

Public Health Goal for 1,2,4-Trichlorobenzene In Drinking Water

Prepared by

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PREFACE

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

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

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

PHGs adopted by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs).

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

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

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

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PUBLIC HEALTH GOAL FOR 1,2,4-TRICHLOROBENZENE IN DRINKING WATER

SUMMARY

A Public Health Goal (PHG) of 0.005 mg/L (0.005 ppm, or 5 ppb) has been developed for 1,2,4-trichlorobenzene (1,2,4-TCB) in drinking water. The principle study selected for derivation of the PHG was that of Robinson et al. (1981). In this study, exposure of rats to 1,2,4-TCB in drinking water *ad libitum* for 95 days resulted in enlargement of adrenal glands in both males and females. A no-observed-adverse-effect-level (NOAEL) of 14.8 mg/kg-day and a lowest-observed-adverse-effect-level (LOAEL) of 53.6 mg/kg-day were identified in females, while a NOAEL of 8.9 mg/kg-day and a LOAEL of 33.0 mg/kg-day were identified in males. The highest experimental NOAEL was used for the PHG calculation. In addition, factors accounting for uncertainty in inter-species extrapolation, potentially sensitive human subpopulations, and use of a study which was less than lifetime were incorporated. The current federal Maximum Contaminant Level (MCL), is also based on the Robinson et al. (1981) study. Since the adoption of the federal standard, a draft report was submitted to the U.S. Environmental Protection Agency (U.S. EPA) under the Toxic Substances Control Act (TSCA) Test Rule, with data indicating that 1,2,4-TCB is carcinogenic in male and female mice. Due to the preliminary nature of the report, the data are not used here as the basis for the proposed PHG. However, because of the potential for a severe effect (cancer), an additional uncertainty factor of 10 was incorporated into the PHG calculation. Based on these considerations, OEHHA derived a PHG for 1,2,4-TCB of 0.005 mg/L (0.005 ppm, or 5 ppb).

INTRODUCTION

The purpose of this document is to develop a PHG for 1,2,4-TCB. California's current drinking water standard for 1,2,4-TCB is 70 ppb. This standard, referred to as the State Maximum Contaminant Level (or State MCL), was adopted by the Department of Health Services in 1994 (California Code of Regulations, Title 22) and is the same value as the federal MCL. In developing a PHG for 1,2,4-TCB, OEHHA staff evaluated the basis for U.S. EPA's MCL. In addition, a search of the scientific literature was conducted to determine if there are any new data that would support the development of a number different than the current value.

In this document, the available data on the toxicity of 1,2,4-TCB are evaluated, with the primary focus on the literature related to oral exposures which are the most appropriate for the establishment of a PHG for drinking water. To determine a safe level for 1,2,4-TCB in drinking water, sensitive groups within the human population are considered. The studies which can be used to identify public health-protective levels have been reviewed and summarized. The results of this evaluation are described below.

CHEMICAL PROFILE

Chemical Identity

1,2,4-Trichlorobenzene (1,2,4-TCB) is the most common of the three isomers of trichlorobenzene. (The other isomers are 1,2,3- and 1,3,5-trichlorobenzene.) The chemical formula for 1,2,4-TCB, as well as pertinent identification numbers, are listed in Table 1.

Table 1. Chemical Identity of 1,2,4-Trichlorobenzene¹

Chemical name	1,2,4-trichlorobenzene
Synonyms	1,2,4-trichlorobenzol hostetex L-pec
Molecular formula	C ₆ H ₃ Cl ₃
CAS registry number	120-82-1
RTECS registry number	NIOSH/DC2100000
Wiswesser line notation	GR BG DG

¹Sources: HSDB (1998), U.S. EPA (1991a)

Physical and Chemical Properties

1,2,4-TCB is a halogenated aromatic compound with three chlorine atoms. It is a colorless liquid at room temperature (25° C; 77° F) or crystalline solid at slightly lower temperatures (below 17° C; 63° F). It is slightly soluble in water and ethanol, very soluble in diethyl ether, and miscible with benzene, petroleum ether and carbon disulfide (U.S. EPA, 1991a). Some of the physical and chemical properties of 1,2,4-TCB are listed in Table 2.

Production and Uses

1,2,4-TCB is used as a solvent in chemical manufacturing, an intermediate in the production of other chemicals, a component of dielectric fluids, and as dye carriers, degreasing agents and lubricants (HSDB, 1998). It is also used as an herbicide for aquatic weed control in irrigation canals, lakes, and ponds (Meister, 1998).

Trichlorobenzenes are typically formed by catalytic chlorination of 1,2-, 1,3- and 1,4-dichlorobenzene in the presence of ferric chloride, followed by fractional distillation (Environment Canada, 1993). In 1982, it was estimated that the annual production of 1,2,4-TCB in the United States was approximately 2,750,000 to 8,070,000 pounds per year (HSDB, 1998).

Table 2. Physical and Chemical Properties of 1,2,4-Trichlorobenzene¹

Property	Value or Information
Molecular weight	181.46
Color/Physical state	colorless liquid (25° C) rhombic crystals (below 17° C)
Odor	aromatic
Odor threshold	3 ppm
Melting point	17° C
Boiling point	213.5° C at 760 mm Hg 84.8° C at 10 mm Hg
Vapor pressure	0.29 mm Hg at 25° C
Flash point	110° C
Solubility in water	34.6 mg/L at 25° C
Log K _{ow}	4.02
Density	1.45 g/ml at 20° C

¹ Sources: HSDB (1998), U.S. EPA (1991a)

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Although data are limited and vary widely, it has been suggested that exposure of the general population to 1,2,4-TCB occurs primarily through inhalation of contaminated air and ingestion of contaminated food, mainly fish (WHO, 1991). Occupational exposure to 1,2,4-TCB would result mainly from inhalation during its manufacture and use.

