Appendix B
Section M

METHYLENE CHLORIDE
MAXIMUM CONTAMINANT LEVEL
SUPPORT DOCUMENT

Office of Science and Research

New Jersey Department of Environmental Protection

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EXECUTIVE SUMMARY

Methylene chloride is a volatile chlorinated hydrocarbon used extensively in commercial and industrial solvent applications. Approximately 85% of the methylene chloride consumed is lost directly to the environment by evaporation. The odor threshold for methylene chloride in the air is 100 ppm. Methylene chloride has been shown to induce hepatocellular and alveolar/bronchiolar tumors in mice and benign mammary tumors in rats. The quantitative cancer risk assessment for methylene chloride was based on a mouse bioassay. A drinking water level of 2.5 ug methylene chloride per liter is associated with a lifetime excess cancer risk of one in a million.

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BACKGROUND INFORMATION AND PROPERTIES

Chemical Properties

Chemical Name	Methylene Chloride
Synonyms	Dichloromethane, methylene dichloride, methane dichoride, DCM
CAS Number	75-09-2
Chemical formula	CH_2Cl_2

Chemical structure

$$\begin{array}{c} H \\ | \\ Cl-C-Cl \\ | \\ H \end{array}$$

Molecular weight	84.94
Physical state (room temperature)	clear, colorless liquid
Melting point	-95 $^{\circ}C$
Boiling point	40 $^{\circ}C$ at 760 mm Hg
Vapor pressure, volatility	349 mm Hg at 20 $^{\circ}C$
Specific gravity, density	1.326 g/mL at 20 $^{\circ}C$
Water solubility	2.0 g/100 mL at 20 $^{\circ}C$
Log octanol/water partition coefficient	1.25
Taste threshold (water)	not available
Odor threshold (water)	not available
Odor threshold (air)	100 ppm
Conversion factors	1 ppm (v/v) = 3.474 mg/m^3

Production and Use

Methylene chloride is commercially produced in the United States predominantly by the hydrochlorination of methanol. The U.S annual production of methylene chloride was estimated to be 269,000 metric tons in 1981. It is widely used as a paint remover, metal degreaser, and aerosol propellant.

Guidelines, Regulations, and Standards

The Occupational Safety and Health Administration (OSHA) workplace standard is 500 ppm (1737 mg/m^3) for an 8-hour time-weighted-average (TWA) exposure with an acceptable ceiling concentration of 1000 ppm (3474 mg/m^3).

An Ambient Water Quality Criteria for halomethanes was published by the U.S. Environmental Protection Agency (U.S.EPA, 1980). The recommended criteria for methylene chloride was based on data for chloroform. Assuming consumption of 2 liters of water and 6.5 grams of fish per day by a 70 kilogram adult, a methylene chloride level of 0.19 ug/L was estimated to limit excess lifetime cancer risk to one in a million.

Health Advisory drinking water guidance describing non-carcinogenic toxicology has been developed for methylene chloride by the Office of Drinking Water (U.S.EPA, 1985b). The lifetime Health Advisory for a 70 kilogram adult is 350 ug/L if one assumes a 20% contribution to the total exposure by drinking water.

ENVIRONMENTAL EXPOSURE

Methylene chloride in surface water evaporates to the atmosphere in a few days or weeks. Methylene chloride can migrate to ground water without adsorbing onto soil.

The Office of Science and Research, New Jersey Department of Environmental Protection, surveyed public water supplies statewide for over 100 substances during the period 1978 through 1981. Methylene chloride was detected in 44% of the samples at a mean concentration of 71 ug/L. Methylene chloride was found in 3.4% of the samples evaluated during initial testing for hazardous contaminents in public water supplies under Assembly Bill A-280. The concentrations observed ranged from 0.5 to 36 ug/L.

