Public Health Goal for 1,1-Dichloroethylene In Drinking Water

Prepared by

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PREFACE

Drinking Water Public Health Goals

Pesticide and Environmental Toxicology Section

Office of Environmental Health Hazard Assessment

California Environmental Protection Agency

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

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365) 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 1,1-DICHLOROETHYLENE IN DRINKING WATER

SUMMARY

The Office of Environmental Health Hazard Assessment (OEHHA) has developed a Public Health Goal (PHG) of 0.01 mg/L (10 µg/L, or 10 ppb) for 1,1-dichloroethylene (DCE, 1,1-DCE; also known as vinylidene chloride) in drinking water. The PHG is based on the most sensitive toxic endpoint, midzonal hepatocellular fatty changes in female rats (Quast et al., 1983). Rats were exposed to 0, 50, 100, or 200 ppm DCE in their drinking water over a period of two years. Midzonal fatty changes were observed in females at all exposure levels. Accordingly, the LOAEL for this study and endpoint is 50 ppm. Based on water consumption, the authors estimated the time-weighted average dose for females exposed to 50 ppm DCE in drinking water to be 9 mg/kg-day. The PHG calculation assumes an adult body weight of 70 kg, a relative source contribution of 20%, a drinking water consumption of 4 Leq/day, and applies an uncertainty factor of 3,000. In only 1 of 18 oncogenicity studies is there suggestive evidence that DCE may be a carcinogen (Maltoni et al., 1984, 1977). Accordingly, the evidence is not compelling enough to justify the derivation of the PHG based on a quantitative estimate of the chemical's carcinogenic potency.

INTRODUCTION

The purpose of this document is to develop a Public Health Goal (PHG) for DCE in drinking water. Primarily data used in our earlier risk assessments was evaluated for the purpose of developing the PHG for DCE. Where appropriate, particularly in the area of metabolism, new information was utilized in the preparation of this document. No new information regarding the toxicity of DCE in experimental animals or in humans was found since the derivation of the current California Maximum Contaminant Level (MCL) (DHS, 1988).

A MCL of 0.006 mg/L (6 ppb) was established by the California Department of Health Services (DHS) in 1988 (DHS, 1988). The U.S. Environmental Protection Agency (U.S. EPA) has set a slightly higher federal MCL and Maximum Contaminant Level Goal (MCLG) of 0.007 mg/L for DCE. Although both agencies use the same study (Quast et al., 1983) and same endpoint (hepatic midzonal fatty changes), U.S. EPA based the response in male rats while OEHHA (formerly in DHS) based the response in females. The difference in dose to the test animals (10 mg/kg-day in males; 9 mg/kg-day in females) accounts for the difference in the state versus federal MCL.

DCE is not listed under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65), as a chemical known to the state to cause cancer or reproductive toxicity. The International Agency for Research on Cancer (IARC) has classified DCE as a Group 3 chemical, "not classifiable as to its carcinogenicity to humans" (IARC, 1987). U.S. EPA has classified DCE as a "Class C" chemical, a "possible human carcinogen" (U.S. EPA, 1998a).

CHEMICAL PROFILE

Chemical Identity

DCE is a simple, unsaturated halogenated hydrocarbon. The chemical formula, synonyms, and CAS number are listed in Table 1 and are adapted from ATSDR's toxicological profile of the chemical (ATSDR, 1994).

Physical and Chemical Properties

DCE, a liquid at room temperature, is very soluble in organic solvents and is also highly volatile. Other important physical and chemical properties of DCE are given in Table 2.

Production and Uses

DCE does not occur naturally, however, it can be found in landfills as a result of the breakdown of polyvinylidene chloride products (U.S. EPA, 1985b). It is produced commercially by the dehydrochlorination of 1,1,2-trichloroethane in the presence of excess base. The commercial grade material typically contains 99.8% DCE. Estimated United States production of DCE in 1989 was 230 million pounds (CMA, 1989).

DCE is used principally for the production of polyvinylidene chloride polymers (PVDC). PVDC is used principally in the food packaging industry as cast and extruded fill (Saran and Velon wraps) and as a barrier coating for paper, cellulose, polypropylene, and other plastics. Extruded filaments of PVDC are also used in the textile industry for furniture and automobile upholstery, drapery fabric and outdoor furniture (Environment Canada, 1994).

Table 1. Chemical Identity of 1,1-dichloroethylene

Chemical name	1,1-dichloroethylene
Synonyms	DCE, 1,1-dichloroethene, 1,1-DCE, vinylidene chloride, VDC, vinylidene dichloride
Chemical formula	$C_2H_2Cl_2$
Chemical structure	$Cl_2C=CH_2$
CAS Registry number	75-35-4

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

Property	Value or Information	References
Molecular weight	96.95	Budavari, 1989
Color	colorless	Grayson, 1985
Physical state	liquid	Budavari, 1989
Odor	mild, sweet odor resembling chloroform	Budavari, 1989
Odor threshold	500 ppm	Torkelson and Rowe, 1981
Melting point	-122.5 ^{o}C	Budavari, 1989
Boiling point	31.7 ^{o}C @ 760 mmHg	Budavari, 1989
Flash point	-16 ^{o}C (open cup); -10 ^{o}C (closed cup)	U.S. EPA, 1985a
Flammability limits	7.3-16%	Weiss, 1986
Autoignition temperature	570.0 ^{o}C	HSDB, 1997
Solubility		
Water	2.5 g/L @ 25 ^{o}C	HSDB, 1997
Organic solvents	soluble in organic solvents	Budavari, 1989
Density	1.213 g/cm^3 @ 20 ^{o}C	Budavari, 1989
Partition coefficients		
Log K_{ow}	1.32	HSDB, 1997
Log K_{oc}	1.81	U.S. EPA, 1982
Vapor pressure	500 mmHg @ 20^{o}C; 591 mmHg @ 25^{o}C	Verschueren, 1983; Torkelson and Rowe, 1981
Henry's law constant	0.19 atm-m^3 / mol @ 20 - 25^{o}C	Pankow and Rosen, 1988
Conversion factors	1 ppm = 3.97 mg/m^3 1 mg/m^3 = 0.25 ppm	Verschueren, 1983

