.4 \text{ } \mu\text{g/L (0.4 ppb)}
 \end{aligned}$$

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);
- q₁^{*} or CSF = Cancer slope factor, CSF or q₁^{*}, which is the upper 95% confidence limit on the cancer potency slope. Both potency estimates are converted to human equivalent [in (mg/kg-day)⁻¹] using BW^{3/4} scaling. A cancer potency value of 0.047 (mg/kg-day)⁻¹ is used here.
- L/day = Adult daily water consumption rate, a default of 2 L/day. As 1,2-DCA is a volatile chemical and is likely to be volatilized into the air during bathing and showering, an addition exposure equivalent of 2 L/day is included to account for this route of exposure.

For approaches that use low-dose extrapolation based on quantitative cancer risk assessment, U.S. EPA does not factor in an RSC. The use of low-dose extrapolation is considered by U.S. EPA to be adequately health-protective without the additional source contributions. In

developing PHGs, we have adopted the assumption that RSCs should not be factored in for carcinogens grouped in U.S. EPA categories A and B, and for C carcinogens for which we have calculated a cancer potency based on low-dose extrapolation.

Thus the PHG for 1,2-DCA based on carcinogenic effects is 0.4 $\mu\text{g/L}$ (0.4 ppb).

RISK CHARACTERIZATION

1,2-DCA has been identified by U.S. EPA as a probable human carcinogen (B2) and it is listed under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65) as a chemical known to the state to cause cancer.

There are three carcinogenicity studies of 1,2-DCA in the literature, they are the gavage study reported by NCI (1978) and the inhalation studies reported by Maltoni et al. (1980) and Cheever et al. (1990). Of the three studies, only the NCI study showed a statistically significant increase of tumor incidences in the exposed rats and mice. The other two long-term inhalation studies did not show an association between tumor incidence and 1,2-DCA exposure in rats and mice of both sexes. In a one-year bioassay, Klaunig et al. (1986) exposed male mice to 1,2-DCA in drinking water and reported no increase in tumor incidences.

In 1988, OEHHA developed cancer potency values with a range of 0.014 to 0.088 $(\text{mg/kg-day})^{-1}$ for 1,2-DCA, using the NCI (1978) carcinogenicity study results. Since that time, studies published by Baertsch et al. (1991) and NTP (1991) showed that 1,2-DCA administered over a short duration but at a high concentration produced more DNA-adducts and greater toxicity than when the compound was administered over a long period of time but at a lower concentration. In an inhalation study, Cheever et al. (1990) showed that inhalation exposure of rats to 50 ppm of 1,2-DCA did not induce tumors at any site. However, when the rats were exposed to both 50 ppm 1,2-DCA and disulfiram (an inhibitor of cytochrome P-450 enzymes), elevated cancer rates were observed in the liver, skin, testes, bile ducts, and mammary glands. It is possible that when 1,2-DCA was administered by injection or by gavage at high doses, the normal detoxifying pathway mediated through the cytochrome P-450 enzymes became saturated and consequently enhanced the carcinogenic potency of 1,2-DCA.

Based on the recently available toxicity information and the pharmacokinetic, metabolic and toxicity studies of 1,2-DCA published earlier there are reasons to believe that the high doses and the gavage administration used in the NCI studies (1978) might have augmented the carcinogenic potential of 1,2-DCA. For this reason, cancer potency values were also derived from the Maltoni et al. (1980) and Cheever et al. (1990) studies. However, the cancer potency values of 1,2-DCA derived from the two negative studies are within the range of values based on the NCI (1978) studies. Therefore, the values derived from the Maltoni et al. (1980) and Cheever et al. (1990) studies support the use of cancer potency values derived from the NCI (1978) studies. A cancer potency value of 0.047 $(\text{mg/kg-day})^{-1}$ was thus developed based on the incidence data of hemangiosarcomas in male rats. The PHG was calculated assuming a de minimis theoretical excess individual cancer risk level of 10^{-6} from exposure to 1,2-DCA. Based on the evaluation described in this document, OEHHA developed a PHG of 0.0004 mg/L (0.4 ppb) for 1,2-DCA in drinking water.

There are a number of uncertainties associated with the development of a PHG for 1,2-DCA:

- selection of the most appropriate bioassay data set available,
- estimation of human exposure, and
- due to genetic variation or exposure to other chemicals, some people may be more susceptible to the carcinogenic hazards posed by 1,2-DCA.

As discussed earlier, the cancer potency of 1,2-DCA was developed using the cancer bioassay data reported by NCI (1978). If bioassay information provided by Cheever et al. (1990) and Maltoni et al. (1980) were used in the dose-response evaluation, cancer potency values ranging from 0.015 to 0.032 (mg/kg-day)⁻¹ could have been estimated.

In the calculation of the PHG for 1,2-DCA, it was assumed that the drinking water consumption rate of an adult is 2 L/day. Furthermore, since 1,2-DCA is a volatile chemical and can be volatilized into the air during bathing and showering, an additional exposure equivalent of 2 L/day was included in the exposure assessment to account for this route of exposure. Depending on a number of factors related to the usage of water contaminated with 1,2-DCA, assuming a total consumption of 4 equivalent L/day could either over- or underestimate human exposure. For example, if drinking water is boiled before consumption, the dose received via the oral route could be less than the one calculated. However, the 1,2-DCA volatilized from the boiling water would be present in the indoor air and human exposure could occur through inhalation.

The study results published by Cheever et al. (1990) suggest that people who have low or impaired microsomal oxidative enzyme activities (e.g., people who takes disulfiram, a drug that inhibits the microsomal oxidative enzymes) may be more susceptible to the carcinogenic hazard posed by 1,2-DCA exposure than the general population. Cheever et al. (1990) showed that rats exposed to 50 ppm 1,2-DCA in air for two years did not exhibit any increase in cancer incidence. In contrast, there was a high incidence of hepatic, testicular, and mammary tumors in rats chronically exposed to both 50 ppm 1,2-DCA in air and 0.05% disulfiram in diet.

OTHER REGULATORY STANDARDS

U.S. EPA promulgated an MCLG of zero and an MCL of 5 ppb (5 µg/L) for 1,2-DCA (U.S. EPA, 1998). The California DHS adopted a MCL for 1,2-DCA of 0.5 µg/L [California Code of Regulations (CCR) Title 22 for organic chemicals Section 64444]. The Occupational Safety and Health Administration has set a time-weighted average level of 1 ppm and a short-term exposure limit of 2 ppm for 1,2-DCA (ATSDR, 1994). Arizona, Massachusetts, and Minnesota promulgated drinking water quality standards of 5 µg/L. While Florida, New Jersey, and Connecticut have established drinking water standards of 3, 2, and 1 µg/L, respectively (ATSDR, 1994).

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