Public Health Goal for
1,4-Dichlorobenzene
in Drinking Water

Prepared by

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PREFACE

Drinking Water Public Health Goal of the Office of Environmental Health Hazard Assessment

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. The PHG describes concentrations of contaminants at which adverse health effects would not be expected to occur, even over a lifetime of exposure. 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 adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires OEHHA to adopt PHGs that meet the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which scientific evidence indicates that no known or anticipated adverse effects on health will occur, plus 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 scientific ambiguity, OEHHA shall use criteria most protective of public health and shall incorporate uncertainty factors of noncarcinogenic substances for which scientific research indicates a safe dose-response threshold.
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 periodically 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. For this reason PHGs are only one part of the information used by DHS for establishing drinking water standards. PHGs established by

OEHHA exert no regulatory burden 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 developed for technical assistance to DHS, but may also benefit federal, state and local public health officials. 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 environmental waters where additional concerns of bioaccumulation in fish and shellfish may pertain. Often environmental water contaminant criteria are more stringent than drinking water PHGs, to account for human exposures to a single chemical in multiple environmental media and from bioconcentration by plants and animals in the food chain.

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SUMMARY

A Public Health Goal (PHG) of 0.006 mg/L (6 ppb) is developed for 1,4-dichlorobenzene (1,4-DCB) in drinking water. The PHG is based on carcinogenic effects observed in experimental animals A National Toxicology Program (NTP) study cited in the development of the PHG provided evidence of hepatocarcinogenicity in both male and female mice. For the calculation of the PHG, cancer potency estimates were made following the 1996 proposed draft guidelines of U.S. EPA for carcinogenic risk assessment in which linearized multistage model is fit to the experimental data in order to establish lower 95% confidence bound on the dose associated with a 10% increased risk of cancer (LED_{10}). The PHG was calculated assuming a *de minimis* theoretical excess individual cancer risk level of 10^{-6} from exposure to 1,4-DCB. Based on these considerations, OEHHA calculates a PHG of 0.006 mg/L (6 ppb) for 1,4-DCB in drinking water.

INTRODUCTION

The purpose of this document is to establish a PHG for 1,4-DCB (also known as *para*-dichlorobenzene). A Maximum Contaminant Level (MCL) of 0.005 mg/L was established by the California Department of Health Services (DHS, currently Office of Environmental Health Hazard Assessment) in 1988 (DHS, 1988a). This level is lower (more stringent) than the federal Maximum Contaminant Level Goal (MCLG) and MCL of 0.075 mg/L for 1,4-DCB. U.S. EPA reported that 1,4-DCB at this level is "the lowest level to which water systems can reasonably be required to remove this contaminant should it occur in drinking water" and believes it would protect against the potential health problems (U.S. EPA, 1995; 1987).

Under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65), 1,4-DCB is listed as a chemical known to the state to cause cancer. In 1994, the Office of Environmental Health Hazard Assessment (OEHHA) reevaluated 1,4-DCB as a carcinogen and based on the weighting of the overall evidence, concluded there is still sufficient evidence to consider 1,4-DCB as a carcinogen (OEHHA, 1994). The International Agency for Research on Cancer (IARC) has classified 1,4-DCB as possibly carcinogenic to humans (Group 2B; IARC, 1987). 1,4-DCB is also listed in the NTP's seventh annual report on carcinogens as a compound "reasonably anticipated" to be a carcinogen (NTP, 1994). U.S. EPA has not classified 1,4-DCB as to its carcinogenic potential.

In this document, we evaluate the available data on the toxicity of 1,4-DCB, primarily by the oral route, and included information available since the previous assessment by DHS (1988a). To determine a public health-protective level of 1,4-DCB in drinking water, sensitive groups are identified and considered, and relevant studies were identified, reviewed and evaluated.

CHEMICAL PROFILE

1,4-DCB (CAS No. 106-46-7) is a chlorinated aromatic compound which is a solid at room temperature, forming colorless to white crystals (monoclinic prisms or leaflets) with an odor of camphor or mothballs. It has a molecular formula of $C_6H_4Cl_2$ with a molecular weight of 147.01 g/mol. 1,4-DCB has a melting point of 53.1°C and a boiling point of 174°C. The vapor pressure of 1,4-DCB at 54.8°C is 10 mm Hg. It has a very low solubility in water of 65.3 mg/L at 25°C, but is soluble in organic solvents including ether, chloroform, carbon disulfide and benzene.

The primary uses of 1,4-DCB are as a space deodorizer, an insecticidal fumigant for moths and a chemical intermediate in the production of polyphenylene sulfide resin (a plastic used in electronics applications) and 1,2,4-trichlorobenzene. Consumption pattern estimates have ranged from 35 to 40% for moth control, 35 to 55% as a space deodorant and the balance for miscellaneous and other uses (HSDB, 1997).

1,4-DCB may be synthesized using a Friedel-Crafts catalyst such as ferric oxide in the chlorination of liquid benzene (Health Canada, 1993). This reaction produces primarily 1,4-DCB with less than ~1% contaminating mono-, di- and trichlorobenzenes, although these by-products may be separated out by subsequent fractionation. 1,4-DCB may also be synthesized using the Sandmeyer process using the appropriate chloroaniline compound as a substrate, or by the chlorination of chlorobenzene (HSDB, 1997).

U.S. production of 1,4-DCB has been estimated at 15×10^6 pounds (1981; HSDB, 1997), while U.S. imports have been estimated at 1.09×10^7 grams (HSDB, 1997).

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

1,4-DCB is not known to occur naturally in the environment. However, the varied uses of 1,4-DCB allow for the introduction of significant quantities into environmental media. In particular, leachates from chemical dumps and effluents from manufacturing may contaminate land and water, and direct volatilization from its use in deodorizing may result in significant air contamination. Volatilization of 1,4-DCB from water also suggests that inhalation is the predominant route of exposure. A recent study examining exposure to 1,4-DCB in the U.S., as gauged by levels of 1,4-DCB in blood and 2,5-dichlorophenol (a metabolite) in urine, demonstrated that over 95% of the population has exposure to this compound (Hill *et al.*, 1995). Estimation of exposure to 1,4-DCB is frequently confounded by the reporting of total dichlorobenzenes (including the *ortho*- and *meta*-isomers).

