Appendix B
Section E

DICHLOROBENZENE
HEALTH-BASED MAXIMUM CONTAMINANT LEVEL
SUPPORT DOCUMENT

Office of Science and Research

New Jersey Department of Environmental Protection

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EXECUTIVE SUMMARY

Large amounts of dichlorobenzenes (DCBs) are produced in the U.S. for use in the manufacture of other organic chemicals and as process solvents. It is estimated that between 196-299 megagrams were lost to the U.S. environment in 1983. In New Jersey drinking water p-DCB levels have been found to range from 1.0 to 10.5 ppb. In humans the DCBs produce acute effects on the respiratory, hematologic, urinary, and central nervous systems. Chronic exposures can result in liver injury and toxic effects on the hematopoietic system. DCBs are not highly acutely toxic to animals. Chronically exposed animals may develop central nervous system, liver and kidney damage, in addition to inhibition of the hematopoietic system. The health-based maximum contaminant level (MCL) for o-DCB is calculated to be 600 ug/L of drinking water. p-DCB has been shown to be carcinogenic in rats and mice. Based on animal carcinogenesis data, an MCL of 6.1 ug/L p-DCB was derived that should result in no more than one in a million risk of cancer to the population from drinking water.

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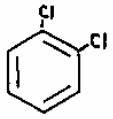
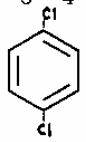
Chemical Properties

Chemical name	ortho-dichlorobenzene
Synonyms	1,2-dichlorobenzene, o-dichlorobenzene, o-DCB, o-dichlorobenzol, Chloroben
CAS number	95-50-1
Chemical formula	$C_6 H_4 Cl_2$
Chemical structure	
Molecular weight	147.01
Physical state (room temperature)	colorless liquid
Melting point	-17 °C
Boiling point	180.5 °C
Vapor pressure	1.0 mm at 20 °C
Specific gravity	1.306 at 20 °C
Water solubility	145 mg/L at 25 °C
Log octanol/water partition coefficient	3.38
Odor threshold, water	0.01 mg/L
Odor threshold, air	2-4 ppm
Saturation concentration	8.0 g/m^3 at 20 °C
Conversion factors	(at 25 °C and 760 mm Hg) 1 ppm = 6.01 mg/m^3 1 mg/L = 166.3 ppm

Chemical Properties

Chemical name	para-dichlorobenzene
Synonyms	1,4-dichlorobenzene, p-dichlorobenzene, p-DCB, p-dichlorobenzol, Paracide
CAS number	106-46-7
Chemical formula	$C_6H_4Cl_2$
Chemical structure	
Molecular weight	147.01
Physical state (room temperature)	colorless, crystalline solid
Melting point	53.1 °C
Boiling point	173.4 °C
Vapor pressure	1.0 mm at 20 °C
Specific gravity	1.458 at 20 °C
Water solubility	123 mg/L at 25 °C
Log octanol/water partition coefficient	3.38
Odor threshold, water	0.03 mg/L
Odor threshold, air	15-30 ppm
Saturation concentration	4.8 g/m^3 at 20 °C
Conversion factors	(at 25 °C and 760 mm Hg) 1 ppm = 6.01 mg/m^3 1 mg/L = 166.3 ppm

Production and Use

The total annual production of dichlorobenzenes (DCBs) in the U.S. for 1983 was estimated to be between 46.7 and 50.2 million kilograms (USEPA, 1983). Almost all of this was in the form of o- or p-dichlorobenzene with m-dichlorobenzene accounting for less than 1% of the total production.

Chlorinated benzenes are used as intermediates in the production of organic chemicals, including other chlorinated benzenes, and in herbicides, pesticides, fungicides, dyes, rubber, process solvents, and deodorizing agents (U.S.EPA, 1980).

Guidelines, Regulations, and Standards

In the U.S. occupational exposure standards have been established for 1,2-dichlorobenzene and 1,4-dichlorobenzene. The maximum allowable concentration (MAC) for 1,2-dichlorobenzene is 50 ppm (300 mg/m^2). OSHA has set a threshold limit value (TLV) standard for 1,4-dichlorobenzene at 75 ppm (450 mg/m^2) (U.S.EPA, 1985)

The American Conference of Governmental Industrial Hygienists (ACGIH) has recommended a short-term exposure limit (STEL) for 1,4-dichlorobenzene of 110 ppm (675 mg/m^2) (U.S.EPA, 1985).

