

Appendix B  
Section D

CHLOROBENZENE  
HEALTH-BASED MAXIMUM CONTAMINANT LEVEL  
SUPPORT DOCUMENT

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New Jersey Department Of Environmental Protection

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#### EXECUTIVE SUMMARY

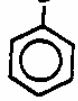
Monochlorobenzene (MCB) is an intermediate in chemical and pesticide production and a process solvent for various organic compounds. Human exposure to MCB has been occupationally related or accidental. Acute exposure to this chemical results in central nervous system depression and hepatic and renal disorders. Effects of chronic exposure involve depression of both the central nervous system and peripheral nervous system, respiratory tract irritation and medullary aplasia. In animals, chronic exposure causes hepatic and kidney histopathic changes and increased liver weights with porphyrin excretion at high doses. The odor/taste threshold was determined to be in a range of 0.41 to 1.5 micrograms per liter (ug/L) (Tarkhova, 1965) and 10 to 20 ug/L (Varshavskaya, 1968). A health based maximum contaminant level of 4.5 ug/L in drinking water is believed adequate to protect the public from these adverse systemic health effects.

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BACKGROUND INFORMATION AND PROPERTIES

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

Synonyms	Monochlorobenzene (MCB) Chlorobenzene Benzene chloride Phenyl chloride Chlorobenzol
CAS #	108-90-7
Chemical formula	C <sub>6</sub> H <sub>5</sub> Cl
Chemical structure	
Molecular weight	112.56
Physical state	colorless liquid (at room temperature)
Melting point	-45.6 °C
Boiling point	132 °C at 760 mm Hg
Vapor pressure, volatility	10 mm Hg at 22.2 °C
Specific gravity, density	1.1058 at 20 °C/4 °C
Water solubility	insoluble; 0.049 (g/100 mL water at 20 °C (Patty's Industrial Hygiene and Toxicology, 1981)
Log octanol/water partition coefficient	2.84
Odor/taste threshold (water)	0.41-1.5 ug/L (Tarkhova, 1965), 10-20 ug/L (Varshavskaya, 1968; as cited in U.S.EPA, 1985b)
Odor threshold (air)	almond-like odor, 0.21 ppm (DPIMR, 1982)
Odor threshold (medium unknown)	0.21 mg/L (HSDB, 1986)
Conversion factors	1 mg/L = 217 ppm 1 ppm = 4.60 mg/m <sup>3</sup> at 25 °C, 760 mm Hg (Patty's Industrial Hygiene and Toxicology, 1981)

## Production and Use

Chlorobenzene (MCB) is produced by the chlorination of benzene in the presence of a catalyst, ferric chloride (U.S.EPA, 1985a). The U.S. imported 8.37 million pounds in 1975. U.S. industry produced 329 million pounds in 1976 (Fishbein, 1979). In New Jersey, industry imported 10-50 thousand pounds and produced 50-100 thousand pounds of MCB in 1978-79 (New Jersey Industrial Survey, 1978-1979). National production in 1981 was 290 million pounds (U.S.EPA, 1985b). This production increased to 515 million pounds in 1983 (U.S.EPA, 1985a).

MCB is an intermediate in the production of chloronitrobenzene, diphenyl oxide, DDT and silicones and is also a process solvent for methylene diisocyanate, various adhesives, polishes, waxes, pharmaceuticals and natural rubber (U.S.EPA, 1985a).

## Guidelines, Regulations, and Standards

The American Conference of Governmental Industrial Hygienists (ACGIH, 1982) and the National Institute for Occupational Safety and Health Administration (NIOSH, 1976) recommended a Threshold Limit Value (TLV) of 75 ppm (350 mg/m<sup>3</sup>) in an occupational environment.

The U.S.EPA proposed two ambient water quality criteria figures based on systemic toxicity data (488 ug/L) and on the taste threshold (20 ug/L). These figures were derived for a 70-kg adult consuming two liters of water per day and 6.5 g of contaminated fish and seafood (U.S.EPA, 1985b).

The World Health Organization (WHO) suggested a guideline of 3 ug/L of MCB to avoid taste and odor problems (WHO, 1984).