Air

Air release of 1,4-DCB has been estimated at 70 to 90% of the total U.S. production, including contributions from its use as a toilet deodorizer (~1.7×10^6 kg), garbage deodorant (~3.7×10^6 kg) and agent for moth control (~7.8×10^6 kg) (IARC, 1982; citing Johnston *et al.*, 1979). Since these are the predominant uses of 1,4-DCB and resulted in significant air exposures, they are the most likely sources and route of exposure to humans.

Air concentrations of 1,4-DCB in central and suburban Tokyo have ranged from 1.5 to 4.2 $\mu g/m^3$ (IARC, 1982; citing Morita and Ohi, 1975). Urban areas would be expected to have higher levels of 1,4-DCB in air relative to rural areas because of greater proximity to sites of production and emission. An indoor air survey of 57 California homes for 1,4-DCB (presumably present from its use in consumer products for deodorizing and moth control) showed overnight air concentrations of 1,4-DCB ranging from 0.4 to 2.8 $\mu g/m^3$ (Health Canada, 1993; citing Wallace *et al.*, 1988). Other estimates of mean indoor air concentrations of 1,4-DCB have ranged from 1.7 to 56 $\mu g/m^3$ (ATSDR, 1993). Factory operations involving the production or use of 1,4-DCB have resulted in considerably higher air concentrations with reported levels generally ranging from 48 to 204 mg/m^3; early reports have estimated concentrations as high as 4,350 mg/m^3 (U.S. EPA, 1980).

Soil

The Toxic Release Inventory (TRI) reported total releases of 1,4-DCB to land of 4,482 pounds for the years 1987 to 1993. California is not among the top five states for total (land plus water) releases of 1,4-DCB. The degradation of lindane has been reported to produce 1,4-DCB (IARC, 1982).

Water

1,4-DCB has been found in ground water in community water system wells in California, including two large and one small wells (DHS, 1986; DHS, 1988b). TRI reported total releases of 1,4-DCB to water of 33,675 pounds for the years 1987 to 1993, more than 80% of which came from a single facility in West Virginia. Concentrations of 1,4-DCB in the U.S. drinking water system have been reported to range from 0.1 to 30 ppb, although higher levels have been reported sporadically (IARC, 1982; U.S. EPA, 1985; DHS, 1988b).

Food

The use of 1,4-DCB in odor control may potentially result in the contamination of food. Such exposure of pigs and chickens to 1,4-DCB has resulted in disagreeable flavors of pork and eggs, respectively (IARC, 1982; citing Schmidt, 1971 and Langner and Hilliger, 1971). Traces of 1,4-DCB have also been found in fish, bovine tissue and pigeons. Polyphenylene sulfide coatings (highly corrosion and temperature resistant plastic) are manufactured by processes involving 1,4-DCB. Some of these coatings may contain residual 1,4-DCB and may come in contact with food and result in contamination.

METABOLISM AND PHARMACOKINETICS

Absorption

The physicochemical properties of 1,4-DCB (low water solubility, high lipid solubility) suggest that the compound would be readily absorbed by most routes of exposure by membrane diffusion (U.S. EPA, 1980). The breadth of toxic endpoints and target organs and the speed of onset of effects observed in both human and animals exposed to 1,4-DCB also suggests rapid systemic absorption by multiple routes of exposure.

Distribution

Humans exposed to 1,4-DCB by inhalation have been shown to accumulate the compound in adipose tissue (U.S. EPA, 1980; citing Morita and Ohi, 1975). The tissue distribution of ^{14}C-labeled 1,4-DCB was compared in rats administered the compound for 2 to 10 days by several routes of exposure including oral, inhalation and subcutaneous (NTP, 1987; citing Hawkins *et al.*, 1980). 1,4-DCB accumulation peaked in four to six days in fat, kidney, lung, liver, plasma and muscle, with fat the site of greatest concentration by at least an order of magnitude. Route of exposure did not appear to influence the distribution significantly. Gender differences in the distribution of 1,4-DCB from whole-body inhalation exposure (500 ppm for 24 hours) was examined in the serum, liver, kidneys and fat of rats (Umemura *et al.*, 1990). Kidney 1,4-DCB

was significantly higher in males relative to females, whereas liver 1,4-DCB was significantly higher in females relative to males.

F344 rats exposed by inhalation to 1,4-DCB for 24 hours exhibited higher organ to serum distribution ratios relative to animals receiving 1,4-DCB by oral gavage (Umemura *et al.*, 1989).

Metabolism and Excretion

Exposed humans convert 1,4-DCB to 2,5-dichlorophenol, which is excreted as glucuronide and sulfate conjugates, and 2,5-dichlorohydroquinone (NTP, 1987; citing Hallowell, 1959; Pagnotto and Walkley, 1965). 2,5-Dichlorophenol has been detected in the urine of exposed humans (HSDB, 1997; citing Menzie, 1969).

The primary metabolites of 1,4-DCB detected in the urine of rats exposed by oral administration included 2,5-dichlorophenyl methyl sulfoxide and 2,5-dichlorophenyl methyl sulfone. Rabbits administered 1,4-DCB orally formed 2,5-dichlorophenol (plus glucuronide and ethereal sulfate conjugates) and 2,5-dichloroquinol (HSDB, 1997; citing Azouz *et al.*, 1955). Similarly, rats exposed to ^{14}C-labeled 1,4-DCB excreted most of the compound as sulfate or glucuronide conjugates of 2,5-dichlorophenol (Klos and Dekant, 1994; NTP, 1987; citing Hawkins *et al.*, 1980). Minor metabolites reported in rats include 2-(*N*-acetyl-cysteine-*S*-yl)-1,4-dichlorobenzene and 2-(*N*-acetyl-cysteine-*S*-yl)-2,3-dihydro-3-hydroxy-1,4-dichlorobenzene (Klos and Dekant, 1994).

Several species and strains of animals (including humans) were compared in the ability of their hepatic microsomes to biotransform 1,4-DCB (Hissink *et al.*, 1997). B6C3F1 mouse microsomes showed the greatest ability to metabolize 1,4-DCB followed by rat then human microsomes.

Approximately 40% of an oral dose of 1,4-DCB was eliminated in the urine of male and female rats three days after administration (Klos and Dekant, 1994). Elimination of 1,4-DCB by rats was reported to be nearly complete five days following exposure by several routes (NTP, 1987; citing Hawkins *et al.*, 1980).

