

Appendix B
Section P

1,2,4-TRICHLOROBENZENE
HEALTH-BASED MAXIMUM CONTAMINANT LEVEL
SUPPORT DOCUMENT

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New Jersey Department of Environmental Protection

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EXECUTIVE SUMMARY

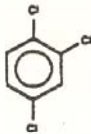
1,2,4-Trichlorobenzene (1,2,4-TCB) is a volatile synthetic chlorinated benzene, mainly used as a dye carrier and a herbicide intermediate. The odor threshold in air is 3 parts per million (ppm). The odor and taste threshold in water has not been reported. In 1983, the amount of 1,2,4-TCB produced was between 3.3×10^6 and 9.83×10^6 pounds. High doses of 1,2,4-TCB induce acute toxicity in both man and animals. Chronic exposure can adversely effect heme synthesis. The chemical induces embryotoxic and developmental effects at levels higher than those that produce liver enzyme changes. A health-based maximum contaminant level of 8.6 micrograms per liter (ug/L) of 1,2,4-TCB in drinking water is recommended to protect the general population from these health effects.

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BACKGROUND INFORMATION AND PROPERTIES

Chemical Properties (U.S.EPA, 1985a, unless otherwise stated)

Synonyms	1,2,4-Trichlorobenzene 1,2,4-TCB Benzene, 1,2,4-trichloro- asym-trichlorobenzene TCB Trojchlorobenzene (Polish) 1,2,4-Trichlorobenzol 1,2,4-Trichlorobenzol
CAS #	120-82-1
TSL #	DC 2100000
Chemical formula	$C_6H_3Cl_3$
Chemical structure	
Molecular weight	181.46
Physical state	colorless liquid (at room temperature) (HSDB, 11/30/84)
Melting point	16.95 °C (HSDB, 11/30/84) (rhombic crystals)
Boiling point	213.5 °C
Vapor pressure	1 mm Hg at 38.4 °C 0.29 mm Hg at 25 °C
Specific gravity	1.4542 at 20 °C
Vapor density	6.26 (Air = 1)
Water solubility	0.000269 moles/liter at 20 °C (HSDB, 11/30/84) 34.6 mg/L at 25 °C
Octanol/water partition coefficient	10,471 (HSDB, 11/30/84)

Log octanol/water partition coefficient	4.02
Odor threshold	3 ppm (HSDB, 11/30/84) (in air)
Conversion factors	1 ppm $\frac{1}{3}$ = 7.42 mg/m ³ 1 mg/m ³ = 0.135 ppm (Verschueren, 1983) (in air)

Production and Use

1,2,4-trichlorobenzene is produced as an intermediate in herbicide manufacture by several different processes. It is a product of the catalyzed chlorination of o-dichlorobenzene and the chlorination of monochlorobenzene. It is also a diazolization product of 2,4-, 2,5-, and 3,4-dichloroaniline when Cu₂Cl₂ treatment is used as a catalysis (HSDB, 11/30/84). It is also formed as a product of the tetrazolization, when Cu₂Cl₂ is used as a catalyst, of 1,3-diaminobenzene (U.S.EPA, 1985a). It is also formed in small quantities during the chlorination of drinking water and during the combustion of chlorine-containing polymers (U.S.EPA, 1985a).

In 1977 production was between 11 and 60 million pounds per year. The U.S. imported 1.94 million pounds per year in 1975 (U.S.EPA, 1985a). Industry in the state of New Jersey imported between 1 and 5 million pounds per year during the period 1978-79 (N.J. Industrial Survey, 1978-1979). In 1983, 1,2,4-TCB production was between 3.3 and 9.83 million pounds per year (U.S.EPA, 1985a).

1,2,4-TCB is used as a solvent in chemical manufacturing, as a heat transfer medium, a synthetic transformer oil, a dielectric fluid, and as a termite exterminating agent (HSDB, 11/30/84).

Regulations, Guidelines, and Standards

Sax (1984) recommends a maximum allowable concentration (MAC) of 50 ppm in air for commercial-grade trichlorobenzene. Coate et al. (1977) recommends a Threshold Level Value (TLV) lower than 25 ppm, preferably at 5 ppm. The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a ceiling level of 5 ppm (40 mg/m³) (ACGIH, 1982). The National Institute of Occupational Safety and Health (NIOSH) determined an ecotoxicity TLV of between 1 and 10 ppm in a 96-hour period (NIOSH. Reg. Tox Effect. Chem. Sub., 1979).