## ENVIRONMENTAL EXPOSURE

### Fate and Transport

Because MCB is highly volatile, contamination of air occurs when it is used as a solvent. The chemical contaminates soil and water during its disposal as a waste solvent (U.S.EPA, 1985a). Once it is in surface water, MCB will settle on the bottom and, as a result, will reach a chronic equilibrium over a long period of time (DPIMR, 1982). This contamination is possible on a national scale since MCB is used in metal cleaning operations all across the country (U.S.EPA, 1985a).

MCB contamination of the air can occur either through direct volatilization or through indirect evaporation from surface waters. It is suspected, but not proven, that free radical oxidation degrades MCB in air (U.S.EPA, 1985a).

MCB degradation in soil occurs at a slower rate than in air. The

chemical is adsorbed onto soil particles and is able to migrate to ground water supplies (U.S.EPA, 1985a). Very little, if any, degradation occurs once MCB reaches ground water (Roberts et al., 1980).

Once in the environment, MCB can bioconcentrate and bioaccumulate in organisms as it moves up through the various trophic levels (biomagnification) (U.S.EPA, 1985a). In fish, trout are most sensitive to exposure, while goldfish are most tolerant (Dow Chemical Company, 1978 and Dalich et al., 1982). MCB has also been reported to bioconcentrate and bioaccumulate in invertebrate species and plants (U.S.EPA, 1978).

#### Ambient Levels

The U.S.EPA (1983) estimated that 191-303 megagrams were lost during MCB production of between 88,769-128,755 megagrams. Most of this estimated loss was subsequently released into the environment (153-259 megagrams) (U.S.EPA, 1983). Dow Chemical, a major producer of MCB, estimated that between 30 to 50% of the product made each year was lost to air. They also estimated that 0.1% of the total amount produced was lost to water (Dow, 1978).

Ambient levels of MCB have been measured in air, surface water, and waste water (Table I). Some of these contamination levels were found in air and water in, or bordering, the state of New Jersey. Harkov et al. (1980) reported MCB levels in 22% of all air samples analyzed at average concentrations ranging from 0.26 to 0.82 ppbv, with a maximum level of 9.1 ppbv. These samples were taken at six sites in the state (Table II). In a later survey, Harkov et al. (1984) measured seasonal differences in MCB contamination of air in three urban sites in New Jersey: Camden, Elizabeth, and Newark. Concentrations appeared larger in the winter (0.18-0.22 ppbv) than in the summer (0.07-0.11 ppbv) across all areas. In two of these areas, Newark and Elizabeth, MCB concentrations have decreased over time. MCB contamination is found at higher levels in industrial situations. NIOSH reported occupational levels in production facilities ranging from negligible to 18.7 mg/m<sup>3</sup> (Cohen et al., 1981).

New Orleans, LA. drinking water supplies were found to contain levels of MCB (U.S.EPA, 1975a and U.S.EPA 1975c). Ground water supplies in Hardeman County, TN., were observed to be contaminated with MCB at levels ranging from trace amounts to 41 ug/L with a mean level of 5.0 ug/L (Clark et al., 1982). Levels ranging from 10-60 ng/L were found in tap water from homes in the old Love Canal area in Niagara Falls (Barkley et al., 1981). Three water supplies, sampled in New Jersey during the initial round of testing in accord with the New Jersey Assembly Bill A-280, had a median level of 0.5 ppb with a range of 0.5 ppb to 1.7 ppb (May 1985). Subsequent testing found levels ranging between 0.34 ppb and 7.00 ppb in four different sources. The water supply with the 7.00 ppb was found in Queen's Square and its use has been discontinued. These people now receive water from Elizabeth Township (N.J.DEP, 1986).

There has been little research on MCB contamination of food (U.S.EPA, 1985b).

## METABOLISM AND PHARMACOKINETICS

### Absorption

Quantitative studies on the absorption of MCB are not available (U.S.EPA, 1985b). Toxic effects reported in humans after inhalation or ingestion indicate that the chemical is absorbed via the respiratory and gastrointestinal tracts (G.I.) (Reich, 1934, Rosenbaum et al., 1947, and Tarkova, 1965). It has been demonstrated in studies of MCB metabolism that absorption occurs in animals (Williams, 1959). Even though definitive G.I. studies do not exist, given the lipophilic nature of MCB and the documented dermal absorption of other chlorobenzenes, some degree of dermal absorption of MCB would be expected (U.S.EPA, 1985a).

