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OFFICE OF RESEARCH AND DEVELOPMENT
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TECHNICAL REPORT DATA (Please read Instructions on the reverse before completing)		
1. REPORT NO. EPA/600/8-89/092	2.	3. RECIPIENT'S ACCESSION NO. PB90-142449/AS
4. TITLE AND SUBTITLE Updated Health Effects Assessment for Methylene Chloride		5. REPORT DATE 6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S)		8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS		10. PROGRAM ELEMENT NO. 11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS Environmental Criteria and Assessment Office Office of Research and Development U.S. Environmental Protection Agency Cincinnati, OH 45268		13. TYPE OF REPORT AND PERIOD COVERED 14. SPONSORING AGENCY CODE EPA/600/22
15. SUPPLEMENTARY NOTES		

16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

17. KEY WORDS AND DOCUMENT ANALYSIS		
a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
18. DISTRIBUTION STATEMENT Public	19. SECURITY CLASS (This Report) Unclassified	21. NO. OF PAGES
	20. SECURITY CLASS (This page) Unclassified	22. PRICE

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

ORD CLEARANCE FORM

1. EPA Report No.	2. Series	3. Lab/Office Draft No.	4 Copyright Permission
	EPA/600/8	ECAO-Cin-H028a	☐ Yes (Attached) ☐ No ☒ N/A

5A. Original Document Title:
Updated Health Effects Assessment for Methylene Chloride

5B. Final Document Title, if changed:

6. Author(s), Affiliation, and Address (identify EPA authors with Lab/Office)

7. Project Officer/FTS Telephone
Chris DeRosa
U.S. EPA/ECAO-Cin 684-7534

8. Contract/IAG/Assistance Agreement No.

10. DU/Obj./PPA/Project/Deliverable Output No.
Y105

9. Product (check one)
- ☐ Peer Reviewed Journal Article (complete block 13)
- ■ Published Reports: Project Report/Summary (magnetic tapes/ floppy diskettes), Method, Research Report, User's Guide, Design Manual, Handbook, Criteria Document, Health Assessment Document, Technology Transfer Report, Proceedings (Conferences, Symposia, Workshops)
- ☐ Symposium Papers and Book Chapters
- ☐ Internal Report (distribution restricted to EPA)
- ☐ Miscellaneous (newsletter, research brief, trade paper) non-peer reviewed journal article (complete block 13)
- ☐ Unpublished Report

11. Technical Information (Program) Manager
Signature Judith Olsen Date 8/21/89
Signature of sender (if other than TI(P)M) Date to CERI

12. Signature/Date
Bennett S. Smith, Document Manager 8/31/89
Chris DeRosa, Branch Chief 9/1/89
for C T DeRosa, Acting Director ECAO-Cin 9/1/89

13. Bibliographic Citation (Include Month/Year)
☐ Accepted _____ ☐ Published _____

14. Distribution (use block 16, if necessary)

15A. This Publication
- ☐ does not have policy implications for EPA
- ☐ has policy implications for EPA (memo attached)

15B. Lab/Office Director Signature
Jerry Parker for Don H Farland
Acting Director OHEA

15C. Date 10/19/89

16. Comments

EPA-362(Cin)(Rev.3/87)

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with methylene chloride. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1987. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria Document for Halomethanes. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA-440/5-80-051. NTIS PB 81-117624.

U.S. EPA. 1982. Errata: Halomethanes Ambient Water Quality Criteria for the Protection of Human Health. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC.

U.S. EPA. 1983. Reportable Quantity for Dichloromethane. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1985a. Health Assessment Document for Dichloromethane (Methylene Chloride). Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA-600/8-82-004F. NTIS PB 85-191559.

U.S. EPA. 1985b. Addendum to the Health Assessment Document for Dichloromethane (Methylene Chloride): Updated Carcinogen Assessment of Dichloromethane (Methylene Chloride). Office of Health and Environmental Assessment, Carcinogen Assessment Group, Washington, DC.

U.S. EPA. 1986c. Integrated Risk Information System (IRIS). Carcinogenicity Assessment for Lifetime Exposure to Methylene Chloride. Online. (Verification date 12/04/86.) Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived nor were larger uncertainty factors employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RFD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1984).

For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980b). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

The major issue of concern is the amply demonstrated carcinogenicity of methylene chloride. Although human data are lacking, animal experiments have clearly demonstrated the carcinogenicity of methylene chloride in mice and strongly suggest carcinogenicity in rats. Methylene chloride has been shown to be mutagenic in Salmonella and to increase the number of chromosomal aberrations in cultured chinese hamster ovary cells.

The U.S. EPA (1985b, 1986c) reported an oral unit risk slope estimate of 7.5×10^{-3} $(mg/kg/day)^{-1}$ based on the arithmetic mean of slope factors derived from the NTP (1985) inhalation data and the NCA (1983) oral data. The U.S. EPA (1985b, 1986c) also reported an inhalation unit risk slope estimate of 1.4×10^{-2} $(mg/kg/day)^{-1}$ based on the combined incidence of carcinomas and adenomas of the lung or liver in B6C3F1 mice from the 2-year NTP (1985) inhalation study. The corresponding unit risk for air is given as 4.1×10^{-6} $\mu g/m^3$. In all of these analyses methylene chloride has been classified in weight of the evidence category B2, probable human carcinogen. A potential revision to the unit risk estimate has been proposed based upon the application of pharmacokinetic modeling (U.S. EPA, 1987). Adoption of a unit risk estimate based upon pharmacokinetic modeling could lead to an estimate 1 to 2 orders of magnitude lower than that currently proposed.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3112 for EPA's Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa and Karen Blackburn were the Technical Project Monitors and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Emergency and Remedial Response, Washington, DC.

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Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Office of Air Quality Planning and Standards
Office of Solid Waste
Office of Toxic Substances
Office of Drinking Water

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
CAS	Chemical Abstract Service
CS	Composite score
EKG	Electrocardiogram
K_{oc}	Soil sorption coefficient
K_{ow}	Log octanol/water partition coefficient
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
ppm	Parts per million
RfD	Reference dose
RfD_I	Inhalation reference dose
RfD_O	Oral reference dose
RFD_S	Subchronic reference dose
RFD_{SI}	Subchronic inhalation reference dose
RfD_{SO}	Subchronic oral reference dose
RV_d	Dose-rating value
RV_e	Effect-rating value
SCE	Sister chromatid exchange
SNARL	Suggested no-adverse-response level
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of methylene chloride (CAS No. 75-09-2), also known as methylene dichloride and dichloromethane, are shown below.