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Air

Owing to its low vapor pressure, air releases of DCE are the largest sources of the chemical in the environment (ATSDR, 1994). It is estimated that approximately the same amount of DCE is released into the atmosphere during its manufacture as during its use. At one point, it was estimated that as much as 2 - 5% of the manufactured DCE is released into the air (Singh et al., 1981). Very small amounts of the material are released during the incineration of polymerized products.

More recent estimates of the amount of DCE released into the air are approximately 650 tons/year, which was approximately 0.8% of the 1985 production (U.S. EPA, 1985a). Estimates of release by the Chemical Manufacturers Association are in the neighborhood of 100 tons DCE/year (CMA, 1989). In any event, discharges to air account for greater than 99% of the total environmental releases (TRI91, 1993). The half-life for DCE in air is estimated to be approximately 2 - 3 days (U.S. EPA, 1980; Tuazon et al., 1988).

Air concentrations of DCE range from ambient levels of 0.005 to 0.84 ppb to concentrations as high as 97 ppb which was measured at a hazardous waste site known to contain DCE (Harkov et al., 1985; LaRegina et al., 1986). Quantitative information regarding the air concentrations of DCE at hazardous waste sites on the National Priority List (NPL) is not available.

Soil

Limited information is available regarding the releases of DCE to soil. It is estimated that approximately 180 lbs/year DCE are disposed of annually in municipal landfills as residual monomer in various plastic products (Neufeld et al., 1977).

Approximately 15 lbs of DCE was released to the soil from manufacturing and processing facilities in 1991, according to the Toxic Release Inventory (TRI) (TRI91, 1993). Note that this is probably an underestimate, as only certain types of facilities are required to report releases.

DCE deposited on or near the soil surface is expected to rapidly volatilize into the air. Soil mobility of DCE is quite high, as the chemical migrates through soil without any significant retardation by adsorption to organic carbon (U.S. EPA, 1982). Accordingly, DCE deposited on or into the soil may end up in groundwater. Because DCE in soil tends to partition into either the air or groundwater, ambient soil concentrations of the chemical are expected to be low.

Water

According to the TRI, approximately 832 pounds of DCE were released to water from manufacturing and processing facilities in 1991 (TRI91, 1993). The chemical has been

measured in raw wastewater from these facilities at mean concentrations of 3 - 760 µg/ml (U.S.EPA, 1981). This data should be used with caution, as only certain types of facilities are required to report. Additional sources of DCE to water, particularly groundwater, are hazardous waste sites at which DCE has been improperly disposed. No quantitative information is available regarding this potential source of contamination.

Concentrations of 1 to 550 µg/ml DCE have been reported in surface waters near industrial sites (Going and Spigarelli, 1977). DCE is infrequently detected in surface waters; there were no detections of the chemical in a 105-city survey of raw surface water (ATSDR, 1994). According to U.S. EPA data (Staples et al., 1985), only approximately 6% of 8,714 surface water samples nationwide contained detectable amounts of DCE. Urban runoff has been reported to contain DCE at concentrations of 1.5 - 4 µg/L in positive samples, which represented approximately 3% of all samples collected (Cole et al., 1984).

In an U.S. EPA survey (U.S. EPA, 1985a), approximately 3% of the drinking water supplies in the US were found to contain DCE, with concentrations ranging from 0.2 - 0.5 µg/L (estimated mean of 0.3 µg/L). DCE was also found in 2.3% (quantification limit of 0.2 ppb) of 945 finished drinking water samples from groundwater sources in a nationwide survey (Rajagopal and Li, 1991; Westrick et al., 1984). In another survey of drinking water wells (part of the 1982 ground water supply survey), DCE was detected in 9 of 466 wells at a median concentration of 0.3 µg/L (Cotruvo, 1985). In California, a survey of 11,696 public drinking water supplies conducted between 1984 and 1992 found 14 supplies which exceeded the federal MCL of 7 ppb (Storm, 1994). One hundred twenty (120) supplies were found to contain DCE at levels ranging from a low of 0.1 ppb to a high of 99 ppb. The mean concentration of positive samples was 2.5 ppb.

Food

Although little information is available concerning concentrations of DCE in food, there is widespread use of DCE-containing polymers in food wraps (e.g. Saran™ Wrap). Concentrations of residual DCE in household films used for food packaging have been reported to be 6.5 to 10.4 ppm (Birkel et al., 1977). Concentrations of DCE in foodstuffs wrapped with commercial films containing DCE residues that averaged 8.8 ppm ranged from <0.005 to 0.01 ppm (Gilbert et al., 1980).

METABOLISM AND PHARMACOKINETICS

Absorption

DCE is well absorbed following inhalation and oral exposures. The low molecular weight and hydrophobic nature of the chemical suggest that dermal absorption is likely, although no specific studies of DCE absorption by this route of exposure were identified in the literature.