Air

Emissions of 1,2,4-TCB into air primarily result from volatilization following industrial use of trichlorobenzenes and from incomplete incineration of trichlorobenzene-containing materials. A 1979 report of concentrations in ambient air in three U.S. cities provided the following mean values (samples were taken hourly, 24 h/day, during two weeks of mobile sampling in the cities indicated): Los Angeles, California, 0.05 µg/m³ (maximum concentration recorded, 0.25 µg/m³), Oakland, California, 0.02 µg/m³ (maximum concentration recorded, 0.11 µg/m³), and Phoenix, Arizona, 0.02 µg/m³ (maximum concentration recorded, 0.08 µg/m³) (HSDB, 1998; and WHO, 1991; citing Singh et al., 1981). In surveys of ambient air from up to 18 sites in Canada taken between October 1988 and April 1990, mean concentrations of 1,2,4-TCB ranged from below the limit of detection (0.1 µg/m³) to 0.27 µg/m³ (Environment Canada, 1993). Reported mean concentrations in ambient air in the Netherlands were less than 0.8 µg/m³ (Environment Canada, 1993; and WHO, 1991; citing Lebret, 1985).

Soil

At the site of a transformer manufacturing plant in Saskatchewan, where up to 30 tons of dielectric fluid containing trichlorobenzenes had been spilled in the mid-1970's, average concentrations of 1,2,4-TCB as high as 1,075 µg/g were measured in near-surface soil (0 to 3 m depth) (Environment Canada, 1993). With the exception of soil near poorly maintained waste sites, the presence of chlorobenzenes in soil has been associated mainly with pesticide use (WHO, 1991). No releases to land were reported in the California Toxic Release Inventory (TRI) for the years 1987-1994. Offsite releases (disposal + recycling) were estimated between 70 and 36,000 pounds/year for the same time period.

Water

1,2,4-TCB was detected in the drinking water supplies of three cities bordering on Lake Ontario; concentrations ranged from 1 to 4 ppt (ng/L), with a mean concentration of 2 ppt (Oliver and Nicol, 1982). Samples taken in 1976-77 from 11 U.S. locations revealed concentrations ranging from 0.01-0.53 ppb, with an average of 0.09 ppb (HSDB, 1998; WHO, 1991).

Maximum concentrations in surface water samples collected from the Niagara River at Niagara-on-the-Lake during 1988-89 were reported to be 2.5 ppt 1,2,4-TCB (Environment Canada, 1993; citing NRDIG, 1990).

In two reports regarding industrial wastewater in the U.S., concentrations of 1,2,4-TCB ranged from 0.25 to 500 µg/L, and 12 to 607 µg/L (WHO, 1991; citing Ware and West, 1977; and Neptune, 1980).

Food

1,2,4-TCB has been measured in fish. Whole fish, mostly trout, taken from each of the Canadian Great Lakes in the early 1980's contained 0.5-5 ppb wet weight (or up to 5 ng/g) (Oliver and Nicol, 1982). Rainbow trout taken from Lake Ontario in 1983 contained an average concentration of 0.6 ppb. Livers of flatfish collected off Southern California municipal wastewater outfalls contained 3.4-26 ppb wet weight, while 1,2,4-TCB was not detected in fish from the control site (HSDB, 1998).

Human milk may also be a source of exposure to 1,2,4-TCB. In a study of breast milk from women in Slovenia, Yugoslavia, in 1981, concentrations 3-5 days after parturition ranged from 'not detected' to 4 ppb (detection limit not specified). The average concentration in these samples was 1 ppb (expressed on a whole milk basis) or 25 ppb (expressed on a fat basis) (HSDB, 1998; and WHO, 1991; citing Jan, 1983). 1,2,4-TCB was also detected in breast milk of Canadian women three to four weeks after parturition; the mean concentration for women in the general population was 0.6 ppb. Concentrations in the breast milk of women of the indigenous population were slightly higher (1.2 ppb) (HSDB, 1998; and WHO, 1991; citing Davies and Mes, 1987).

METABOLISM AND PHARMACOKINETICS

Absorption

Trichlorobenzenes appear to enter the systemic circulation readily by ingestion, inhalation, and dermal absorption; however, no quantitative data were located on rates of absorption by any exposure route (U.S. EPA, 1991a). Following administration of ¹⁴C-1,2,4-TCB by oral gavage, 16 rats and two monkeys excreted 84% and 40% of the administered dose, respectively, in 24-hour urine, while fecal elimination accounted for only 11% and 1%, respectively (Lingg et al., 1982). Inhalation and dermal absorption of trichlorobenzenes can be inferred from systemic effects observed in toxicity studies (U.S. EPA, 1991a; citing Kociba et al., 1981; Brown et al., 1969).

Distribution

It appears that initial distribution of 1,2,4-TCB is mainly to the highly perfused tissues, particularly the liver, kidneys, and adrenals. Distribution of ¹⁴C-1,2,4-TCB was studied in rats for two weeks following seven days of oral daily dosing (U.S. EPA, 1991a; citing Smith and Carlson, 1980). Adrenals initially had the highest concentration of radiolabel, however concentrations rapidly declined. 1,2,4-TCB was found to accumulate in abdominal fat and liver, while concentrations in adrenals, muscle, kidney, heart, and spleen were less than twice background within 6-11 days following dosing.