TOXICOLOGY

Toxicological Effects in Animals

Acute Toxicity

The median lethal dose (LD_{50}) of 1,4-DCB to rats and mice has been estimated between 1 and 5 g/kg body weight by either oral, inhalation, subcutaneous or intraperitoneal routes (as reviewed in HSDB, 1997 and NTP, 1987). Death resulted from respiratory paralysis following the appearance of symptoms including tearing and salivation, excitement then ataxia and dyspnea. *Post-mortem* examination revealed effects on the liver (enlargement, necrosis), kidney (necrosis), lungs (edema, hemorrhage) and the eyes and nose (irritation).

Fischer 344 rats (five/sex/dose) were administered 0, 60, 125, 250, 500 or 1,000 mg/kg-day 1,4-DCB by oral gavage for 14 days (NTP, 1987). Because no compound-related effects were

observed either micro- or macroscopically, a second experiment was undertaken with doses of 0, 500, 1,000, 2,000, 4,000 or 8,000 mg/kg-day 1,4-DCB. All rats in the three highest dose groups and all but one of the female rats in the 1,000 mg/kg-day dose group died before the end of the study.

B6C3F1 mice (five/sex/dose) were administered 0, 60, 125, 250, 500 or 1,000 mg/kg-day 1,4-DCB by oral gavage for 14 days in a repeat of a higher-dose study which resulted in the deaths of many animals at various doses (NTP, 1987). No compound-attributable deaths were observed.

Male and female rats (five/sex/group) and mice (four/sex/group) were administered 0, 150, 300 or 600 mg/kg-day for four days in an investigation of the proliferation of cells in the liver and kidneys (Umemura *et al.*, 1992). Among male rats administered 300 mg/kg, the proximal tubule epithelial cells of the kidney showed an increased cumulative fraction of proliferating cells. Male and female rats and mice exhibited increased proliferative fraction of cells in the livers of exposed animals in all exposed groups.

Rats administered 770 mg/kg-day 1,4-DCB over five days developed modest porphyrinuria, increased porphobilinogen and increased δ-aminolevulinic acid (Rimington and Ziegler, 1963).

Rats and mice exposed to 1,4-DCB by gavage for either five days (mice, 600 mg/kg-day) or three weeks (rats, 300 mg/kg-day) exhibited increased cell proliferation of the liver of rats and mice and in the kidneys of rats as gauged by increased bromodeoxyuridine and [^{3}H]thymidine incorporation (Eldridge *et al.*, 1990).

The toxicity of 1,4-DCB was compared by oral and inhalation routes of exposure in F344 rats (Umemura *et al.*, 1989). Rats were exposed to either 125 or 500 ppm 1,4-DCB by inhalation for 24 hours (whole-body) or treated once by oral gavage with 500 mg/kg body weight. Among animals exposed by inhalation, evidence of renal toxicity (eosinophilic droplets, swelling/ desquamation of tubular epithelium) was observed. Several serum parameters were also altered only among animals exposed by inhalation including elevations in blood urea nitrogen (BUN), hepatic glutamic exaloacetic transaminase and glutamic pyruvate transaminase.

Rats (three/sex) were exposed to 500 ppm 1,4-DCB for 24 hours in whole-body inhalation chambers (Umemura *et al.*, 1990). Male rats showed evidence of epithelial swelling and desquamation of renal tubules as well as "eosinophilic bodies" in the cytoplasm and an increase in BUN level.

No evidence of hepatotoxicity was observed among male F344 and Sprague-Dawley rats administered 1,4-DCB intraperitoneally at doses ranging from 0.9 to 5.4 mmol/kg (0.13-0.79 g/kg) (Stine *et al.*, 1991).

Male F344 rats (four/group) were injected intraperitoneally once with 2, 3, or 4 mmol/kg 1,4-DCB (0.29, 0.44 or 0.59 g/kg) (control animals received corn oil) and were examined for signs of liver and kidney toxicity (Valentovic *et al.*, 1993). Renal cortical slice accumulation of tetraethylammonium was increased among rats in the high-dose group.

Subchronic Toxicity

Fischer 344 rats (10/sex/dose) were treated by oral gavage with 0, 300, 600, 900, 1,200 or 1,500 mg/kg-day for five day/week for 13 weeks (NTP, 1987). Survival was considerably decreased among both males and female rats at the higher doses. Animals in the two highest dose groups exhibited evidence of liver effects (degeneration and necrosis), bone marrow hypoplasia, splenic and thymic lymphoid depletion and necrosis of the epithelia of the small intestine and nose. Kidney effects observed in males surviving at least 45 days in all exposed groups included multifocal degeneration of the cortical tubular epithelia, the formation of eosinophilic droplets in the epithelial cytoplasm from the proximal convoluted tubules and tubular cell degeneration. Kidney effects were not observed among female rats. Changes in the organ to brain weight ratio were reported for the liver (male and female rats at doses ≥ 900 mg/kg-day) and kidneys (male rats at 600 to 1,200 mg/kg-day). Several blood parameters were also altered among exposed animals including hematocrit, red blood cell count, hemoglobin concentration, percentage reticulocytes, mean corpuscular volume, serum triglycerides, serum cholesterol, serum protein and alkaline phosphatase. Several of these alterations were observed among all exposed groups, with the male rats more strongly affected than the female rats. A lower-dose study at 0, 37.5, 75, 150, 300 or 600 mg/kg-day was also conducted because of the high mortality observed in the initial study. Male rats in the high-dose group showed moderate cortical tubular degeneration of the kidney.

B6C3F1 mice (10/sex/dose) were administered 1,4-DCB by oral gavage at 0, 600, 900, 1,000, 1,500 or 1,800 mg/kg-day 1,4-DCB for five days/week for 13 weeks (NTP, 1987). Mortality was high among male and female mice in the high-dose groups. Among animals in all dose groups, the incidence of hepatocellular degeneration was increased and was dose-dependent in severity. Among animals in the two highest dose groups, lymphoid necrosis of the thymus and hematopoietic hypoplasia of the spleen and bone marrow were observed. Organ to brain weight ratios were altered for the liver (males and females at 900 to 1,500 mg/kg-day), spleen (all treated male mice) and ovary (high-dose female mice). Several blood parameters were also altered in many treated groups including white blood cell count, platelets, serum triglycerides, serum cholesterol and total serum protein. Because of the absence of no-observed-adverse-effect-level (NOAEL) in this experiment a second 13-week experiment was undertaken at doses of 0, 84.4, 168.8, 337.5, 675 or 900 mg/kg-day 1,4-DCB. Hepatic effects described as centrilobular to midzonal hepatomegaly was observed in male and female mice in the two highest dose groups.