### Distribution

Sullivan et al. (1983) conducted an inhalation and pharmacokinetic study on male Sprague-Dawley rats. They were exposed to 0, 100, 400, or 700 ppm MCB 8 hours per day for 1 to 5 consecutive days. A steady state concentration was attained during the first 8 hours of exposure. The tissue concentration was proportional to the exposure concentration with the exception of adipose tissue in which MCB tissue levels increased 8 to 10 times when the exposure concentration was increased from 100 to 400 ppm. Tissue levels increased 3 to 5 times when the exposure concentration was increased from 400 to 700 ppm.

### Metabolism

Following subcutaneous injection of rats, monochlorobenzene was metabolized to 4-chlorophenylmercapturic acid and conjugates of 4-chlorophenol and 4-chlorocatechol (Shimada, 1981). Based on this information, Shimada proposed that MCB metabolism involves an initial oxidation to form 4-chlorobenzene-1,2-epoxide. Studies that used perfused rat livers suggested that MCB is metabolized to conjugates of 3-chlorophenol following hydrolysis of a 3-chlorobenzene-1,2-epoxide intermediate (Selander et al., 1975).

It is thought that one of the reactive intermediates is the epoxide precursor of the phenols, catechols, and mercapturic acid compounds. Metabolites have been found to covalently bind to protein in the proximal convoluted tubules in the kidney where necrosis later developed in mice (Reid and Ilette, 1972 and Reid, 1972).

### Excretion

There are species differences in elimination of MCB (Williams et al.,

Table I

Ambient Levels of MCB in Air, Surface Water, and Wastewater  
in the United States - 1976-1980\*

Source	Concentration	Reference
Air	+ND to 13 ug/m <sup>3</sup>	Pellizzari et al., 1979, Singh et al., 1981, and Brodzinsky and Singh, 1982
Surface Water	+ND to 10 ug/L	Shackleford and Keith, 1976, Sheldon and Hites, 1978, Elder et al., 1981, and ORVWSC, 1982
Waste Water	667 ug/L (mean)	Neptune, 1980

+ND = not detected

\* Source: Adapted from U.S. EPA, 1985a.



Table II

Chlorobenzene Levels Found in Air in New Jersey (ppbv)\*

Site	Number of Samples	Trace	Average	Range	<u>Quantifiable Samples</u>	
					Number of Samples	Average
Overall	263	53	--	--	173	0.54
Elizabeth	54	7	0.82	0.0-9.1	45	0.98
Rutherford	46	2	0.67	0.0-12.0	38	0.81
Newark	50	13	0.39	0.0-5.7	35	0.55
South Amboy	48	13	0.26	0.0-3.9	24	0.51
Batsto	42	17	0.28	0.0-2.8	14	0.82
Camden	--	--	--	--	--	--

\*Source: Harkov, R., Katz, R., Bozzelli, Jr., and Kebbekus, B., 1980.

1975). The major urinary metabolite in the 13 species studied was p-chlorophenylmercapturic acid (19-65%) (Williams et al., 1975). Table III lists some of the species studied. The amounts of metabolites will vary depending on the saturation of metabolic pathways (U.S.EPA, 1985a). Sullivan (1981) determined that metabolic pathways are saturable in rats. As cited earlier, male Sprague-Dawley rats were exposed to 0, 100, 400, or 700 ppm MCB via inhalation for an 8-hour period. Urinary metabolites were measured in samples taken at 16- and 48-hours post exposure. The two higher exposure doses resulted in saturation of the detoxification pathways through the depletion of glutathione available for conjugation. This tends to increase the incidence and extent of toxicity. MCB is also eliminated unchanged by the respiratory tract. As dosage increases, the amount excreted via this route increases (Sullivan et al., 1983).

#### Human Exposure and Body Burden

Human exposure to MCB occurred in the past in occupational settings and through accidental ingestion (U.S.EPA, 1985b). Recently, however, ambient levels of the chemical have been found in air, soil and water (U.S.EPA, 1985a). No epidemiological studies are available regarding the health effects of MCB exposure. Clark et al. (1982) performed an epidemiological study on people exposed to a multitude of organic chemicals, including MCB, which had leached from a hazardous waste dump into the water supply. This is one of the few studies to find a positive, statistically significant, conclusive correlation between potable water contaminated with leachate from a waste dump and adverse health effects in humans. The adverse effects included hepatomegaly and elevated liver function test values.