Metabolism

It appears that the first step of metabolism of 1,2,4-TCB is the production of an arene oxide intermediate (demonstrated in rabbits, rats, and monkeys) while subsequent metabolic steps vary among the species examined. In rabbits, following single oral doses of 500 mg/kg or i.p. doses of 60-75 mg/kg 1,2,4-TCB, the major phenols formed were 2,4,5- and 2,3,5-trichlorophenol (Jondorf et al., 1955; Kohli et al., 1976). Similar phenolic metabolites were found in rats and monkeys following single oral doses or i.v. administration of 10 mg/kg 1,2,4-TCB (Lingg et al., 1982). Urinary metabolites identified from the oral administration of 1,2,4-TCB to rabbits include glucuronide conjugates (27%), sulfuric acid conjugates (11%) and 2,3,5- and 2,4,5-trichlorophenylmercapturic acid (0.3%) (Jondorf et al., 1955). In monkeys, the major urinary metabolites identified were an isomeric pair of 3,4,6-trichloro-3,5-cyclohexadiene-1,2-diol glucuronides (48-61%), glucuronides of 2,4,5- and 2,3,5-trichlorophenol (14-37%) and unconjugated trichlorophenol (1-37%). In the rat, mercapturic acids (i.e., two isomers of N-acetyl-S-(trichloro-phenyl)-L-cysteine) accounted for 60-62% of the urinary metabolites, in addition to thiols (28-33%) and phenols (1-10%). In the rat, conjugation of the intermediate with glutathione was thought to account for the sulfur-containing urinary metabolites, while in the monkey, the absence of sulfur-containing metabolites seemed to preclude the involvement of glutathione (Lingg et al., 1982).

Excretion

In rats, 84% of an oral dose and 78% of an i.v. dose of ¹⁴C-1,2,4-TCB (10 mg/kg) were excreted in urine within 24 hours; 11 and 7%, respectively, were identified in feces in the same time period. In monkeys, 40% of an oral dose and 22% of an i.v. dose were excreted in urine within 24 hours, while <1% was measured in feces (Lingg et al., 1982). In another study, rats were administered 181.5 mg/kg-day of ¹⁴C-1,2,4-TCB orally for seven days (Smith and Carlson, 1980). By fifteen days after dosing, fecal elimination essentially ceased, accounting for a total of approximately 4% of the administered dose. In contrast, radioactivity was still detected in urine 21 days after dosing, accounting for approximately 72% of the total administered radioactivity.

U.S. EPA estimated a half-life for 1,2,4-TCB in rabbits of 8.5 days (U.S. EPA, 1991a). The half-life in rats has been estimated at 93 hours (WHO, 1991).

TOXICOLOGY

Toxicological Effects in Animals

Acute Toxicity

LD₅₀ estimates have been reported for CFE rats (756 mg/kg bw) and CF₁ mice (766 mg/kg bw) following ingestion of a single oral dose of 1,2,4-TCB (Brown et al., 1969). A somewhat lower LD₅₀ estimate (approximately 300 mg/kg bw) was reported in male and female ddY mice following oral administration of 1,2,4-TCB (Yamamoto et al., 1978).

Single i.p. injections of 37 mg/kg 1,2,4-TCB in rats resulted in significantly increased bile duct-pancreatic fluid (BDPF), decreased BDPF protein concentration, and increased bile flow (Yang et al., 1979; cited by U.S. EPA, 1991a).

An acute toxicity study was conducted to further examine TCB-related adrenal enlargement observed in rats in a multigeneration reproduction study (Robinson et al., 1981). Groups of preweanling female rats (9-10/dose) were administered 0, 250 or 500 mg/kg 1,2,4-TCB by i.p. injection at 22, 23, and 24 days of age. At 25 days of age, the following treatment-related changes were noted: decreased body weight and increased adrenal weight (high-dose rats compared to controls), decreased uterus weight and increased liver weight (both treatment groups compared to controls). In addition, U.S. EPA conducted a one-month study which repeated part of the Robinson et al. (1981) study. Rats (5/group) were administered 0 or 53 mg/kg-day 1,2,4-TCB by gavage. Histopathologic examination showed moderate vacuolization of the zona fasciculata (thick middle layer of the adrenal gland) in TCB-treated rats, while control rats showed only slight vacuolization. There was a 14% increase in absolute adrenal gland weight and a 13% increase in adrenal gland/body weight ratio observed in TCB-treated rats compared to controls (U.S. EPA, 1997; citing Cicmanec, 1991).

Rats administered doses up to 730 mg/kg-day by gavage for 15 days showed hepatic porphyria, hepatomegaly in porphyric rats, and severe liver damage (intense necrosis and fatty changes) (Rimington and Ziegler, 1963; cited by Environment Canada, 1993).

Dermal application of 0.5 ml undiluted 1,2,4-TCB to guinea pigs five days per week for three weeks resulted in focal necrosis of the liver (Brown et al., 1969).

Subchronic Toxicity

In subchronic inhalation studies, male rats, rabbits and dogs were exposed to 1,2,4-TCB (0, 223 or 742 mg/m³) 7 hours/day, 5 days/week for 44 days. Increased liver weights (rats and dogs) and increased kidney weights (rats) were reported at the highest concentration. A reversible increase in urinary excretion of porphyrins was noted in low- and high-dose rats; however, the authors interpreted this change as being a physiologic rather than a toxic effect (Kociba et al., 1981). In an abstract it was reported that male and female rats were exposed to 22.3 or 74.2 mg/m³, 6 hours/day, 5 days/week for 90 days. A slight, reversible increase in urinary porphyrins was observed at 74.2 mg/m³ (Watanabe et al., 1978). Male rats, rabbits and monkeys were exposed to concentrations of 1,2,4-TCB up to 741 mg/m³ 7 hours/day, 5 days/week, for 26 weeks. Transient changes in liver (hepatocytomegaly) and kidney (hyaline degeneration of the cortex) were reported in rats at all concentrations; however, no exposure-related effects were observed in any species after 26 weeks (Coate et al., 1977).