In order to protect fresh water aquatic life, the U.S.EPA proposed that 1,2,4-TCB levels should average less than 210 ug/L in a 24 hour period, but not exceed 470 ug/L at any time. They proposed a level of 3.4 ug/L in a 24 hour period not to exceed 7.8 ug/L at any time to protect salt

water aquatic life. The level set to protect the general public from organoleptic effects is 13 ug/L. This figure is based more on aesthetic characteristics rather than adverse health effects.

No federal standards have been set for 1,2,4-TCB levels in drinking water. The Soviet Union considered 30 ug/L appropriate to protect against organoleptic effects from exposure through drinking water (U.S.EPA, 1980).

ENVIRONMENTAL EXPOSURE

Fate and Transport

The atmospheric residence time of 1,2,4-TCB is unknown; however Singh et al. (1981) determined the residence time for an unspecified isomer as 116 days. It is known that the chemical is degraded by chemical or sunlight-catalyzed reactions in the atmosphere and is removed from the atmosphere by adsorption onto particulate material.

The chemical is easily volatilized from water. Its water solubility at 25 °C is 34.6 mg/L (U.S.EPA, 1985a). The half-life of 1,2,4-TCB in river water is approximately 1.8 to 28 days (Zaeteman et al., 1980). The chemical may also be degraded by microbial populations in both natural and waste-treated waters. It has been noted by Roberts et al. (1980) that no degradation occurred in ground water (U.S.EPA, 1985a).

In soil, once the chemical is adsorbed onto particulate matter, its movement through the soil and air is dependent upon soil composition and vapor phase diffusion. It is thought that a strain of pseudomonas bacteria degrades 1,2,4-TCB to chlorophenols (U.S.EPA, 1985a).

As reflected in its water solubility and octanol/water partition coefficient, this chemical tends to bioconcentrate in the tissues specifically in fat, under ambient water concentrations. As the substance moves up the food chain, it tends to bioaccumulate (U.S.EPA, 1985a).

It is thought that inhalation is a primary route of exposure in humans. Given our position in the trophic levels, exposure can also occur through the consumption of contaminated food and water (U.S.EPA, 1985a).

Ambient Levels

1,2,4-TCB is released to the environment in three ways: 1) through manufacture and transport, 2) through the use of industrial and consumer products that contain the chemical, and 3) through the disposal of TCB-contaminated wastes (U.S.EPA, 1985a).

In 1983, between 9,085 and 27,330 pounds of 1,2,4-TCB were lost through manufacturing processes. Ambient levels in air measured in 35

locations in the U.S. averaged 136 nanograms/cubic meter (ng/m^3) for all TCBs. In production areas, the level was $181 \text{ ng}/\text{m}^3$; in urban-suburban areas, the level was $128 \text{ ng}/\text{m}^3$ (Brodzinsky and Singh, 1982). In 1981, Singh et al. reported a mean ambient level in air of $52.0 \pm 36.9 \text{ ng}/\text{m}^3$ in Los Angeles; $23.4 \pm 15.8 \text{ ng}/\text{m}^3$ in Phoenix and $22.6 \pm 18.1 \text{ ng}/\text{m}^3$ in Oakland (U.S.EPA, 1985a).

Oliver and Nichol (1982) have measured chlorinated benzene concentrations in the Great Lakes region. Soil and sediment levels in Lake Ontario ranged from 7 to 94 ng/g for TCBs.

1,2,4-TCB and other TCB isomers have been found in many surface and drinking waters in levels ranging from 0.1 ng/L to 8,000 ng/L (U.S.EPA, 1985a). In New Jersey, two public water supplies were found to be contaminated with 1 ppb 1,2,4-TCB during Round 2 of the Assembly Bill A-280 testing (N.J.DEF, Division of Water Resources, 1986). In industrial waste water, 1,2,4-trichlorobenzene has been found at concentrations ranging from 12 to 607 ug/L (Neptune, 1980).

There have been no studies designed to determine if 1,2,4-TCB is a contaminant of human food supplies (U.S.EPA, 1985a).