Chemical class:	halogenated aliphatic hydrocarbon (purgeable halocarbon)	
Molecular weight:	84.93	
Vapor pressure at 20°C:	362.4 mm Hg	Callahan et al., 1979
Water solubility at 25°C:	13,030 mg/ℓ	Horvath, 1982
Density at 20°C (reference water 4°C)	1.3225	Windholz, 1983
Vapor density	2.93 (air=1)	U.S. EPA, 1985a
Log K_{ow}:	1.25	Hansch and Leo, 1985
K_{oc}:	27.5	Sabljic, 1984
K_{oc}:	8.8 g/mℓ	U.S. EPA, 1986b
Bioconcentration factor:	2.3 [estimated from log K_{ow} and the equation given by Veith et al. (1979)]	Veith et al., 1979
	5.25 [estimated from equation given by Veith et al. (1979)	U.S. EPA, 1985a
Half-lives in air:	53-127 days	Singh et al., 1981; Makide and Rowland, 1981
water:	1-6 days (estimated)	
Tropospheric lifetime	1.4 yrs (calculated)	Altshuller, 1980
Evaporation half-life	18-25 min (experimental)	Dilling, 1977
	20.7 min (theoretical)	
	0.9±0.3 yrs (calculated)	Singh et al., 1983
	0.3 yrs (calculated)	Cox et al., 1976
	0.39 yrs (calculated)	Davis et al., 1976

Loss of methylene chloride from water will be due primarily to volatilization (Dilling, 1977; NLM, 1987). The aquatic half-life listed above was estimated from a reaeration rate ratio of 0.650 and oxygen reaeration rate constants of 0.19-0.96 day^{-1} (Mabey et al., 1981). On prolonged contact with water, DCM hydrolyzes very slowly, forming HCl as the primary product (Fells and Moelwyn-Hughes, 1958). Adsorption to suspended solids and sediments and bioaccumulation in aquatic organisms will not be significant fate processes.

The half-life of methylene chloride in soil was not found in the available literature. Evaporation is expected to be the predominant loss mechanism from the soil surface. The evaporation half-life from soil would be expected given its larger surface area to be shorter than its evaporation half-life from water. The aqueous solubility and relatively low K_{oc} value of this compound suggest that in cases where DCM is not volatilized quickly, leaching would also play a role in determining the fate of this compound in soils (NLM, 1987). In subsurface soil and sediment sampling detected DCM in 60 of 118 cases. Concentrations were from 427 to 433 ppb. Ambient soil concentrations of DCM are unknown (U.S. EPA, 1981). Biodegradation of chlorinated aliphatic hydrocarbons such as methylene chloride may be slow (Wilson et al., 1983); therefore, under conditions in which methylene chloride leaches into soil, it may leach into groundwater. "Recent evidence indicates that DCM is biodegradable under both aerobic and anaerobic conditions. Brunner and Leisinger (1978) first reported the isolation of a facultatue methylotroph with the ability to utilize DCM as a sole carbon source for growth." Wood et al. (1978) also has been able to demonstrate the degradation of DCM under anaerobic conditions. Detection of this compound in groundwater supplies supports this prediction (Page, 1981).

However, these results are equivocal as Page (1981) does not give adequate details pertaining to the methodology used. The methodology used varies greatly and can influence the limit of detection (LOD) and accuracy and bias of results. "Contamination, absorption, and adsorption are common problems of the methods used to analyze air and water for DCM content (National Academy of Science, 1978)." However, DCM has been detected at 32 of 204 surface water sites from which samples were collected (Ewing et al., 1977).

In the atmosphere, reaction with photochemically generated hydroxyl radicals is expected to be the predominant removal mechanism (NLM, 1987; Cox et al., 1976; Davis et al., 1996). This compound may travel long distances from its emission sources because of its relatively long lifetime in the atmosphere. Based on a tropospheric to stratospheric turnover time of 30 years and a half-life of 53-127 days for methylene chloride, <1% of the tropospheric methylene chloride is expected to diffuse into the stratosphere. However, there is a great disparity in the reported residence time of DCM in the atomosphere. Cox et al. (1976) argues conunicingly for a residence time or only 0.3 years based on photo kinetiz studies. Values, however, range from the Cox et al. (1976) figure of 0.3 years to the Altoherller (1980) estimate of 1.4 years.

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL MAMMALS

2.1. ORAL

Absorption through the intestinal mucosa appears to be fairly rapid and complete in humans (Roberts and Marshall, 1976). Prichard and Angelo (1982) have described a physiologically based pharmacokinetic model (Bishoff model) for mice and have used it to simulate the distribution, metabolism and elimination of DCM after both acute and chronic dosing. Preliminary results indicate that the kinetics depend on route and vehicle used for administration. Administration of DCM in water by oral gavage orby intravenous injection yields similar blood and tissue profiles; administration in 50% polyethylene glycol/water shows a rapid blood elimination and a slow liver elimination, while oral gavage with corn oil as a vehicle. In subsequent and more extensive investigations, Angelo et al. (1986a) administered gavage doses of ^{14}C-methylene chloride at 50 mg/kg/day in water or 50 or 1000 mg/kg/day in corn oil once daily on 14 consecutive days to groups of six young adult male B6C3F1 mice. Angelo et al. (1986b) also treated groups of six young adult male F344 rats were treated by gavage with ^{14}C-methylene chloride at 50 or 200 mg/kg/day in water for 14 consecutive days. Cumulative 24-hour recovery of exhaled radioactivity exceeded 90% of the administered dose in both species at all dose levels, measured on days 1, 7 and 14 of treatment. These data indicate that methylene chloride is almost completely absorbed from the gastrointestinal tracts of both rats and mice.

Yesair et al. (1977) administered single gavage doses of ^{14}C-methylene chloride in water or corn oil to mice and followed the appearance of radioactivity in the plasma for the following 96 hours. Plasma levels of radioactivity peaked later and higher, remaining higher throughout the experiment when the test chemical was administered in corn oil rather than in water.

Withey et al (1983) have investigated the absorption of DCM in fasting rats following oral gavage of equivalent doses (125 mg/kg) in 4 mℓ of water or corn oil. The post-absorption peak blood concentration averaged three times higher for a water vehicle than for corn oil (121 µg/mℓ versus 44 µg/mℓ), while the time to peak blood concentration averaged 3 times longer for corn oil than for the water vehicle (16.3 vs. 5.2 minutes). These observations suggests that gastrointestinal absorption may be greater when water is used as the vehicle. No differences in absorption rates between corn oil and water were discussed by Angelo et al. (1986a).

2.2. INHALATION

Riley et al. (1966) described the kinetics of absorption and excretion in a 70 kg man exposed for 2 hours to 100 ppm methylene chloride in air. As exposure progressed, the concentration in alveolar air increased, suggesting approach to steady state conditions. However, equilibrium had not been reached after 2 hours and exposure was discontinued and methylene chloride in exhaled air was monitored. The postexposure decline in concentration of methylene chloride in exhaled air appeared to be exponential and roughly proportional to the amount absorbed during the exposure period. The retention factors expressed as a percentage of inhaled dose in this and related studies are summarized in Table 2-1.

DiVincenzo and Kaplan (1981) exposed groups of 4-6 volunteers to 50, 100, 150 or 200 ppm methylene chloride for 7.5 hours. Serial breath excretion curves were obtained. Pulmonary absorption was rapid during the first hour, then began to decline as steady-state was approached. Postexposure methylene chloride concentrations in exhaled air dropped rapidly. By 7 hours after treatment was terminated, expired air from those volunteers exposed to 50, 100 or 150 ppm contained <0.1 ppm methylene chloride.

TABLE 2-1

Absorption of Methylene Chloride by Human Subjects*
(Sedentary conditions)

Inhalation Concentration (ppm)	Exposure (hours)	Retention (%)	Reference
50	7.5	70	DiVincenzo and Kaplan, 1981
100	7.5	60	
150	7.5	63	
200	7.5	60	
662	0.30	74	Lehmann and Schmidt-Kehl, 1936
806	0.50	75	
1152	0.50	72	
1181	0.50	70	
44-680	2.00	31	Riley et al., 1966
100	2.00	53	DiVincenzo et al., 1972
100	4.00	41	
200	2.00	51	
250	0.50	55	Astrand et al., 1975
500	0.50	55	
750	1.00	34	Engstrom and Bjurstrom, 1977

*Source: U.S. EPA, 1985a

The concentration in expired air from those exposed to 200 ppm declined to 1 ppm 16 hours after treatment. Exposure and post-exposure blood concentrations of DCM were directly proportional to the magnitude of exposure (Di Vincenzo and Kalplan, 1981a).