In a subchronic oral study, rats were exposed to 1,2,4-TCB in diet for 13 weeks at concentrations up to 1000 ppm (82 mg/kg_{bw}-day for males, 101 mg/kg_{bw}-day for females). Liver-to-body weight ratios were significantly higher in animals from the high dose group. In addition, mild to severe histopathologic changes were found in liver, thyroid and kidney. These changes were significant in high-dose animals and were more severe in males than females (Cote et al., 1988). In a 90-day oral gavage study, male rats were exposed to 0, 10, 20, or 40 mg/kg-day. At 40 mg/kg-day there was a significant increase in liver-to-body weight ratios that persisted throughout a 30-day recovery period. Changes in enzymes (e.g., cytochrome c reductase activity, cytochrome P450 levels, glucuronyltransferase activity, benzopyrene hydroxylase activity) were observed at all dose levels and were often dose-related (Carlson and Tardiff, 1976).

Genetic Toxicity

1,2,4-TCB was not mutagenic in seven strains of *Salmonella typhimurium* and in *Escherichia coli*-WP2, with or without metabolic activation (U.S. EPA, 1994b). 1,2,4-TCB, as well as the other TCB isomers, did not induce chromosomal aberrations in Chinese hamster cells, with or without metabolic activation (Schoeny et al., 1979; Lawlor et al., 1979; Sofuni et al., 1985; as cited by Environment Canada, 1993; and U.S. EPA, 1991a). Negative results were also reported for 1,2,4-TCB in rat hepatocyte primary culture (HPC) / DNA repair tests. Results from an assay using adult rat liver epithelial cells (ARL assay) indicate that 1,2,4-TCB is able to induce cellular transformation (U.S. EPA, 1994a). Eight-week-old mice injected i.p. with 1,2,4-TCB showed a dose-related increase in the number of micronucleated cells in bone marrow (U.S. Air Force, 1989; as cited by U.S. EPA, 1994b).

Developmental and Reproductive Toxicity

Female Sprague-Dawley rats (approximately 14/group) were administered 0, 75, 150, or 300 mg/kg 1,2,4-TCB by gavage on days 6-15 of gestation. At necropsy (day 22 of gestation) no gross skeletal or visceral abnormalities were observed in pups from treated dams. Mild osteogenic effects were noted in some pups, but these effects were not considered of teratological significance. There were no treatment-related effects in regard to the number of resorptions/dead fetuses, litter size, and fetal weight between treated dams and controls. Histological lesions were noted in the lenses of eyes in pups from the mid-dose group. Among high-dose dams, liver weights were increased compared to controls, while histological examination revealed mild changes in liver and thyroid. In dams from the two highest dose groups, mixed function oxidase activity (aminopyrine-N-demethylase) was significantly increased, while hemoglobin and hematocrit levels were significantly decreased (Black et al., 1988).

Pregnant rats (6 or more dams/group) were administered 1,2,4-TCB by gavage (0, 36, 120, 360 or 1200 mg/kg-day) on days 9-13 of gestation. The study was terminated on day 14 of gestation. All six dams in the high-dose group died by the third day of treatment. Administration of 360 mg/kg-day resulted in some maternal lethality (2/9 dams) and caused a significant decrease in body weight. Embryonic growth retardation was observed in fetuses of the 360 mg/kg-day group, including: head length, crown-rump length, somite number, and protein content. 1,2,4-TCB exposure during the period of organogenesis did not increase resorptions, embryoletality, or cause teratogenic effects. This study also demonstrated significantly increased activity of several hepatic enzymes in dams at 120 and 360 mg/kg-day. Histological examination revealed moderate hepatocellular hypertrophy in dams fed 360 mg/kg-day (Kitchin and Ebron, 1983).

In a multigeneration reproductive study, rats were exposed to 0, 25, 100 or 400 ppm 1,2,4-TCB in drinking water *ad libitum*, beginning with the birth of the F₀ generation. Each treatment group consisted of 17-23 litters (each litter contained 4 females, and 3 or 4 males). Females of the F₀ and F₁ generations were bred, with non-sibling males from the same treatment group, at approximately day 90. Blood and organs were obtained from 10 rats/sex/group (approximately one animal per litter) at day 37 and day 95 in the F₀ generation, and at day 95 in the F₁ generation. The experiment was terminated at day 32 (weaning) of the F₂ generation. A significant treatment-related decrease in water intake was noted in F₀ high-dose females at day 35 and in both sexes of F₀ high-dose rats at day 83; however, differences did not occur at other time points or in other generations. Using water consumption data, the authors calculated doses of 1,2,4-TCB corresponding to each treatment group (0, 25, 100 or 400 ppm) for F₀ rats. For females at day 29 concentrations of 1,2,4-TCB in drinking water correspond to doses of 0, 8.3, 28.0, 133.2 mg/kg-day, respectively. For males at day 29 doses were 0, 8.5, 27.6 or 133.6 mg/kg-day. For females at day 83 doses were 0, 3.7, 14.8 or 53.6 mg/kg-day. And for males at day 83 dose were 0, 2.5, 8.9 or 33.0 mg/kg-day. No treatment-related effects were noted with respect to fertility, neonatal weight, maternal weight, litter size, viability, postweaning growth, locomotor activity, or blood chemical analyses. Administration of 400 ppm 1,2,4-TCB resulted in significant enlargement of adrenal glands in both sexes in the F₀ and F₁ rats at 95 days (Robinson et al., 1981).