Ambient water quality criteria have been adopted to protect human health from the toxic properties of DCB ingested in water and contaminated aquatic organisms. These criteria include a recommended ambient water concentration of no more than 400 ug/L of DCB (U.S.EPA, 1980).

The National Academy of Sciences (NAS) established a suggested-no-adverse-response-level (SNARL) of 0.094 mg/L for chronic exposures to p-DCB in drinking water. The NAS SNARL for o-DCB is 0.3 mg/L (NAS 1977, 1983).

Health Advisories have been developed for the DCBs by the U.S. EPA. The lifetime Health Advisory for o-DCB (and m-DCB) is 0.62 mg/L, and 0.75 mg/L for p-DCB (U.S.EPA, 1985).

The World Health Organization (WHO, 1984) has recommended an acceptable drinking water level of 1.0 mg/L for o- and p-DCB based on odor threshold (WHO, 1984).

ENVIRONMENTAL EXPOSURE

Fate and Transport

Dichlorobenzenes are volatile compounds which readily evaporate to the atmosphere from water and soil. In the atmosphere DCBs may be degraded by chemical or photolytic reactions, or may be adsorbed onto particles that

settle out or are removed by rain. The estimated residence time for all isomers of DCB in the atmosphere is 38.6 days, with a half-life of about 3 days. DCBs are reactive to hydroxy radicals in air and chlorophenols are the most likely degradation products.

Although some studies indicate that the degradation of chlorobenzenes is possible by microbial communities in soil and water, these reactions generally occur very slowly. DCBs have been reported to be persistent in soil and are generally resistant to microbial degradation.

Chlorobenzenes are lipophilic and tend to bioaccumulate in animal and human tissues after uptake from ambient air, water, and food.

Ambient Levels

Dichlorobenzenes are released into the environment during manufacture and transport; through use as pesticides, solvents, and other industrial and consumer products; and through the disposal of manufacturing wastes In 1983 it was estimated that of the 296-490 megagrams of DCBs lost in the U.S. during manufacture, 196-299 megagrams were lost to the environment (U.S.EPA, 1984).

In the 1978-1981 New Jersey potable water monitoring project, DCB was detected in 2% of approximately 500 water samples collected statewide from public water supplies. The average detected value for this isomer was 20 ug/L (N.J. DEP, 1984). During 1984-1985 the New Jersey Department of Environmental Protection (NJDEP) found p-DCB in 0.3% of the water supply samples tested in the initial round of sampling under the Assembly Bill A-280 amendments to the New Jersey Safe Drinking Water Act (NJSDWA). The median p-DCB concentration in the contaminated samples was 5.8 ug/L, with a maximum of 10.5 ug/L (N.J.DEP, 1985).

METABOLISM AND PHARMACOKINETICS

Absorption

The dichlorobenzenes have a low water and high lipid solubility, and are therefore likely to diffuse through most biological membranes, including the surfaces of the lungs, gastrointestinal tract, and skin. Quantitative studies on the absorption of DCBs in humans and animals are lacking. The available data indicate that absorption occurs fairly rapidly through the lungs and gastrointestinal tract (U.S.EPA, 1985).

Distribution

Once absorbed, through either inhalation or ingestion, the DCBs are rapidly distributed to the blood, adipose tissue, kidney, liver, lung, heart, brain, and muscle. Distribution is primarily to adipose tissue,

which can have initial levels 10-32 times higher than blood concentrations. This is true for both single-dose and repeated exposures by either inhalation or ingestion (U.S.EPA, 1985).

Metabolism

The metabolism of the DCBs in rabbits and rats has been investigated; little data is available on humans. The primary metabolites are dichlorophenols which are formed by hydroxylation of arene oxide intermediates and conjugated with glucuronic and sulfonic acids. (Hawkins et al., 1980).