METABOLISM AND PHARMACOKINETICS

Absorption

The data on the pharmacokinetics of 1,2,4-TCB exposure are not well documented. Studies using male Charles River rats and female rhesus monkeys indicate that given a 10 mg/kg oral dose, 11 and 1% was excreted in the feces, respectively; while 84 and 40% was excreted via the urinary tract (Lingg et al., 1982). It is also known that the chemical is absorbed via the respiratory tract (Kociba et al., 1981) and the skin (Brown et al., 1969). The specific rates of absorption are unknown since these studies were not designed to provide this information.

Distribution

1,2,4-TCB is recognized as a lipophilic compound. Smith and Carlson (1980) subjected male Sprague-Dawley rats to an oral dose of 181.5 mg/kg per day over a seven day period. Bioconcentration occurred in all tissues assayed on the first post-exposure day, including abdominal fat, liver, adrenal, muscle, kidney, heart, and spleen specimens. Abdominal fat and liver tissues were the only ones to show any detectable levels after 16 post-exposure days.

Metabolism

The initial step in the metabolism of 1,2,4-TCB involves the formation

of arene oxide intermediates that are then altered in some species to form 2,3,5-trichlorophenol and 2,4,5-trichlorophenol (Lingg et al., 1982 and U.S.EPA, 1985a). In the rat, Lingg et al. determined that these intermediates conjugate with glutathione resulting in the formation of 2,4,5- and 2,3,5-isomers of N-acetyl-S-(trichlorophenyl)-L-cysteine (60-62% of urinary metabolites). Minor urinary metabolites include 2,4,5- and 2,3,5-trichlorothiophenol (28-33%) and free 2,3,5- and 2,3,4-trichlorophenol (1-10%) (Lingg et al., 1982). In the monkey, the arene oxide intermediates metabolize further to form: an isomeric pair of 3,4,6-trichloro-3,5-cyclohexadiene-1,2-diol glucuronides (48-61% of urinary metabolites); glucuronides of 2,4,5- and 2,3,5-trichlorophenol (14-37%); and unconjugated trichlorophenols (1-37%) (Lingg et al., 1982). The rabbit produced 5-day urinary metabolites of 1,2,4-TCB of glucuronid conjugates (27%), sulfuric acid conjugates (11%) and 2,3,5- and 2,4,5-trichlorophenylmercapturic acid (0.3%). The major phenols formed were 2,4,5- and 2,3,5-trichlorophenol (Jondorf et al., 1955 and Kohli et al., 1976).

Excretion

A study by Lingg et al. (1982) showed that within 24 hours after single oral or intravenous (i.v.) dose of 10 mg/kg, rats excreted 84% and 78%, respectively, in the urine. Monkeys given the same dose under the same conditions excreted 40% and 22%, respectively, in the urine. The rat excreted 11% of the oral dose and 7% of the i.v. dose in the feces, while the monkeys excreted less than one percent of either dose in the fecal material.

Human Exposure and Body Burden

The target tissues for 1,2,4-TCB exposure are adipose and other fatty tissues (U.S.EPA, 1985a). One highly susceptible population would be breast-fed infants, since human milk has a high fat content (U.S.EPA 1985a), but there have been no reports of 1,2,4-TCB in human tissues that resulted from ingestion. However, there has been a reported level of TCB in the breath of Love Canal residents at levels ranging from a trace amount to 90 ng/m³ (Barkley et al., 1980). It is thought that at these doses the bioaccumulation is negated by the metabolism and elimination of the TCB from the body (U.S.EPA, 1985a).

It is thought that most exposure to 1,2,4-TCB occurs through the ingestion of contaminated water and the inhalation of contaminated air (U.S.EPA, 1985a).

HEALTH EFFECTS

Overview

1,2,4-TCB exposure has occurred at high levels for both acute and

chronic periods. In humans, high acute doses cause respiratory irritation and organic damage to the kidneys. Lower acute doses may cause eye and throat irritation (HSDB, 1984 and U.S.EPA, 1985a). High chronic doses have caused medullary aplasia (HSDB, 1984).