Chronic Toxicity and Carcinogenicity

In a dermal exposure study, 0.03 mL applications of a 30% or 60% solution of 1,2,4-TCB in acetone were painted on the skin of mice, twice weekly for two years (75 mice/sex/dose for treated animals; 50 mice/sex for controls). Skin painting with 1,2,4-TCB produced clinical signs of general toxicity (i.e., excitability, panting), as well as local skin thickening, keratinization and inflammation of the epidermis. TCB exposure also resulted in decreased survival, increased spleen weights, decreased adrenal weights, and minor hematological effects. Histopathology showed some organ sites had increased non-neoplastic lesions (type/severity not specified). No increase in tumor incidence was reported. However, among male mice, nine different tumors were found in the high-dose group compared to two in each the low-dose group and control group. Among females, 11 different tumors were reported compared to 3 in the low dose group and 8 in controls. The authors do not state whether these tumors were found in different individual animals or whether there were multiple tumors in the same animal. Overall, the study design and reported results were inadequate for making conclusions about carcinogenicity in animals or humans (Yamamoto et al., 1982; U.S. EPA, 1991a; Environment Canada, 1993).

More recently, an interim report was submitted by the Chemical Manufacturers Association (CMA) to U.S. EPA regarding preliminary data obtained from a two-year oral carcinogenicity study of 1,2,4-TCB conducted in mice (U.S. EPA, 1993a; U.S. EPA, 1993b). We were not able to find out from U.S. EPA or CMA whether the data have been finalized. However, through a search of a publicly accessible database, we found that the report was finalized in 1994. Due to the short timeframe allowed for adopting PHGs, we were not able to obtain the final report prior to the finalization of this technical support document. Therefore, we are not able to confirm that the preliminary data have not changed.

In this study, 50 mice/sex/group were exposed to 0, 150, 700 or 3200 mg/kg-day of 1,2,4-TCB in diet for 104 weeks. Survival was significantly reduced in high-dose animals compared to controls. Among high-dose mice, only 5/50 males and 0/50 females survived to termination compared with 74-90% survival in all other groups. The increase in mortality of high-dose animals began at approximately week 65-70, and progressed rapidly for the remainder of the study. Mean body weights were significantly lower in high-dose males and females throughout the study relative to control animals. In other treatment groups, body weights were inconsistent compared with controls, but were frequently higher over the course of the study.

Most deaths in high-dose mice occurred as a result of hepatocellular neoplasms, primarily carcinomas. Hepatocellular carcinomas were present in 100% of high-dose males, 92% of high-dose females, and approximately 55% of mid-dose males and females (Table 3). The tumors were reported to be mostly large and often multiple, frequently with pulmonary metastases. Hepatocellular adenomas were also increased in incidence (except for in high-dose males, in which it was noted that they were likely overwhelmed by the extent of carcinoma development). Incidences of combined adenomas and carcinomas were not provided. In addition to hepatic neoplastic lesions, 1,2,4-TCB resulted in enlargement of hepatocytes from many mid- and high-dose males, including animals with and without concurrent hepatic neoplasia. Other hepatic alterations (focal necrosis, portal inflammation and fibrosis, regenerative changes) were also attributed to TCB exposure, but were

considered either secondary to, or influenced by, the severe degree of hepatic neoplasia observed in the animals. Mean terminal liver weights were significantly increased in males of all treatment groups compared to controls, and in low- and mid-dose females compared to controls (all high-dose females died prior to termination).

Histological examination also revealed degenerative changes to the adrenals, bilateral degeneration of the testes (0/50 in controls, 9/50 in high-dose), and empty, contracted seminal vesicles. However, low- and mid-dose groups had not been histopathologically examined in full at the time of the report. Thus, it is unclear if these effects were caused directly by TCB exposure or if they were secondary to prolonged sickness as was observed in the high-dose animals.

A similar oral carcinogenicity study was conducted in F344 rats (50/sex/group) and submitted to the U.S. EPA along with the results of the mouse study (U.S. EPA, 1994b). In this study 1,2,4-TCB was not carcinogenic in either sex of rats.

Table 3. Tumor incidence data from mice exposed to 1,2,4-trichlorobenzene.¹

Dose group (mg/kg-day)	Male Mice		Female Mice	
	hepatocellular adenoma	hepatocellular carcinoma	hepatocellular adenoma	hepatocellular carcinoma
0	4/49 ²	8/49	3/50	1/50
150	7/50	5/50	4/50	1/50
700	16/50	27/50	16/50	28/50
3200	2/50	50/50	8/50	46/50

¹These data were presented in an initial pathology report with draft (unaudited) histopathology summary incidence tables submitted to U.S. EPA by Miles, Inc. (U.S. EPA, 1993a and b). This study was conducted under the Toxic Substances Control Act (TSCA) Section 4 Test Rule.

²Tumor incidence is shown as (number of animals with the tumor / number of animals examined).

Toxicological Effects in Humans

Information on the health effects in humans from exposure to 1,2,4-TCB or trichlorobenzenes as a group is very limited.

In one case report, it was documented that an individual exposed to 3-5 ppm 1,2,4-TCB suffered from eye and respiratory irritation. In a second report, two cases are described. A 68-year-old woman, with long-term exposure from soaking her husband's work clothes in trichlorobenzene (isomer not identified), developed aplastic anemia. Anemia was also reported to develop in a 60-year-old man who was exposed occupationally for over 30 years to mono-, di- and trichlorobenzene, as well as to DDT (U.S. EPA, 1991a; and WHO, 1991; citing Rowe, 1975; and Girard et al., 1969).

WHO (1991) identified two additional case reports. An adult male who had inhaled TCB vapors for several hours during the repair of a pump developed massive hemoptysis (Ehrlicher, 1968) and 7 cases of chloracne were documented in 15 TCB production workers

exposed for 2-6 months (exposure concentrations unknown; Popovki et al., 1980). WHO noted, however, that the TCB isomer was not specified in either report, and no details of confounding factors or doses were available for evaluation.

