

**Public Health Goal for
1,2-DICHLOROBENZENE
in Drinking Water**

Prepared by

**Pesticide and Environmental Toxicology Section
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency**

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LIST OF CONTRIBUTORS

PHG PROJECT MANAGEMENT

Project Officer

Anna Fan, Ph.D.

Chemical Prioritization

Report Outline

Joseph Brown, Ph.D.

Coordinator

David Morry, Ph.D.

Yi Wang, Ph.D.

Document Development

Michael DiBartolomeis, Ph.D.

Coordinator

George Alexeeff, Ph.D.

Hanafi Russell, M.S.

Yi Wang, Ph.D.

Public Workshop

Michael DiBartolomeis, Ph.D.

Coordinator

Judy Polakoff, M.S.

Organizer

Methodology/Approaches/Review

Comments

Joseph Brown, Ph.D.

Robert Howd, Ph.D.

Coordinators

Lubow Jowa, Ph.D.

David Morry, Ph.D.

Rajpal Tomar, Ph.D.

Yi Wang, Ph.D.

REPORT PREPARATION

Author

John Faust, Ph.D.

Primary Reviewers

Richard Lam, Ph.D.

Jolanta Bankowska, Ph.D.

Secondary Reviewer

Michael DiBartolomeis, Ph.D.

Final Reviewers

Anna Fan, Ph.D.

William Vance, Ph.D.

Editor

Michael DiBartolomeis, Ph.D.

SUPPORT

Administrative Support

Edna Hernandez

Coordinator

Laurie Bliss

Sharon Davis

Kathy Elliott

Vickie Grayson

Michelle Johnson

Juliet Rafol

Genevieve Shafer

Tonya Turner

Library Support

Mary Ann Mahoney

Valerie Walter

Website Posting

Robert Brodberg, Ph.D.

Edna Hernandez

Laurie Monserrat, M.S.

Judy Polakoff, M.S.

Hanafi Russell, M.S.

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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 0.6 mg/L (600 ppb) is developed for 1,2-dichlorobenzene (1,2-DCB) in drinking water. There is inadequate evidence to establish the carcinogenicity of 1,2-DCB to humans, and therefore the proposed PHG is based on noncarcinogenic adverse effects observed in experimental animals in a subchronic oral exposure study. The use of this study is consistent with the U.S. Environmental Protection Agency (U.S. EPA) in the establishment of its MCL for drinking water exposure. The National Toxicology Program (NTP) study cited numerous adverse effects in rats exposed to 250 and 500 mg/kg-day for 90 days which included hepatotoxicity and organ and body weight changes. These types of effects are consistent with other reports on the toxicity of 1,2-DCB. The no-observed-adverse-effect-level (NOAEL) for 1,2-DCB was identified as 125 mg/kg-day. Based on these data, OEHHA develops a PHG of 0.6 mg/L (600 ppb) for 1,2-DCB in drinking water.

INTRODUCTION

The purpose of this document is to develop a PHG for 1,2-DCB in drinking water. U.S. EPA determined that 1,2-DCB is not classifiable as to human carcinogenicity (Group D; IRIS, 1992). The International Agency for Research on Cancer (IARC) determined that there were inadequate data upon which to base an evaluation of the carcinogenicity of 1,2-DCB (IARC, 1982).

In this document, we evaluate the available data on the toxicity of 1,2-DCB, with the primary focus on the literature related to oral exposures which may be most appropriate for the establishment of an PHG for drinking water. To determine a public health protective level for 1,2-DCB in drinking water, an effort was made to identify potential sensitive groups in the general population (and if there was inadequate information to identify whether or not there are any, appropriate uncertainty factors were incorporated into the PHG). The studies which can be used to identify public health protective levels are reviewed and evaluated.

CHEMICAL PROFILE

1,2-dichlorobenzene (1,2-DCB; CAS No. 95-50-1) has the molecular formula $C_6H_4Cl_2$ and a molecular weight of 147.01 g/mol. At room temperature, it is a colorless to pale yellow liquid with a pleasant, aromatic odor (HSDB, 1997). 1,2-DCB has a melting point of $-17^\circ C$ and a boiling point of $180^\circ C$. It is miscible with numerous organic solvents including alcohol, ether, benzene and acetone. Its solubility in water is 137 mg/L at $25^\circ C$ and it has a vapor pressure of 1.47 mm Hg at $25^\circ C$ (HSDB, 1997). The odor threshold has been estimated at 50 ppm 1,2-DCB (HSDB, 1997).

PRODUCTION AND USE

The primary uses of 1,2-DCB are as a chemical intermediate and as a solvent. An important use for 1,2-DCB is in the production of several chemicals, mainly 3,4-dichloroaniline (via 3,4-dichloronitrobenzene) and several herbicides including diuron, propanil and neburon (NTP, 1985). As a solvent, one of the key uses of 1,2-DCB is in the manufacture of toluene diisocyanate. Together these account for approximately 70 to 90% of total 1,2-DCB use. 1,2-DCB is also an insecticide/fumigant used in the control peach tree borers, bark beetles, grubs and termites. Other minor uses include its use as a solvent for waxes, gums, resins, tars, rubbers, oils and asphalts and

as a degreaser for metals (e.g., engines), leather and wool. It is also an intermediate in the manufacture of certain dyes. As an emulsion, 1,2-DCB has been used as a deodorizing agent in garbage and sewage.