Excretion

Elimination of DCBs and their metabolites occurs within 5-6 days after exposure, with release from adipose tissue occurring the slowest. o-DCB and its metabolites are eliminated slightly more rapidly than p-DCB. Some metabolites are excreted in the bile, but are then reabsorbed by the enterohepatic pathway and excreted in the urine (Hawkins et al., 1980).

Human Exposure and Body Burden

It is estimated that in the U.S. approximately 1.6 million people are exposed to either o- or p-DCB in drinking water at levels ranging from 0.5 ug/L to 5 ug/L. No individuals are thought to be exposed to levels of m-DCB above 0.5 ug/L. Current data suggest that a majority of the persons using public drinking water supplies would be exposed to intake levels of the DCB isomers below 0.014 ug/kg per day (U.S.EPA, 1984).

Average concentrations of p-DCB in human adipose tissue have been reported to be between 2.3 and 1.7 ug/g, and levels in blood range from 4 to 16 ug/mL with an average of 9.5 ug/mL (U.S.EPA, 1984).

HEALTH EFFECTS

Overview

The dichlorobenzenes can have toxic effects on the respiratory tract and central nervous and hematologic systems, and can cause liver or kidney damage in humans after acute high level exposure. Chronic exposure may also result in adverse effects on the reticuloendothelial and hematopoietic systems. DCBs have been found to produce acute effects in animals similar to those in humans. Central nervous system (CNS), liver and kidney damage are the most predominant health effects of chronic exposure. p-DCB has been shown to be carcinogenic in rats and mice.

Human

Acute. Very little data are available on acute exposures to DCBs in humans. It has been reported, however, that exposure to o- or p-DCB by inhalation may produce immediate effects on the CNS, skin, and respiratory tract. Common symptoms of such exposure include eye and upper respiratory tract irritation, vomiting, headache, rhinitis, and periorbital swelling (U.S.EPA, 1984).

Ingestion of p-DCB has been noted to affect the hematologic and urinary systems as well as the CNS, causing listlessness, jaundice, methemoglobinemia, anemia, hypothermia, oliguria, and other urinary abnormalities (U.S.EPA, 1984).

Epidemiologic data are insufficient to evaluate dose - response relationships. Zapata-Gayon et al. (1982) found that short-term exposure to o-DCB (8 hours per day for 4 days) produced alterations in the chromosomes of human leukocytes (U.S.EPA, 1985a).

Chronic. Repeated exposure to DCBs over a period of more than one year has resulted in toxic effects to the reticuloendothelial and hematopoietic systems. Seventeen of 23 exposure cases have involved pathological changes in the blood or liver, including chronic lymphoid leukemia, acute hemolytic anemia, aplastic anemia or bone marrow hyperplasia. Together these findings suggest a common pathologic action for the DCB on bone marrow and other organs of the blood-forming system (U.S.EPA, 1985a).

Animal

Acute. The LD_{50} for rats after oral administration of o-DCB ranges from 500 to 1,500 mg/kg. The oral LD_{50} for p-DCB ranges from 500 to 2,500 mg/kg (U.S.EPA, 1984, 1985).

Relatively high oral doses are needed to produce acute effects. These effects initially include increased lacrimation, salivation, and excitation, followed by ataxia, dyspnea and death from respiratory paralysis. Pathological findings from acute exposures identify injury to the liver, kidney, heart, thymus, spleen, and stomach, and brain edema. Liver damage is manifest as necrosis, degeneration, or porphyria, depending upon the isomer to which an individual is exposed (U.S.EPA, 1984, 1985a).