Female rats were administered 18.8, 188 or 376 mg/kg-day 1,4-DCB five days/week for 192 days (NTP, 1987; citing Hollingsworth *et al.*, 1956). Liver and kidney weight changes were observed in the two highest dose groups, while only the highest dose group showed slight liver injury (focal necrosis, cirrhosis). Rabbits administered 500 or 1,000 mg/kg 1,4-DCB for five days/week over 219 days exhibited liver effects in the low-dose group (enlargement, necrosis).

Fischer 344 rats (five/sex/dose) were treated daily with 0, 75, 150, 300 or 600 mg/kg-day by oral gavage for either 4 or 13 weeks (Bomhard *et al.*, 1988). Relative and absolute kidney weights were increased among male rats in all but the 75 mg/kg-day dose group after 13 weeks. Male rats showed increased urinary LDH, increased epithelial cell secretion and increased hyaline droplet formation in the cytoplasm of renal cortical cells over all the doses tested. After both 4 and 13 weeks, male rats showed evidence of renal damage (tubular cellular necrosis, dilated tubules with cast formation in the outer medulla) in all but the lowest dose group.

Noncarcinogenic Chronic Toxicity

1,4-DCB was administered to F344/N rats and B6C3F1 mice (50/sex/group) in corn oil by gavage for five days/week at doses of 0, 150 or 300 mg/kg-day (male rats) and 0, 300 or 600 mg/kg-day (female rats and mice of both sexes) for two years (NTP, 1987). Male rats exhibited numerous renal effects including increased severity (but not incidence) of nephropathy and hyperplasia of the renal pelvis, mineralization of the collecting tubules of the medulla (increased incidence in low- and high-dose groups) and focal hyperplasia of the tubular epithelium (increased incidence in high-dose groups) and pelvic urothelium (increased incidence in low-and high-dose groups). Renal effects also tended to increase in severity with increasing dose. Parathyroid hyperplasia incidence was also increased among male rats at both doses relative to control animals. Female rats in the high- and low-dose groups exhibited significantly increased incidence of nephropathy.

Among mice in the NTP studies, numerous types of liver toxicity were observed including cytomegaly, karyomegaly, hepatocellular degeneration and cellular necrosis and the incidences were significantly increased over control animals in both dose groups. Follicular cell hyperplasia of the thyroid, adrenal gland medullary hyperplasia and focal hyperplasia of the adrenal gland capsule were significantly increased among 1,4-DCB exposed male mice. Kidney toxicity was also observed with significant increases in nephropathy in high-dose male mice and tubular regeneration in high-dose female mice.

Male and female Alderley Park (Wistar-derived) rats and female SPF Swiss mice (75 to 79/sex/group) were exposed by inhalation to 0, 75 or 500 ppm 1,4-DCB for five hours/day, five days/week for 76 weeks (rats) or 57 weeks (mice) (Riley *et al.*, 1980, unpublished report; summarized in Loeser and Litchfield, 1983). Animals were then exposed to control air for a period of 36 weeks (rats) or 18 weeks (mice). Among high-dose rats, liver, kidney, heart and lung weights were increased in both sexes and urinary coproporphyrin levels were elevated in males.

Developmental and Reproductive Toxicity

A two-generation reproductive study conducted by the Chlorobenzene Producers Association has been described by the U.S. EPA (IRIS, 1994) and has been used in the development of a reference concentration (RfC) (Chlorobenzene Producers Association, 1986). Three weeks prior to mating, rats (28/sex/group) were exposed to 0, 50, 150 or 450 ppm 1,4-DCB for six hours/day, seven days/week. F_1 weaning were similarly exposed for 11 weeks before mating. Liver weights were significantly increased among male rats in the 150 and 450 ppm dose groups. Male and female rats exhibited significantly increased kidney weights as well. Male rats in the mid-dose groups exhibited decreased body weight and weight gain, signs of eye and nose irritation and evidence of decreased grooming.

Male mice injected intraperitoneally with 800 mg/kg-day 1,4-DCB in chloroform developed abnormal sperm (Murthy *et al.*, 1987; as cited by DHS, 1988a).

Pregnant rats and rabbits were exposed to 0, 100, 300 or 800 ppm 1,4-DCB for six hours/day over days 6 to 15 (rats) or 6 to 18 (rabbits) of gestation (Hayes *et al.*, 1985). Maternal weight gain was transiently decreased among rabbits in the highest dose group. An increase in the number of resorptions among dams exposed to 300 ppm, but not 800 ppm, was considered to be unrelated to exposure. No other significant toxic effects were noted. In a similar experiment, pregnant rats

exposed to 0, 75, 200 or 500 ppm 1,4-DCB for six hours/day over days 6 to 15 of gestation produced no indications of teratogenicity, fetotoxicity, embryotoxicity or maternal toxicity (Hodge *et al.*, 1977).

Pregnant female CD rats were administered 1,4-DCB by oral gavage with 0, 250, 500, 750 or 1,000 mg/kg-day on days 6 to 15 of gestation (Giavini *et al.*, 1986). At doses ≥ 500 mg/kg-day, maternal weight gain and food consumption was decreased. In the high-dose group, fetal weight was significantly decreased. Among fetuses in the two highest dose groups, the number of skeletal variations was significantly increased and a dose-related increase in the frequency of extra ribs was observed among fetuses from the dose groups ≥ 500 mg/kg-day.

Male mice exposed to 0, 75, 225 or 450 ppm 1,4-DCB for six hours/day for five days exhibited no evidence of dominant lethal toxicity (Anderson and Hodge, 1976).