Absorption of methylene chloride increased with duration of exposure and physical activity (presumably due to an increase in ventilation, and cardiac output) and with duratin of exposure (Astrand et al., 1975). Elevated ventilation doubled absorption but decreased retention from 55 to 40% of inhaled dose.

Engstrom and Bjurstrom (1977) demonstrated that methylene chloride absorption was related directly to degree of obesity in human subjects. Obese subjects (fat = 25% of body weight) absorbed 30% more methylene chloride than lean subjects (fat = 8% of body weight) when exposed to 750 ppm for 1 hour. Biopsy and analysis of subcutaneous fat revealed a substantial (10.2 and 8.4 mg/kg wet tissue) concentration in adiposa 1 and 4 hours postexposure, respectively. Although the concentrations in fat were somewhat lower in obese than in lean subjects, the total amount of body fat resulted in greater total methylene chloride absorption in obese subjects.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. No reports of subchronic oral exposure of humans to methylene chloride have been located in the available literature. Bornmann and Loeser (1967) exposed 30 male and 30 female Wistar rats for 3 months to drinking water containing 0.125 g methylene chloride/ℓ (125 ppm). Assuming rats drink 0.049 ℓ/day and that their average body weight is 0.35 kg, this dose corresponds to 17.5 mg/kg bw/day. No differences in behavior, appearance, body weight or survival of treated rats were observed compared with an equal number of control rats. No significant differences in hematologic values, urinalysis or plasma levels of nonesterified fatty acids were found in 8-10 male rats from each group. Blood glucose levels in 10 treated males were slightly elevated compared with 10 control males, but all values fell within the normal range. Estrous cycles, as evaluated by microscopic examination of vaginal smears, indicated no changes that were due to treatment. Necropsy and histopathological examination of ~20 animals of each sex and group revealed no lesions in any internal organ examined.

Recently, Kirschman et al. (1986) reported on groups of 20 male and 20 female Fischer 344 rats and identical numbers of B6C3F1 mice provided with drinking water containing 0, 0.15, 0.45 or 1.5% (0, 1500, 4500 or 15,000 ppm) methylene chloride for 90 days. Assuming rats drink 0.049 ℓ/day and that their average body weight is 0.35 kg, these doses corresponds to 0, 210, 630 or 2100 mg/kg bw/day. Assuming mice drink 0.0057 ℓ/day and that their average body weight is 0.03 kg, these doses correspond to 0, 285, 855 or 280 mg/kg bw/day. Slightly decreased water intake was observed in treated rats along with a slight decrease in body weights in middle-dose males and high-dose females. Minor hematological changes were observed in

rats at ≥4500 ppm and clinical chemistry parameters that reflected potentially compromised liver function were observed sporadically in all treated groups. Urinary pH was reduced in all treated groups of rats in a dose-related manner and high-dose females had elevated kidney weights. No histopathologic changes were observed in rats at an interim kill after 1 month of treatment. At termination, however, high-dose rats of both sexes and some middle-dose females had centrilobular necrosis. Dose-related increased hepatocellular vacuolization occurred in all treated groups.

Treated mice also had depressed fluid intake, and slightly reduced body weights were observed in both sexes at ≥855 mg/kg/day. There was no histopathologic evidence of toxicity in mice at an interim sacrifice performed at 1 month. At termination, a mild centrilobular fatty change, which was more apparent in males, was observed in mice at ≥855 mg/kg/day.

3.1.2. Inhalation. Inhalation exposure of humans to methylene chloride is likely to be a result of occupational exposure; consequently, long-term exposure can be expected. Studies of occupational exposure of humans to methylene chloride are discussed in Section 3.2.2. Subchronic exposure can be expected the use of consumer products containing methylene chloride, such as aerosol cans and paint stripping products. Historically, subchronic inhalation exposure of astronauts to methylene chloride vapors emanating from materials used in the interiors of spacecrafts has been a concern. Consequently, several investigators (Thomas et al., 1972; Haun et al., 1971, 1972; Weinstein et al., 1972; MacEwen et al., 1972) exposed several species of laboratory animals to atmospheric methylene chloride for up to 14 weeks. The U.S. EPA (1983) summarized results of these studies follows. Mice exposed to 25 or 100 ppm (112.9 or 451.6 mg/kg bw/day) methylene chloride continuously for 14 weeks had increases in spontaneous locomotor activity at

112.9 but not 451.6 mg/kg/day. No gross or histological lesions were found at necropsy, except that livers of mice exposed to 451.6 mg/kg/day stained positive for fat. Hexobarbital sleep time was unaffected, but hepatic levels of cytochromes were somewhat altered. Rats subjected to the same exposure regimens had nonspecific renal tubular degeneration and regeneration, and hepatic cytoplasmic vacuolization and positive fat staining at both exposure levels (55.3 and 221.3 mg/kg/day). Rats appeared to be the more sensitive species. No specific macro- or microscopic organ changes or changes in hematologic or clinical chemistry values were noted in a small number of monkeys in these studies (58.6 and 234.5 mg/kg/day). Carboxyhemoglobin levels, the result of metabolism of methylene chloride to carbon monoxide and subsequent action on hemoglobin, were elevated in monkeys at both exposure levels (58.6 and 234.5 mg/kg/day) and in dogs only at the higher exposure of 117.6 mg/kg/day but not at 29.4 mg/kg/day. There was no cumulative increase in carboxyhemoglobin over the period of exposure. No overt signs of toxicity or changes in body weights relative to controls were noted in any of these four species.

Higher levels of continuous exposure were also investigated. Exposure of the same four species to 1000 or 5000 ppm (mice; 4516.2 or 22,581.2 mg/kg/day rats; 2213 or 11,067.3 mg/kg/day dog; 1176.2 or 5881.2 mg/kg/day monkeys; 2344.9 or 11,724.9 mg/kg/day) resulted in signs of severe toxicity at 5000 ppm: narcosis for the first 24 hours and pronounced lethargy for the remainder of the exposure period, reduced food consumption, and high rates of mortality in mice (22,581.2 mg/kg/day), dogs (5881.2 mg/kg/day) and monkeys. Rats were somewhat less sensitive; none died. Liver and kidney damage were common findings in all species. At 1176.2 mg/kg/day dogs were severely affected and died. Mice and rats did not show overt signs of

toxicity, but body weight gain was slightly depressed in the rats. Less severe histopathological changes than had been seen at the highest dose were noted in the livers of all four species and in the kidneys of rats exposed to 2213.5 mg/kg/day. Monkeys showed no significant changes in hematologic or clinical chemistry values.

Male SPF Wistar rats exposed to 500 ppm (1106.7 mg/kg/day) vapors of methylene chloride for 10 days had significantly elevated liver cytochrome P-450 levels (Norpoth et al., 1974). However, this effect was not seen in animals exposed to 5000 ppm. Likewise, Weinstein et al. (1972) reported no changes in liver enzymes in mice after 28 days of exposure to 250 ppm (1129.1 mg/kg/day) methylene chloride.