In a recent health survey of workers engaged in the production of pentachlorophenol, the prevalence of chloracne was 95.2% (20/21 workers) in a trichlorobenzene tank area (isomer not specified) where dioxin and dibenzofurans levels were thousands of parts per million (Cheng et al., 1993).

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

There are no adequate data in humans regarding adverse health effects from exposure to 1,2,4-TCB to establish a dose-response relationship.

Of the studies conducted in experimental animals, the most relevant for the purposes of calculating a PHG for 1,2,4-TCB in drinking water is the study by Robinson et al. (1981). In this multigeneration study, two generations of rats were exposed to 0, 25, 100 or 400 ppm 1,2,4-TCB in drinking water for 95 days. Administration of 400 ppm 1,2,4-TCB resulted in significant enlargement of adrenal glands in both sexes. A NOAEL of 14.8 mg/kg-day was identified in this study based on a dose-rate calculation made by the authors. Robinson et al. (1981) conducted an acute toxicity study to further examine the TCB-related adrenal enlargement observed in rats of the multigeneration study. Groups of female rats were administered 0, 250, or 500 mg/kg 1,2,4-TCB by i.p. injection at 22, 23 and 24 days of age. At 25 days of age high-dose rats had increased adrenal weight compared to controls. To more specifically characterize the changes noted in the Robinson et al. (1981) report, U.S. EPA conducted an in-house study (U.S. EPA, 1997; citing Cicmanec, 1991), and found that the TCB-related increases in adrenal weights were associated with the histopathologic lesions, vacuolization of the zona fasciculata of the cortex. Therefore, the NOAEL of 14.8 mg/kg-day was selected for the calculation of the PHG.

Higher LOAELs and NOAELs were identified in other studies, including that by Carlson and Tardiff (1976). In this 90-day oral gavage study, rats were exposed to 0, 10, 20 or 40 mg/kg-day. Changes in enzymes were observed at all dose levels and were often dose-related. Although enzyme induction is a sensitive endpoint, it is not considered an adverse effect. Thus, for this study, 20 mg/kg-day is identified as the NOAEL and 40 mg/kg-day is considered a LOAEL based in significant increase in liver-to-body weight ratios.

Therefore, the NOAEL of 14.8 mg/kg-day identified in the Robinson et al. (1981) study was selected for the calculation of the PHG for 1,2,4-TCB in drinking water.

Carcinogenic Effects

At present, there is inadequate evidence from human data, experimental animal data and genotoxicity studies to establish that 1,2,4-TCB is a human carcinogen. From the interim report submitted by the Chemical Manufacturers Association to U.S. EPA, there appears to be evidence for a strong carcinogenic effect in both male and female B6C3F1 mice, with nearly all of the mice in the high-dose group (50/50 males and 46/50 females) developing

hepatocellular carcinomas. The effect appears to be treatment-related (U.S. EPA, 1993a; U.S. EPA, 1993b).

For the purposes of establishing the most sensitive sex of B6C3F1 mice, cancer potencies/slope factors were calculated for the incidences of carcinomas in both males and females. Cancer potencies were generated with the Tox_Risk program (Version 3.5) which fit the linearized multistage (LMS) model to the data on tumor incidence (ICF Kaiser International, 1993). In accordance with U.S. EPA's proposed guidelines for carcinogenic risk assessment, the LMS model was used to estimate the lower 95% confidence limit on the dose associated with a 10% increase in tumor development (LED₁₀) (U.S. EPA, 1996). At doses below this point, a linear dose-response was assumed with which a cancer slope factor (CSF) was calculated. A theoretical excess individual cancer risk from exposure to 1,2,4-TCB was limited to the *de minimis* level of 10⁻⁶. The results of these analyses are presented in Table 4 below. For comparison purposes, estimates of cancer potency were also made using the LMS model polynomial exclusively (q₁^{*}).

Following U.S. EPA draft proposed guidance (U.S. EPA, 1996), interspecies scaling of cancer potencies derived from experimental animals (CSF_{animal} or q₁^{*}_{animal}) to human potencies (CSF_{human} or q₁^{*}_{human}) was based on the following relationship:

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

where, the default body weight is 70 kg for humans and 0.035 kg for mice.

Table 4. Cancer Potencies for 1,2,4-TCB Based on Results in Mice (U.S. EPA 1993a and b).

Data sets for Mice	q ₁ [*] _{animal} (mg/kg-d) ⁻¹	q ₁ [*] _{human} (mg/kg-d) ⁻¹	χ ²	p	k	MLE ₁₀ (mg/kg-d)	LED ₁₀ (mg/kg-d)	CSF _{animal} (mg/kg-d) ⁻¹	CSF _{human} (mg/kg-d) ⁻¹
Liver Carcinomas Female	1.0E-3	7.0E-3	8.06	0.02	3	126	100	1.0E-3	6.7E-3
Liver Carcinomas Male	5.2E-4	3.5E-3	1.02	0.6	3	385	186	5.4E-4	3.6E-3

Note: The q₁^{*} is the carcinogenic potency determined exclusively from the polynomial by the linearized multistage (LMS) model (previous cancer risk assessment methodology). χ² is the value of the Chi-squared goodness of fit statistic; p is the significance of the Chi-squared value where a criterion of p≥0.05 is considered an adequate fit of the polynomial equation to a data set; k is the number of non-zero doses used in the fitting procedure. MLE₁₀ is the maximum likelihood estimate of the dose that corresponds to a 10% extra tumor response. LED₁₀ is the 95% lower confidence limit on the MLE₁₀ dose. The CSF is the carcinogenic slope factor calculated from the LED₁₀ (derived by dividing 10% or 0.1 by the LED₁₀).