Genetic Toxicity

NTP testing provided no evidence of mutagenicity in four strains of *Salmonella typhimurium* (with or without metabolic activation), no induction of forward mutations in the mouse lymphoma L5178Y/TK$^{+/-}$ assay (without metabolic activation), no increased sister-chromatid exchange or chromosomal aberrations in Chinese hamster ovary (CHO) cells (with or without metabolic activation) and no increased micronucleation in mouse erythrocytes by 1,4-DCB (NTP, 1987). Another mouse lymphoma assay did not provide clear evidence of mutagenicity (McGregor *et al.*, 1988). Some of NTP's findings have been repeated by other groups, both before and after the NTP report (Galloway *et al.*, 1987; Myhr *et al.*, 1990; Prasad, 1970). Likewise, in a battery of *in vitro* and *in vivo* mutagenicity tests, no mutagenicity was observed in assays in *Salmonella typhimurium* or *Escherichia coli*, dominant lethal assays and cytogenetic assays (Loeser and Litchfield, 1983; Lawlor *et al.*, 1979; Anderson *et al.*, 1990; Shimizu *et al.*, 1983).

1,4-DCB has been shown to bind covalently to DNA of the liver, kidney, lung and stomach in male BALB/c mice within one day following intraperitoneal injection, with repair occurring within three days (Lattanzi *et al.*, 1989). No evidence of DNA binding was observed in male Wistar rats. Liver and lung microsomes from both rat and mouse did, however, induce an interaction of 1,4-DCB with calf thymus DNA. This binding was inhibited by the addition of SKF-525A and enhanced by the addition of GSH. Similar testing of cytosolic fractions also demonstrated DNA binding of 1,4-DCB, although to a lesser degree. Metabolites of 1,4-DCB were also found to covalently bind DNA to a low level (relative to protein binding) in male Wistar rats (den Besten *et al.*, 1992).

Clastogenic activity was significantly increased in the bone marrow of NMR1 mice treated intraperitoneally with 1,4-DCB (Mohtashamipur *et al.*, 1987).

Carcinogenicity

1,4-DCB was administered to F344/N rats and B6C3F1 mice (50/sex/group) in corn oil by gavage five days/week at doses of 0, 150 or 300 mg/kg-day (male rats) and 0, 300 or 600 mg/kg-day (female rats and mice of both sexes) for two years (NTP, 1987). Among male rats, a dose-dependent increase in renal tubular cell adenocarcinoma and a marginal increase in mononuclear cell leukemia were observed (Table 1). NTP concluded that there was clear evidence of carcinogenicity of 1,4-DCB for male rats, but no evidence of carcinogenicity for female rats.

Table 1. Tumor Incidence in 1,4-DCB Treated Male F344/N Rats (NTP, 1987)

Dose (mg/kg-day)	Tubular cell Adenocarcinoma	Mononuclear Cell Leukemia
0	1/50	5/50
150	3/50	7/50
300	7/50	11/50

Liver tumor incidence was significantly increased among both male and female mice (Table 2). Hepatoblastomas were also observed in four high-dose male mice. There was a marginal trend toward increased follicular cell adenomas of the thyroid among female mice (0/48, control; 0/45, low-dose; 3/46, high-dose) and a marginal but significant increase in the incidence of pheochromocytoma among male mice (0/47, control; 2/48, low-dose; 4/49, high-dose). NTP concluded that there was clear evidence of carcinogenicity of 1,4-DCB for both male and female B6C3F1 mice.

Table 2. Tumor Incidence in 1,4-DCB-Treated B6C3F1 Mice (NTP, 1987)

Dose (mg/kg-day)	Hepatocellular Carcinoma		Hepatocellular adenoma		Combined Hepatocellular Adenoma or Carcinoma	
	Male	Female	Male	Female	Male	Female
0	14/50	5/50	5/50	10/50	17/50	15/50
300	11/49	5/48	13/49*	6/48	22/49	10/48
600	32/50*	19/50*	16/50*	21/50*	40/50*	36/50*

* Statistically significant increase in incidence ($p < 0.05$)

Male and female Alderley Park (Wistar-derived) rats and female SPF Swiss mice (75-79/sex/group) were exposed by inhalation to 0, 75 or 500 ppm 1,4-DCB for five hours/day, five days/week for 76 weeks (rats) or 57 weeks (mice) (Riley *et al.*, 1980; summarized in Loeser and Litchfield, 1983). No treatment-related carcinogenic effects were observed among the animals exposed in this regimen.

No carcinogenic effects were observed among several species exposed to 1,4-DCB by inhalation and orally for six to seven months (Hollingsworth *et al.*, 1956).

Kidney Tumors and $\alpha_{2\mu}$-Globulin Binding

The appearance of renal tubule tumors in male rats raises the possibility that the tumors were induced by a mechanism involving the hyperplastic response mediated by the binding of the test compound to $\alpha_{2\mu}$-globulin. This binding leads to accumulation in the renal proximal tubules which results in nephrotoxicity, hyperplasia and a subsequent carcinogenic response, a mechanism hypothesized for certain strains of male rats (including Fisher 344/N) but determined to be irrelevant to humans for the purposes of risk assessment because of the absence of significant amounts of $\alpha_{2\mu}$-globulin in humans (U.S. EPA, 1991). There is some evidence that the

development of kidney tumors observed in the male F344 rats exposed to 1,4-DCB by oral gavage is subsequent to the nephrotoxic action of 1,4-DCB from its (or a metabolite's) binding to $\alpha_{2\mu}$-globulin and accumulation in the tubules. The evidence comes from several observations:

1. 1,4-DCB induces renal tumors only in male rats and not in female rats or mice.
2. 1,4-DCB produces renal toxicity and cell proliferation only in male rats and in the proximal tubules in the P2 segment and there are associated hyaline droplets which contain $\alpha_{2\mu}$-globulin (Bomhard *et al.*, 1988; Charbonneau *et al.*, 1989).
3. A rat strain lacking $\alpha_{2\mu}$-globulin did not develop nephropathy or hyaline droplet accumulation in response to 1,4-DCB exposure (Dietrich and Swenberg, 1991).
4. 1,4-DCB and its primary metabolite (2,5-dichlorophenol) have been shown to reversibly bind to $\alpha_{2\mu}$-globulin both *in vitro* and *in vivo* (Charbonneau *et al.*, 1989).

From this evidence it appears plausible that the $\alpha_{2\mu}$-globulin mechanism may play a role in the etiology of the renal tumors in male rats. Because this mechanism may be irrelevant to humans, the nephropathy and carcinogenesis at this site have not been used for risk assessment in the development of the PHG for 1,4-DCB.