The target organs in non-lethal acute exposure in animals are the liver, brain ganglion cells, and mucous membranes (Coate et al., 1977). Subchronic exposure tends to affect primarily the liver (Carlson, 1977 and Watanabe et al., 1977). High doses may be embryotoxic and adversely affect the physical development of the fetus (Kitchin and Ebron, 1983). There is no available evidence that 1,2,4-TCB is either a mutagen or a carcinogen (U.S.EPA, 1985a).

It is believed that exposure to halogenated aromatic compounds can interfere with heme synthesis in the liver. (Heme is used in the synthesis of many enzymes and cytochromes, including microsomal cytochrome P-450.) The studies considered for the risk assessment identify liver and urinary porphyrin levels as the most sensitive endpoints of toxicity. It was reported that the effects in the rat resemble those in the human more closely than other experimental animals (Watanabe et al., 1977). Many studies have been done comparing interspecies differences in porphyrin production (Jondorf et al., 1955, Kohli et al., 1976, and Lingg et al., 1982).

Human

Acute. An odor threshold of 3 ppm has been determined in occupational exposure. Minimum eye, throat, and respiratory tract irritation occurs at exposures of 3 to 5 ppm in sensitive people. Dermal contact with 1,2,4-TCB can cause irritation. A case report of acute exposure involved a worker who inhaled a very large amount and subsequently suffered hemorrhaging in the lungs. Another effect of over-exposure can be organic damage to the kidneys with resultant diuresis (HSDB, 1984 and U.S.EPA, 1985a).

Chronic. A 68-year old woman who soaked her husband's work clothes in 1,2,4-TCB before washing developed aplastic anemia involving medullary aplasia, leukocytopenia and thrombocytopenia (Girard et al., 1969 as cited in HSDB, 1984). A 40-year old man who worked for three years with mono-, ortho-di-, and trichlorobenzene developed anemia (Girard et al., 1969 as cited in HSDB, 1984).

Animal

Acute. The oral LD₅₀ in CFE rats was 756 mg/kg (95% confidence limits (CI): 556-939 mg/kg) and the oral LD₅₀ in CF mice was 766 mg/kg (95% CI: 601-979 mg/kg) with a mixture of 92% 1,2,4-TCB and 8% 1,2,3-TCB (Brown et al., 1969). Other oral LD₅₀ values were: rats, 650 mg/kg; mice, 615 mg/kg; rabbit, 812 mg/kg; guinea pig, 1,218 mg/kg; and unknown, mammal, 700 mg/kg (HSDB, 1984). The target organs in non-lethal acute inhalation

exposure in laboratory animals such as rats, dogs, and cats were the liver, brain ganglion cells, and mucous membranes (Coate et al., 1977). A dose of 500 mg/kg per day over a ten-day exposure period induced porphyria in male rats as indicated by high liver levels of coproporphyrin, protoporphyrin, uroporphyrin, and catalase (Rimington and Ziegler, 1963).

Subchronic/Chronic. The endpoints of toxicity in subchronic exposure studies were liver and urinary tract excretion of porphyrins. The available literature suggests that the liver is the most sensitive target organ following subchronic exposure to 1,2,4-TCB (Watanabe et al., 1977 and Carlson, 1977). Other organs affected by subchronic exposure include the adrenals, kidneys, and to some extent, muscle, heart, and spleen (Smith and Carlson, 1980).

A summary of studies performed to assess 1,2,4-TCB induced effects is given in Table I. The toxic mechanism of 1,2,4-TCB exposure was proposed to be that the cell membrane and organelles of liver cells were altered in some way by the chemical or a metabolite. This damage resulted in a change in membrane permeability and as a result, porphyrins were excreted. Some porphyrinogenic chemicals and/or their metabolites may also have caused the induction of amino-levulinic acid (ALA) synthetase and the inhibition of uroporphyrinogen decarboxylase (UPD). Both of these mechanisms resulted in an increase in concentration of uroporphyrinogen and heptacarboxylporphyrinogen. These two biochemicals were then excreted into the urine and oxidized to uroporphyrin and heptacarboxylporphyrin (Hill, 1985).