Although the potency generated from the tumor incidence in females was greater than that from males, the p-value of the least squares coefficient (χ²) indicates the lack of an adequate fit of the polynomial equation to the data set. Therefore, the most sensitive site, gender and species for tumor development from 1,2,4-TCB was the hepatocellular carcinomas observed in male mice in the study submitted to U.S. EPA (U.S. EPA, 1993a and b). In this case, the p-value indicates a reasonable fit of the model polynomial to this data set. The CSF_{human} calculated from this data set is 3.6 × 10⁻³ (mg/kg-day)⁻¹. This value has been selected as the

most appropriate for the calculation of the PHG for drinking water for carcinogenic endpoints.

CALCULATION OF PHG

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

Noncarcinogenic Effects

Calculation of a public health-protective concentration (C, in mg/L) for 1,2,4-TCB in drinking water follows the general equation for noncarcinogenic endpoints:

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

where,

NOAEL/LOAEL	=	No-observed-adverse-effect-level or lowest-observed-adverse-effect-level
BW	=	Adult body weight
RSC	=	Relative source contribution
UF	=	Uncertainty factor(s)
W	=	Daily water consumption rate

The principle study selected for derivation of the PHG for 1,2,4-TCB was that of Robinson et al. (1981). In this study, exposure of rats to 1,2,4-TCB in drinking water ad libitum for 95 days resulted in enlargement of adrenal glands in both males and females. A NOAEL of 14.8 mg/kg-day and a LOAEL of 53.6 mg/kg-day were identified in females, while a NOAEL of 8.9 mg/kg-day and a LOAEL of 33.0 mg/kg-day were identified in males. The highest experimental NOAEL was used for the PHG calculation. In addition, a default value of 70 kg was selected for adult human body weight (BW). The RSC of 20% was used in the calculation in the absence of information suggesting this value is not appropriate. A cumulative uncertainty factor (UF) of 10,000 was applied: 10 to account for interspecies extrapolation, 10 for potentially sensitive human subpopulations, 10 for use of a study which was less than lifetime, and an additional factor of 10 for uncertainty from potential severe endpoints (carcinogenicity). Net exposures to VOCs in water could be higher than estimated using the default of 2 L/day for daily water consumption, due to inhalation of vapors and dermal exposure during showering or bathing. U.S. EPA estimates that for

VOCs, bathing/showering could add an exposure equivalent to drinking 2 L/day, thus the total estimate for water intake in the PHG calculation is 4 liter equivalents per day (L_{eq}/day).

Therefore:

$$C = \frac{14.8 \text{ mg/kg-day} \times 70 \text{ kg} \times 0.2}{10,000 \times 4 L_{eq}/day}$$

$$C = 0.00518 \text{ mg/L (ppm)}$$

$$= 0.005 \text{ mg/L (rounded)}$$

$$= 5 \text{ } \mu\text{g/L (ppb)}$$

Based on this calculation of a health-protective concentration, OEHHA derived a PHG of 0.005 mg/L (0.005 ppm, or 5 ppb) for 1,2,4-TCB in drinking water.

Carcinogenic Effects

The following general equation can be used to calculate the public health-protective concentration (C) for 1,2,4-TCB in drinking water (in mg/L):

$$C = \frac{BW \times R}{q_1^* \text{ or CSF} \times L/day} = \text{mg/L}$$

where,

- BW = Adult body weight (a default of 70 kg)
- R = *De minimis* level for lifetime excess individual cancer risk (a default of 10^{-6})
- q_1^* or CSF = q_1^* is the upper 95% confidence limit on the cancer potency slope calculated by the LMS model; CSF (cancer slope factor) is a potency derived from the lower 95% confidence limit on the 10% tumor dose (LED_{10}). $CSF = 10\% / LED_{10}$. Both potency estimates (q_1^* and CSF) are converted to human equivalent [in $(\text{mg/kg-day})^{-1}$] using $BW^{3/4}$ scaling.
- L/day = Daily volume of water consumed by an adult (a default of 2 L/day, or 4 L_{eq} for VOCs).

The purpose of calculating two potency estimates for a carcinogen is based on the fact that our current experience-base is almost wholly with the LMS model whereas the new methodology, proposed by U.S. EPA (1996) in its proposed guidelines for carcinogen risk

assessment, is based on the LED₁₀ which has little or no experience-base and may present problems. The LMS model focuses on the linear low-dose extrapolation, while the new method places a higher premium on fitting the observed data to estimate the ED₁₀ and the 95% lower bound (LED₁₀), the point from which the low-dose extrapolation is made. In the case of 1,2-DCP, the potency estimates calculated using the two methodologies were consistent ($3.6 \times 10^{-3} \text{ (mg/kg-day)}^{-1}$ and $3.5 \times 10^{-3} \text{ (mg/kg-day)}^{-1}$). See Table 4.

The cancer slope factor selected for calculating the PHG was derived using the LED₁₀ methodology. Using the incidence of hepatocellular carcinomas observed in male mice in the study submitted by the Chemical Manufacturers Association to U.S. EPA, a cancer potency estimate of $3.6 \times 10^{-3} \text{ (mg/kg-day)}^{-1}$ was determined. A risk level of 10^{-6} is generally considered *de minimis*. The default value of 70 kg was used for the estimation of adult human body weight (BW). Net exposures to VOCs in water could be higher than estimated using the default of 2 L/day for daily water consumption, due to inhalation of vapors and dermal exposure during showering or bathing. U.S. EPA estimates that for VOCs, bathing/showering could add an exposure equivalent to drinking 2 L/day, thus the total estimate for water intake in the PHG calculation is 4 liter equivalents per day (L_{eq}/day).