Following inhalation exposure, DCE is rapidly absorbed as substantial levels of parent compound were found in the venous blood of rats 2 minutes after the onset of exposure (Dallas et al., 1983, McKenna et al., 1978a). Absorption via the inhalation route is dose and time dependent; the percentage absorbed decreased with respect to duration of exposure until equilibrium (approximately 80% uptake) was reached in approximately one hour. The cumulative uptake of DCE following inhalation exposure was linear for levels of 150 ppm or less; at 300 ppm, a steady-state was never achieved indicating that absorption is saturable at high levels of exposure (Dallas et al., 1983).

Almost complete absorption of DCE at doses of 0.5 to 350 mg/kg occurs in rats following oral (gavage) exposures with corn oil as a vehicle (Jones and Hathway, 1978a,b; Putcha et al., 1976). The degree of absorption (at 200 mg/kg) was unaffected by vehicle, as the dose was completely absorbed if given in Tween 80, corn oil or mineral oil (Chieco et al., 1981). These authors found that the rate of DCE absorption was dependent on the vehicle, with the rate of absorption decreasing according to vehicle in the following order: Tween 80 > corn oil > mineral oil.

Distribution

Radioactivity is rapidly distributed to all tissues of the rat and mouse following either oral or inhalation exposure to radiolabeled DCE (Jones and Hathway, 1978a; McKenna et al., 1978a). The highest levels of radioactivity were found at 72 hours in the liver and kidneys of animals exposed orally. Peak levels were found in the livers and kidneys of animals at two hours following inhalation exposure. Livers, kidney and lungs of fasted rats had consistently higher levels of radioactivity than non-fasted rats when exposed at either 10 or 200 ppm (McKenna et al., 1978a). These same authors found that although a higher tissue burden of DCE was found in fasted rats in these target tissues, overall accumulation of radioactivity was less in fasted rats.

Metabolism

Biotransformation of DCE involves oxidation via the cytochrome P-450 system and subsequent detoxification by conjugation with glutathione and cellular macromolecules. The oxidative pathway is saturated at relatively low doses, irrespective of route of administration (Andersen and Jenkins, 1977; D'Souza and Andersen, 1988, Dallas et al., 1983).

DCE is oxidized by the rat and mouse liver cytochrome P-450 system to the epoxide, 2-chloroacetyl chloride and to 2,2-dichloroacetaldehyde (Liebler et al., 1985, 1988; Liebler and Guengerich, 1983). Greater amounts (approximately six times) of DCE is metabolized in mice versus rats (Dowsley, 1995). It appears that the cytochrome P-450 isozyme, CYP2E1, is responsible for the oxidation of DCE in the liver and lungs of both species (Kainz et al., 1993; Lee and Forkert, 1994; 1995; Forkert et al., 1996; Dowsley et al., 1996) and in the kidneys of male mice (Speerschneider and Dekant, 1995). The principal product of metabolism by this isozyme is the DCE epoxide, albeit more of the 2,2-dichloroacetaldehyde is produced in murine lungs than liver (Dowsley et al., 1996). These metabolites undergo secondary reactions, principally conjugation with glutathione and cellular macromolecules. The major metabolites found in vitro are glutathione conjugates

thought to originate from the epoxide (Dowsley et al., 1995, 1996). These metabolites are formed by the addition of either one or two molecules of glutathione to DCE epoxide and are: 2-S-glutathionyl acetate (GTA) and 2-(S-glutathionyl) acetylglutathione (GAG), respectively. Products of glutathione conjugation with the other oxidative metabolites of DCE are found in significantly smaller quantities, as are the unconjugated oxidative products themselves (Dowsley et al., 1995). Conjugation of the epoxide with glutathione is clearly a detoxification mechanism, as pretreatment of animals with glutathione depleting agents enhances toxicity (Forkert and Moussa, 1991, 1993; Moussa and Forkert, 1992; Forkert, 1997). In addition, cytotoxicity due to DCE exposure occurs after the depletion of cellular glutathione (Jaeger et al., 1974; Jenkins and Anderson, 1978).

The oxidative metabolic pathway for DCE is saturable, occurring at an oral dose of approximately 10 to 50 mg/kg in the rat. From this dose level, the percentage of the administered dose that is metabolized begins to decrease and the percentage of the dose as unchanged DCE in expired air begins to increase as the dose increases. This saturation of metabolism occurs with inhalation exposures exceeding 200 ppm (794 mg/m^3) (Dallas et al., 1983).

Excretion

Elimination of DCE and metabolites occurs primarily via the urine and in the expired air of exposed animals. The rate of excretion is relatively rapid, as most of the dose is eliminated within the first 72 hours (Jaeger et al., 1977). At low doses (less than 10 mg/kg oral), most of the dose is excreted as glutathione conjugates in the urine and in the bile (McKenna et al., 1978b). As the dose increases, oxidative metabolism becomes saturated and greater amounts of the dose become eliminated unchanged via the lungs. The amount eliminated via exhalation approaches 100% with large oral doses (350 mg/kg) or with high (>200 ppm) inhalation exposures (Jones and Hathway, 1978b, D'Sousa and Andersen, 1988).

Toxicokinetics and PB-PK Modeling

D'Sousa and Anderson (1988) developed a physiologically based pharmacokinetic model for DCE in rats. The model demonstrated that DCE has saturable oxidative metabolism and the rate and degree of metabolism is affected by the rate of absorption. Additionally, these authors showed that the percentage of DCE exhaled unchanged, metabolized and conjugated with glutathione is different for different routes of exposure and dose levels. The authors provided experimental verification for their model. This model predicts that human metabolism will produce less of the reactive DCE-epoxide than rats at equivalent mg/kg oral or ppm inhalation concentrations.