Longer-term exposures to methylene chloride produces liver toxicity. ICR mice exposed to 100 ppm (451.6 mg/kg/day) methylene chloride for 10 weeks had centrilobular fat accumulation and decreased glycogen levels (Weinstein and Diamond, 1972). Inhalation of 451.6 mg/kg/day methylene chloride for 100 days produced cytoplasmic vacuolization and positive fat staining in mice (Haun et al., 1972). These effects were also observed in the liver of rats and dogs exposed to 25-100 ppm (rats; 55.3-221.3 mg/kg/day, dogs; 29.4-117.6 mg/kg/day) for 100 days. Kidney damage was also reported in this study. Rats exposed to 55.3 and 221.3 mg/kg/day methylene chloride had nonspecific renal tubular degenerative and regenerative changes.

Taken collectively, these studies suggest that subchronic exposure to methylene chloride produces behavioral effects in animals. The liver and kidneys of animals are also likely target organs for methylene chloride toxicity. Lesions in rats exposed to 25 or 100 ppm methylene chloride appear to be more severe than lesions in mice exposed to the same concentrations. Monkeys and dogs seem to be the least affected of those species

studied. At higher exposure concentrations (1176.2 mg/kg/day), dogs appear to be most sensitive and to experience treatment-related mortality.

3.2. CHRONIC

3.2.1. Oral. No reports of chronic oral exposure of humans to methylene chloride have been found in the available literature. Currently a 2-year gavage study with rats has been sponsored by NTP (1988), but results are not yet available.

A 24-month toxicity and carcinogenicity bioassay was performed in F344 rats and B6C3F1 mice (NCA, 1982a,b, 1983; Serota et al., 1986a,b). Details of the experiments are discussed in Section 4.2.1. of this document. Rats and mice received doses of 0.5, 50, 125 and 250 mg/kg/day methylene chloride in their drinking water for 2 years. In rats, a statistically significant reduction in body weight, water consumption and food consumption were noted at dose levels of 125 and 250 mg/kg/day. Minimal effects were noted on the hematological and serum chemistry parameters monitored in rats. Treatment-related alterations in histomorphology were observed in rats of both sexes at all dose levels tested except the lowest. Increases in foci of cellular alterations and fatty changes were most prominent.

In mice (NCA, 1983; Serota et al., 1986b), no treatment-related changes were observed in survival, body weight, water consumption, clinical observation, leukocyte counts and gross necropsy findings. Histomorphologic alterations of the liver were observed in both male and female mice in the high-dose group.

3.2.2. Inhalation. In humans, mild intoxication by methylene chloride results in somnolence, lassitude, anorexia and mild lightheadedness, followed by greater degrees of disturbed central nervous system function and

depression. Permanent disability has not been reported. When fatalities have occurred the cause has been attributed to cardiac injury and heart failure (NAS, 1978).

Further reports of human intoxication from methylene chloride were presented by NIOSH (1976). Most of the case reports were concerned with acute exposure and are not discussed here. Most of the epidemiologic studies lack data on the concentration of methylene chloride in breathing space air or they are complicated by exposure to other chemicals. Welch (1987) reported that workers from several industries, including auto parts production and plastic and prosthesis manufacturing, presented a variety of CNS complaints, including headaches, dizziness, nausea, memory loss, parasthesia, tingling in the hands and feet, and loss of consciousness. These effects occurred during certain painting and cleaning operations. Methylene chloride levels up to 100 ppm were measured and the duration of exposure was 6 months to 2 years. Assuming a breathing rate of 20 m^3/day, 5-day workweek, an 8-hour workday exposure and a body weight of 70 kg, this corresponds to a dose of 23.6 mg/kg/day. However, workers were also exposed concommitantly to a mixture of other chemicals and as such, the behavioral effects noted in this study cannot be unequivocally ascribed to methylene chloride.

Weiss (1967) reported a case of toxic encephalosis in a chemist exposed for several hours per day for 5 years to methylene chloride used in a salt-recrystallization operation. Measurements revealed concentrations of 660-3600 ppm (2293-12,505 mg/m^3) methylene chloride in workroom air with a mean of 900 ppm (3126 mg/m^3) in the breathing zone. Assuming a breathing rate of 20 m^3/day, 5 day workweek, an 8 hour workday exposure, and a body weight of 70 kg, this dose corresponds to 212.7 mg/kg/day. This worker also had physical contact with liquid methylene chloride.

Exposure of 56 workers to 28-173 ppm methylene chloride (in a 9:1 methylene chloride:methanol atmosphere) resulted in statistically significant changes in mental tiredness ($p<0.05$) and physical tiredness and sleepiness ($p<0.01$) (Cherry et al., 1983). These paramenters were significantly different only for the morning shift and correlated with blood carboxyhemoglobin levels at the end of the shift. Furthermore, performance deterioration on the morning shift correlated ($p<0.01$) with the end-of-the-shift blood concentrations of methylene chloride.

Other epidemiological studies have not revealed adverse effects in humans occupationally exposed to methylene chloride. Friedlander et al. (1978) reported an epidemiological study of male workers at Eastman Kodak exposed primarily to TWA concentrations of 30-125 ppm (104-434 mg/m^3) (Assuming a breathing rate of 20 m^3/day a 5-day workweek, an 8-hour workday, and a body weight of 70 kg, these doses correspond to 7.1 and 29.5 mg/kg/day) methylene chloride (estimated both from air monitoring and blood carboxyhemoglobin levels) for up to 30 years. A proportionate mortality study, where death certificates from 334 exposed workers who died from 1956-1976 were used. A cohort mortality study that involved all 751 workers employed in the exposure area in 1964 and a separate analysis of a subgroup of 252 of these workers exposed for a minimum of 20 years by 1964 were also performed. Data from this subgroup were analyzed separately to study effects requiring long latency periods. The follow-up period in the cohort mortality study was 13 years. Control groups consisted of other Eastman Kodak male employees working in production but not exposed to methylene chloride, New York State male cause- and age-specific mortality rates, and U.S. male age-specific mortality rates. Follow-up of workers aged $\geq$25 years

was >97% as of 1964. None of these studies revealed any indication of increased risk of death from circulatory disease including ischemic heart disease, cancer or other causes.

Ott et al. (1983a) investigated mortality and current cardiac health in workers from a fiber production plant in which methylene chloride was used as a solvent. Given that metabolism of methylene chloride to carbon monoxide results in an increase in percentage of carboxyhemoglobin with a commensurate decrease in the oxygen-carrying capacity of the blood, these authors suggested that exposure to methylene chloride may lead to an increase in the incidence of ischemic cardiac disease. Data on mortality were obtained in a fiber manufacturing plant from a cohort of workers who were exposed for at least 3 months between January 1, 1954 and January 1, 1977 to a TWA of ~140 ppm (~486 mg/m^3) methylene chloride. Assuming a breathing rate of 20 m^3/day, a 5-day workweek, and 8-hour workday and a body weight of 70 kg, this dose corresponds to 33.1 mg/kg/day. A control cohort was composed of workers who were not exposed to methylene chloride. Another control group provided the expected death data for 5-year intervals matched by race (white and non-white) and sex. Mortality data indicated no increase in deaths in either men or women from circulatory system diseases, ischemic heart disease as a separate category, or malignant neoplasms associated with exposure to methylene chloride.