1,2-DCB is produced along with other chlorobenzene compounds (including *para*-DCB) by the chlorination of benzene or monochlorobenzene in the presence of a catalyst, usually ferric chloride (IARC, 1982). The chemical mixtures produced by this reaction can then be separated by distillation and crystallization. 1,2-DCB can also be produced by the Sandmeyer process which uses chloroaniline as a substrate. Technical grade 1,2-DCB contains 98.7% 1,2-DCB plus 1.3% other isomers.

In 1979, production in the United States (U.S.) was estimated to be 26 million kilograms of 1,2-DCB (HSDB, 1997). Imports have been estimated at over one million kilograms of 1,2-DCB in 1975 (HSDB, 1997). No more recent data were available on the production of 1,2-DCB.

ENVIRONMENTAL OCCURRENCE

1,2-DCB is not known to occur naturally. The introduction of significant quantities of 1,2-DCB into the environment may result from its use as an industrial solvent and chemical intermediate.

Air

Significant release of 1,2-DCB to air may result from its use as a solvent. It has been estimated that 5 to 10% of the annual U.S. production of 1,2-DCB is released to air (IARC, 1982). Air sampling taken in the vicinity of chemical plants and wasted disposal sites have found levels ranging from 0 to 1.3 $\mu\text{g}/\text{m}^3$ (IARC, 1982). The California Toxic Release Inventory (CTRI) for the years 1987 to 1994 reported 1,2-DCB emissions to air of 5,403 to 62,493 pounds/year. Aerial fallout collected on the coast of southern California in 1977 showed levels of 1,2-DCB of less than 53 ng/m^2 (IARC, 1982). The incineration of organic matter containing chlorine has been proposed as another potential source of environmental contamination (Health Canada, 1993; citing Young and Voorhees, 1989).

Soil

No releases of 1,2-DCB to land were reported in the CTRI for the years 1987 to 1994. Offsite (disp + recy) releases were estimated between 38,480 and 93,644 pounds/year for the years 1987 to 1993. The nationwide U.S. EPA TRI for 1987 to 1993 estimated releases to land of 171,663 pounds 1,2-DCB. The degradation of lindane in soil has been reported to produce 1,2-DCB (IARC, 1982).

Water

A potentially significant source of water contamination by 1,2-DCB is from its use as a deodorizer. Water contamination can also result from leaching from chemical waste dumps. No 1,2-DCB, however, has been reported to be introduced into water in the CTRI for the years 1987 to 1994. Emission to sewers and Publicly-Owned-Treatment-Works (POTW) ranged from 0 to 350 pounds/year for the same years. The nationwide TRI for 1987 to 1993 estimated releases to water of 75,967 pounds 1,2-DCB. California is not among the top five states in amount released to water and land (<2400 pounds).

Drinking water has been reported to contain levels of 1,2-DCB ranging from 1 µg/L (\leq 1975) and 2.5 µg/L (1976 to 1977) (IARC, 1982; citing Shackelford and Keith, 1976). Effluents from southern California sewage plants have been reported to contain 1,2-DCB at levels ranging from 2 to 12 µg/L (IARC, 1982). There have also been other reports of drinking water contamination with 1,2-DCB (NTP, 1985; citing Dowty *et al.*, 1975; Kavlock *et al.*, 1979).

Food

Significant and/or probable sources of exposure to 1,2-DCB in food have not been identified. However, "proper or improper uses or accidents" may result in the contamination of food commodities (U.S. EPA, 1980a). Furthermore, the lipid solubility of dichlorobenzenes suggests the potential for bioconcentration such that consumption of fish or shellfish may result in exposure to 1,2-DCB.

METABOLISM AND PHARMACOKINETICS

Absorption

Because of their relatively high lipid solubility and relatively low water solubility, dichlorobenzenes are likely to be absorbed by most routes of exposure by membrane diffusion (U.S. EPA, 1980a). Rapid respiratory absorption has been suggested by the appearance of principal metabolites in urine following occupational exposure to *para*-DCB (U.S. EPA, 1980a; citing Pagnotto and Walkley, 1966). Gastrointestinal and skin absorption of chlorinated benzenes has also been suggested by both case reports of poisonings and animal experimentation (U.S. EPA, 1980a; citing Jacobs *et al.*, 1974a; Jacobs *et al.*, 1974b; Ware and West, 1977).

Distribution

Distribution of 1,2-DCB is likely to occur to all highly perfused sites because of its ready absorption by several routes of exposure. Rats were fed a mixture of Rhine River contaminants including 1,2-DCB such that the received doses were 0.4, 0.8 or 2 mg 1,2-DCB/kg body weight for 4 to 12 weeks (Jacobs *et al.*, 1974a,b). 1,2-DCB was found to accumulate in adipose tissue (both abdominal and renal) to a greater extent than in the liver, kidney, heart and blood.