Chronic: In inhalation studies, Hollingsworth et al. (1958) found decreased spleen weights in male guinea pigs exposed to o-DCB for 7 hours per day, 5 days per week for 6-7 months at 560 mg/m^3. Using the same exposure regimen for p-DCB at 580 mg/m^3, he found no adverse effects on several parameters examined in rats, guinea pigs, mice, rabbits and monkeys. At 950 mg/m^3 the investigator noted growth reduction in guinea pigs, and increased liver and kidney weights, and histological liver changes (cloudy swelling, granular degeneration) in rats. No adverse

effects were reported in rabbits, mice or monkeys. In rats and guinea pigs exposed to p-DCB at 2,050 mg/m^3 for 6 months, growth depression, increased liver and kidney weights, and liver pathology (necrosis, fatty degeneration, swelling, fibrosis) were recorded. When exposed to 4,800 mg/m^3 of p-DCB for up to 69 exposures for 8 hours per day, 5 days per week, rats, guinea pigs and rabbits experienced severe irritation, CNS depression, liver, kidney and lung pathologies, and death (Hollingsworth et al., 1956).

Rats exposed to approximately 450 mg/m^3 of p-DCB for 5 hours per day, 5 days per week, for 76 weeks were found to have some increases in liver weights. At approximately 3,000 mg/m^3 exposed rats exhibited slightly elevated protein and coproporphyrin outputs and increased liver and kidney weights (Loeser and Litchfield, 1983).

Pike (1944) found that rabbits exposed to p-DCB at about 800 ppm for 8 hours, 5 days per week for as long as 12 weeks, developed tremors, weakness, nystagmus, and reversible non-specific eye changes. Similar toxic effects developed in rabbits fed p-DCB at 1,000 mg/kg for 5 days per week for several months (Pike, 1944).

Chronic: In oral studies, rats administered o-DCB and p-DCB via stomach tubes, 5 days per week for a total of 138 doses, had increased liver and kidney weights at doses of 188 mg/kg and 376 mg/kg. Cloudy swelling of the liver also developed in rats at the higher dose of 376 mg/kg. Exposure to p-DCB at 376 mg/kg caused liver cirrhosis and focal necrosis. No effects were noted at the lowest dose of 18.8 mg/kg (Hollingsworth et al., 1956, 1958).

Hollingsworth also fed p-DCB to rabbits by intubation at a level of 500 mg/kg per dose for a total of 263 doses in 367 days, and 1,000 mg/kg per dose for a total of 92 doses in 219 days. CNS depression, weight loss and liver pathologies were noted at both dose levels with some deaths occurring at the higher level (Hollingsworth et al., 1956).

Varshavskaya (1968) administered o-DCB to rats at doses of 0.001, 0.01 and 0.1 mg/kg per day for 9 months. At the two highest dose levels, the investigator reported depression of higher nervous system function, inhibition of the hematopoietic system and altered blood, liver, and kidney enzyme activities. No effects were noted at the lowest dose level.

B6C3F Mice and F344/N rats were given o-DCB at doses of 30, 60, 125, 250 or 500 mg/kg per day corn oil by gavage, 5 days per week for 13 weeks. At 500 mg/kg o-DCB decreased survival in male and female mice and female rats was observed. In addition, centrolobular necrosis of the liver, hepatocellular degeneration, and depletion of lymphocytes in the thymus and spleen of both sexes were noted at the highest dose. At 500 mg/kg renal tubular degeneration was observed in male rats, and multifocal mineralization of the myocardial fibers of the heart and skeletal muscle

were seen in mice. At the dose of 250 mg/kg, necrosis of individual hepatocytes was observed in rats of both sexes and male mice. Minimal hepatocellular necrosis was detected in a few rats at a dose of 125 mg/kg, but no hepatic alteration was observed in mice at this dose. Slight hematologic changes were noted in the 500 mg/kg dose group of male and female rats; no other marked hematologic changes were observed at any other dose level or in mice (NTP, 1985).

Two-year toxicology/carcinogenesis studies of o-DCB were conducted by NTP (1985). o-DCB was administered in corn oil by gavage 5 times per week for 103 weeks to groups of 50 male and 50 female F344/N rats and B6C3F mice at doses of 60 and 120 mg/kg. Controls only received corn oil by gavage. The only compound-related effect observed was an increase in tubular regeneration in the kidneys of male mice (control, 8/48, 17%; low dose, 12/50, 24%; high dose, 17/49, 35%). No other compound-related effects in rats or mice were noted.