TOXICOLOGY

Toxicological Effects in Animals

The following sections on animal toxicity are representative of toxicity studies concerning DCE that are available in the literature, and are intended to give the reader an overview of the toxic profile of the chemical. For a more detailed discussion of the toxicity of 1,1-dichloroethylene, see reviews contained in ATSDR (1994) and WHO (1990).

Acute Toxicity

Oral LD_{50} values in rats (in oil vehicles) are approximately 1500 and 1800 mg/kg in males and females, respectively (Jenkins et al., 1972; Ponomarkov and Tomatis, 1980). Young or fasted rats (e.g. those with lower glutathione levels) are significantly more sensitive to the acute effects of DCE; LD_{50}s in these animals are approximately 50 mg/kg (Andersen and Jenkins, 1977). Mice are more sensitive than rats to the acute toxic effects of DCE, LD_{50}s in this species are reported as approximately 200 mg/kg for non-fasted, adult males and females (Jones and Hathway, 1978a).

The situation regarding inhalation toxicity is similar; 4-hour LC_{50} values for fasted male rats are approximately 30 times lower than those reported for rats with access to food (approximately 400 ppm versus 10,000 - 15,000 ppm) (Jaeger et al., 1974). Identical situations are seen in mice and hamsters. As is the case for oral exposure, mice are significantly more sensitive to the acute effects of DCE than are rats; 4-hour LC_{50} values are approximately 40 and 200 ppm in males and females, respectively (Henschler, 1979; Oesch et al., 1983; Short et al., 1977c).

The principal target organs of DCE toxicity are the liver and kidney. The most sensitive end-point of acute DCE toxicity is liver damage. Increases in enzyme markers of liver damage (aspartate transaminase, AST and alanine transaminase, ALT) have been observed in fasted rats with oral doses of 50 mg/kg (Andersen and Jenkins, 1977; Jenkins and Andersen, 1978; Molsen et al., 1989). Histological evidence of liver damage is seen with oral doses of as little as 100 mg/kg, the observed effects being centrilobular and midzonal necrosis (Kanz et al., 1991). Renal effects of tubular necrosis are seen at higher doses (200-400 mg/kg) (Jenkins and Anderson, 1978). Pulmonary injury (involving Clara cells) and gastrointestinal effects (edema of the forestomach) have also been observed in rats and mice exposed to DCE at relatively high levels (100 - 200 mg/kg) (Moussa and Forkert, 1992; Chieco et al., 1981).

As previously noted, the food intake and dosing vehicle influence the hepatotoxicity of DCE. Fasting exacerbates DCE toxicity (Andersen and Jenkins, 1977; Andersen et al., 1980; Chieco et al., 1981; Jenkins and Andersen, 1978). The hepatotoxic effects are attenuated by administration in a vehicle that increases the rate of absorption (e.g. aqueous Tween 80 versus corn or mineral oil) (Chieco et al., 1981).

Subchronic Toxicity

As is the case with acute toxicity, the liver, kidney and lung are the organs most effected by sub-chronic exposure to DCE. After a 90 day continuous inhalation exposure to concentrations of 10, 61, 101, or 189 mg/m^3, no histopathological changes were observed in the livers of rats, guinea pigs, rabbits, Beagles or squirrel monkeys exposed to concentrations of 101 mg/m^3 or less (Prendergrast et al., 1967). At the highest dose, livers from surviving dogs, monkeys and rats showed hepatic changes including fatty metamorphosis, focal necrosis and bile-duct proliferation. In addition, all rats showed hypertrophy of the kidney tubules and inflammatory changes were seen in the lungs of most animals. Doses were not estimated by the authors. In the same study, 30-eight hour exposures to 395 mg/m^3 resulted in a high incidence of lung congestion in all species except dogs. Hepatic effects (fatty infiltration and necrosis) were seen in guinea-pigs.

At a level of 500 ppm for 6 hours/day over the course of 20 days, exposed rats developed nasal irritation and displayed liver cell degeneration. At an exposure level of 200 ppm, nose irritation was observed, but there were no other effects noted (Gage, 1970).

Minimal recoverable liver cell cytoplasmic vacuolation was observed in rats exposed 6 hrs/day, 5 days/week for 90 days to either 25 or 75 ppm DCE. At both dose levels, gross examination revealed unremarkable pathology (Quast et al., 1977).

Both mice and rats demonstrated liver toxicity when exposed to 15, 30, or 60 ppm DCE in air for 23 hours/day for up to 7 days as evidenced by increased serum levels of aspartate transaminase (AST) and alanine transaminase (ALT) (Short et al., 1977a,b). In mice, severe renal tubular nephrosis was observed in all animals at exposures as low as 15 ppm for one day; no renal lesions were observed in rats. No mice survived longer than 2 days at the 60 ppm exposure level.

Dogs were exposed to daily oral doses of 6.25, 12.5 or 25 mg/kg for 97 continuous days. No adverse effects related to DCE exposure were noted in body weights, food consumption, urinalysis, blood chemistry, organ weights and ratios or upon necropsy and subsequent histopathology (Norris, 1977; Quast et al., 1983).

DCE was administered in the drinking water to rats for 90 days at concentrations of 0, 60, 100, or 200 mg/L. At the highest concentration (equivalent to a dose of approximately 19 - 26 mg/kg-d), only minimal, reversible liver cytoplasmic vacuolization was observed in the animals. No abnormalities were seen in gross pathology or organ/body weight ratios (Quast et al., 1977).