Metabolism and Excretion

Metabolites identified from the oral administration of 1,2-DCB to Chinchilla rabbits include 3,4-dichlorophenol (major), 2,3-dichlorophenol (minor), 3,4-dichlorophenylmercapturic acid (minor) and 3,4- and 4,5-dichlorocatechol (minor) (IARC, 1982; Azouz *et al.*, 1955). Glucuric (~50%), ethereal sulfate (~20%) and mercapturic acid compounds (~5%) were the major conjugates in urine and peaked one day after administration. Another study in which [¹⁴C]-1,2-DCB was orally administered to rats at doses of 10, 50 or 250 mg/kg identified ~60% mercapturic acids, ~30% sulfates and ~10% phenols in the urine (Hissink *et al.*, 1996). Elimination of 1,2-DCB occurs relatively slowly with most elimination complete five to six days after administration (Parke and Williams, 1955).

TOXICOLOGY

Toxicological Effects in Animals

Acute Effects

Median lethal doses for 1,2-DCB in mice, rats, rabbits and guinea pigs ranged from 1,875 to 3,375 mg/kg for single doses administered in olive oil (Varshavskaya, 1967b as described in U.S. EPA, 1980a). Effects observed included reddening of the mucous membranes, tearing and salivation, difficulty breathing, disturbed movement (ataxia, paraparesis, paraplegia), excitation then sleepiness and death within three days. *Post-mortem* examination revealed pathological changes to the liver (necrosis), brain (edema), stomach (hemorrhage) and kidneys.

In a 10-day oral gavage study, Sprague-Dawley rats (10/sex/dose) were administered 0, 37.5, 75, 150 or 300 mg/kg-day (Robinson *et al.*, 1991). Among male rats in the high-dose group, final body weight, absolute organ weight (heart, kidney, spleen, testes, thymus) and relative organ weight (spleen, thymus) were significantly decreased. Absolute and relative liver weight and hepatocellular necrosis were increased in this dose group as well. High-dose male rats also showed increased water consumption and alanine aminotransferase levels (ALT). Leukocyte counts were increased among male rats in both the 150 and 300 mg/kg-day dose groups.

Prior to the testing by NTP of 1,2-DCB for chronic toxicity (see below), 14-day studies in B6C3F1 mice and Fischer 344 rats were undertaken by Battelle's Columbus Laboratories (NTP, 1985). Animals (five/sex/group) were administered 0, 250, 500, 1,000, 2,000 or 4,000 mg/kg-day (mice - first experiment), 0, 30, 60, 125, 250 or 500 mg/kg-day (mice - second experiment) and 0, 60, 125, 250, 500 or 1,000 mg/kg-day (rats) in corn oil on 14 consecutive days. In the first mouse experiment, there was no survival among mice in the top three dose groups and overall survival was less than 20%. *Post-mortem* examination of male mice in the 500 mg/kg dose group showed liver effects including paleness, mottling, focal necrosis, cyto- and karyomegaly, chronic moderate multifocal granulomatous hepatitis and/or centrilobular degeneration. In the second mouse experiment, all but two mice survived the exposure. Hepatocellular necrosis was observed in two of four male mice. Female mice in the high-dose group exhibited signs of hepatocellular necrosis (1/4), multifocal hepatitis (1/4), cytomegaly and karyomegaly (2/4) and hepatocellular degeneration (1/4). All effects were found to be mild.

All rats in the high-dose group died by the fifth day of the study. Male rats in the 250 and 500 mg/kg dose group and female rats in the 500 mg/kg showed decreased weight gain over the test period. Gross examination of tissues from animals in the high-dose group as well as some rats in lower dose groups showed discoloration of the liver, abnormally colored small intestine contents and congestion of brain vascularization.

1,2-DCB administered in liquid paraffin at doses up to 455 mg/kg for 15 days produced hepatic porphyria in male rats as evidenced by increased porphyrin precursors in the liver, urine and feces (Rimington and Ziegler, 1963). Other indications of hepatic toxicity included decreased catalase activity and necrosis. The study design precluded the determination of a no-observe-adverse-effect level (NOAEL).

Male F344 and Sprague-Dawley rats were administered 1,2-DCB intraperitoneally at doses ranging from 0.9 to 5.4 mmol/kg (Stine *et al.*, 1991). Plasma ALT levels in F344 rats were elevated within 24 hours at doses between 1.8 and 5.4 mmol/kg, suggesting liver injury. Histopathological examination of the liver showed evidence of centrilobular injury. These authors also report a substantial difference in strain sensitivity to the hepatotoxic effects of 1,2-DCB, with F344 rats considerably more sensitive than Sprague-Dawley rats. At 1,2-DCB levels which produced minimal hepatic injury (0.9 mmol/kg), pretreatment with phenobarbital increased the degree of hepatotoxicity markedly, suggesting an involvement of cytochrome P₄₅₀ in the mediation of the injury.

Male F344 rats (four per group) were injected once with 2, 3 or 4 mmol/kg 1,2-DCB (control animals received corn oil) and were examined for signs of liver and kidney toxicity (Valentovic *et al.*, 1993). After 24 hours, plasma transaminase (ALT/GPT) was significantly increased in a dose-dependent manner accompanied by centrilobular necrosis, indicating acute hepatotoxicity. Urine output, urinary protein and liver weight were increased both one and two days after injection of 4 mmol/kg 1,2-DCB. Kidney weight was significantly increased and renal cortical slice accumulation of cations was decreased two days after injection of 4 mmol/kg 1,2-DCB.