The National Toxicology Program (NTP) conducted two 13-week studies of the effects of p-DCB on F344/N rats. In the first study, rats were dosed with 300 to 1,500 mg/kg of p-DCB. Histologic changes were observed in the kidney of all male rats at all dose levels; therefore, another 13-week study was conducted at doses of 38-600 mg/kg. Doses of 1,200 or 1,500 mg/kg producted cellular degeneration in liver, bone marrow, spleen, thymus, and nasal turbinales in both male and female rats. Renal tubular cell degeneration was observed in male rats receiving 600 mg/kg or more in the first study, but only equivocal changes were detected at 150 mg/kg. Changes in the hematocrit were observed in all males receiving doses of 300 to 1,200 mg/kg. No hematologic effects were observed in female rats.

The effects on $B6C3F_1$ mice exposed to p-DCB for 13 weeks was also reported (NTP, 1986). The mice received doses of 600 to 1,800 mg/kg in corn oil by gavage for five days per week. Hepatocellular degeneration was observed in both sexes at all doses. The white blood cell count was reduced in all dosed males and in females receiving 1,000 mg/kg or more. Hepatic porphyria was not found in mice at any dose level. A second 13-week study was performed at doses of 85 to 900 mg/kg. In this study, cytomegaly was observed in male and female mice at doses of 675 mg/kg or more, but not at 338 mg/kg. No renal toxicity was observed in either study.

A two-year study of the effects of p-DCB on B6C3F mice and F344/N rats was conducted by NTP (1976). The doses selected for the two-year studies were 150 and 300 mg/kg for male rats and 300 and 600 mg/kg for female rats and both sexes of mice. Selection of doses was based on the toxicity seen in the preliminary 13-week studies. Male rats dosed with p-DCB had an increase in nephropathy, epithelial hyperplasic of the renal pelvis, mineralization of the collecting tubules, and focal hyperplasia of renal tubular epithelium. Female rats had a dose-related increase in nephropathy. p-DCB increased the incidences of non-neoplastic liver

lesions in male and female mice, including alteration in cell size (cytomegaly and karyomegaly), hepatocellular degeneration, and individual cell necrosis. The incidence of nephropathy was increased in male mice; renal tubular regeneration increased in female mice.

Behavioral and Central Nervous System

CNS depression has been observed in rats, rabbits, and guinea pigs exposed via inhalation to o- and p-DCB at levels ranging from 3,239 to 100,000 mg/m^3 for acute exposure (Hollingsworth et al., 1958).

Subchronic exposures (5-14 weeks) to p-DCB by inhalation at dose levels ranging from 900 mg/m^3 to 100,000 mg/m^3 has been reported to result in respiratory excitation, tremors, weakness, nystagmus, and CNS depression and collapse in rabbits, rats, guinea pigs or mice (U.S.EPA, 1985).

Oral doses of p-DCB at levels of 500 and 1000 mg/kg also produced CNS depression in rabbits that were given 92 doses in 219 days (Hollingsworth et al., 1956).

Varshavskaya (1967) found changes in conditioned reflexes among rats administered o-DCB for 5 months at 0.01 and 0.1 mg/kg per day

Behavioral and CNS effects on humans exposed to DCBs have been reported in the literature from both occupational and nonoccupational case studies. Acute and chronic exposures to DCBs, primarily o- and p-DCB, have been found to cause many general symptons indicative of CNS depression. These include pallor, headaches, dizziness, asthenia, numbness, clumsiness, exhaustion, dyspnea, anorexia, malaise, tremors, and mental sluggishness. Exposure profiles and chemical mixtures were often not well defined in many of the studies but the primary route of exposure was commonly via inhalation (Ware and West, 1977; U.S.EPA, 1980).

Reproductive, Embryotoxic, and Teratogenic

Data on the reproductive, embryonic and teratogenic toxicity of the DCBs is limited, however; they have been demonstrated to cross the placenta (Dowty et al., 1976).

Hayes et al. (1985) observed no fetotoxic or teratogenic effects in fetuses of rats or rabbits exposed to o-DCB via inhalation at levels reaching 400 ppm. Rabbits exposed to p-DCB at levels of up to 500 ppm were also without adverse fetotoxic or teratogenic effects (Hayes et al., 1985).