METABOLISM AND PHARMACOKINETICS

Absorption

Methylene chloride is expected to be completely absorbed after

ingestion through the intestinal mucosa. McKenna and Zempel (1981) noted 92 to 96% recovery of radioactivity in urine, feces, and exhaled air of rats following single oral (gavage) doses of 1 or 50 mg/kg (^{14}C)-methylene chloride in water.

Distribution

Methylene chloride is distributed throughout the body after being inhaled or ingested by humans or laboratory animals. It distributes into adipose tissue and across the blood-brain barrier. Single oral doses of 1 or 50 mg/kg (^{14}C)-methylene chloride to rats was found in the liver, kidney, and lung (McKenna and Zempel, 1981; McKenna et al., 1982).

Metabolism

Methylene chloride and other dihalomethanes are biotransformed to both carbon monoxide and carbon dioxide (U.S. EPA, 1985c). Carbon monoxide is the end product of microsomal oxidation, and carbon dioxide is an end product of cytosolic metabolism. The microsomal pathway is a cytochrome P-450 mediated process that requires NADPH and molecular oxygen. The cytosolic pathway is glutathione dependent and does not require molecular oxygen.

Excretion

Pulmonary excretion and hepatic metabolism are the primary route of methylene chloride elimination from the body. Small amounts of methylene chloride are eliminated via the kidney. The plasma half-life of inhaled methylene chloride in humans is estimated to be 40 minutes (DiVincenzo et al., 1972). Elimination from the human muscle and adipose tissue has been estimated to occur in 60-80 minutes and 240 minutes, respectively (Stewart et al., 1972a,b).

Human Exposure and Body Burden

Post-exposure breath methylene chloride concentrations can be correlated with exposure time, duration, and blood COHb levels (Stewart et al., 1976; Peterson, 1978).

HEALTH EFFECTS

Overview

Methylene chloride exposure is associated with fatty degenerative changes and glycogen depletion in the liver and kidney of experimental animals following high doses. Exposure to high methylene chloride concentrations causes central nervous system effects, including depression, anesthesia, coma, and death. Carbon monoxide is a primary

methylene chloride metabolite resulting in carboxyhemoglobinemia.

Subchronic or chronic exposure of experimental animals to low levels of methylene chloride can cause histomorphological alterations in the liver, including increased fat content and vacuolization. Methylene chloride in two-year studies induced hepatocellular and alveolar/bronchiolar neoplasms in mice and benign mammary gland neoplasms in rats.

Human

The typical acute presentation of methylene chloride poisoning is headache, nausea, and drowsiness (Friedlander et al., 1978). A case report of delirium from methylene chloride exposure has been presented (Tariot, 1983).

Animal

The oral LD_{50} values for methylene chloride were reported as 1,987 mg/kg for mice and 2,121 mg/kg for rats (Kimura et al., 1971; Aviado et al., 1977).

Behavorial and Central Nervous System

Methylene chloride acts primarily on the central nervous system progressing from drowsiness to coma (Barrowcliff and Knell, 1979; Gamberale et al., 1975). The acute effects of methylene chloride toxicity are similar to carbon monoxide poisoning, presumably due to carboxyhemoglobin formation as a result of metabolism (Putz et al., 1976).

Reproductive, Embryotoxic, and Teratogenic

In both prenatal and postnatal evaluation, methylene chloride caused no gross teratogenic effects in animals at the exposure levels used (Schwetz et al., 1975; Bornschein et al., 1980; Hardin and Manson, 1980). No studies were found on endocrine, gonadal, or fertility effects in animals. Attention is drawn to the lack of data on reproductive effects in humans.

Schwetz et al. (1975) exposed mice and rats to methylene chloride at 1250 ppm for 7 hours per day from days 6 through 15 of pregnancy. There were no effects on implantation sites, live fetuses, resorptions or fetal body weight in either mice or rats. The only anomaly, was a significantly increased incidence of extra sternebrae in the treated mice, occurring in 50% of treated litters compared with 14 percent of the controls. In the rats, there were significant increases in litters affected by dilated renal pelvis and delayed ossification of sternebrae, as well as a significant decrease in lumbar ribs or spurs.