Subchronic Effects

In a 90-day oral gavage study designed to meet the needs of the U.S. EPA for toxicity data, Sprague-Dawley rats (10/sex/dose) were administered daily doses of 0, 25, 100 or 400 mg/kg-day (Robinson *et al.*, 1991). In addition to significantly decreased body weights at the end of the study, male rats in the high-dose group exhibited decreased absolute and relative organ weights (spleen) and increased absolute organ weight (kidney, liver) and increased relative organ weight (heart, kidney, liver, brain, testes). Female rats in the high-dose group also exhibited increased absolute and relative weight of both kidney and liver. Other effects observed included increased ALT (high- and mid-dose males), blood urea nitrogen (BUN) (high-dose males) and total bilirubin (high-dose males and females). Liver lesions described as centrilobular degeneration, hypertrophy and single cell necrosis were observed among male and female rats in the high-dose group.

Beyond the 14-day studies described above, 13-week subchronic studies were also undertaken by Battelle's Columbus Laboratories as part of the dose range-finding for the chronic NTP study (NTP, 1985). Mice and rats (five/sex/group) were administered 1,2-DCB at 0, 30, 60, 125, 250 or 500 mg/kg-day in corn oil for five days/week for 13 weeks.

Male mice in the two highest dose groups and female mice in the high-dose group exhibited decreased weight gain over the course of the experiment. By the end of the experiment, male and female mice in the high-dose group and female mice in the 250 mg/kg dose group exhibited persistent rough coats and lethargic behavior. An observation of relatively low white cells counts among male mice was attributed to unusually low counts among the control group. Of the two mice in the high-dose group surviving the regimen, one mouse showed signs of hepatocellular necrosis accompanied by increased SGPT levels. Total liver porphyrin was elevated among female mice in the two highest dose groups and there was a positive dose-response trend. Treated male mice in the high-dose group exhibited increased uroporphyrin and female mice in the high-dose group exhibited increased coporphyrin levels. Relative liver weight was increased among male and female mice in the high-dose group and to a lesser degree among female mice in the 250 mg/kg dose group. Microscopic examination of animals in the high-dose group exhibited evidence of hepatic centrilobular necrosis, hepatocellular necrosis, foci of mineralization of the myocardial

fibers of the heart, necrosis and myositis of skeletal muscle, splenic and thymic lymphoid depletion and splenic lymphocyte necrosis (only one female). Two male mice in the 250 mg/kg dose group exhibited evidence of hepatocellular necrosis. No effects were observed in the mice in the 125 mg/kg dose group.

Table 1 identifies effects which were observed among rats in the 13-week NTP study (1985). A dose-dependent decrease in final body weights was observed in male rats with the final body weight of the high-dose group 19% below that of the control animals. Relative organ weights also changed significantly for the lung (increased), thymus (decreased), right kidney (increased) and brain (increased) of male rats in the high-dose group. Absolute organ weights of the heart (decreased), liver (increased), spleen (decreased), thymus (decreased) and testes (decreased) were also significantly altered in this group. Relative and absolute uterine weights were increased for female rats in the high-dose group. The change in liver weight for both male and female rats was found to be dose-dependent. Urinary uroporphyrin and coproporphyrin levels were significantly increased in male and female rats in the high-dose group (the only group examined for this effect). Several blood parameters were significantly decreased among rats in the high-dose group including hematocrit, hemoglobin, RBC count (males only), lymphocytes (males only) and mean corpuscular volume. An increase in the number of platelets observed in female rats in all but the lowest dose group of female rats was not considered to be biologically significant. Small changes in certain blood parameters (serum cholesterol, triglycerides, protein) were speculated to be a reflection of hepatic effects. The liver damage found upon microscopic examination included centrilobular hepatocellular degeneration or necrosis.

Table 1. Effects Observed in the 13-Week Study of 1,2-DCB in Rats (NTP, 1985)

Effect	dose (mg/kg-day)									
	30		60		125		250		500	
	M	F	M	F	M	F	M	F	M	F
Relative liver weight (↑)					✓	✓	✓	✓	✓	✓
Liver necrosis							✓	✓	✓	✓
Renal tubular Degeneration									✓	
Thymic lymphoid Depletion									✓	
Serum cholesterol	✓				✓	✓	✓	✓	✓	✓

Rats (10 females/group) were treated by gavage with 0, 18.8, 188 or 376 mg/kg-day for five days/week for 192 days (Hollingsworth *et al.*, 1958). Among animals in the high- and mid-dose groups, liver and kidney weights were increased; however, only animals in the high-dose group exhibited liver pathology (cloudy swelling). In an inhalation study, several species (rats, mice, guinea pigs, monkeys) were exposed to 0, 49 ppm (rats, guinea pigs, mice) or 93 ppm (rats, guinea pigs, rabbits, monkeys) 1,2-DCB for seven hours/day, five days/week for six to seven months. Among animals in the high-dose group, body weight gain was reduced (rats) and spleen weights were increased (guinea pigs).

White rats were administered 0, 0.001, 0.01 or 0.1 mg/kg-day 1,2-DCB for nine months (Varshavskaya, 1967a; as described in U.S. EPA, 1988). No effects were observed among animals in the lowest dose group. Among rats in the high-dose group, adrenal gland weight was increased as well as an increase in urinary 17-ketosteroids. At both the high- and mid-dose, acid phosphatase was increased and alkaline phosphatase was decreased.