In a review by Loeser and Litchfield (1983) of a rat embryotoxicity and teratogenicity inhalation study, p-DCB was found to have adverse effects on pregnant rats and their fetuses. Dams were exposed for 6 hours per day from days 6-15 (inclusive) of pregnancy to atmospheres of 0, 75, 200 or 500 ppm. Results showed that 1 dam at 75 ppm, 1 at 200 ppm,

and 5 at 500 ppm delivered litters one day earlier than expected, otherwise no differences among the dams were noted. The only fetal effects noted were gastroschisis and malrotation of the right hind limb in one fetus from both 5 and 200 ppm groups, and one fetus with agnathia and cleft palate in the 500 ppm group (Loeser and Litchfield, 1983).

Genetic

The mutagenicity of the DCBs has not been extensively studied. o-DCB, however, has been found to be clastogenic based on a study showing a significant increase in chromosomal aberrations in leukocytes of humans accidentally exposed to o-DCB vapors for 4 8-hour workdays (Zapata-Gayon et al., 1982).

Mutagenicity tests on o- and p-DCB were negative in five strains of Salmonella (TA98, TA100, TA1535, TA1537, and TA1538) with or without microsomal activation (Lawlor et al., 1979).

Studies of o-DCB were also negative for mutagenicity in four Salmonella strains (TA98, TA100, TA1535 and TA1537) when tested with or without metabolic activation at doses as high as 1,300 ug per plate (NTP, 1982).

Several studies of mold and plant cell cultures treated with dichlorobenzenes have reported mutations and chromosomal aberrations under various exposure regimens. Test species included Aspergillus nidulens, Allium, Nothoscordum fragans, and Lens esculenta (U.S.EPA, 1985).

Carcinogenicity

The NTP (1985) has released a report on the carcinogenesis studies of o-DCB in rats and mice. Two-year bioassay studies of o-DCB were conducted by administering the test chemical in corn oil by gavage 5 times per week for 103 weeks to groups of 50 male and 50 female F344/N rats and B6C3F1 mice at doses of 60 and 120 mg/kg. Groups of 50 rats and 50 mice of each sex received corn oil by gavage on the same schedule and served as vehicle controls. Under the conditions of these studies, there was no evidence of carcinogenicity for o-DCB in male and female F344/N rats or B6C3F1 mice. This assay, however, may not have been sufficiently sensitive since the doses used may have been less than the maximum tolerated dose (MTD) as estimated by subchronic studies.

The NTP has released a draft report (1986) about the carcinogenicity of p-DCB. p-DCB was administered by gavage to male F344/N rats at doses of 0, 150, or 300 mg/kg and to male and female B6C3F mice at doses of 0, 300, or 600 mg/kg per day for 2 years (50 animals per group). A dose-related increase in the incidence of tubular cell adenocarcinomas was detected in the kidneys of male rats (1/50; 3/50; 7/50; incidence in control, low-dose, and high-dose groups, respectively) and one tubular cell adenoma was observed in a high-dose male rat. There was a marginal increase in the

incidence of mononuclear cell leukemia in dosed male rats compared with that of vehicle controls (5/50; 7/50; 11/50). p-DCB increased the incidence of hepatocellular carcinomas in high dose male mice (14/50; 5/48; 19/50) and hepatocellular adenomas in dosed male mice (5/50; 6/48; 21/50). Pheochromocytomas (benign or malignant, combined) of the adrenal gland occurred more frequency in dosed male mice, and the incidence in the high-dose group was significantly greater than that in the vehicle controls (0/47; 2/48; 4/49).

Two long-term inhalation studies have been conducted in mice and rats to assess the chronic toxicity and carcinogenic potential of p-DCB. In one study mixed groups of Swiss strain mice (75 males and 75 females per group) were exposed to airborne concentrations of 0, 75 and 500 ppm of p-DCB, 5 hours per day, 5 days per week for 57 weeks for all female groups and the 500 ppm males, and for 61 weeks for the 0, and 75 ppm males (Loeser and Litchfield, 1983).