NTP (1982) performed an oral gavage study in rats and mice as a dose-finding study for their chronic bioassay of the compound. Groups of 10 mice or rats of both sexes were dosed by gavage five times per week at 0, 5, 15, 40, 100, or 250 mg/kg DCE in corn oil for 13 weeks. Three high-dose female rats died during the first week; severe centrilobular necrosis of the liver was observed in these animals. No centrilobular necrosis was seen in any of the other treated rats. Focal areas of cellular alteration were observed in 30% of the high-dose rats of both sexes. A high incidence of liver fibrosis, pigmentation, bile duct hyperplasia, and hepatocellular atrophy was observed in males and females at the two

highest doses, albeit the effects seen in the 100 mg/kg group were more moderate than those seen in the 250 mg/kg group. Fatty metamorphosis was seen in all treatment groups, however, there was no distinct dose-response.

All male mice exposed to 250 mg/kg died within 24 hours; 9/10 of the females at the same dose died within 48 hours. Deaths occurred in 1/10 females receiving 5 mg/kg or 15 mg/kg; 1/10 males receiving 40 mg/kg; and 2/10 males and 3/10 females receiving 100 mg/kg. Centrilobular necrosis and hemorrhage were observed in animals dying at the 250 mg/kg dose. Cellular atypia of the liver (less severe than in rats) was observed in the majority of animals at the 100 mg/kg dose, but not at 250 mg/kg. Other effects seen were cellular necrosis, liver congestion, and fatty metamorphosis, which was the most frequently observed change. The incidence and severity of these hepatic effects were dose-related and more severe in males than in females.

Genetic Toxicity

DCE is mutagenic in bacterial test systems with S-9 activation. DCE is mutagenic in *Salmonella* tester strains at concentrations of 3.3×10^{-4} to 3.3×10^{-2} M or in air at a concentration of 5% for 3 hours (Bartsch et al., 1975; Jones and Hathway, 1978c; Simmon et al., 1977). No activity was observed in the absence of the S-9 fraction. DCE has been shown to be mutagenic in *Escherichia coli* and *Saccharomyces cerevisiae* in the presence of metabolic activation (Greim et al., 1975; Bronzetti et al., 1981) and was mutagenic to *S. cerevisiae* in a mouse host-mediated assay (Bronzetti et al., 1981).

In most mammalian systems, DCE has failed to elicit mutagenic responses. The chemical has yielded negative results in mammalian (rat and mouse) dominant lethal assays (Short et al., 1977c; Andersen et al., 1977). Likewise, significant positive results were not observed in Chinese hamster V79 cells (Drevon and Kuroki, 1979). In the presence of a S-9 activation system, a weak but significant increase in the incidence of sister chromatid exchanges and chromosomal aberrations was observed in the Chinese hamster cell line (Sawada et al., 1987).

In vivo studies have yielded mixed results. No chromatid or chromosomal aberrations were observed in femoral bone marrow cells of rats exposed to 25 or 75 ppm DCE via inhalation for six months (Quast et al., 1986). However, increases in chromosomal aberrations in Chinese hamster bone marrow cells were observed after DCE exposure (WHO, 1990).

Radiolabeled DCE binds to DNA in the livers and kidneys of both rats and mice (Reitz et al., 1980). Inhalation exposure to 10 or 50 ppm DCE for 6 hours leads to detectable levels of DNA adduct in these tissues. Binding was greater in mice versus rat and in kidney versus liver. It was estimated that 30 adducts/10^6 nucleotides were formed in mouse kidneys at the 50 ppm exposure level.

Developmental and Reproductive Toxicity

Inhalation exposure to DCE is both fetotoxic and produces developmental effects in laboratory animals with exposure conditions that result in maternal toxicity (Murray et al., 1979; Short et al., 1977a). Soft tissue anomalies in rats and skeletal defects in rats, mice and rabbits were observed at air concentrations of DCE ranging from 15 to 449 ppm.

Exposures ranged from four to 13 days and encompassed the sensitive phase of gestation for each species. An oral dose of 40 mg/kg-d given to pregnant rats via drinking water on days 6 through 15 of gestation resulted in no increase in the incidence of malformation over that observed in the controls (Murray et al., 1979).

A more recent study demonstrated various cardiac malformations (predominantly atrial septal defects, aortic valve defects and mitral valve defects) in fetuses from maternal rats exposed before and during (the entire) pregnancy to DCE in the drinking water at concentrations of 110 and 0.15 ppm (Dawson et al., 1993). The authors did not estimate the average daily dose of DCE to the dams.

Continuous exposure of rats over three generations to concentrations of 0, 50, 100, or 200 ppm (0, 7, 14, or 29 mg/kg) continuously in drinking water resulted in no effects on reproductive function and parameters (six sets of litters were evaluated). Reversible, dose-related mild hepatocellular fatty changes were observed, however (Nitschke et al., 1983).

Chronic Toxicity and Carcinogenicity

A total of 18 carcinogenicity and/or long-term bioassays have been performed on DCE. Of the eighteen studies, eleven involved exposure via the inhalation route, five bioassays were by the oral route, one was application to the skin, and one was by subcutaneous injection. No attempt will be made in this document to summarize all of these studies. For greater detail, the reader is referred to the reviews found in ATSDR (1994) and U.S. EPA (1990).