In another study of cardiac function, Ott et al. (1983b) collected 24-hour EKGs on 50 workers from two fiber producing plants. Data regarding 24 workers from the plant where exposure to TWA concentrations of 60-475 ppm (208-1650 mg/m^3) (assuming a breathing rate of 20 m^3/day, 5-day workweek, an 8-hour workday and a body weight of 70 kg, these doses correspond to 14.2-112.3 mg/kg/day) methylene chloride occurred were compared with data

from 26 workers from a similar plant not using methylene chloride. No significant changes in ventricular or supraventricular ectopic activity, nor episodic ST-wave segment depression were associated with exposure to methylene chloride.

Other epidemiologic studies (Skory, 1980; Skory et al., 1980a,b) apparently revealed no adverse health effects attributable to methylene chloride; however, exposure data from these studies were not available in the secondary source from which this discussion was taken.

Cherry et al. (1981) reported that a group of 46 men who were occupationally exposed to 75-100 ppm (261-347 mg/m^3) (assuming a breathing rate of 20 m^3/day, a 5-day workweek, an 8-hour workday and a body weight of 70 kg, these doses correspond to 17.7-23.6 mg/kg/day) methylene chloride for an unspecified length of time complained of excessive neurological symptoms. Clinical examinations, motor conduction velocity measurements, EKGs and a battery of psychological tests "designed to detect minimal brain damage" were administered to 29 of the exposed men and an equal number of age-matched unexposed men employed at similar jobs. The results revealed no evidence of cardiac abnormalities or neurological or behavioral impairment associated with exposure to methylene chloride.

Burek et al. (1980, 1984) and Dow Chemical Co. (1980) studied chronic inhalation exposure of animals to methylene chloride. Sprague-Dawley rats (SPF-derived, 129/sex/exposure concentration) and golden Syrian hamsters (~108/sex/exposure concentration) were exposed to 0, 500, 1500 or 3500 ppm (rats: 0, 197.6, 592.9 and 1383.4 mg/kg/day; hamster: 0, 288.0, 864.1 and 2016.2 mg/kg/day) methylene chloride of >99% purity. Exposures were for 6 hours/day, 5 days/week (except "holidays") for up to 2 years. Rats were subjected to interim kills at 6, 12, 15 or 18 months for cytogenetic or general chemical and histopathological examinations.

During the first week of exposure, rats in the high concentration group exhibited a slight decrease in physical activity, but appeared to return to normal activity for the remainder of the trial. During the first 2 months, rats in all groups suffered a disease believed to be sialodacryoadenitis, a transient viral involvement of the salivary glands. No increased mortality was associated with the disease. None of the exposure levels affected body weights, clinical chemistries, or hematologic or urinalysis values in rats. Carboxyhemoglobin levels ranged from 0-5.3% in controls and 8.9-20.4% in exposed rats but did not appear to be dose- or duration-related. Significant increases in mortality occurred only in the high-dose females starting at the 13th month of exposure.

Mean liver weights were increased at the 18-month interim kill, in both male and female rats in the high-dose group. Histopathologic alterations related to methylene chloride were found only in the liver. A dose-related increase in hepatocellular vacuolization, indicative of fatty degeneration, was noted in all exposed groups of rats. Multinucleated hepatocytes, a spontaneous geriatric change in female rats, were observed after 12 months *in exposed and treated groups alike.* A significant increase in the number of foci of altered hepatocytes was observed in high-dose females. Males exposed to 592.9 or 1383.4 mg/kg/day had an increased incidence of hepatocellular necrosis and coagulation necrosis. Some females exposed to 197.6 mg/kg/day ppm for 12 months appeared to have slightly increased hepatic hemosiderin. Female rats exposed to 1383.4 mg/kg/day and male rats exposed to 592.9 mg/kg/day methylene chloride had a decreased incidence or severity of chronic progressive glomerulonephropathy, another normal geriatric change, compared with controls. Male rats exposed to 1383.4 mg/kg/day exhibited less severe nonrenal lesions (uremic pneumonitis, mineralization

of organs and blood vessels, brain malacia, myocardial degeneration, etc.) that were associated with chronic progressive renal disease.

In this study, hamsters appeared to be less sensitive than rats to methylene chloride. Although carboxyhemoglobin levels were higher in hamsters (0.3-4.0% in control groups, 22.2-34.6% in treatment groups) than in rats, no clear evidence of toxicity was observed in hamsters. Methylene chloride-exposed hamsters exhibited a decrease in the incidence of age-related amyloid deposition relative to controls.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Pertinent data associating oral exposure of humans to methylene chloride with terata or reproductive effects were not located in the available literature. The estrous cycle in female rats was reported to be unaffected by exposure to 0.125 g methylene chloride/ℓ in their drinking water for 3 months (17.5 mg/kg/day) (Bornmann and Loeser, 1967).

3.3.2. Inhalation. Pertinent data regarding teratogenicity or reproductive dysfunction in humans exposed by inhalation to methylene chloride were not located in the available literature. Methylene chloride has been shown to cross the placental barrier in laboratory animals (Anders and Sunram, 1982). Schwetz et al. (1975) exposed Swiss-Webster mice and Sprague-Dawley rats to 1250 ppm methylene chloride for 7 hours/day on days 6-15 of gestation (mice, 1646.5 mg/kg/day; rats, 806.9 mg/kg/day). Mouse fetuses were collected and examined on day 18 and rat fetuses were collected and examined on day 21 of gestation. Dams of both species were minimally affected; slightly increased carboxyhemoglobin formation was the only effect reported. Delayed development (manifestations unspecified) was the only effect noted in rat fetuses. In mouse fetuses, slightly advanced ossification of the sternebrae were noted, which suggested accelerated development.

The teratogenic effect of methylene chloride in rats was also investigated by Hardin and Manson (1980). Groups of 26-28 Long-Evans hooded rats were exposed to 4500 ppm mg/m^3) methylene chloride for 6 hours/day (2490.1 mg/kg/day) (group 1, before and during gestation; group 2, before gestation; group 3, during gestation). "Before gestation" exposures were the 3 weeks immediately preceding mating and "during gestation" exposures included the first 17 days of gestation. Gravida from 16-18 dams/group were examined on day 20 of gestation. A slight but significant decrease in fetal body weight occurred in groups exposed during gestation compared with controls and the group exposed only before gestation. No other abnormalities were reported. In a companion paper, Bornschein et al. (1980) studied the behavioral effects of methylene chloride on pups from 10 dams per group. Methylene chloride had no effects on behavior, body weights, food and water consumption, wheel running activity, and avoidance learning up to 400 days of age.

3.4. TOXICANT INTERACTIONS

No studies of toxic interactions of methylene chloride with other xenobiotics have been found in the available literature. Some case histories in humans, however, suggest that interactions with other compounds may occur. Functional circulatory disorders in workers exposed for >3 years to methylene chloride and other organochlorine compounds at "permissible" levels have been reported (Dunavskii, 1972). The symptoms, including chest pain, EKG irregularities, bradycardia, decreased myocardial contractility and altered adaptation to physical stress, were not attributed to methylene chloride alone.

The metabolism of methylene chloride to carbon monoxide forms the basis for concern about combined exposure to methylene chloride and carbon monoxide. Fodor and Roscovanu (1976) reported that exposure of human

subjects to 500 ppm (assuming a breathing rate of 20 m^3/day, with continuous exposure, this dose corresponds to 496.3 mg/kg/day) of methylene chloride (for an unspecified duration) resulted in levels of carboxyhemoglobin in blood comparable with those produced by the TLV for carbon monoxide, 50 ppm. Mixed exposures could pose a health threat to occupationally exposed workers, smokers or cardiorespiratory patients. Savolainen et al. (1977) expressed concern that exposure to methylene choride in combination with other lipophilic solvents may result in enhanced central nervous system and metabolic effects.