Breast-fed infants would be very susceptible to maternal exposure to MCB. Other high risk groups include those who have skin, liver, kidney, or chronic respiratory diseases (NIOSH/OSHA, 1981). MCB was found in the air, soil, tap water, and body tissues of Love Canal residents (U.S.EPA, 1985a). In an analysis of blood, breath, and urine of nine residents of Love Canal, Barkley et al. (1980) found blood levels from 0.05 to 17.0 ng/mL; a trace of MCB in their breath and levels ranging from 20 to 120 ng/L in their urine. These data are included in the same study that found levels ranging from 10 to 60 ng/L in tap water from homes in Love Canal. Elder et al. (1981) found MCB levels in the soil at Love Canal in the ppm range. Pellizzari et al. (1979) found ambient air concentrations that ranged between 'not detected' to 6,072 ng/m<sup>3</sup>.

Exposure to MCB was quantified at two sites in New Jersey (Pellizzari et al., 1985). Table IV lists concentrations in breath, daytime occupational and outdoor air, and overnight house and outdoor air in the three sampling periods. An understanding of these results should be tempered by the knowledge that the analytic method of measurement probably had fluctuations in accuracy and precision. Nevertheless, some body burden can be assumed from the data shown in Table IV (Pellizzari et al., 1985).

## HEALTH EFFECTS

### Overview

Acute exposure to monochlorobenzene causes severe central nervous system (CNS) effects, liver and kidney maladies and respiratory distress in both man and lower mammals. Chronic exposure also results in CNS effects, and liver and kidney histologic changes in both man and laboratory animals. Male rats developed neoplastic hepatic nodules in a weak dose dependent relationship when compared to control groups (NTP, 1985). Reproductive effects of MCB exposure, including seminiferous tubule atrophy in rats and dogs, occurred at high doses (Monsanto Company, 1977a, 1978).

### Human

Acute. Acute exposure to MCB can cause a multitude of clinical reactions: eye and nose irritation, headaches, dizziness, a paralysis, hepatic and renal disorders, and cyanosis (with methemoglobinemia) (U.S.EPA, 1985a). These reactions can take several hours to develop (HSDB, 1986). For example, a two-year old boy accidentally ingested between 5 to 10 mL of MCB. He became cyanotic within 2 hours. He lost consciousness and displayed head and neck twitching. He regained consciousness after 3 hours and all bodily functions returned to normal within 8 hours (Reich, 1934). Tarkhova (1965) exposed human volunteers to 0.02 ppm (0.1 mg/m<sup>3</sup>), 0.04 ppm (0.2 mg/m<sup>3</sup>), and 0.06 ppm (0.3 mg/m<sup>3</sup>) MCB and monitored encephalographic patterns. Exposure at the 0.04 ppm and 0.06 ppm doses induced electroencephalographic changes within minutes.

Dermal exposure to MCB may cause skin irritation. Moderate erythema and slight superficial necrosis may develop with repeated exposure (HSDB, 1986).

There are severe toxic effects to humans at 400 ppm after a 60-minute exposure. The clinical threshold of MCB effects occurs at 200 ppm in 60 minutes (Verschueren, 1983).

Chronic. Case reports of exposure to MCB have been reported in occupational settings (U.S.EPA, 1985a). In one case report (Rosenbaum et al., 1947) workers exposed to MCB for 1 to 2 years developed symptoms such as headaches, sleepiness, and dyspepsia. Other toxic symptoms included peripheral nervous system abnormalities, including muscular twitchings and numbness. Another group of workers exposed for less than 1 year showed no symptoms of toxicity (Rosenbaum et al., 1947). Another case (Girard et al., 1969) involved a 70-year old woman who was occupationally exposed to glue containing 70% MCB for 6 years. She developed headaches, upper respiratory tract and eye irritations, and medullary aplasia.

### Animal

Acute. There have been many studies designed to determine the LC<sub>50</sub>

Table III

Species Variation in Urinary Metabolites of <sup>14</sup>C-Monochlorobenzene\*  
Percentage of 24-hour Excretion of <sup>14</sup>C

Species	4-chlorophenol	4-chlorocatechol	4-chlorophenyl- mercapturic acid
Man	33	31	19
Rhesus Monkey	19	37	40
Dog	14	45	42
Rabbit	29	38	26
Rat	23	22	49
Mouse	20	31	42 *

\*Source: Williams, R., Hirom, P., and Renwick, A. 1975.