In the other study Alderly Park Wistar-derived albino rats (76-79 animals per sex per group) were exposed to airborne concentrations of 0, 75, or 500 ppm of p-DCB for 5 hours per day, 5 days per week for 76 weeks (Loeser and Litchfield, 1983). No evidence for carcinogenicity was found in either study, however, the animals were not exposed for 104 weeks, the usualduration of dosing for carcinogenicity studies in these species.

QUANTITATIVE RISK ASSESSMENT

Studies Useful for Risk Assessment

Several studies may be useful for assessing the effects of chronic DCB exposure.

There are no studies in the literature pertaining to m-DCB that would be appropriate for evaluating health effects in humans. Data obtained in mutagenicity tests and short-term studies suggest, however, that m-DCB is somewhat more toxic than p-DCB and behaves more like the ortho isomer. This has led to the assumption that Acceptable Daily Intakes (ADIs) developed for o-DCB will also be applicable to m-DCB.

A number of studies for o-DCB are available in which dose-response data are described and which allow for the estimation of a no-observed-adverse-effect level (NOAEL). Animals are exposed both by gavage and by inhalation for periods of time constituting a subchronic or chronic exposure. Since gavage studies are more appropriate for the development of MCLs in drinking water and several are available for evaluation, only these studies will be used in the quantification of toxicological effects. Studies of the longest duration and employing the lowest doses would be the most appropriate to estimate the risk of chronic ingestion of low levels of o-DCB.

The two-year NTP (1985) study involving rats and mice is the longest and most complete toxicity study made with o-DCB. Varshavskaya (1966) identified toxic effects at doses lower than NTP, but the description of the study lacked many essential experimental details and this raised the question of whether the effects observed were the result of exposure to o-DCB. The NTP chronic study identified a dose-related increased in tubular regeneration in the kidney of male rats (control, 8/48, 17%; 60 mg/kg dose, 12/50, 24%; 120 mg/kg dose, 17/49, 35%). Although the statistical significance of this data was not given, the marginal increase in tubular regeneration might be considered as a lowest-observed-adverse-effect level (LOAEL), upon which a health-based MCL would be derived.

The Office of Drinking Water, U.S.EPA, had considered p-DCB to be a noncarcinogen and derived a health advisory for p-DCB in drinking water based on subchronic toxicity information. The new NTP carcinogenicity/toxicity study (1986) demonstrated the potential of p-DCB to increase the incidence of benign and malignant tumors in both sexes of rats and mice. This was sufficient evidence to classify p-DCB under EPA's catagory B2, probable human carcinogen. Therefore, a risk analysis based on the NTP study (1986) was carried out using male rats, which had the highest dose-related incidence of a malignant tumor (kidney adenocarcinomas) and received the lowest dose, 150 mg/kg. The incidence of renal adenocarcinomas in male rats was: 1/50 for controls, 3/49 for the 150 mg/kg dose group, and 7/50 for the 300 mg/kg dose group.

Calculation of a Health-Based Maximum Contaminant Level (MCL)

Maximum contaminant levels for DCBs in drinking water are presented as ADI concentrations for o-DCB (and m-DCB) and p-DCB.

Based on the NTP (1985) study, the MCL for o-DCB (and m-DCB) is calculated as follows:

$$ADI = \frac{(60\ mg/kg/day)\ (5/7)}{(100)\ (5)}$$

$$ADI = 0.085\ mg/kg/day$$

$$MCL = \frac{ADI\ (0.2)\ (70)}{2\ L/day}$$

$$MCL = 0.60\ mg/L$$

$$= 600\ ug/L$$

5/7 = conversion of 5 day per week exposure to 7 day per week exposure.

70 kg = assumed weight of an adult human.

0.2 = relative source contribution from drinking water.

100 = uncertainty factor appropriate for use with a NOAEL from a chronic animal study.

5 = convert a LOAEL to a NOAEL.

2 L/day = assumed water consumption by an adult.

60 mg/kg per day = LOAEL (NTP, 1985)

The incidence of renal adenocarcinomas in male rats obtained from the NTP study (1986) was fitted to the multistage model using the K.S. Crump & Co. (1982) version of GLOBAL 82. The multistage model is given by:

$$P(d) = 1 - \exp(-q_o - q_1 d - \ldots - q_k d^k)$$

$q_i \geq 0$, $i = 0,1,\ldots,k$, where d is dose, P(d) is the lifetime probability of cancer at dose d and k, qo, ... q_k are parameters. In practice, k is set equal to the number of dose groups less one.