Christenson and Hulzinga (1971) reported the case of a 17-year-old male who died after using a mixture of 80% methylene chloride and 14.9% methanol to remove paint. Barbiturate derivatives were found in the blood, brain, urine and stomach contents. Death was ascribed to the combination of methylene chloride and barbiturates.

Two reports of phosgene poisoning related to methylene chloride (Gerritsen and Buschmann, 1960; English, 1964) pointed out that phosgene, a combustion product of methylene chloride, is highly toxic. Both cases involved the use of methylene chloride as a paint remover in an enclosed area heated with a portable kerosene heater. One case (Gerritsen and Buschmann, 1960) involved a woman who was exposed for a 3-hour period during 1 day when she was 7 months pregnant; she expectorated blood-tinged sputum and felt tightness in her chest. The next day she was hospitalized with dyspnea, cyanosis, and elevated pulse and body temperature. She was treated and discharged 8 days later. She gave birth to a healthy infant 2 months later.

The second case (English, 1964) involved a 67-year-old male who was exposed for 8 hours to methylene chloride in a small unventilated room heated with a portable kerosene heater. He experienced breathlessness, headache, giddiness and a tightness across the chest. Upon hospitalization the next day he was cyanotic, sweating, and tachypneic with extensive coarse rales in both lungs. He was discharged after 5 weeks but experienced lassitude, weakness and hypochondriosis for an additional 3 months.

4. CARCINOGENICITY

4.1. HUMAN DATA

Several epidemiological studies that were reviewed briefly in Section 3.2.2. examined the health effects associated with occupational exposure to methylene chloride. Friedlander et al. (1978) and Ott et al. (1983a) reported no excess cancer mortality in exposed cohorts compared with controls. This study has been recently updated through 1984 (Hearne et al., 1987). Workers were exposed to an average workplace concentration of 26 ppm (assuming a breathing rate of 20 m^3/day, a 5-day workweek, an 8-hour workday and a body weight of 70 kg, this dose corresponds to 6.1 mg/kg/day) methylene chloride for an average of 22 years. Again, there was no increase in deaths from malignant neoplasms, respiratory cancer, or liver cancer in exposed workers compared with the general population. An increase in the incidence of deaths due to pancreatic cancer was observed but was not statistically significant.

4.2. BIOASSAYS

4.2.1. Oral. An NTP-sponsored gavage bioassay of methylene chloride in rats is currently underway; results are not yet available (NTP, 1988).

A 24-month toxicity and carcinogenicity bioassay was performed in F344 rats (NCA, 1982a,b; Serota et al., 1986a) and B6C3F1 mice (NCA, 1983; Serota et al., 1986b). In the rat study, groups of 85 males and 85 females were administered methylene chloride in their drinking water. Target doses were 0, 5, 50, 125 or 250 mg/kg bw/day for 24 months. Consumption was monitored and actual consumption closely paralleled target doses. A second control group of 50 rats/sex and a high-dose group (250 mg/kg bw/day) of 25 rats/sex were added for 78 weeks followed by a 26-week recovery period. There was a statistically significant increase ($p<0.05$) in the combination of neoplastic nodules and hepatocellular carcinomas in female rats relative to controls.

These incidences (0/134, 1/85, 4/83, 1/85, 6/85 in combined control, 5, 50, 125 and 250 mg/kg bw/day groups, respectively), however, were within those observed in historical controls. The U.S. EPA (1985a) concluded therefore, that this study did not provide sufficient evidence for methylene chloride carcinogenicity in F344 rats.

In the mouse experiment, groups of 50 females and 60-200 males were treated with methylene chloride in the drinking water. Target doses were 0, 60, 125, 185 or 250 mg/kg bw/day for 24 months. Daily consumption was monitored and showed that consumed dose was similar to target dose. A significant ($p<0.05$) increase in the combined incidence of hepatocellular adenoma and carcinoma was recorded in male mice (24/125, 51/200, 30/100, 31/99 and 35/125 in combined control, 60, 125, 185 and 250 mg/kg bw/day groups, respectively). This data is not considered to be sufficient evidence of carcinogenicity of methylene chloride in mice.

4.2.2. Inhalation. Burek et al. (1980, 1984) and Dow Chemical Co. (1980) evaluated the carcinogenicity of methylene chloride based on a chronic (2-year) inhalation exposure regimen. Sprague-Dawley rats and golden Syrian hamsters were exposed to methylene chloride at 0, 500, 1500 or 3500 ppm 6 hours/day, 5 days/week for up to 2 years (assuming rats have a breathing rate of 0.223 m^3/day and a body weight of 0.35 kg these doses correspond to 0, 197.6, 592.9 and 1383.4 mg/kg/day. Assuming a hamster has a breathing rate of 0.13 m^3/day and a body weight of 0.149 kg, these doses correspond to 0,288.0, 864.1 and 2016.2 mg/kg/day. No exposure-related differences in the incidences of benign or malignant tumors were observed in male hamsters. There was a statistically significant increase ($p=0.032$) in the incidence of benign tumors in female hamsters exposed to 2016.2 mg/kg/day ppm methylene choride. However, this increase was attributed to increased longevity in

that group and subsequently, a higher probability of developing these tumors. After corrections for survival differences between the groups, the data is not statistically significant.

An increase in the number of benign mammary tumors per tumor-bearing rat (but not in the number of tumor-bearing rats) was observed at all dose levels in females and in males in the high dose group. There was a statistically significant increase ($p<0.001$) in salivery gland sarcomas in male rats given 1383.4 mg/kg/day methylene chlroide (Table 4-1). These tumors appeared to arise from mesenchymal rather than epithelial tissue. According to the investigators, interpretation of the significance of these findings is equivocal. Studies of chronic methylene chloride exposure at high levels in a wide variety of laboratory species have established the liver as the primary target organ. The apparent relationship between methylene chloride and the salivary gland was unusual and appeared to be inconsistent with previously reported data. Early in the course of treatment, these rats had apparently contracted a viral disease, sialodacryoadenitis, in the salivary glands. It was suggested that the combination of the virus with methylene chloride may have increased the incidence of salivary gland neoplasia. The fact that these sarcomas appeared to arise from mesenchymal tissue rather than from epithelial (glandular) tissue further confounded interpretation. Burek et al. (1984) expected primary salivary gland neoplasms to arise from epithelial cells.