Table IV

Monochlorobenzene Concentrations ( $\mu\text{g}/\text{m}^3$ ) in Subjects' Breath, Daytime Occupational and Outdoor Air, and Overnight House and Outdoor Air over Three Sampling Periods in New Jersey\*

Source	<u>Sampling Period</u>					
	Aug-Nov median	1981 range	July-Aug median	1982 range	Jan-Feb median	1983 range
Breath+	1.12	0.39-2.04	0.68	0.20-2.52	0.25	0.20-0.31
Daytime occupational air	2.02	0.51-4.00	2.35	0.56-4.80	0.49	0.21-0.72
Daytime outdoor air	1.45	0.73-2.32	1.10	1.08-1.24	0.21	0.14-0.34
Overnight house air	1.48	0.37-2.96	1.31	0.39-3.08	0.37	0.30-0.90
Overnight outdoor air	1.04	0.60-6.00	0.72	0.20-1.36	0.16	0.16-0.26

+ Sample taken at night

\*Source: Pellizzari, E. et al., 1985.

and LD<sub>50</sub> of various animal species to MCB exposure. Estimates for the LC<sub>50</sub> in rats and mice vary depending on the exposure period:

Rat	22,000 ppm	2.5 hours	Eastman Kodak (1978)
	2,965 ppm	6.0 hours	Bonnet et al. (1982)
Mice	1,886 ppm	6.0 hours	Bonnet et al. (1982)

Estimates of the oral LD<sub>50</sub> in rats are 2.91 g/kg body weight (Irish, 1963); 2.14 g/kg (Monsanto Company, 1965); and 400-1600 mg/kg (Eastman Kodak, 1978). An estimate of the LD<sub>50</sub> value in rabbits is 2.83 g/kg (Irish, 1963; Eastman Kodak, 1978).

In general, acute effects of high-dose MCB exposure were bronchiolar necrosis (Reid et al., 1973), changes in enzymatic and physiological functions involving the liver (Ogata et al., 1981 and Ariyoshi et al., 1975), and necrosis of the proximal tubules and vacuolated convoluted tubules of the kidney. These effects were similar in different strains of mice and rats (Reid et al., 1971).

The National Toxicology Program (NTP, 1983) published major research on the acute (1- and 14-day exposure periods), subchronic (91 days), and chronic (103 weeks) toxicity of MCB ingestion in male and female Fischer 344/N rats and B6C3F1 hybrid mice. In the 1-day study, five rats and mice of each sex were given a single oral dose of 0, 250, 500, 1000, 2000, or 4000 mg/kg MCB in corn oil by gavage followed by an observation period of 14 days. Mortality was the endpoint measured. Most deaths occurred within the first four days after exposure. Mice showed a higher sensitivity to MCB exposure. Of those given 1000 mg/kg per day or more, most died within the first three days after administration. Most of the rats in the 4000 mg/kg per day dose category died.

In the 14-day study, groups of five rats of each sex were exposed to a dose of 0, 125, 250, 500, 1000, or 2000 mg/kg per day of MCB in corn oil, 5 days per week for 14 days. All rats in the 1000 and 2000 mg/kg per day dosage groups died during the study period. Five mice of each sex were given doses of 0, 30, 60, 125, 250, or 500 mg/kg using the same experimental schedule as the rats. Accidental deaths occurred in the mice which were unrelated to chemical exposure.

The subchronic and chronic NTP studies are discussed below.

Subchronic/Chronic. Monsanto Company (1978) conducted inhalation studies with beagle dogs (groups of 8) and Charles River rats (groups of 15 of each sex) exposed 62 times over a 90 day period at 0.0, 0.75 (165 ppm), 1.50 (319 ppm), and 2.0 mg/L (434 ppm) of MCB. Both species were exposed 6 hours per day, 5 days per week. There were no effects in the rats but 2 of the 8 dogs lost weight and had symptoms of conjunctivitis and moribundity at the 1.5 mg/L dose. The 2.0 mg/L dose caused various liver and kidney

symptoms such as elevated liver enzyme levels and cytoplasmic vacuolation of renal collecting tubules. Death occurred in 5 of 8 dogs after 25-29 days.