Manson and her colleagues assessed the reproductive toxicity of methylene chloride before, as well as during, pregnancy (Hardin and Manson, 1980; Bornschein et al., 1980). Groups of 30 rats were exposed to 4500 ppm for 6 hours per day, 7 days per week before mating only, before mating and pregnancy, or during pregnancy. The premating exposure period was approximately three weeks while during-pregnancy exposure was from days 1 through 17. Approximately two-thirds of the rats were killed for teratology on day 21 of pregnancy, while the remainder were allowed to litter out for postnatal evaluation.

In the teratology study (Hardin and Manson, 1980), there were no significant effects on implantation sites, live fetuses or resorptions, however fetal body weight was reduced by about 10 percent in the groups exposed before and during gestation, or during gestation only. In the postnatal part of the study (Bornschein et al., 1980), there were no significant effects on birth weight or postnatal growth rate up to 400 days of age. There was a trend among the female offspring toward lower body weights in the groups exposed before mating.

Genetic

The activity of methylene chloride in short-term tests is summarized in Table I. Methylene chloride is mutagenic in <u>Salmonella</u> <u>typhimurium</u>, although it is negative as a mutagen in other prokaryotic and eukaryotic systems tested (Barber et al., 1981; Green, 1983; Osterman-Golkar et al., 1983). Methylene chloride induced chromosomal aberrations in Chinese hamster ovary cells and gave negative results in other mammalian systems (Jongen et al., 1981; Thilagar and Kumaroo, 1983).

Carcinogenicity

The carcinogenic potential of methylene chloride has been adequately reviewed (IARC, 1979; EPA, 1985a; EPA, 1985c; FDA, 1985). Methylene chloride has been classified as an animal carcinogen (EPA, 1986; FDA, 1985). Methylene chloride induced hepatocellular and alveolar/bronchiolar carcinoma in both sexes of B6C3F1 mice and mammary fibroadenoma in female F344/N rats (NCA, 1983; NTP, 1986).

In a 24-month oncogenicity study, methylene chloride was administered in deionized drinking water to eight-week-old B6C3F1 mice (NCA, 1983). The mice were divided into four dose groups and two control groups of various sizes. The two control groups were treated identically and were combined for statistical analysis. Target doses of methylene chloride in milligrams per kilogram body weight per day were: 0 (125 males and 100 females), 60 (200 males and 100 females), 125 (100 males and 50 females), 185 (100 males and 50 females), and 250 (125 males and 50 females). Actual daily doses received by the male mice were 60.55, 123.61, 177.48, or 234.29 mg/kg per day. The

Table I

Genetic Toxicology of Methylene Chloride

Process	Endpoint	Test System	Conclusions	References
Gene Mutation	Base-pair substitution, Frameshift	Ames Salmonella with and without metabolic activa- ation	*Positive*	Barber et al., 1981; Green, 1983
		Chinese hamster epithelial (V79) and ovary (CHO) cells HGPRT locus	Negative	Osterman- Golkar et al., 1983; Jongen et al., 1981
Chromosomal Rearrangement Homologous recombination	Sister chromatid exchange	Chinese hamster ovary cells in vitro with and without metabolic activation	Negative	Thilagar and Kumaroo, 1983
Chromosomal Rearrangement Non-homologous recombination	Chromosomal aberrations	Chinese hamster ovary cells in vitro with and without metabolic activation	Positive	Thilagar and Kumaroo, 1983

female mice received average daily doses of 59.46, 118.19, 172.41, or 237.76 mg/kg per day. Food and water were freely available.

All surviving animals were sacrificed after 104 weeks on the study. A complete necropsy was peformed on every animal, whether found dead, sacrificed when moribund, or sacrificed at the end of the study. Selected results are presented in Table II.

For the female mice, the incidence of tumors of any type in the treatment groups was not significantly increased over the controls at any dose level. In male mice, no single type of tumor was significantly increased in the treated groups when compared to the controls. However, the number of treated male mice with either hepatocellular carcinoma or adenoma was significantly increased over the incidence in controls.