Nitschke et al. (1982) conducted a 2-year inhalation toxicity and oncogenicity study where rats were exposed to 0, 50, 200 or 500 ppm, 6 hours/day, 5 days/week for 20 (males) or 24 months (females). Assuming rats have a breathing rate of 0.223 m^3/day and a body weight of 0.35 kg, these doses correspond to 0, 19.8, 79.1 and 197.7 mg/kg/day respectively. Interim

TABLE 4-1

Summary of Salivary Gland Region Sarcoma Incidence in Male Rats in a 2-Year Inhalation Study with Dichloromethane[a]

Dose (mg/kg/day)	Incidence[b]	Fisher's Exact Test
0	1/93 (1%)	NA
197.6	0/94 (0%)	NA
592.9	5/91 (5.5%)	(p=0.10, NS)
1383.4	11/88 (12.5%)	(p=0.002)

[a]Source: Burek et al., 1980, 1984; Dow Chemical Co., 1980

[b]Cochran-Armitage test for linear trend, $p<0.0001$

NS = Not significant; NA = not applicable

necropsies were performed at 6, 13, 15 and 18 months. No treatment-related increase in tumor incidence was observed. This study has been criticized for using doses too low to elicit a positive response. Consequently, the National Toxicology Program has performed an inhalation study in rats and mice (NTP, 1985). The final draft of this study has been released (NTP, 1986). In this experiment, 50 male and 50 female F344/N rats were exposed to air containing 0 (chamber controls), 1000, 2000 or 4000 ppm (0, 3474, 6947 or 13,894 mg/m^3), 6 hours/day, 5 days/week for 102 weeks. Concurrently, 50 male and 50 female B6C3F1 mice were exposed by the same schedule to air containing 0, 2000 or 4000 ppm methylene chloride (0, 1612.9 or 3225.9 mg/kg/day). During week 3 of treatment, rats of both sexes in the 395.3 mg/kg/day group were exposed to 790.5 mg/kg/day and rats of both sexes in the 790.5 mg/kg/day group were exposed to 395.3 mg/kg/day.

In rats of both sexes, a significant increase ($p<0.05$ males; $p<0.001$ females) in mammary tumors (fibroadenoma, adenoma, fibroma: combined incidence) was observed in the high-dose groups (Table 4-2). Similarly, the incidence of subcutaneous fibroma or sarcoma (combined) according to authors, in male rats was significantly higher in the high-dose group than in controls ($p<0.01$). The incidence of these tumors was combined because they all occurred in the mammary chain and were considered to be of the same etiologic origin. However, combining tumor incidences is not a valid statistical procedure. Furthermore, historical incidence of these tumors, which are generally much higher than experimental controls, are generally ignored in NTP's discussion. In light of these facts the results and conclusions of the NTP (1985, 1986) bioassay are equivocal. The incidence of other tumor types were also increased although not statistically significant. These included the combined incidence of neoplastic nodules and

TABLE 4-2

Tumor Incidence in Rats Treated with Methylene Chloride[a]

Tumor Type	Historical Controls[e]	Control	395.3	790.5	1581.0
MALES					
Fibroadenoma, adenoma, fibroma of mammary gland	>3±3%	0/50 (0%)	0/50 (0%)	2/50 (4%)	5/50[b] (10%)
Subcutaneous (combined) tumors of mammary area	>5±3%	1/50 (2%)	1/50 (2%)	4/50 (8%)	9/50[c] (18%)
FEMALES					
Fibroadenoma, adenoma, fibroma of mammary gland	>28±10%	7/50 (14%)	13/50 (26%)	14/50 (28%)	23/50[d] (46%)

[a]Source: NTP, 1986; percentages based on animal groups of 50 each.

[b]$p<0.05$; Fisher's exact Test as compared to control incidences.

[c]$p<0.01$ as compared to control incidences.

[d]$p<0.001$ as compared to control incidences.

[e]Historical incidence +/- standard deviation (NTP studies) in 1727 animals. Historical controls were not used to derive statistical significance.

hepatocellular carcinomas in female rats, adrenal gland pheochromocytoma and interstitial cell tumors in males, squamous cell metaplasia in females, pituitary gland adenoma or carcinoma and mononuclear cell leukemias in both sexes. In male rats, the incidence of mesothelioma derived from the tunica vaginalis was found to be significantly higher in both the high and intermediate groups than in controls, but the incidence in controls in this experiment was unusually low compared with historical controls thereby making interpretation of these results equivocal.

An increase in the incidence of lung tumors in treated mice was highly significant ($p<0.001$) (Table 4-3). The latency period was significantly reduced in treated mice. Lung tumors were believed to be responsible for the reduced survival observed in high-dose group males and females. Also noteworthy was the incidence of liver tumors in treated mice ($p=0.014$ males; $p<0.001$ females) (see Table 4-3).

The results of the NTP (1985) bioassay were used in combination with data from the drinking water mouse study (NCA, 1983) by the U.S. EPA (1985b) to derive cancer potency estimates for oral and inhalation exposure to methylene chloride (Section 6.3.). Subsequent to the U.S. EPA (1985b) analysis, the NTP study was finalized and became available in a published form (NTP, 1986). The relevant tumor incidence data had not changed between the 1985 and 1986 versions of the study and publication of the more recent version is not expected to alter the quantitative estimation of carcinogenic potency.

4.3. OTHER RELEVANT DATA

Several experiments regarding the mutagenicity of methylene chloride are summarized in Table 4-4. Simmon et al. (1977) reported that methylene chloride was mutagenic to Salmonella typhimurium strain TA100 when assayed in a desiccator in which the atmosphere contained the test compound.

TABLE 4-3

Tumor Incidence in Mice Treated with Methylene Chloride[a]

Tumor Type	Historical[e] Controls	Control	1612.9 mg/kg/day	3225.9 mg/kg/day
MALES				
Alveolar/bronchiolar adenomas	17±8%[f]	3/50 (6%)	19/50[b] (38%)	24/50[b] (48%)
Alveolar/bronchiolar carcinomas	17±8%f	2/50 (4%)	10/50[c] (20%)	28/50[b] (56%)
Multiple lung tumors	-----	0/50 (0%)	10/50 (20%)	28/50 (56%)
Hepatocellular adenoma and carcinoma	30±8%	22/50 (44%)	24/49 (49%)	33/49[c] (67%)
Hepatocellular carcinoma	----	13/50 (26%)	15/49 (31%)	26/49[d] (53%)
Multiple liver tumors	----	21/50 (4%)	11/49 (22%)	16/49[c] (33%)
FEMALES				
Alveolar/bronchiolar adenomas	7±4%[f]	2/50 (4%)	23/48[b] (48%)	28/48[b] (58%)
Alveolar/bronchiolar carcinomas	7±4%[f]	1/50 (2%)	13/48[b] (27%)	29/48[b] (60%)
Multiple lung tumors	----	0/50 (0%)	11/48 (23%)	29/48 (60%)
Hepatocellular adenoma and carcinoma	30±8%	3/50 (6%)	16/48[b] (33%)	40/48[b] (83%)
Hepatocellular carcinoma	----	1/50 (2%)	11/48[b] (23%)	32/48[b] (67%)

TABLE 4-3 (con't)

Tumor Type	Historical[e] Controls	Control	1612.9 mg/kg/day	3225.9 mg/kg/day
Multiple liver tumors	----	0/50 (0%)	3/48 (6%)	28/48 (58%)

[a]Source NTP, 1986

[b]$p<0.001$; Fisher exact test as compared to control incidence

[c]$p=0.014$ as compared to control incidences

[d]$p=0.005$ as compared to control incidences

[e]Historical incidence $\pm$ standard deviartion (NTP) in historical controls were not used to derive statistical significance.

[f]Combined incidence of Alveolar/Bronchiolar Adenoma or Carcinoma.