Dilley (1977) used lower doses than Monsanto Company (1978). They exposed groups of 32 male, 125 gram, Sprague-Dawley rats to 0 ppm, 75 ppm, and 250 ppm MCB for 7 hours per day, 5 days per week for 120 exposures (6 months). Rats developed focal lesions of the adrenal cortex, lesions in the tubules of the kidneys, and congestion of both the liver and kidneys at the 75 ppm dose. After 11 weeks there was an increase in liver-to-body-weight ratios. At the higher dose, rats had more severe chronic symptoms such as histopathological changes in the kidneys, liver, and adrenals as early as 11 weeks, and the livers were congested and the adrenal cells showed vacuolation in the zona fasciculata.

Other studies have looked at the health effects in rats inhaling MCB (Khanin, 1977, Tarkhova, 1965, Pislaru, 1960, and Gabor and Raucher, 1960). The rodents had similar toxic responses as did those in the Dilley (1977) and Monsanto Company (1977) studies at similar or greater dose levels.

Monsanto Company (1977a, b) also did oral exposure route studies using beagle dogs and Charles River rats. The dogs (4 of each sex per group) were given oral doses of MCB in capsules at 27.3, 54.6, and 272.5 mg/kg per day, 5 days per week for 13 weeks. Toxic symptoms were diarrhea, vomiting, conjunctivitis, and minimum histologic changes in the liver, kidneys, and hematopoietic tissues at the 54.6 mg/kg per day dose. In the highest dose level 4 out of 8 dogs died in 3 to 5 weeks. The no observed adverse effect level (NOAEL) was 27.3 mg/kg per day. The rats (18 of each sex per group) were given 0, 12.5, 50, 100, or 250 mg/kg per day in corn oil, 5 days per week for 13 weeks over 93 to 99 days. The NOAEL was 50 mg/kg per day. Liver and kidney weights were increased at 100 mg/kg per day. Retarded growth occurred in males at the highest dose.

Irish (1963) exposed rats to 0, 14.4, 144, or 288 mg/kg per day for 192 days. These rats suffered similar toxic effects as those in the Monsanto Company study (1977).

In the 13-week National Toxicology Program (NTP) subchronic study (NTP, 1985) groups of 10 B6C3F<sub>1</sub> mice or Fischer 344/N rats of each sex were administered 0, 60, 125, 250, 500, or 750 mg/kg per day MCB in corn oil 5 days per week by gavage. The mice had symptoms at lower doses than the rats. The lowest observed adverse effect level (LOAEL) was 60 mg/kg per day. One male mouse in the 60 mg/kg per day dosage level developed hepatic necrosis. The male mice had increased liver weights with a 27% drop in body weight at the 125 mg/kg per day. Effects at the 250 mg/kg per day were a 50% reduction in female weight gain, increased excretion of coproporphyrins in females, and lesions of the liver, kidney, bone marrow, and spleen. There was an 82% drop in male body weight. The other two higher doses were fatal to males within one week with lesions of the liver,

kidney, bone marrow, and spleen. The females had polyuria, centrilobular hepatocellular necrosis, and a 50% drop in weight gain. The 750 mg/kg per day dose was lethal to females within 10 weeks. They showed similar effects as the males at this dose.

The rats showed no response at doses lower than 250 mg/kg per day. At this dose there was a 10% drop in male weight gain and minimal centrilobular hepatocellular necrosis. Both males and females showed similar effects at the 500 mg/kg per day dose: myeloid depletion of bone marrow, excretion of porphyrins, centrilobular hepatocellular necrosis, and lymphoid depletion of the thymus and spleen. These effects were greater at the 750 mg/kg per day dose in both sexes. In addition, reduced survival, decreased body weights, and hematologic effects, including reduced white blood cell (WBC) count in females and increased reticulocyte percentage in males, were found in the highest dose group.

The two-year NTP study (1985) is discussed under Carcinogenicity. Neoplastic hepatic nodules occurred in male rats at the high dose. Treated female rats did not show this response and their mean-body weights were greater than the control group during the second year of the study. No other toxic effects were observed during the course of the study.

#### Behavioral and Central Nervous System

Mice exposed for five minutes to MCB vapor had reduced respiratory rates. The  $RD_{50}$  was 1,054 ppm. The estimated NOAEL in humans was determined to be 11 ppm. This reduction in breathing rate is in agreement with the knowledge that MCB causes sensory irritation in the respiratory system (DeCaurriz et al., 1981).