In a study sponsored by the National Coffee Association (NCA, 1982), methylene chloride was administered to eight-week-old Fischer 344 rats via deionized drinking water. The rats were divided into four treatment groups of 85 rats per sex and control group with 135 rats per sex. The target doses provided were 0, 5, 50, 125, or 250 mg methylene chloride/kg body weight/day. The male rats received average daily doses of 5.85, 52.28, 125.04, or 235.00 mg/kg per day. The female rats consumed an average of 6.47, 58.32, 135.59, or 262.81 mg/kg per day. Food and water were freely available to the animals.

All surviving animals were sacrificed after 104 weeks on the study. A complete necropsy was peformed on every animal, whether found dead, sacrificed when moribund, or sacrificed at the end of the study.

For the male rats, the incidence of tumors of any type in the treatment groups was not significantly increased over the controls at any dose level. The treated female rats showed a significantly increased incidence of hepatic neoplastic nodules when compared to the controls. The number of treated female rats with either neoplastic nodules or hepatocellular carcinoma was also significantly increased over the concurrent controls.

The incidence of neoplastic nodules in female rats was 0/118 (number of rats with lesion per number examined) in the control group, 2/68 in the 5 mg/kg per day group, 4/68 in the 50 mg/kg per day group, 2/69 in the 125 mg/kg per day group, and 4/67 in the 250 mg/kg per day group. The number of female rats with either neoplastic nodules or hepatocellular carcinoma was 0/118 in the control group, 2/68 in the 5 mg/kg per day group, 6/68 in the 50 mg/kg per day group, 2/69 in the 125 mg/kg per day group, and 6/67 in the 250 mg/kg per day group.

In a two-year study conducted by the National Toxicology Program (NTP, 1986), eight-week-old F344/N rats and B6C3F1 mice of both sexes were exposed to methylene chloride by inhalation. The rats were exposed

to methylene chloride concentrations of 0, 1000, 2000, or 4000 ppm, while mice were exposed to concentrations of 0, 2000, or 4000 ppm methylene chloride. The inhalation exposures were performed 6 hours a day, 5 days a week for 102 weeks. Both rats and mice were randomly distributed so that there were 50 animals per sex per treatment group. Food was freely available to the animals except during the exposure period, while water was available at all times via an automatic watering system.

Animals were killed when moribund or at the conclusion of the study (104 weeks). A complete necropsy and histological examination was performed on each animal. Selected results are presented in Table II. The National Toxicology Program concluded the following:

> Under the conditions of these inhalation studies, there was some evidence of carcinogenicity of dichloromethane for male F344/N rats as shown by an increased incidence of benign neoplasms of the mammary gland. There was clear evidence of carcinogenicity of dichloromethane for female F344/N rats as shown by increased incidences of benign neoplasms of the mammary gland. There was clear evidence of carcinogenicity of dichloromethane for male and female B6C3F1 mice, as shown by increased incidences of alveolar/bronchiolar neoplasms and of hepatocellular neoplasms.

In a two-year study conducted by Dow Chemical Company, 8-week-old Sprague-Dawley rats and Syrian Golden Hamsters of both sexes were exposed to methylene chloride by inhalation (Burek et. al., 1984). Approximately 95 rats and hamsters per sex per treatment group were given 0, 500, 1500, or 3500 ppm methylene chloride 6 hours a day, 5 days a week. Additional animals were used for interim sacrifices and cytogenetic studies. Water was freely available at all times, while food was provided only during non-exposure periods.

The final sacrifice was performed 24 months after the first exposure. All animals were necropsied and tissues were fixed in 10% formalin. "Conventional methods" were used for sectioning and staining "representative organs and tissues." Selected results are presented in Table II.