Extra risk above background is defined as

$$[P(d) - (0)]/[1 - P(0)],$$

for the multistage model. Extra risk may be interpreted as the probability of the occurrence of a cancer at a dose d, given that no cancer would have occurred without any dose.

Animal-to-human extrapolation is based on the assumption that both animals and humans are equally susceptible (in terms of extra risk) to the carcinogen when the dose is measured in the same units for both species (Crump and Howe, 1980).

In this report, the mg/m^2 body surface area per day will be used for animal-to-human extrapolation. When the surface area conversion basis is used, then the human dose (Dh) measured in mg/kg per day is given by

$$Dh = Da\ (Wa/Wh)^{1/3},$$

where Da is the animal dose (mg/kg per day), Wa and Wh are the weights for

animals and humans, respectively, measured in the same units.[1]

The intermitent dose of 150 and 300 mg per day administered 5 out of 7 days per week is adjusted to an average daily dose by:

$$Da \times \frac{5}{7} = Da\ (av)$$

$$150\ mg/kg \times \frac{5}{7} = 107\ mg/kg/day$$

$$300\ mg/kg \times \frac{5}{7} = 214$$

then $Dh = 107 \left(\frac{.35}{70}\right)^{1/3} = 18.29\ mg/kg/day$

$$Dh = 214 \left(\frac{.35}{70}\right)^{1/3} = 36.38\ mg/kg/day$$

The upper 95% confidence limit on the slope, or potency (q_1^*), derived from the model is 0.0097. The dose that represents 95% upper bound on the 10^{-6} risk is 1.75×10^{-4} mg/kg per day.

The health-based maximum contaminant level (MCL) that would deliver the human dose is calculated by:

$$MCL\ (ug/L) = \frac{Dh(mg/kg/d) \times Wh\ (kg) \times 1000\ (ug/mg)}{V(L/d)}$$

where V = water volume consumed daily by humans

$$MCL\ (ug/L) = \frac{1.75 \times 10^{-4}\ mg/kg/day \times 70\ kg \times 1000\ (ug/mg)}{2\ L/day}$$

$$MCL = 6.1\ ug/mL$$

As a result, the 95% upper bound on the 10^{-6} risk level was determined to be 6.1 ug/L from the multistage model.

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1 Let Wa and Wh be in kg, and let Sa and Sh be the surface areas of animals and humans, respectively, in m^2. Surface area is approximately proportional to body weight to the 2/3 power; this means that Sa = KWa and $Sh = KWh^{2/3}$ for some constant K. The animal dose mg/m^3 per day that is equivalent to Da is therefore $DaWa/Sa = DaWa^{1/3}K$. Under the surface area method for converting risk, this also represents that equivalent human dose in mg/m^3 per day. Converting the units of this dose to mg/kg per day yields $Dh = (DaWa^{1/3}/K)\ (Sh/Wh) = DaWa^{1/3}/K)\ (KWh^{2/3}Wh = Da\ (Wa/Wh)^{1/3}$.

Assumptions and Uncertainty

It is assumed that: (1) rats are at least as sensitive to a given oral dose of DCB as an adult human; (2) an adult human weighs 70 kg; and (3) drinking water sources will represent 20% of the total exposure to DCBs.

The uncertainties in applying dose-response data from animals to humans and the inherent variability in the human population are addressed in the calculations by incorporating a safety factor of 100 into the equation. An additional factor of 5 is included to account for the uncertainties in converting a LOAEL (based on a very minimal effect) to a NOAEL.

Conclusions

A health-based maximum contaminant level concentration of 600 ug/L was derived for o-DCB (and m-DCB) which should result in no adverse effects in the population.

From the analysis of animal carcinogenesis data, a MCL of 6.1 ug/L in drinking water was derived for p-DCB that should result in no more than 1 excess cancer in a million.

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