#### Reproductive, Embryotoxic, and Teratogenic

One study (Monsanto Company, 1977) exposed groups of four dogs of each sex to 27.3, 54.6, or 272.5 mg/kg per day of MCB orally by capsule over a 90-day exposure period. The male dogs (3 of 4) in the high dose group developed tubular atrophy and epithelial degeneration of the seminiferous tubules with resultant decreased spermatogenesis. These effects occurred at a dose sufficient to kill the dogs or make them severely ill. One other study (Monsanto Company, 1978) exposed male dogs via inhalation to 0.75 mg/L (165 ppm), 1.5 mg/L (424 ppm), or 2.00 mg/L (434 ppm) MCB, for 5 days per week over three months. In the high dose group two dogs developed bilateral atrophy of their seminiferous tubules. Mortality in this group was high with 5 out of 8 dying after day 25 to 29. The same study protocol (Monsanto Company, 1978) was used for rats with the exception that there were 15 of each sex per dose group. The male rats in the high dose group had gonadal atrophy, but the females developed significantly higher gonad-to-body-weight ratios compared to non-exposed females.

In a teratology study, John et al. (1984) examined the embryotoxic and



teratogenic potential of MCB in rats and rabbits. Groups of 32 to 33 Fischer 344/N rats and groups of 30 New Zealand white rabbits were exposed to 0, 75, 210, or 590 ppm of MCB on days 6 to 15 of gestation (rats) and on days 6 to 18 (rabbits). The only maternal toxicity in rats was a reduction in weight in the 590 ppm dose group. No embryotoxic or teratogenic effects appeared even though the incidence of some minor variants, such as the delayed ossification of the cervical vertebrae, were significantly increased at the 75 and 590 ppm groups. Since these variants were not seen in the 210 ppm dose group, they were considered a fetotoxic effect, and not indicative of a teratogenic response to MCB exposure. The rabbits did show some visceral malformations, such as mean fetal crown-rump length in the 210 ppm dose, spina bifida (1 case) and a few heart abnormalities in the 210 and 590 ppm dosage groups. A second part of the study by John et al. (1984) looked at these effects using 0, 10, 30, 75, or 590 ppm doses in groups of 30 to 32 rabbits exposed during days 6-18 of gestation. The results of this study were negative: there was no increase in malformations. The only effect was a slight delay in skeletal development in the highest dose group. This dose was toxic to the mothers.

#### Genetic

The mutagenic potential of MCB has been evaluated in various test systems, such as bacterial, fungal, and mammalian test systems (DuPont, 1977, Keskinova, 1968, Merck, 1978, Monsanto Company, 1976, Prasad, 1968, and Simmon et al., 1979). All of these were negative with the exception of two studies: Keskinova (1968) showed positive results in the ability of MCB to induce reversion of vitamin B<sub>1</sub> prototrophy in Streptomyces antibioticus; Simmon et al. (1979) had<sup>1</sup> positive results for mitotic crossing over in Saccharomyces cerevisiae.

#### Carcinogenicity

The U.S.EPA (1985c) categorized MCB as a Group C Carcinogen. This means there is no human evidence of its carcinogenicity and limited animal evidence. The NTP (1985) completed a two-year bioassay in mice and rats, to determine the carcinogenic potential of MCB. The NTP tested the chemical because it is produced in large volume in this country, there is a lack in chronic toxicity data, and its has appeared in water supplies (Dowtey et al., 1975).

Kluwe et al. (1985) reported the toxic results of the two-year NTP study. F344/N rats of both sexes and female B6C3F<sub>1</sub> mice were divided into groups of 50 animals each and given, by gavage, MCB in corn oil in the following doses: 0, 60, or 120 mg/kg, five days per week for 103 weeks. Groups of 50 male B6C3F<sub>1</sub> mice were given doses of 0, 30, or 60 mg/kg, on the assumption they are<sup>1</sup> more sensitive to MCB. All other experimental conditions remained the same. Survival was significantly reduced in the high dose male rats. Male rats developed neoplastic hepatic nodules in the

following proportions (dose): 2/50 (0 mg/kg), 4/49 (60 mg/kg), and 8/49 (120 mg/kg). This trend was statistically significant. Treated female rats did not show this response but their mean-body weights were greater than the control group's during the second year of the study. No other toxic signs were observed during the course of the study.