Carlson and Tardiff (1976) exposed six male CD rats per dose group to 0, 10, 20, or 40 mg/kg per day 1,2,4-TCB in corn oil for 90 days. There was a 30-day recovery period. Five responses were evaluated: weight gain, liver weight, hemoglobin content, packed cell volume and indicators of xenobiotic metabolism. The effects observed involved liver weight and alterations in xenobiotic metabolism. There was a statistically significant increase ($p < 0.05$) in liver-to-body weight ratios that persisted through the recovery period in rats in the 40 mg/kg dose group. There were various changes in xenobiotic metabolism following the 90-day administration period. At a 10 mg/kg or greater dose, cytochrome c reductase activity was increased (recovery occurred in 30 days), azoreductase activity was increased, and glucuronyltransferase activity was decreased. At a 20 mg/kg or greater dose, cytochrome P-450 levels increased (recovery occurred in 30 days). Benzopyrene hydroxylase activity increased 2-fold at 40 mg/kg.

Carlson (1977) continuously exposed groups of 5 female rats to oral doses of 0, 50, 100, or 200 mg/kg per day TCB in corn oil for 30, 60, 90, or 120 days (see Table I). The rats weighed between 0.120 and 0.140 kg at the beginning of the study. The lowest observed adverse effect level (LOAEL) was 50 mg/kg per day for the 120-day exposure period. At this level a significant increase in liver porphyrins was observed. The control groups may have had some exposure to 1,2,4-TCB.

The study conducted by Watanabe et al. (1977) exposed male and female rats (30 males and 73 females, divided into three dose-exposure groups) to 0, 22.3 (1 ppm), or 74.2 mg/m³ (3 ppm) TCB (see Table I). Animals were exposed for 6 hours per day, five days a week for three months. The average weight of the rats at the beginning of the study was 0.200 kg for the males and 0.175 kg for the females. The overall average weight at the beginning of the study was 0.182 kg. The overall average weight at the end of the study was 0.423 kg. The authors used 99.6% pure 1,2,4-TCB. The other 0.4% was 1,2,3-TCB. The authors reported a no observed adverse effect level (NOAEL) of 22.3 mg/m³ (3 ppm). In the 74.2 mg/m³ dose group there was an increase in urinary porphyrin excretion.

Behavioral and Central Nervous System

Behavioral and CNS effects of 1,2,4-TCB exposure have been observed in animal studies. A response by rats to an acute, high dose (5-10 mg/m³) of an unspecified TCB isomer was immediate nervousness, followed within 30 minutes by death (Gurfein and Pavlova, 1960). In an acute and subchronic inhalation study using less lethal doses given to cats, dogs, rats, rabbits, and guinea pigs; brain ganglion cells were affected (Coate et al., 1977). In a subchronic study, conducted by Sasmore and Palmer (1981), male rats exposed for 13 weeks to 7,423 mg/m³ (1,000 ppm) 1,3,5-TCB for 6 hours per day, 5 days per week, showed a significant increase in liver-to-brain weight ratios 4 weeks after exposure terminated. This effect was not seen at 13 weeks. Monkeys exposed to levels as high as 742 mg/m³ (100 ppm) for 7 hours per day, 5 days per week showed no changes in ophthalmic parameters or operant behavior (Coate et al. 1977).

In humans, no apparent clinical behavioral or CNS effects have been observed (U.S.EPA, 1985a).

Reproductive, Embryotoxic, and Teratogenic

Kitchin and Ebron (1983) determined that doses of 120 and 360 mg/kg per day of 1,2,4-TCB administered to Sprague-Dawley rats during days 9-13 of gestation were strong inducers of hepatic enzymes. Pregnant rats were treated with 0, 36, 120, 360, or 1,200 mg/kg/day 1,2,4-TCB in corn oil on days 9-13 of gestation. They were sacrificed on day 14 of gestation. The embryotoxic effects of a 360 mg/kg per day dose were a significant increase in fetal mortality and reductions in head length, crown-to-rump length, somites, and protein content. This was accompanied by a 22% maternal mortality rate. No reproductive or teratogenic effects were observed.

Robinson et al. (1981) conducted a two generation study on Charles River rats in which the drinking water contained 1,2,4-TCB at 0, 25, 100, or 400 mg/L. The only result was enlarged adrenal glands in the F₀ and F₁ generations.