The male rats showed a statistically significant increase in the incidence of sarcomas in the salivary gland region. The authors point out that the rats in this study were affected by the common viral disease (sialodacryoadenitis) early in the study, and that this virus, which primarily affects the salivary glands, may have contributed to this tumor response. This apparent relationship between methylene chloride exposure and salivary gland tumors has not been repeated in other studies.

Table II

Incidence of Tumors in Mice and Rats
Induced by Methylene Chloride

Dose Levels		Responses
Experimental ppm	Adjusted mg/kg/day	(# Animals with tumor/ # animals at risk)

NCA - Male Mice Hepatocellular Carcinoma or Adenoma

---	0	24/125
---	60.55	51/200
---	123.61	30/100
---	177.48	31/99
---	234.29	35/125

Burek - Male Rats Salivary Gland Region Sarcoma

0	0	1/92
500	96.14	0/95
1500	288.42	5/95
3500	672.97	11/97

NTP - Male Mice Hepatocellular Carcinoma or Adenoma

0	0	22/50
2000	1719.51	24/50
4000	3439.03	33/50

NTP - Female Mice Hepatocellular Carcinoma or Adenoma

0	0	3/50
2000	1897.47	16/48
4000	3794.95	40/48

NTP - Male Mice Alveolar/Bronchiolar Carcinoma

0	0	2/50
2000	1719.51	10/50
4000	3439.03	28/50

NTP - Female Mice Alveolar/Bronchiolar Carcinoma or Adenoma

0	0	3/50
2000	1897.47	30/48
4000	3794.95	41/48

NTP - Female Rat Mammary Fibroadenoma

0	0	5/50
1000	235.86	11/50
2000	471.72	13/50
4000	943.43	22/50

Female rats and male hamsters did not have significantly increased tumors of any type. The total number of benign tumors was increased in the female hamsters. The authors did not feel this increase was treatment related, and the exact tumor incidence was not reported.

In a two-year inhalation study, Sprague-Dawley rats of both sexes were exposed to 0, 50, 200, or 500 ppm methylene chloride for 6 hours per day, 5 days per week for 20 months (males) and 24 months (females) (Nitschke et al., 1982). The male rats were distributed into groups of 85 (0 and 500 ppm) and 90 (50 and 200 ppm). The female rats were distributed into groups of 85 (0 and 50 ppm) and 90 (200 and 500 ppm). Five rats per sex per dose group were sacrificed after 6, 12, 15, and 18 months of exposure. Food and water were provided to the animals except during exposure periods.

For the purpose of this report, only those animals were considered which died spontaneously, were killed when moribund, or were sacrificed at the termination of the study. "Conventional methods" were used for processing representative sections of organs and tissues that were histologically examined.

The male rats did not show a significantly increased incidence of any tumor type when compared to the controls. However, the female rats showed a significantly increased incidence of benign mammary tumors (adenoma, fibroadenoma, or fibroma) when compared to the controls. The incidence of mammary adenoma, fibroadenoma, or fibroma in the female rats was 52/70 in the control group, 58/70 in the 50 ppm groups, 61/70 in the 200 ppm group, and 55/70 in the 500 ppm group.

QUANTITATIVE RISK ASSESSMENT

Studies Useful for Risk Assessement

Animal bioassay data were employed for the methylene chloride risk assessment. The rationale applied for the selection of animal studies useful for quantitative risk assessment was based upon the guidelines set forth in Crump and Howe (1980). Experimental designs judged most suitable involved treatment of animals for 85% and observation of animals for 90% of their average life span. In the NCA (1982, 1983), NTP (1986), Burek et al. (1984), and Nitschke et al. (1982) studies, the rats were treated and observed for 80% of their average life span, whereas the mice were treated and observed for 98% and 100% of the life span, respectively. The oral exposure route used by the NCA studies closely mimics the expected human route of exposure. The study of choice is the NCA (1983) study in mice.