Of the eleven inhalation exposures, none were conducted for the lifetime of the animals; all were for 12 months or less. Only one of the studies, that conducted by Maltoni et al. (1977, 1984), provided positive results. This study serves as the basis for the U.S. EPA's inhalation unit risk for DCE and, as discussed below, serves as a supporting study for U.S. EPA's oral slope factor which is based on the NTP (1982) bioassay (U.S. EPA, 1998a).

Maltoni et al. (1977, 1984) exposed both sexes of Swiss mice to 10 and 25 ppm DCE 4 hours/day, 4-5 days per week for 12 months. Twenty-five parts per million was considered to be the maximum tolerated dose as the groups exposed to 50 ppm and higher died after 2-7 days of exposure. Animals were followed until their spontaneous death, at which point they were autopsied. Animals were divided into two control groups of 100 animals/sex and 90 animals/sex, one 10 ppm group of 30 animals/sex, and two 25 ppm groups of 30 animals/sex and 120 animals/sex. The additional control group served as controls to the second 25 ppm groups which was started two weeks into the study.

Statistically significant increases in kidney adenocarcinomas were seen in the 25 ppm groups of male mice. The incidence of these tumors in males was 0/54 and 0/66 in the controls, 0/25 in the 10 ppm group, and 3/21 and 25/98 in the two 25 ppm groups. No increases in other tumor types were observed in mice. It is important to note that the kidney tumors were observed along with a significant degree of renal pathology (tubular necrosis). It has been suggested that the nephrotoxicity seen in Swiss mice from DCE exposure may be an integral part of the tumorigenesis of DCE. Specifically, DNA synthesis associated with tissue regeneration coupled with the weak genotoxic activity of DCE may be the mechanism responsible for the renal adenocarcinomas seen only in this strain and species (Green, 1990; Reitz et al., 1980; Speerschneider and Dekant, 1995).

The same investigators also exposed both sexes of Sprague Dawley rats to 10, 25, 50, 100, and 150 ppm under the same conditions as the mice (4 hours/day, 4-5 days/week for 52 weeks). A statistically significant increase in mammary tumors (total tumors) was seen at the 10 and 100 ppm doses. No dose-related response was observed, thus these tumors are considered non-treatment related.

Only two of the oral studies were conducted for two years: the NTP (1982) and the Quast et al. (1983) drinking water study. Neither study produced positive results, however, it appears that doses less than the MTD were used in both studies.

In the NTP (1982) study, groups of 50 rats or mice of either sex were dosed with DCE in corn oil, five days per week for 104 weeks. Rats were exposed to either 0, 1, or 5 mg/kg/dose, while mice were exposed to 0, 2, or 10 mg/kg/dose. Histopathological examination revealed an increased (non-significant) incidence of liver necrosis in high-dose male and low dose female mice and renal inflammation in high dose rats of both sexes. No significant increases in compound-related tumors were observed in the study. A non-significant increase in adrenal pheochromocytomas were observed in male rats, however (6/50, 5/48, and 13/47 in the controls, 1 mg/kg, and 5 mg/kg groups, respectively). This tumor incidence data was used by U.S. EPA in the derivation of their oral slope factor for DCE.

Quast et al. (1983) exposed groups of 48 Sprague-Dawley rats of either sex to 50, 100, or 200 ppm DCE in their drinking water for a period of two years. Control groups consisted of 80 animals per sex. The time-weighted average DCE doses reported by the authors were 7, 10, or 20 mg/kg-d for the males and 9, 14, or 30 mg/kg-d for the females. The doses were calculated based on water analysis and consumption and animal body weights. There were no significant differences between the treated animals and controls in the following parameters: appearance and demeanor, mortality, body weight, food consumption, hematology, urinalysis, clinical chemistry, organ weights, or organ/body weight ratios, nor were there difference in water consumption. The sole treatment-related effect observed was in the liver and was characterized by a minimal amount of hepatocellular swelling with midzonal fatty change. This effect was seen in the high dose males and in the females at all doses. No exposure-related neoplastic changes were observed in the test groups.

In the skin application studies by Van Duuren et al. (1979), DCE was found to be an incomplete carcinogen. DCE served as an initiator when applied to the skin of ICR/Ha mice followed by treatment with phorbol myristate acetate treatment. Weekly subcutaneous injections of 2 mg DCE per mouse (same strain) for approximately 78 weeks failed to elicit a carcinogenic response.

Toxicological Effects in Humans

General Toxicity

Exposure to high concentrations of DCE (> 4000 ppm; 15,880 mg/m^3) results in a rapid onset of CNS depression followed by unconsciousness if exposure is continued (Irish, 1963). Skin contact with DCE causes irritation, which may be partly due to the presence of hydroquinone monomethyl ether inhibitor (Chivers, 1972). Dermatitis has been reported in

an individual whose skin was exposed to plastic film (DCE/vinyl chloride polymer in the absence of a stabilizer) (Osbourne, 1964). Eye contact causes conjunctivitis and transient corneal injury (Gibbs and Wessling, 1983).

No effect on serum levels of enzymatic markers of liver damage was found in 133 human subjects occupationally exposed to DCE (WHO, 1990).

Genetic Toxicity

No information was found regarding genotoxic effects of DCE in humans, however, there is evidence that human liver can activate DCE into a metabolite mutagenic to Salmonella typhimurium TA 1535 (Jones and Hathway, 1978c).

Developmental and Reproductive Toxicity

One human study is available suggesting neural tube defects in humans after transplacental exposure to DCE from contaminated water (NJDH 1992a, 1992b - from ATSDR, 1994). ATDSR (1994) suggests that these results be interpreted with caution as the evidence is considered only suggestive.