TABLE I

Studies that Assessed Liver and Urinary Porphyrin
Excretion after Exposure to 1,2,4-Trichlorobenzene*

Species	Route	Dose	Duration and Frequency of Exposure	Study NOAEL ¹ or LOAEL ²	Reference
Rat	Inhalation	0,223, 742 mg/m ³	7hrs/day; 5 days/wk, 30 exposures over 44 days	LOAEL 223mg/m ³	Kociba et al., 1981
Rat	Inhalation	0,22.3 74.2 mg/m ³	6 hrs/day;5 days/wk, 3 months	NOAEL 22.3 mg/m ³	Watanabe, et al., 1978
Rat	Oral	50,100 or 200 mg/kg/ day	30,60,90 or 120 days	LOAEL 50 mg/kg/ day at 120 days	Carlson, 1977
Rabbits	Dermal	30,150 or 450 mg/kg day	5 days/wk, 4 weeks	NOAEL 150 mg/kg day	Rao et al., 1982

1) NOAEL: No Observed Adverse Effect Level

2) LOAEL: Lowest Observed Adverse Effect Level

* adapted from U.S.EPA, 1985b.

Black et al. (1983) conducted a teratogenicity study on Wistar rats, by gavage, of doses of 75-600 mg/kg on days 6-15 of gestation. No teratogenic effects were observed in the offspring, but the mothers suffered from thyroid and liver lesions with reduced hemoglobin and hematocrit levels.

Genetic

There is no evidence in the available literature that 1,2,4-TCB is mutagenic in Salmonella typhimurium (Schony et al., 1979 and Lawlor et al., 1979). Schony et al. (1979) evaluated the mutagenicity and hepatic enzyme induction potential of 1,2,4-TCB in the Salmonella bioassay using the strains TA98, TA100, TA1535, and TA1537. The results were negative when tested with or without metabolic activation with Aroclor 1254. Schony et al. used eight concentrations of trichlorobenzene that ranged from 102 to 1.4×10^5 ug/plate. The toxic dose, the dose that kills one or more strains on the mutagenesis plates, was 1599 ug/plate.

In an abstract, Lawlor et al. (1979) reported testing a variety of compounds, including 1,2,4-TCB in the Salmonella plate incorporation mutagenesis assay using five doses. The strains used were TA98, TA100, TA1535, TA1537, and TA1538 with and without metabolic activation by Aroclor 1254 induced rat liver microsomes. The results appeared to be negative but due to insufficient reporting of experimental procedures this can not be quantified.

Carcinogenicity

There is currently no evidence that 1,2,4-TCB is carcinogenic in the animal species studied. There are no human data available to evaluate this effect (U.S.EPA, 1985b). It is classified as a Group D carcinogen by the U.S.EPA (inadequate animal evidence and no human evidence of carcinogenicity). Yamamoto et al. (1982) conducted a two-year dermal painting study of 1,2,4-TCB effects on 400, four week old Slc:ddy mice. The mice were exposed to 0%, 30%, and 60% solutions of 1,2,4-TCB (0.03 ml) painted onto their skin twice a week for two years. Each dose group contained 75 mice of each sex and there were 50 control animals per sex. Tumors of the lung, stomach, bladder, and mammary glands did develop, but no single tumor type was increased significantly over incidence in the control group. However, mean survival time was significantly reduced in the 60% group (both male and female mice) and in females in the 50% group. Due to this drop in survival, the study is not appropriate for making conclusions about carcinogenicity in humans.

QUANTITATIVE RISK ASSESSMENT

Studies Useful for Risk Assessment

It is maintained that the rat is an appropriate model for humans in the study of 1,2,4-TCB as a systemic toxicant. This chemical causes

similar effects in exposed rats as does another chlorinated aromatic compound, hexachlorobenzene (HCB). Both humans and rats have similar porphyric effects during the initial period of HCB exposure. In rats, similar porphyrinogenic effects occurred at doses between 10 to 40 mg/kg per day that occurred in humans at a dose of about 50 mg/kg per day (Watanabe et al., 1977).

Studies considered for the calculation of a health-based, maximum contaminant level (MCL) included Kociba et al., 1981, Carlson and Tardiff, 1976, Carlson, 1977, Rao et al., 1982, and Watanabe et al., 1981. Carlson and Tardiff (1976) identified a NOAEL of 20 mg/kg per day, but did not use porphyrin excretion as the experimental endpoint as did the other studies.