Toxicological Effects in Humans

Acute Toxicity

The evidence of adverse health effects to humans is limited to case reports of accidental exposure. Effects from human exposure described in case reports include (reviewed in DHS, 1988a): pulmonary granulomatosis, vertigo, asthenia, anemia and granulocytopenia (Perrin, 1941); cataracts, hepatitis (Berliner, 1939); death from hepatic failure (Cotter, 1953); swelling around the eyes, dyspnea, headache, nausea and vomiting, fatigue, cough, rhinitis (Weller and Crellin, 1953, Cotter, 1953); hemolytic anemia (Campbell and Davidson, 1970; Hallowell, 1959); and allergic purpura (Nalbandian and Pearce, 1965). Other effects described include headache, runny nose, puffy eyes and swelling of the lower extremities (HSDB, 1997). Longer exposures to high concentrations have been reported to result in weakness, dizziness, weight loss, tingling of the hands and liver injury. The case reports do not always present clear evidence that 1,4-DCB is the etiologic agent for the symptoms which appear.

Exposure of occupationally exposed human subjects to 1,4-DCB vapors at concentrations of 50 to 80 ppm was found to be irritating to the eyes and nose (Hollingsworth *et al.*, 1956). The irritation was more severe at 160 ppm 1,4-DCB.

Subchronic Toxicity

One year after discontinuing an exposure to 1,4-DCB in the home which resulted in hepatic enlargement, jaundice and weight loss, an individual developed cataracts in the lenses of the eyes (HSDB, 1997). Another individual in the same home who also exhibited signs of jaundice and weight loss developed less severe cataracts six months after exposure. A case report has also been made of reversible ataxia following long-term exposure to 1,4-DCB (Miyai *et al.*, 1988).

Developmental and Reproductive Toxicity

No information regarding the developmental and/or reproductive toxicity of 1,4-DCB to humans has been located in the scientific literature.

Genetic Toxicity

Cultured human lymphocytes were reported to have an increase in sister-chromatic exchange in response to exposure to 1,4-DCB (Carbonell *et al.*, 1991). Details were not presented on the purity of the test compound.

Carcinogenicity

Case reports of chronic lymphoid leukemia (two cases), acute myeloblastic leukemia (two cases) and myeloproliferative syndrome (one case) were observed in individuals exposed to 1,2- and 1,4-DCB from repeated use of a mixture of the compounds as a solvent/cleaning fluid (NTP, 1987; Girard *et al.*, 1969). There was no indication of exposure to benzene. In its evaluation of this study, IARC reported that it "suggested an association between leukemia and exposure to dichlorobenzenes" (IARC, 1982).

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

Numerous studies have identified adverse noncarcinogenic effects resulting from exposure to 1,4-DCB. However, no data are available from epidemiological studies of human populations or case reports of human exposures. The few case reports which are available, as well as the limited number of chamber studies, are limited by adequate estimation of exposure levels or by insufficient exposure duration for establishing effects which may result from long-term exposure.

The NTP (1987) chronic gavage studies demonstrated several noncarcinogenic adverse effects at the lowest dose tested in both male and female rats and mice. In the case of male rats, renal effects as well as hyperplasia of the parathyroid were observed at 150 mg/kg-day. The renal toxicity observed in male rats was attributed to the $\alpha_{2\mu}$-globulin mediated response, a response confirmed by many other studies to be specific for certain strains of male rats. Among female rats, renal effects were observed at the low-dose of 300 mg/kg-day. Likewise, of male and female mice administered 300 mg/kg-day exhibited adverse effects, particularly hepatotoxicity. From these studies a lowest-observed-adverse-effect level (LOAEL) of 150 mg/kg-day was identified.

With the exception of renal effects observed in male rats and changes in clinical chemistry and serum parameters for which there was no clear toxicological correlate, the LOAEL observed in rats in a subchronic exposure study was 900 mg/kg-day (liver, bone marrow, spleen, thymus, small intestine and upper respiratory effects); the NOAEL is therefore 600 mg/kg-day (NTP, 1987). The initial mouse portion of the subchronic studies demonstrated adverse liver effects at all doses tested with an LOAEL of 600 mg/kg-day. A follow-up study with lower doses established an LOAEL of 675 mg/kg-day for hepatotoxicity in male and female mice and an NOAEL of 337.5 mg/kg-day.

Hollingsworth *et al.* (1956) demonstrated liver and kidney weight changes in female rats treated for approximately 27 weeks with 188 and 376 mg/kg-day, although no microscopic evidence of injury was reported at the lower level. The NOAEL from this study is 18.8 mg/kg-day.

The developmental study by Giavini *et al.* (1986) provided evidence of fetal effects at doses greater than 500 mg/kg-day, establishing an NOAEL of 250 mg/kg-day. The two-generation inhalation teratogenicity study by the Chlorobenzene Producers Association (1986; as described in IRIS, 1994) demonstrated an LOAEL of 150 ppm 1,4-DCB for effects on liver weight on the parental generation of male rats, with an NOAEL of 50 ppm 1,4-DCB. U.S. EPA estimated a human equivalent exposure level (adjusted for duration) of 75 mg/m^3, which when assuming a 70 kg body weight, a 20 m^3/day breathing rate and a 100% fractional absorption, converts to a daily dose of 21 mg/kg-day. There is considerable uncertainty, however, in the route-to-route extrapolation.

Carcinogenic Effects

Several studies have been conducted evaluating the carcinogenicity of 1,4-DCB, the most complete and current of which is that conducted by (NTP, 1987). This lifetime oral exposure study was conducted in both sexes of two species (rats and mice) with two doses of 1,4-DCB with an adequate number of animals (50/group). Clear evidence of exposure-related tumor development was demonstrated in male rats (renal tumors) and male and female mice (liver tumors). However, as described above, the renal tumors in the male rats have been evaluated cautiously because of the potential involvement of the $\alpha_{2\mu}$-globulin-mediated mechanism, which U.S. EPA determined to be irrelevant to human risk assessment (U.S. EPA, 1991). Since 1,4-DCB produced renal toxicity in female rats and mice as well as male rats, the appearance of renal tumors in male rats has remained part of the weight-of-evidence for the carcinogenicity of this compound.