Chronic Effects (Non carcinogenic)

F344/N rats and B6C3F1 mice (50/sex/dose) were treated by gavage five times/week with 0, 60 or 120 mg/kg 1,2-DCB for 103 weeks (NTP, 1985). Survival among male rats in the high-dose group was significantly decreased, although aspiration of the treatment compound into the lungs and error in administration were likely contributing factors. Among male mice in the high-dose group there was an increase in the incidence of kidney tubular regeneration (control, 8/48; low-dose, 12/50; high-dose, 17/49), although this incidence is below that of several other control groups studied in the same laboratory at approximately the same time.

Developmental and Reproductive Toxicity

Bred Fischer 344 rats (30 or 32/group) and inseminated New Zealand White rabbits (28 or 30/group) were exposed to 0, 100, 200 or 400 ppm 1,2-DCB by inhalation for six hours/day on Days 6 to 15 (rats) or 6 to 18 (rabbits) of gestation in order to examine teratogenic potential (Hayes *et al.*, 1985). Among rat dams in the high-dose group liver weight was increased. Among rat dams in all exposed groups, maternal weight gain was decreased. Among rabbit dams, maternal weight gain was decreased during the first three days of exposure to 400 ppm 1,2-DCB. There was no evidence of teratogenic or fetotoxic effects in rats or rabbits up to 400 ppm 1,2-DCB.

Genetic Toxicity

No evidence of mutagenicity was found when 1,2-DCB was tested in several strains of *Salmonella*, both with and without metabolic activation (NTP, 1985; Anderson *et al.*, 1972; Lawlor *et al.*, 1979; Loveday *et al.*, 1990; Myhr and Caspary, 1991; Haworth *et al.*, 1983). 1,2-DCB increased the frequency of reverse mutations of the *meth₃* (methionine-requiring) locus of *Aspergillus nidulans* (Prasad, 1970).

Carcinogenicity

F344/N rats and B6C3F1 mice (50/sex/dose) were treated by gavage five times/week with 0, 60 or 120 mg/kg-day 1,2-DCB for 103 weeks (NTP, 1985). Among low-dose male rats, the incidence of pheochromocytomas was increased, although the incidence was not significantly elevated in the high-dose group and there was no evidence of a dose-dependent trend (9/50, 16/50, 6/49; all non-malignant). Among male and female mice, the incidence of malignant histiocytic lymphoma was increased, although the incidence of total lymphoma was not increased. There was a positive trend test showing for the incidence of combined alveolar and bronchiolar carcinomas in male mice. NTP concluded there was no evidence of carcinogenicity of 1,2-DCB in either F344/N rats or B6C3F1 mice at the doses tested.

Toxicological Effects in Humans

Acute Effects

Short-term exposure to high concentrations of 1,2-DCB has been suggested to result in depression of the central nervous system, although this effect is weak (reviewed in HSDB, 1997). Exposure

to 1,2-DCB vapors has also been reported to result in transient irritation of the eyes, nose and throat while oral exposure has resulted in stomach discomfort with nausea and vomiting.

Subchronic Effects

There are several case reports of poisoning, primarily from inhalation exposure to 1,2-DCB vapors, although the exposures usually involved exposure to other chlorinated benzene compounds (reviewed in U.S. EPA, 1980a; U.S. EPA, 1988). Dermal exposure was probably also significant in several of these cases. Quantitative estimates of exposure were not available. Among the effects observed in some, but not all cases, were irritation of the upper respiratory tract and eyes, nausea, vomiting, fatigue, headache, contact dermatitis, anemia, peripheral lymphadenopathy, acute hemolytic anemia, jaundice and leukocytosis. These observations suggest a broad spectrum of target organs in the toxicity produced by 1,2-DCB.

Twenty-six workers (8 male and 18 female) were accidentally exposed to 1,2-DCB for approximately eight hours/day for four days at levels thought to be in excess of 100 ppm (Zapata-Gayon *et al.*, 1982). The workers developed clinical symptoms including headache, malaise, dizziness, nausea and irritation of the mucous membranes.

In another study, long-term exposure to 1,2-DCB in the air in an industrial setting was not found to produce indications of toxicity, as determined by intermittent medical examinations which included blood work and urinalysis (Hollingsworth *et al.*, 1958). Air concentration were estimated between 1 and 44 ppm 1,2-DCB (mean, 15 ppm).

Developmental and Reproductive Toxicity

No data regarding the developmental or reproductive toxicity of 1,2-DCB to humans were located in the literature.

Genetic Toxicity

The occupationally-exposed workers described above (n = 26; Zapata-Gayon *et al.*, 1982) showed increased incidence of chromosomal aberrations in peripheral leukocytes relative to an unexposed control group (n = 11), with approximately equal single and double breaks. There was some increase in chromosomal aberrations still evident after six months.

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-dichlorobenzene from repeated use of a mixture of the compounds as a solvent and cleaning fluid (Girard *et al.*, 1969; Tolot *et al.*, 1969; as described in IARC, 1982 and U.S. EPA, 1980a). There was no indication of exposure to benzene.

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

There are inadequate quantitative exposure data from the case reports and epidemiological studies of adverse human health effects from exposure to 1,2-DCB to establish a dose-response relationship.