Carlson (1977) continuously exposed rats to oral doses of 0, 50, 100, or 200 mg/kg per day TCB for 30, 60, 90, or 120 days. The rats weighed between 0.120 and 0.140 kg at the beginning of the study. The lowest observed adverse effect level (LOAEL) was 50 mg/kg per day for the 120-day exposure period. Although the route of exposure is appropriate and the study duration is adequate, this study was not selected for calculation of the MCL because 1) only female rats were used in the study, 2) only five rats were in each treatment group, and 3) it is unclear, but the control groups may have had some exposure to 1,2,4-TCB.

The study conducted by Watanabe et al. (1977) exposed male and female rats (30 males and 73 females, divided into three dose-exposure groups) to 0, 22.3 (1 ppm), or 74.2 mg/m³ (3 ppm) TCB. Animals were exposed for 6 hours per day, 5 days per week for three months. The average weight of the rats at the beginning of the study was 0.200 kg for the males and 0.175 kg for the females. The overall average weight at the beginning of the study was 0.182 kg. The authors used 99.6% pure 1,2,4-TCB. The other 0.4% was 1,2,3-TCB. The major negative attribute of this study was that the exposure route was inhalation. The authors reported a no observed adverse effect level (NOAEL) of 22.3 mg/m³ (3 ppm). At 74.2 mg/m³ there was an increase in urinary porphyrin excretion. This study provides dose-response data that identifies both a NOAEL and LOAEL. The NOAEL and LOAEL of 22.3 and 74.2 mg/m³ are equivalent to oral doses of 2.38 and 7.92 mg/kg per day, respectively. (The equivalent dose is obtained by multiplying the intermittent exposures of 22.3 and 74.2 mg/m³ by 6/24 (6 hours per day), 5/7 (5 days per week), and 0.253 m³ per day (estimated rat inhalation rate) and dividing by 0.423 kg (the average body weight of the rats at the end of the exposure period). No other study identified a LOAEL lower than the NOAEL reported for this study.

Both studies observed liver porphyria which is considered a sensitive endpoint of 1,2,4-trichlorobenzene toxicity. In addition, Watanabe et al. (1977) used more rats per sex per dose group than Carlson (1977).

Calculation of the Health-Based Maximum Contaminant Level

The U.S.EPA (1984b) outlined a method to convert the inhalation dose

to an absorbed dose in the mouse or rat. Route to route extrapolation is appropriate when pharmacokinetic data exist to convert the inhalation dose to the equivalent effective oral dose (also referred to as the absorbed dose). This method is outlined below, giving the equations used to estimate the respiratory rate and absorbed dose in the rat, the extrapolation to an absorbed dose (ADI) in the human followed with the calculation of the health-based MCL. Data from the study by Watanabe et al. (1977) is used in the calculations.

Estimation of Breathing Rate (BR):

In order to calculate the absorbed dose in the rat, its breathing rate needed to be estimated. Anderson et al. (1977) reported that the inhalation rate can be estimated based on the observation that 25-gram mice breathe 34.5 L/d and 113 gram rats breathe 105 L/d. To estimate the inhalation rate (I) for mice or rats of other body weights (BW), a surface area proportionality can be used:

$$\begin{aligned} \text{For mice: } & 0.0345 (BW/0.025)^{2/3} \text{ m}^3/\text{d} \\ \text{For rats: } & 0.105 (BW/0.113)^{2/3} \text{ m}^3/\text{d} \end{aligned}$$

$$\begin{aligned} I &= 0.105 (0.423/0.113)^{2/3} \text{ m}^3/\text{d} \\ &= 0.253 \text{ m}^3/\text{d} \end{aligned}$$

The hourly respiratory rate (BR) is:

$$\begin{aligned} \text{BR} &= 0.253 \text{ m}^3/\text{d} \times 1 \text{ d}/24 \text{ hrs} \\ &= 0.011 \text{ m}^3/\text{hr} \end{aligned}$$

Estimation of the Absorbed Dose in the Rat (AD):

$$\text{AD} = \frac{(\text{Cr}) (\text{De}) (\text{d}) (\text{A}) (\text{BR})}{\text{BW}}$$

where:

- AD = Absorbed Dose in the rat (mg/kg/day)
- Cr = NOAEL (22 mg/m³)
- De = hours of exposure per Day (6 hrs/day)
- d = number of days exposed per week (5/7)
- A = pulmonary Absorption factor (assumed to be 0.50)
- BR = Breathing Rate in the rat (0.011 m³/hr)
- BW = average Body Weight of the rats at the end of the treatment period (0.423 kg)

$$\text{AD} = \frac{22.3 \text{ mg/m}^3 (6 \text{ hrs/d}) (5 \text{ d}/7\text{d}) (0.50) (0.011 \text{ m}^3/\text{hr})}{0.423 \text{ kg}}$$

$$= 1.235 \text{ mg/kg/day}$$

Extrapolation to an Absorbed Dose in the Human (ADI):

$$ADI = \frac{AD}{(OAF)(SF)}$$

where:

ADI = Average Daily Intake in the human (mg/kg/day)

OAF = Oral Absorption Factor, assumed to be 100%

SF = Safety Factor of 1000 is assumed for a subchronic study

$$ADI = \frac{1.235 \text{ mg/kg/day}}{(1)(1000)}$$

$$= 0.001235 \text{ mg/kg/day}$$

Calculation of the Health-Based Maximum Contaminant Level (MCL):

$$MCL = \frac{ADI (AAW) (SC)}{WC}$$

where:

MCL = health-based Maximum Contaminant Level

AAW = Average Adult Weight, assumed to be 70 kg

SC = Source Contribution of 0.20 from drinking water

WC = average drinking Water Consumption of a 70 kg adult, assumed to be 2 liters/day

$$MCL = \frac{0.001235 \text{ mg/kg/day} (70 \text{ kg}) (0.20)}{2 \text{ L/day}}$$

$$= 0.0086 \text{ mg/L}$$

$$= 8.6 \text{ ug/L}$$

The health-based MCL for 1,2,4-trichlorobenzene is 8.6 ug/L.

There is some discussion in the scientific community on the most appropriate method to convert an inhalation dose, NOAEL or LOAEL, to an ADI. The method used in this assessment converts the NOAEL to an absorbed dose in the laboratory animal using a surface area adjustment. This absorbed dose is then used to extrapolate to an absorbed dose in the human (ADI). Another method extrapolates directly from a NOAEL or LOAEL to the ADI for humans using a standard average human daily respiratory rate (20 m³/day). The former is the one used in the risk assessment of 1,2,4-TCB and resulted in a MCL of 8.6 ug/L after calculating the absorbed dose in the rat of 1.235 mg/kg per day, an inhalation rate in the rat of 0.011 m³/hr, and an ADI of 0.001235 mg/kg per day. The U.S.EPA (1984b) outlined this method to convert the inhalation dose to an absorbed dose in the laboratory animal to an ADI. The former method uses experimental data to estimate the absorbed dose in the laboratory animal. In contrast, the latter method uses the assumption of an average human respiratory rate (20

m³/day) and a direct human-to-animal weight conversion. The MCLs obtained using both methods are similar; 8.6 ug/L compared with 7.7 ug/L respectively.

Assumptions and Uncertainty

It is assumed that: 1) the rat is the best model of 1,2,4-TCB effects in man, 2) an adult human consumes 2 L of water per day, 3) 0.20 represents the drinking water contribution to total 1,2,4-TCB exposure (U.S.EPA, 1985b), 4) the conversion from an inhalation dose in the rat to an oral dose in the human is feasible, and 5) the value of 0.50 is an accurate estimate of the pulmonary absorption of 1,2,4-TCB under the experimental conditions in the Watanabe et al. study. Two experts from the U.S.EPA's Office of Drinking Water, Criteria and Standards Division suggested using a pulmonary absorption value between 0.30 and 0.50. This range takes into account the physiological variables of respiration rate and volume and also the CNS effects caused by the small amount of trichlorobenzene absorbed into the system. The value of 0.50 was used in the estimation of the absorbed dose from the dose given to the research animals in the Watanabe et al. study (1977).

Conclusions

The health-based maximum contaminant level of 8.6 ug/L of drinking water is believed adequate to protect the public from any toxic systemic effects from 1,2,4-trichlorobenzene exposure through the ingestion of potable water. There is no evidence that the chemical is carcinogenic in animals or humans.

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