Other evidence from the NTP studies of rats and mice was also weighted for the evaluation of the carcinogenicity of 1,4-DCB. The development of liver tumors in mice provides strong evidence for the carcinogenicity of 1,4-DCB; the tumors developed in both sexes to a high degree (72%, female; 80% , male) and a rare liver tumor (hepatoblastoma) also developed in 1,4-DCB-exposed male mice. While the relevance of liver tumors in male mice is considered more significant in terms of human risk assessment, the appearance of this tumor type in both male and female of mice lends strength to the weight-of-evidence. Pheochromocytomas also developed in a dose-dependent manner to a significant degree in male mice, although the marginal nature of the observation does not alone provide definitive evidence of carcinogenicity in male mice. Male rats also showed an increase in mononuclear cell leukemia which occurred with a significantly increased trend in incidence with increasing dose by NTP's life-table analyses. The possibility that the development of this tumor type is compound-related, however, cannot be ruled out. Some evidence of genotoxicity also supports the contention of carcinogenicity of 1,4-DCB. While reverse and forward mutation assays are generally negative, Lattanzi *et al.* (1989) and den Besten *et al.* (1992) showed the binding of 1,4-DCB to DNA in rats and mice.

Overall, there is sufficient evidence relating to the carcinogenicity of 1,4-DCB in both mice and rats and in other studies to consider the compound a nonthreshold carcinogen.

For the purpose of establishing the most sensitive site of tumor formation in the most sensitive sex and strain of experimental animals, cancer potencies or cancer slope factors (CSFs) were calculated for the tumor incidences reported to be statistically significantly increased and exposure-related in the NTP (1987) study. A cancer potency for pheochromocytomas in male mice was

found to be less than for liver tumors and was not presented. For the generation of the potencies, the GLOBAL86 program was used which fit the linearized multistage model to the data on tumor incidence (Howe and van Landingham, 1986). The results of these analyses are presented in Table 3. Adjustment for intercurrent mortality is based upon the following relationship:

$$q_{animal} = q_1^* \times \left(\frac{T}{T_e}\right)^3$$

where, T is the life-span of the experimental animals (104 weeks for rats and 80 weeks for mice) and T_e is the duration of the experiment (104 weeks; the CSF_{animal} was adjusted similarly).

Conversion of cancer potencies from experimental animals (q_{animal} or CSF_{animal}) to human potencies (q_{human} or CSF_{human}) were based on the following relationship:

$$q_{human} = q_{animal} \times \left(\frac{bw_h}{bw_a}\right)^{\frac{1}{4}}$$

where, bw_h and bw_a are human and animal body weight defaults, respectively. The default human body weight is 70 kg, mouse body weight is 0.03 kg and rat body weight is 0.35 kg.

The male mouse combined incidence of hepatocellular adenomas and carcinomas was the most sensitive gender and site for tumor development. The p-value of the least squares coefficient (χ^2) indicates a reasonable fit of the model polynomial to this experimental dataset. In accordance with U.S. EPA's draft proposed guidelines for carcinogen risk assessment, the linearized multistage model was also used to estimate the lower 95% confidence limit on the dose associated with a 10% increase in tumor development (LED_{10}) (U.S. EPA, 1996). At doses below this point, a linear dose-response was assumed with which a cancer slope factor (CSF) was calculated. For 1,4-DCB, the value for the cancer potency estimate determined by using the multistage model for estimates outside of the range of observation (estimated for a *de minimis* theoretical excess individual cancer risk level of 10^{-6}) is comparable to that determined using the linear assumption for this range [5.7×10^{-3} $(mg/kg\text{-}day)^{-1}$ compared to 5.4×10^{-3} $(mg/kg\text{-}day)^{-1}$]. Given the slight difference in the value generated from the linear default assumption and the absence of a compelling scientific reason to depart from the linear assumption at low doses, the value of 5.4×10^{-3} $(mg/kg\text{-}day)^{-1}$ is used as the estimate of the cancer potency for the calculation of a PHG for 1,4-DCB.

Table 3. Cancer Potencies for 1,4-DCB Based on NTP (1987) (GLOBAL86)

Data sets B6C3F1 Mice	q_1^* $(mg/kg\text{-}d)^{-1}$	q_{human} $(mg/kg\text{-}d)^{-1}$	χ^2	p	k	MLE_{10} (mg/kg-d)	LED_{10} (mg/kg-d)	CSF_{animal} $(mg/kg\text{-}d)^{-1}$	CSF_{human} $(mg/kg\text{-}d)^{-1}$
Combined Liver Tumors Male	1.8E-3	5.7E-3	0.48	0.49	2	130	58	1.7E-3	5.4E-3
Combined Liver Tumors Female	4.6E-4	1.5E-3	4.0	0.046	2	210	230	4.4E-4	1.4E-3
Liver Carcinomas Male	5.8E-4	1.8E-3	1.9	0.16	2	230	180	5.5E-4	1.7E-3
Liver Carcinomas Female	5.3E-4	1.7E-3	0.37	0.54	2	280	200	5.1E-4	1.6E-3
Liver Adenomas Male	1.1E-3	3.5E-3	0.42	0.52	2	150	92	1.1E-3	3.4E-3
Liver Adenomas Female	4.0E-4	1.3E-3	1.1	0.29	2	350	260	3.8E-4	1.2E-3

CALCULATION OF PHG

Noncarcinogenic Effects

The calculation of a health protective concentration (C, in mg/L) for 1,4-DCB in drinking water can be calculated using the general equation for noncancer endpoints:

$$C = \frac{NOAEL \times BW \times RSC}{UF \times W}$$

where NOAEL is the no adverse effect level of the principle study, BW is the human body weight default, RSC is the relative source contribution of drinking water to the total exposure, UF is the uncertainty factor(s) associated with the determination of the value, and W is the drinking water consumption rate.