Therefore,

$$\begin{aligned} C &= \frac{70 \text{ kg} \times 10^{-6}}{[3.6 \times 10^{-3} \text{ (mg/kg-day)}^{-1}] \times 4 \text{ L}_{\text{eq}}/\text{day}} \\ &= 0.00486 \text{ mg/L} \\ &= 0.005 \text{ mg/L (rounded)} \\ &= 0.005 \text{ ppm} \\ &= 5 \text{ ppb} \end{aligned}$$

A public health-protective concentration was calculated for the cancer endpoint because of the evidence for a carcinogenic effect of 1,2,4-TCB in mice. However, due to the preliminary nature of the data, the PHG cannot be based on the cancer effect until the data are confirmed. We were not able to obtain the final report from the Chemical Manufacturers Association or U.S. EPA prior to the adoption deadline. Therefore, we have included this calculation for comparative reasons only.

Based on the available draft cancer data, a public health-protective concentration of 5 ppb is calculated for 1,2,4-TCB. This is the same value calculated based on the noncancer endpoint. OEHHA concludes that a PHG for 1,2,4-trichlorobenzene in drinking water of 5 ppb contains an adequate margin of safety to protect against potential carcinogenic and noncarcinogenic adverse effects.

RISK CHARACTERIZATION

There are a number of areas of uncertainty in regard to the development of the PHG for 1,2,4-TCB. Of particular concern is the potential carcinogenicity of 1,2,4-TCB. From the study submitted to U.S. EPA (U.S. EPA 1993a and b), there appears to be evidence for a

strong carcinogenic effect in two sexes of B6C3F1 mice. With more than half of the mice in the mid-dose group and nearly all of the mice in the high-dose group developing carcinomas, the carcinogenic effect appears to be treatment-related. However, the data are limited. First, the data for the combined incidence for hepatocellular carcinomas and adenomas are not provided in the interim report. These incidences would be useful to give a clearer indication of the nature of the dose-response. In addition, there is some uncertainty in the quality of the data since the report was not finalized. However, the data were submitted to U.S. EPA under TSCA requirements. They also appear in a fact sheet distributed by the U.S. EPA's Office of Pollution Prevention and Toxics (OPPT) (U.S. EPA, 1994b). Therefore, OEHHA determined that the data were useful to assess the dose-response relationship, and to calculate a public or health-protective concentration for comparative purposes. And finally, it was noted in the OPPT fact sheet that, "The validity of these findings for assessing human cancer risk is questionable." U.S. EPA indicated that the mouse liver tumors could have been caused by a secondary mechanism due to liver toxicity. In light of the above, these data are not used as the basis of the proposed PHG for 1,2,4-TCB. Instead, the proposed PHG is based on the noncarcinogenic endpoint (i.e., enlargement of adrenal glands) as reported by Robinson et al. (1981). In order to account for uncertainty from potentially severe endpoints (cancer), an additional uncertainty factor of 10 was incorporated into the calculation. Calculations made on cancer data available to date indicate that the proposed PHG for 1,2,4-TCB in drinking water, based on the noncancer endpoint derived from the Robinson et al. (1981) study, contains an adequate margin of safety to protect against potential carcinogenic effects.

There are other areas of uncertainty in regard to the development of the PHG for 1,2,4-TCB. There are the general toxicological concerns regarding extrapolation from experimental animals. These areas of uncertainty are acknowledged in the use of uncertainty factors. There is also uncertainty in determining the relative source contribution (RSC) of 1,2,4-TCB in drinking water. For PHGs, OEHHA's use of the RSC, with few exceptions, followed U.S. EPA drinking water risk assessment methodology. The RSC range is 20% to 80% (0.2 to 0.8) depending on the scientific evidence. In the derivation of the PHG for 1,2,4-TCB, a RSC of 20% was selected. Although data are limited and vary widely, it has been suggested that exposure of the general population to 1,2,4-TCB occurs primarily through inhalation of contaminated air and ingestion of contaminated food, mainly fish (WHO, 1991). Occupational exposure to 1,2,4-TCB will result mainly from inhalation during its manufacture and use. Therefore, in the calculation of a PHG for 1,2,4-TCB, a default value of 20% was used for the RSC.

While the limited available data in humans do not indicate any subpopulations who may be especially sensitive to the adverse effects of 1,2,4-TCB, the information at present is inadequate to fully assess this issue. It is considered that the uncertainty factor of 10-fold to account for human variability plus another 10-fold for uncertainty about a possible severe endpoint (cancer) should be adequate to protect potentially sensitive populations.

OTHER REGULATORY STANDARDS AND GUIDELINES

U.S. EPA has classified 1,2,4-TCB as a group [D] carcinogen (or not classifiable), based on inadequate or no human and animal evidence of carcinogenicity (U.S. EPA, 1991b).

The U.S. EPA has established both a Maximum Contaminant Level Goal (MCLG) and a Maximum Contaminant Level (MCL) of 0.07 mg/L for 1,2,4-TCB. This value is based on increased adrenal gland weights observed in rats as reported by Robinson et al. (1981). From this study, a NOAEL of 100 ppm (14.8 mg/kg-day) was identified. U.S. EPA applied an uncertainty factor of 1000 (to account for sensitive human subpopulations, extrapolation from an animal study, and for use of a study which was less than lifetime) and derived an RfD of 0.01 mg/kg-day and a DWEL of 0.35 mg/L. Applying a relative source contribution of 20%, U.S. EPA calculated the MCLG of 0.07 mg/L for 1,2,4-TCB in drinking water.

New Jersey, Maine and Arizona have state drinking water guidelines for 1,2,4-TCB of 9, 70 and 140 µg/L, respectively.

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