Methylene chloride significantly increased the incidence of hepatocellular carcinoma or adenoma in female mice (NTP, 1986) and male

mice (NCA, 1983; NTP, 1986). The hepatocellular carcinoma and hepatocellular adenoma tumors were combined according to National Toxicology Program guidelines (McConnell et al., 1986). Therefore, the data set used for the methylene chloride risk assessment is male mice with hepatocellular carcinoma or adenoma for the NCA (1983) study.

<u>Calculation of the Health-Based Maximum Contaminant Level</u>

The dose-response relationship between methylene chloride and hepatocellular carcinoma or adenoma in male mice obtained from the NCA (1983) study was modeled by using regression techniques. The multistage model was utilized in this analysis for low dose extrapolation with quantal data. The multistage model is given by:

$$P(d) = 1 - \exp(-q_0 - q_1 d - \ldots - q_k d^k), \quad q_i \geq 0, \quad i = 0, 1, \ldots k,$$

where $P(d)$ is the lifetime probability of cancer at dose d, and k is set to the number of dose groups less one.

The multistage model was implemented by using an updated version of the computer program GLOBAL82. All calculations were provided by K.S. Crump and Company (Crump, 1986).

Risk has been defined as "extra risk", i.e.,

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

where $P(d)$ is the lifetime probability of dying of liver cancer when exposed to methylene chloride dose d, and $P(0)$ is the lifetime probability of dying of liver cancer when not exposed to methylene chloride. A risk level of one in a million was selected for a lifetime exposure scenario. The 95% upper confidence limit on risk is linear at low doses and will be considered a plausible upper bound on risk.

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 dose is measured in the same unit for both species (Crump and Howe, 1980). The units of mg/m^2 body surface area per day will be used for animal-to-human extrapolation. If D_A represents animal dose in mg/kg per day, then the human dose (D_H) is given by

$$D_H = D_A (W_A / W_H)^{1/3},$$

where W_A and W_H are the weights of animals and humans, respectively.

The multistage model fitted to the male mouse data from the NCA (1983) study with the combined hepatocellular-carcinoma or adenoma-data set provided an animal dose of 9.35×10^{-4} mg/kg per day. The standard assumption is that a 70 kg adult consumes 2 liters of water per day. Therefore, the human dose (in micrograms per liter) is as follows:

$$= \text{human dose (mg/kg/day)} \times (1000 \text{ ug/mg}) \times (70\text{kg})/(2 \text{ L/day})$$
$$= \text{animal dose (mg/kg/day)} \times (W_A/W_H)^{1/3} \times 35,000.$$
$$= \text{animal dose (mg/kg/day)} \times (0.03 \text{ kg}/70 \text{ kg})^{1/3} \times 35,000$$
$$= \text{animal dose (mg/kg/day)} \times 35,000/13$$
$$= (9.35 \times 10^4) \times 35,000/13$$
$$= 2.5 \text{ ug/L}$$

A drinking water level of 2.5 micrograms methylene chloride per liter is associated with a lifetime excess cancer risk of one in a million.

Assumptions and Uncertainty

The extrapolation of liver cancer risk from animal bioassay data to human liver cancer risk was carried out by assuming that animals and humans were equally sensitive relative to a particular measure of dose. The interspecies conversion factor used was mg/m^2 surface area per day. This is equivalent to (mouse weight per human weight)$^{1/3}$. Mouse and human weights used are 0.03 and 70 kilograms, respectively.

A 70 kilogram adult was assumed to consume two liters of drinking water per day for life. The 95% upper confidence level on risk was considered a plausible upper bound on risk. The risk level applied was one in a million excess cancer risk.

Conclusions

Methylene chloride was classified as a probable human carcinogen (EPA Group B2). Methylene chloride induced hepatocellular carcinoma or adenoma and alveolar/bronchiolar carcinoma or adenoma in mice and benign tumors of the mammary gland in rat. The quantitative estimation of liver cancer risk was based on the NCA mouse bioassay (NCA, 1983). A drinking water level of 2.5 micrograms methylene chloride per liter was associated with a lifetime excess cancer risk of one in a million.

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