In the case of 1,4-DCB, the experimental NOAEL for the principle study was 18.8 mg 1,4-DCB/kg body weight-day, which is then adjusted for discontinuous exposure because of the dosing regimen (5 days/wk). The adult human body weight (BW) default is 70 kg. The RSC of 20% was used in the calculation in the absence of information suggesting this

value is not appropriate. A cumulative uncertainty factor of 1000 has been applied which incorporates uncertainty contributions for interspecies extrapolation (10), uncertainty from the subchronic nature of the principle study (10), and potentially sensitive human subpopulations (10). The adult human water consumption default value is 2 L/day. Thus:

$$C = \frac{18.8\ {}^{mg}/_{kg\text{-}day} \times \left(\frac{5}{7}\right) \times 70\ kg \times 0.2}{1000 \times 2\ {}^{L}/_{day}} = 0.1\ {}^{mg}/_{L}$$

Carcinogenic Effects

The calculation of a public health-protective concentration (C, in mg/L) for 1,4-DCB in drinking water can be calculated using the general equation for a carcinogenic endpoint:

$$C = \frac{R \times BW}{CSF \times L/day}$$

where,

R	=	*De minimis* theoretical excess lifetime individual cancer risk level (10^{-6})
BW	=	Adult male default body weight (70 kg)
CSF	=	Cancer slope factor derived from the critical study [5.4×10^{-3} $(mg/kg\text{-}day)^{-1}$]
L/day	=	Volume of water consumed daily by an adult (2 L/day).

For 1,4-DCB, the cancer slope factor (CSF_{human}) derived from the principal study is 5.4×10^{-3} $(mg/kg\text{-}day)^{-1}$ and the adult human body weight default is 70 kg. The adult human water consumption default value is 2 L/day. A risk level of 10^{-6} is generally considered to be *de minimis*.

Therefore,

$$PHG = \frac{10^{-6} \times 70\ kg}{5.4 \times 10^{-3}\ (mg/kg\text{-}day)^{-1} \times 2\ L/day}$$

$$= 0.0065\ mg/L = 0.006\ mg/L\ (rounded) = 6\ ppb.$$

OEHHA calculates a PHG of 0.006 mg/L (6 ppb) for 1,4-DCB in drinking water based on its carcinogenic potential. The calculation of this PHG has incorporated uncertainty such that potentially sensitive subpopulations should be protected from carcinogenic effects from drinking water exposure to 1,4-DCB at this level. The cancer potency value derived from the NTP carcinogenic bioassay has been used for the calculation of the PHG.

RISK CHARACTERIZATION

The primary sources of uncertainty in the development of the PHG for 1,4-DCB in drinking water are also the general issues of uncertainty in any risk assessment, particularly inter- and intra-species extrapolation. There is also some degree of uncertainty regarding the evidence for the putative mechanism involving the accumulation of protein droplets containing $\alpha_{2\mu}$-globulin in the development of renal tumors in response to 1,4-DCB exposure (recently reviewed in Melnick *et al.*, 1996). Among the concerns about the relationship are: 1) evidence that certain compounds which

induce $\alpha_{2\mu}$-globulin accumulation and nephropathy do not appear to lead to renal tumor development (gabapentin, lindane), 2) ligand binding to $\alpha_{2\mu}$-globulin is not required for protein droplet accumulation, 3) renal cell replication rates do not correlate with carcinogenicity and 4) compounds which induce $\alpha_{2\mu}$-globulin accumulation frequently also produce tumors at other sites. These observations have lead to the suggestion that $\alpha_{2\mu}$-globulin may be serving to concentrate or deliver a compound which is actually carcinogenic to the kidney and the inter-species difference is more a matter of the delivered dose rather than an issue of irrelevance because of the absence of $\alpha_{2\mu}$-globulin in humans. While this uncertainty regarding potential mechanism has not been addressed quantitatively in the current risk assessment (renal toxicity and carcinogenicity in male rats were not used in the dose-response evaluations), the issue remains present and may become important in future assessments as more data become available. No evidence of synergy with other chemicals in the toxicity of 1,4-DCB was found in the literature.

The PHG of 6 ppb was calculated based on the carcinogenic potency of 1,4-DCB. In calculating the PHG, a *de minimis* theoretical excess individual cancer risk level of 10^{-6} was assumed. The corresponding levels for cancer risk levels of 10^{-5} or 10^{-4} are 60 and 600 ppb, respectively.

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 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.

U.S. EPA follows a general procedure in promulgating MCLGs:

1. if Group A and B carcinogens (i.e., strong evidence of carcinogenicity) MCLGs are set to zero,

2. if Group C (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,

3. if Group D (i.e., inadequate or no animal evidence) an RfD approach is used to promulgate the MCLG.

For approaches that use low-dose extrapolation based on quantitative 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. This is an area of uncertainty and scientific debate and it is not clear how this assumption impacts the overall health risk assessment.

OTHER STANDARDS AND CRITERIA

The U.S. Environmental Protection Agency's (U.S. EPA's) Maximum Contaminant Level (MCL) and Maximum Contaminant Level Goal (MCLG) for 1,4-DCB is 0.075 mg/L (75 ppb). This value was based upon the exposure level of 150 mg/kg-day which U.S. EPA determined to be the NOAEL in the subchronic portion of the NTP rat study. For its calculation, U.S. EPA adjusted the dose based upon the treatment regimen (exposure of 5 of 7 week days), included 3 uncertainty factors of 10 each (subchronic study duration, interspecies extrapolation, potentially sensitive human subpopulations), an assumed human body weight of 70 kg, 2 L/day water consumption, 20% relative source contribution for drinking water, plus an additional safety factor of 10 for possible carcinogenic effects. The current California MCL is 0.005 mg/L (5 ppb).

U.S. EPA has established an ambient water criterion of 400 µg/L for dichlorobenzenes ingested through water and contaminated aquatic organisms and an ambient water criterion of 2.6 mg/L for dichlorobenzenes ingested through contaminated aquatic organisms alone (U.S. EPA, 1980). U.S. EPA has established an inhalation reference concentration (RfC) of 75 mg/m^3 for noncarcinogenic effects based upon increased liver weights in parental male rats in a reproductive study (IRIS, 1994).

The Occupational Safety and Health Administration (OSHA) has set a permissible exposure level (PEL) of 75 ppm (eight hour time-weighted-average) and a ceiling value of 110 ppm for 1,4-DCB.

Various states have set guidelines for drinking water concentrations and acceptable ambient air concentrations. These are shown in Table 4.

Table 4. State Drinking Water Guidelines

State	Drinking Water Guideline
Alabama	75 ppb
Arizona	75 ppb
Connecticut	75 ppb
Maine	27 ppb
Massachusetts	5 ppb
Minnesota	10 ppb
Wisconsin	75 ppb

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