Chronic Toxicity and Carcinogenicity

A few epidemiological studies regarding DCE have been reported, all of them except one have been confounded by concomitant exposure to vinyl chloride (ATSDR, 1994). In the one study without vinyl chloride as a confounding factor, Ott et al. (1976), examined the mortality and health of 138 employees exposed to DCE. These investigators reported no findings that were statistically related to DCE exposure. IARC (1986) concluded that this study was not adequate to permit an assessment of human carcinogenicity primarily due to the small cohort size. Accordingly, the epidemiological data as a whole are too limited to adequately assess the human carcinogenicity of DCE at this time.

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

The most sensitive endpoint of DCE toxicity is hepatotoxicity. Relatively small doses of DCE over a long period of time (2 years in animal studies) results in hepatic effects of midzonal fatty changes and hepatocellular swelling. The study by Quast et al. (1983) was selected as the representative study for the development of the PHG. This selection was made because the study was of sufficient duration, had sufficient numbers of animals, was representative of effects seen in test animals from DCE exposure, and the effects seen at the doses administered are supported by similar studies (e.g. NTP, 1982; Nitchske et al., 1983). In addition, the route of exposure in this study is the most relevant to the derivation of the

PHG (e.g. drinking water). Indeed, both Environment Canada (1994) and U.S. EPA (1987) use this study as the basis for their Maximum Acceptable Concentration (MAC) and MCL, respectively.

The critical effect observed was midzonal fatty accumulation in the livers of male rats exposed to 200 ppm DCE and in female rats at all exposure levels. The dose levels, as calculated by the authors, were 9, 14 or 30 mg/kg-d for the females. This effect was observed in the females at all doses, accordingly, the dose of 9 mg/kg-d is considered the LOAEL.

Carcinogenic Effects

No dose-response assessment for the potential carcinogenic effects of DCE was performed due to the lack of appropriate data from which a quantitative estimate of the chemical's potency can be based. In all studies by the route most relevant to the PHG (oral), no dose-related, statistically significant increases in tumors have been demonstrated. U.S. EPA based their oral potency factor of 0.6 $(mg/kg\text{-}d)^{-1}$ on the non-significant increase in adrenal pheochromocytomas in male rats (NTP, 1982) and supported the value on the basis of it's similarity (within a factor of two) of the potency derived from the Maltoni et al. (1977, 1984) inhalation studies where significant increased incidences of renal adenocarcinomas were observed in male Swiss mice. Because there is no clear dose-response and the increase in tumor incidence in the high dose group versus the incidence in the controls is not significant, OEHHA does not interpret the pheochromocytoma data as a treatment-related effect. Accordingly, we feel that it is inappropriate to use the incidence data for these tumors as a basis for the calculation of a quantitative potency.

OEHHA has also determined that the tumor data (mouse renal adenocarcinomas) from the Maltoni et al. (1977, 1984) study should not be used for the derivation of the PHG. First, the route of exposure (inhalation) adds uncertainty to an oral risk estimation. Perhaps more importantly, is that statistically significant treatment-related increases in tumor incidence has only been observed in one sex (males) of one strain (Swiss) of one species (mice) in spite of the fact that 18 oncogenicity studies have been performed with DCE. Consequently, DCE is not listed as a carcinogen by IARC or by the State of California under Proposition 65. In addition, recent evidence suggests that due to species differences in metabolism of DCE (specifically the presence of cytochrome CYP2E1), this effect (adenocarcinomas) may be specific to the Swiss mouse and has little relevance to other species, such as humans (Green, 1990; Reitz et al., 1980; Speerschneider and Dekant, 1995). These authors have provided evidence that the P-450 isozyme (CYP2E1), which is responsible for the metabolism of DCE to the predominant reactive species, is not present in the kidneys of non-susceptible species such as the rat. Samples from human kidney have assayed negative for the presence of the isozyme CYP2E1 (Speerschneider and Dekant, 1995). Furthermore, as discussed above in the animal carcinogenicity section, a plausible mechanism for the origin of renal tumors in Swiss mice has been proposed. Accordingly, OEHHA feels that the issue of carcinogenicity is unresolved and that using the Maltoni et al. (1977, 1984) data as the basis for the PHG for this chemical would be inappropriate.

Since only one cancer bioassay out of eighteen performed is positive and there is metabolism data supporting an increased sensitivity of male Swiss mice to DCE carcinogenesis, there is no clear evidence that DCE exposure poses a carcinogenic risk to

humans. The weight-of evidence suggests an approach other than a strict cancer potency slope calculation. Accordingly, the PHG will be calculated using a non-cancer endpoint, taking into consideration uncertainty surrounding DCE carcinogenesis in humans.

CALCULATION OF PHG

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

Noncarcinogenic Effects

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

$$C = \frac{\text{NOAEL (or LOAEL)} \times \text{BW} \times \text{RSC}}{\text{UF} \times \text{W}}$$

where,

NOAEL	=	No-observed-adverse-effect-level (If a NOAEL is not available, a LOAEL, or lowest-observed-adverse-effect-level may be used)
BW	=	Adult body weight (a default of 70 kg)
RSC	=	Relative source contribution (default of 20%)
UF	=	Uncertainty factors (10 to account for inter-species extrapolation, 10 for potentially sensitive human subpopulations, 3 for the use of a LOAEL in the place of a NOAEL, and 10 for insufficiencies in the database)
W	=	Daily water consumption rate: default of 2 L/day; higher values are used for L-equivalents/day (Leq/day) for volatile organics to account for inhalation and dermal exposures from the use of contaminated tap water.