Several studies in experimental animals have identified levels of 1,2-DCB which have resulted in adverse effects. The single available chronic exposure study (NTP, 1985) demonstrated a statistically significant increase in the incidence of kidney tubular regeneration among animals exposed to 120 mg/kg-day (the highest dose tested). The establishment of this level as a lowest-observed-adverse-effect level (LOAEL) is questionable, however, given that concurrent experiments conducted by NTP showed incidences as high for this effect among other control animal populations as for those in the high-dose group exposed to 1,2-DCB. In the establishment of its MCL for 1,2-DCB, U.S. EPA identified the subchronic NTP (1985) study in which rats were exposed by gavage as the study with the most appropriate NOAEL for establishing a guidance value for drinking water exposure. The NOAEL identified in the subchronic segment of NTP (1985) of 125 mg/kg-day for hepatotoxicity was considered more appropriate by U.S. EPA than the lower NOAEL identified in Hollingsworth *et al.* (1958) (18.8 mg/kg-day) because of the limited number of experimental doses used in the latter study (three). In addition, the limited experimental detail presented in Hollingsworth *et al.* (1958) makes interpretation of the results more difficult. Another study for which an NOAEL is reported as lower than that observed in the subchronic portion of the NTP study suffered from lack of experimental detail or questionable significance of toxicological endpoints (Varshavskaya, 1967a).

The only new subchronic toxicity study described since U.S. EPA's evaluation of the literature is that of Robinson *et al.* (1991). This study identified an LOAEL of 400 mg/kg-day for changes in body and organ weight as well as pathological changes to the liver. An NOAEL of 100 mg/kg-day was therefore identified from this study. Since 1,2-DCB was administered daily in this study there would be no adjustment for discontinuous exposure, thus the cumulative dose level for the NOAEL would be higher in this study than that for the NOAEL observed in NTP (1985). The difference, however, is very slight. This study is also limited by the number and range of doses used, which limits the evaluation of a potential dose-response (clear effects were only observed in the high-dose group, whereas in NTP (1985), clear effects were observed in the two highest dose groups).

Higher LOAELs and NOAELs than these observed in the subchronic NTP (1985) study were reported in the teratological investigation by Hayes *et al.* (1985) and the 10-day oral study by Robinson *et al.* (1991). We conclude that NTP (1985) presents the most sensitive indication in the available literature of noncarcinogenic toxicity showing a dose-response.

Carcinogenic Effects

At present there is inadequate evidence from human data, experimental animal data and genotoxicity studies to establish that 1,2-DCB is a human carcinogen, a conclusion also reached by U.S. EPA (1992) and IARC (1982). No new data regarding the carcinogenicity of 1,2-DCB were located in the literature since the U.S. EPA and IARC evaluations. In the absence of information, no dose-response assessment for carcinogenic effects can be made.

CALCULATION OF PHG

Calculation of a public health-protective concentration (C, in mg/L) for 1,2-DCB in drinking water follows the general equation for noncarcinogenic endpoints:

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

where,

NOAEL	=	No-observed-adverse-effect-level (125 mg/kg-day)
BW	=	Adult male body weight (70 kg)
RSC	=	Relative source contribution of 20% (0.2)
UF	=	Uncertainty factor of 1,000 (see below)
L/day	=	Adult daily water consumption rate (2 L/day)

For 1,2-DCB, the experimental NOAEL for the principal study was 125 mg/kg-day for hepatotoxicity, which is then adjusted for discontinuous exposure because of the dosing regimen (five days/wk). The adult human body weight default is 70 kg. An RSC of 20% was used in the calculation in the absence of any specific information on the contribution of drinking water exposure to total exposure to 1,2-DCB. A UF of 1,000 is applied to account for inter-species extrapolation (10), uncertainty from the subchronic nature of the principal study (10) and potentially sensitive human subpopulations (10). The adult human water consumption default value is 2 L/day.

Therefore,

$$\begin{aligned} C &= \frac{125 \text{ mg/kg-day} \times (5/7) \times 70 \text{ kg} \times 0.2}{1,000 \times 2 \text{ L/day}} \\ &= 0.625 \text{ mg/L} = 0.6 \text{ mg/L (rounded)} = 600 \text{ ppb.} \end{aligned}$$

OEHHA calculates a PHG of 0.6 mg/L (600 ppb) for 1,2-DCB in drinking water. This value is identical to the federal MCL of 600 ppb.

RISK CHARACTERIZATION

The primary sources of uncertainty in the development of the PHG for 1,2-DCB in drinking water are those areas associated with the inter-species extrapolation and the estimation of the RSC. Evidence from experimental animals demonstrates a consistent level of toxicological effect for exposure to 1,2-DCB. Therefore, there is a fair degree of confidence that the level of effect used in the calculation of the PHG is adequate. In the absence of information concerning specific sensitive subpopulations and the relative sensitivity of the effects of humans to rodents, default uncertainty factors have been applied. Likewise, an uncertainty factor has been applied to adjust for effects which may not have been observed in the subchronic study due to its limited duration. These uncertainty factors are consistent with those used by U.S. EPA in calculating its MCL for 1,2-DCB. No evidence of synergy with other chemicals in the toxicity of 1,2-DCB was found in the literature.