Male mice had significantly reduced ( $p = 0.031$ ) survival in the 30 mg/kg dose group. This was thought to be related to gavage errors and aspiration of material into the lungs. The mice, unlike the male rats, had no carcinogenic or systemic toxic responses that differed between treated and control groups.

The National Academy of Sciences (NAS, 1983) used NTP (1982) data to calculate a carcinogenic risk estimate of MCB in drinking water. The result was an estimate of 2.4 ug/L per day for an excess lifetime cancer risk of 1 in a million (assuming the consumption of 2 L of water per day).

#### QUANTITATIVE RISK ASSESSMENT

##### Studies Useful for Risk Assessment

There are two subchronic studies that used oral exposure to determine MCB health effects in laboratory animals (Monsanto Company, 1977; NTP, 1985). These studies are more relevant for the calculation of a health-based maximum contaminant level (MCL) to guard against water-related exposure than studies which used exposure by inhalation (Dilley, 1977). The three studies are discussed in an earlier section.

##### Calculation of the Health-Based Maximum Contaminate Level

Monsanto Company (1977) exposed dogs to MCB via capsule vehicle in doses of 27.3, 54.6, and 272.5 mg/kg per day; five days per week for 90 days. There were four dogs of each sex per dose group. The NOAEL was 27.3 mg/kg per day. At higher doses the dogs suffered from diarrhea and vomiting, and had histological changes in the liver, kidneys, and hematopoietic tissues. These responses are similar to those found in humans exposed to MCB. A problem with this study was the small sample size.

There is also an additional safety factor of 10 applied to the systemic toxicity risk assessment of a Group C carcinogen (U.S.EPA, 1985c, Pg. 46949).

$$ADI = \frac{(NOAEL) (AAW) (d)}{(SF) (10^a) (UF)}$$

where: ADI = Average Daily Intake  
NOAEL = No Observed Adverse Effect Level

AAW = Average Adult Weight, assumed to be 70 kg.  
d = days of exposure per week  
SF = Safety Factor, assumed to be 1000 for a subchronic exposure period  
10<sup>a</sup> = additional safety factor of 10, used in a systemic toxicity risk assessment of a Group C carcinogen (U.S.EPA, 1985c)  
UF = Uncertainty Factor, used to adjust for small sample size (U.S.EPA, 1985c)

$$\text{ADI} = \frac{27.3 \text{ mg/kg/day} \times 5/7}{1000 \times 10 \times 3}$$

$$= 0.00065 \text{ mg/kg/day}$$

The health-based maximum contaminant level is calculated as follows:

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

where: SC = Source Contribution, assumed to be 0.20.

DWI = Daily Water Intake assumed to be 2 L per day for a 70 kg adult

$$\text{MCL} = \frac{(0.00065 \text{ mg/kg/day}) (70 \text{ kg}) (0.20)}{2 \text{ L/day}}$$

$$= 0.0045 \text{ mg/L}$$

$$= 4.5 \text{ ug/L}$$

The health-based maximum contaminant level (MCB) is estimated to be 4.5 ug/L.

#### Assumptions and Uncertainty

The major assumption was that the dog is the best model available to extrapolate health effects to humans. The dog was judged to be an appropriate human model for the toxic endpoint considered in this risk assessment, as was described previously.

Other uncertainties involved in the risk estimate include the general assumptions of average adult weight, daily water consumption and source contribution, and the use of an additional safety factor of 10 when calculating a MCL using the ADI approach, on a Group C carcinogen based on its systemic toxicity (U.S.EPA, 1985c). Because of the small sample size used in the Monsanto Company study (1977) a safety factor of 3 adjusted the risk estimate. The U.S.EPA (1985c) proposed guidelines that suggest the use of an extra safety factor between 1 and 10 when it is scientifically

justified due to study inadequacies.

#### Conclusions

Monochlorobenzene is a very toxic chemical capable of inducing central and peripheral nervous system effects, adverse liver and kidney histologic changes and hematopoietic changes in mammals. Dogs and humans have similar responses to the chemical (Monsanto Company, 1977). The risk assessment involved a study (Monsanto Company, 1977) that used the dog as the animal model. The health-based MCL estimated from these data was 4.5 ug/L. It is believed that this level is appropriate to protect the public from any known, adverse, systemic health effect related to primary exposure to MCB through potable water.

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