In the case of DCE, the LOAEL from the principal study was 9 mg/kg-day for midzonal fatty changes and hepatocellular swelling (Quast et al., 1983). The adult human body weight is set at 70 kg, the standard default value. The OEHHA default value of 20% for the RSC was used in the calculation as there is no information suggesting this value is inappropriate. A total uncertainty factor of 3,000 is used (10 for interspecies extrapolation, 10 for intraspecies extrapolation, 3 for the use of a LOAEL in the place of a NOAEL, and

10 for insufficiencies in the database). The uncertainty factor for inter and intra-species extrapolation (total of 100) are standard OEHHA default factors. An UF of 3 was selected for using a LOAEL in the place of a NOAEL because the critical effect was not particularly severe (fatty changes in the liver). An additional UF of 10 was applied due to insufficiencies in the carcinogenicity database. All available carcinogenicity studies (18 total) have deficiencies (dose too low, exposure duration too short, etc.). The OEHHA default value of 4 Leq/day for volatile organic compounds was used as the daily water consumption rate due to the volatility of DCE in order to account for any compound inhaled or dermally absorbed due to the use of contaminated tap water.

Therefore:

$$C = \frac{LOAEL \times BW \times RSC}{UF \times W} = \frac{9\ mg/kg\text{-}day \times 70\ kg \times 0.20}{3{,}000 \times 4\ Leq/day}$$

$$= 0.01\ mg/L = 10\ \mu g/L = 10\ ppb$$

Therefore, the PHG for DCE is 10 ppb.

RISK CHARACTERIZATION

The PHG of 10 ppb was calculated based on the hepatic effects seen in rats following a two year exposure to DCE in their drinking water. Midzonal fatty changes were observed in the livers of female rats exposed to DCE were the most sensitive effect observed and were seen at doses as low as 9 mg/kg-day.

Sources of uncertainty in the development of the PHG for DCE in drinking water are also the general issues of uncertainty in any risk assessment, particularly mode of action, inter- and intra-species extrapolation, and relative source contribution (RSC).

An additional source of uncertainty, specific for this chemical, concerns the suitability of the toxicology database, particularly that for carcinogenicity. Most bioassays conducted with DCE are insufficient by today's standards; they are either for too short of a duration or were performed at doses well below the MTD (and/or below the dose which would have been expected to yield the maximum amount of toxic metabolite - see metabolism section). The issue of carcinogenicity is unclear, and is reflected in the U.S. EPA's classification of DCE as "C" and IARC's classification of "Group 3." The suggestive evidence is sufficient (mutagenicity, positive in a single animal test, structural similarity to a *known* human carcinogen -vinyl chloride), however, to consider the possibility that the chemical may be a human carcinogen. Accordingly, this issue was taken into account in the generation of the PHG via the use of an uncertainty factor.

The PHG of 10 ppb differs from the California MCL of 7 ppb because of different uncertainty factors were applied and water consumption was handled differently in the two calculations. The PHG applies a total UF of 3,000, while the California MCL applied an uncertainty factor of 10,000. The latter uncertainty factor included factors of 100 for interspecies extrapolation, 10 for the use of a LOAEL in place of a NOAEL and 10 for uncertainties in the carcinogenicity database. The current PHG calculation substitutes 3 for

10 for the use of a LOAEL in the place of a NOAEL because the critical effect (fatty changes in the liver) was not particularly severe. The second difference is that the MCL calculation used a water consumption of 2 L/d while the current calculations uses 4 Leq/d, per OEHHA guidance for volatile chemicals, to account for inhalation and dermal exposures from the use of contaminated tap water. U.S.EPA's MCL of 6 ppb is different from the California MCL even though the endpoint was the same (fatty changes in the liver). U.S.EPA used a NOAEL of 10 mg/kg-d derived from male rats instead of 9 mg/kg-d from female rats (both sexes were exposed to 200 ppm DCE in their drinking water; Quast et al., 1983) which was used by DHS and in this document.

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 defaults are 20%, 40%, and 80% (0.2, 0.4, and 0.8); other values may be used depending on the scientific evidence.

U.S. EPA follows a general procedure promulgating MCLGs for Group C chemicals (i.e., limited evidence of carcinogenicity) either an RfD approach is used (as with a noncarcinogen), but an additional UF of 1 to 10 (usually 10) is applied to account for the limited evidence of carcinogenicity, or a quantitative method (potency and low-dose extrapolation) is used and the MCLG is set in the 10^{-5} to 10^{-6} cancer risk range. For this case of DCE, OEHHA has generally followed a procedure similar to that of U.S. EPA in that the PHG was based on a non-cancer endpoint with an additional uncertainty factor applied to account for the incomplete nature of the cancer database.

OTHER REGULATORY STANDARDS

The U.S. Environmental Protection Agency's MCL and MCLG for DCE are both set at 0.007 mg/L (7 ppb). The current California MCL is 0.0063 mg/L or rounded to 6 ppb. All three standards (MCL, MCLG, California MCL) are based on hepatic midzonal fatty changes observed in the Quast et al. (1983) study. The Canadian Maximum Acceptable Concentration of 14 ppb is based on the same study.

Several states have set guidelines for DCE concentrations in drinking water, which are shown in the table below.

Table 1. State Drinking Water Guidelines

State	Drinking Water Guideline
Alabama, Arizona, Connecticut, Maine	7 ppb
California, Minnesota	6 ppb
New Jersey	2 ppb

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