There are limited data available to suggest departure from the default value of 20% for the RSC of drinking water to the total exposure of humans to 1,2-DCB. Therefore, this value has been used in the calculation of the PHG. Some uncertainty exists in this value because of potentially limited exposure from food sources and increased exposure from dermal and inhalation routes (such as exposures from showering/bathing). Because these exposure considerations tend to both increase and decrease the fraction exposure from drinking water sources, the default value has been unadjusted in the calculation of the PHG. The use of an RSC in calculating a PHG for 1,2-DCB is consistent with U.S. EPA in its calculation of an MCL.

With these factors in mind, the level of exposure established by the PHG should be adequately protective from potential adverse health effects from drinking water exposure to 1,2-DCB.

OTHER STANDARDS AND REGULATORY LEVELS

U.S. EPA promulgated a Maximum Contaminant Level Goal (MCLG) and an MCL for 1,2-DCB of 0.6 mg/L which U.S. EPA concluded would protect against the potential health problems identified in its report and is “the lowest level to which water systems can reasonably be required to remove this contaminant should it occur in drinking water” (U.S. EPA, 1995; U.S. EPA, 1991a,b). This value was based on hepatotoxicity observed in subchronic rodent studies with a Drinking Water Equivalent Level (DWEL) of 3.0 mg/L (U.S. EPA, 1996) and an RSC of 20%. The current California MCL is also 0.6 mg/L (600 ppb).

U.S. EPA has also established an ambient water criterion of 400 µg/L for dichlorobenzenes (as a class) 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, 1980b).

The Occupational Safety and Health Administration (OSHA) has established an eight-hour time-weighted average TWA ceiling concentration of 50 ppm 1,2-DCB. The National Institute of Occupational Safety and Health (NIOSH) has established a 15 minute ceiling concentration of 50 ppm.

The American Congress of Governmental Industrial Hygienists (ACGIH) has established an eight-hour TWA average threshold limit value of 25 ppm 1,2-DCB for dermal exposure, a short-term exposure limit (STEL) of 50 ppm.

Table 2. State Drinking Water Guidelines

State	Drinking Water Guideline
Arizona	620 ppb
Maine	85 ppb
Minnesota	600 ppb
New Jersey	600 ppb
Wisconsin	600 ppb

REFERENCES

- Anderson KJ, Leighty EG, Takahashi MT (1972). Evaluation of herbicides for possible mutagenic properties. *J Agric Food Chem* **20**:649-56.
- Azouz WM, Parke DV, Williams RT (1955). The metabolism of halogenobenzenes. Ortho- and para-dichlorobenzenes. *Biochem J* **59**:410-5.
- Dowty B, Carlisle D, Laseter J (1975). New Orleans drinking water sources tested by gas chromatograspectrometry. *Environmental Science and Technology* **9**:762-95.
- Girard R, Tolot F, Martin P, Bourret J (1969). [Severe hemopathy and exposure to chlorine derivatives of benzene (apropos of 7 cases)] (French). *J Méd Lyon* **50**(164):771-3.
- Haworth S, Lawlor T, Mortelmans K, Speck W, Zeiger E (1983). Salmonella mutagenicity test results for 250 chemicals. *Environ Mutagen* **5**(Suppl 1):3-142.
- Hayes WC, Hanley TR Jr, Gushow TS, Johnson KA, John JA (1985). Teratogenic potential of inhaled dichlorobenzenes in rats and rabbits. *Fundam Appl Toxicol* **5**(1):190-202.
- Health Canada (1993). 1,2-Dichlorobenzene (Priority Substances List Assessment Report). Canadian Environmental Protection Act.
- Hissink E, van Ommen B, Bogaards JJ, van Bladeren PJ (1996). Hepatic epoxide concentrations during biotransformation of 1,2- and 1,4-dichlorobenzene. The use of *in vitro* and *in vivo* metabolism, kinetics and PB-PK modeling. *Adv Exp Med Biol* **387**:129-33.
- Hollingsworth RL, Rowe VK, Oyen F, Torkelson TR, Adams EM (1958). Toxicity of o-dichlorobenzene. Studies on animals and industrial experience. *AMA Arch Indust Health* **17**:180-7.
- HSDB (1997). Hazardous Substances Data Bank. Micromedex, Inc. **31**.
- IARC (1982). Ortho- and para-dichlorobenzenes. International Agency for Research on Cancer. *IARC Monog Eval Carcinog Risks Hum* **29**:213-38.
- Jacobs A, Blangetti M, Hellmund E (1974a). Speicherung chlorierter Rheinwasserschadstoffe im Fettgewebe von Ratten [German article - Accumulation of noxious chlorinated substances from Rhine River water in the fatty tissue of rats]. *Vom Wasser* **43**:259-73.
- Jacobs A, Blangetti M, Hellmund E, Koelle W (1974b). Accumulation of organic compounds, identified as harmful substances in Rhine water, in the fatty tissue of rats [Abstract]. Kernforschungszentrum Karlsruhe, Berlin. KFK 1969. UF 1-7. 1.
- Kavlock R, Chernoff N, Carver B, Kopfler F (1979). Teratology studies in mice exposed to municipal drinking-water concentrates during organogenesis. *Food Cosmet Toxicol* **17**(4):343-7.
- Lawlor T, Haworth SR, Voytek P (1979). Evaluation of the genetic activity of nine chlorinated phenols, seven chlorinated benzenes and three chlorinated hexanes (Abstract). *Environ Mutagen* **1**(2):143.

Loveday KS, Anderson BE, Resnick MA, Zeiger E (1990). Chromosome aberration and sister chromatid exchange tests in Chinese hamster ovary cells *in vitro*: V. Results with 46 chemicals. *Environ Mol Mutagen* **16**(4):272-303.

Myhr BC, Caspary WJ (1991). Chemical mutagenesis at the thymidine kinase locus in L5178Y mouse lymphoma cells: Results for 31 coded compounds in the National Toxicology Program. *Environ Mol Mutagen* **18**(1):51-83.

NTP (1985). Toxicology and carcinogenesis studies of 1,2-dichlorobenzene (o-dichlorobenzene) F344/N rats and B6C3F₁ mice (gavage studies). National Toxicology Program, Technical Report Series **255**.

Pagnotto LD, Walkley JE (1966). Urinary dichlorophenol as an index of paradichlorobenzene exposure (Abstract). *Industrial Hygiene Association Journal* **26**:137.

Parke DV, Williams RT (1955). Studies in detoxication: The metabolism of halogenobenzenes. (a) Metadichlorobenzene. (b) Further observations on the metabolism of chlorobenzene. *Biochem J* **59**:415.

Prasad I (1970). Mutagenic effects of the herbicide 3',4'-dichloropropionanilide and its degradation products. *Can J Microbiol* **16**:369-72.

Rimington GE, Ziegler G (1963). Experimental porphyria in rats induced by chlorinated benzenes. *Biochem Pharmacol* **12**:1387-97.

Robinson M, Bercz JP, Ringhand HP, Condie LW, Parnell MJ (1991). Ten- and ninety-day toxicity studies of 1,2-dichlorobenzene administered by oral gavage to Sprague-Dawley rats. *Drug Chem Toxicol* **14**(1-2):83-112.

Shackelford WM, Keith LH (1976). Frequency of Organic Compounds Identified in Water (EPA-600/4-76-062), Athens, GA, Environmental Research Laboratory, U.S. Environmental Protection Agency. 37, 72, 76-7.

Stine ER, Gunawardhana L, Sipes IG (1991). The acute hepatotoxicity of the isomers of dichlorobenzene in Fischer-344 and Sprague-Dawley rats: isomer-specific and strain-specific differential toxicity. *Toxicol Appl Pharmacol* **109**(3):472-81.

Tolot R, Soubrier B, Bresson J, Martin P (1969). [Rapidly developing proliferative myelosis. Possible etiologic role of chlorine derivatives of benzene] (French). *J Med Lyon* **116**:761-8.

U.S. EPA (1996). Drinking water regulations and health advisories. U.S. Environmental Protection Agency, Office of Water. EPA 822-B-96-002.

U.S. EPA (1995). National primary drinking water regulations: o-dichlorobenzene. U.S. Environmental Protection Agency, Office of Water. EPA 811-F-95-004 e-C.

U.S. EPA (1992). Carcinogenicity assessment for lifetime exposure. 1,2-Dichlorobenzene. Integrated Risk Information System. U.S. Environmental Protection Agency.

U.S. EPA (1991a). U.S. Environmental Protection Agency. January 30. *Federal Register* **56**:3526.

U.S. EPA (1991b). U.S. Environmental Protection Agency. July 1. *Federal Register* **56**:30266.

U.S. EPA (1988). Drinking water health document for o-dichlorobenzene. U.S. Environmental Protection Agency, Criteria and Standards Division, Office of Drinking Water, Washington DC. PB89-192231.

U.S. EPA (1980a). Ambient water quality criteria for dichlorobenzenes. U.S. Environmental Protection Agency Office of Water Regulations and Standards, Criteria and Standards Division. Washington DC. (EPA-440/5-80-039).

U.S. EPA (1980b). U.S. Environmental Protection Agency, Criteria and Standards Division. November 28. *Federal Register* **45**:79318.

Valentovic MA, Ball JG, Anestis D, Madan E (1993). Acute hepatic and renal toxicity of dichlorobenzene isomers in Fischer 344 rats. *J Appl Toxicol* **13**(1):1-7.

Varshavskaya SP (1967a). Comparative sanitary toxicological features of chlorbenzol and dichlorbenzol (ortho- and para-isomers) in sanitary protection of water bodies [Russian with English abstract]. *Gig Sanit* **33**:15-21.

Varshavskaya SP (1967b). The hygienic standardization of mono- and dichlorobenzenes in reservoir waters. *Nauch Tr Aspir i Ordin Pervyi Mosk Med Institut* **175**.

Ware S, West WL (1977). Investigation of selected potential environmental contaminants: halogenated benzenes. EPA 560/2-77-004. Rep EPA Contract No. 68-01-4183. U.S. Environmental Protection Agency. Office of Toxic Substances, Washington DC.

Young CM, Voorhees KJ (1989). Thermal decomposition of 1,2-dichlorobenzene. *American Chemical Society* **3**(1):280-7.

Zapata-Gayon C, Zapata-Gayon N, Gonzalez-Angulo A (1982). Clastogenic chromosomal aberrations in 26 individuals accidentally exposed to ortho-dichlorobenzene vapors in the National Medical Center in Mexico City. *Arch Environ Health* **37**(4):231-5.