TABLE 4-4

Mutagenicity and Genotoxicity of Methylene Chloride*

Assay	Indicator Organism	Application	Concentration or Dose	Activating System	Response	Comments	Reference
Reverse mutation	Salmonella typhimurium TA1535, TA1537, TA1538, TA98, TA100	vapor exposure	0-800 µL/9 L desiccator	±S-9	+ +	Data reported only for TA100; positive with or without S-9 activation	Simmon et al., 1977
Reverse mutation	S. typhimurium TA100	vapor exposure	0-1 mL/9 L desiccator	±S-9	+ +	S-9 may enhance, but not required for mutagenicity	Simmon and Kauhanen, 1978
Reverse mutation	S. typhimurium TA1535, TA100	vapor exposure	0-8.3% in air	±S-9	+ +	S-9 enhanced mutagenicity; dose-response was evident in TA100	Green, 1983
Reverse mutation	S. typhimurium TA1535	vapor exposure	0-10% theoretical in air	none	+	Clear-cut dose-response clearly evident	McGregor, 1979
Reverse mutation	S. typhimurium TA1535, TA1537, TA1538, TA98, TA100	vapor exposure	NR	+S-9	+	Positive result only when conducted in gas tight chamber	Nestmann et al., 1980
Reverse mutation	S. typhimurium TA98, TA100	vapor exposure	0-1 mL/ chamber	±S-9	+ +	Positive in both TA98, TA100	Snow et al., 1979
Reverse mutation	S. typhimurium TA98, TA100	NR	NR	S-9	+	Data available in abstract form only	Kanada and Uyeta, 1978
Reverse mutation	S. typhimurium TA98, TA100	vapor exposure	0-57,000 ppm	±S-9	+ +	Response positive and dose-related	Jongen et al., 1978
Reverse mutation	S. typhimurium TA1535, TA98, TA100	vapor exposure	0-10,000 ppm		+ +	Positive dose-related response only in air tight chamber	Barber et al., 1981
Reverse mutation	S. typhimurium TA100	vapor exposure	0-8.4%	±S-9	+ +	Positive dose-related response, S-9 activation did not enhance response	Green, 1980
Reverse mutation	S. typhimurium TA1535, TA1537, TA1538, TA98, TA100	vapor exposure	0-750 mL/ desiccator	±S-9	+ +	Weak positive response	Gocke et al., 1981
Reverse mutation	S. typhimurium TA100	vapor exposure	0-1.4%	±S-9, cytosal, microsomes	+ +	Activation with cytosol yielded maximum response	Jongen et al., 1982

TABLE 4-4 (cont.)

Assay	Indicator Organism	Application	Concentration or Dose	Activating System	Response	Comments	Reference
Rec assay	Bacillus subtilis	NR	NR	NR	-	Data available only in abstract form	Kanada and Uyeta, 1978
Mitotic recombination	Saccharomyces cerevisiae D7	NR	0-209 mM	NA	+	D7 strain metabolizes methylene chloride to active intermediates	Callen et al., 1980
Mitotic recombination	S. cerevisiae D3	NR	NR	NR	-	Minimal data presented	Simmon et al., 1977
Sex-linked recessive lethal	Drosophila	fed or injected	NR	NA	-	Votalization not prevented	Abrahamson and Valencia, 1980
Sex-linked recessive lethal	Drosophila	fed	0-620 mM	NA	+	Conclusion; methylene chloride is mutagenic to sperm	Gocke et al., 1981
Sex-linked recessive lethal	Panagrelus redivivus	NR	10^{-6} to 10^{4} mol/L	NA	+	Equivocal positive results	Samoiloff et al., 1980
Mutations in cell-culture	CHO and V79 cells	cell culture	0-5%	NA	-	Equivocal negative results	Jongen et al., 1981
Chromosomal aberration	rat bone marrow cells	inhalation	0-3500 ppm	NA	-	NC	Dow Chemical Co., 1980
Chromosomal aberration	NMRI mice/bone marrow	1.p. injection	0-3400 mg/kg bw	NA	+ -	Results equivocal	Gocke et al., 1981
Sister-chromatid exchange	SCE/V79 cells	cell culture	0-4.0%	NA	+	Positive dose-response	Jongen et al., 1981
Chromosomal abberation	CHO cells	cell culture	0-10 µL/mL	± S-9	+	Similar results in three replications	Thilagar and Kumaroo, 1983
Sister-chromatid exchange	CHO cells	cell culture	0-10 µL/mL	± S-9	+ -	Marginal but not significant response	Thilagar and Kumaroo, 1983
Chromosomal abberation	rat/mouse lung/liver DNA	inhalation	4000 ppm/3 hours	NA	-	Concluded that methylene chloride is not genotoxic	CEFIC, 1986

[a]Compound and purity not reported

NR = Not reported; NA = not applicable; NC = no comment

Metabolic activation was not required. The response was strongly dose-related. This is typical of the response of many strains of S. typhimurium to methylene chloride (see Table 4-4). In S. cerevisiae D3, however, mitotic recombination was not increased by methylene chloride (Simmon et al., 1977) although positive results were obtained in S. cerevisiae D7 (Callen et al., 1980). Additionally, Abrahamson and Valencia (1980) reported that methylene chloride was negative when tested for sex-linked recessive lethals in Drosophila melanogaster, although positive results were obtained by Gocke et al. (1981).

Thilagar and Kumaroo (1983) investigated the ability of methylene chloride to induce SCE and chromosomal aberrations in cultured Chinese hamster ovary cells. They observed extensive chromosomal aberrations, both with and without Aroclor 1242- and 1254-induced rat S-9 fraction activation. Negative results were reported in the SCE assay. These authors discovered that using plastic rather than glass for the tests markedly reduced the magnitude of the positive response. This observation suggests that methylene chloride may bind to plastic, decreasing its effective concentration in these assays.

In general, methylene chloride is mutagenic to several strains of Salmonella typhimurium. Metabolic activation with S-9 is not required but may enhance mutagenicity. Five studies reported a dose-response relationship (Green, 1980, 1983; McGregor, 1979; Jongen et al., 1978; Barber et al., 1981). The evidence for mutagenicity in other test systems is not so clear cut however. In Saccharomyces cerevisiae, an increase in mitotic recombinations were observed in the D7 strain (Callen et al., 1980) but not in the D3 strain (Simmon et al., 1977). Likewise, in Drosophila, positive (Gocke et al., 1981) and negative (Abrahamson and Valencia, 1980) results have been reported.

The mammalian cells, in vitro exposure to methylene chloride produces an increase in chromosome abberations in CHO cells (Thilagar and Kumaroo, 1983) and in sister-chromatid exchange in SCE/V79 cells (Jongen et al., 1981). However, other reports are negative or equivocal (Jongen et al., 1981; Dow Chemical Co., 1980; Goche et al., 1981; Thilagar and Kumaroo, 1983).

The in vivo interaction of methylene chloride and its metabolites with F344 rat and B6C3F1 mouse lung and liver DNA was measured after inhalation of 4000 ppm ^{14}C-methylene chloride for 3 hours (CEFIC, 1986). The DNA was isolated from the tissue 6, 12 and 24 hours after the start of exposure and then analyzed for total radioactivity and the distribution of radioactivity in enzymatically hydrolyzed DNA samples. Low-levels of radioactivity were found in DNA from the lungs and livers of both rats and mice. Higher levels were found in mouse DNA and protein than in the rat. The radioactivity was found to be associated with normal constituents of DNA. Under the conditions of this study, there was no evidence for alkylation of DNA by methylene chloride and it was concluded that methylene chloride was not genotoxic (CEFIC, 1986).

There is clear evidence of mutagenicity in yeast. Results are mixed for Drosophila and mammalian cells in cultures, and were largely negative in mammalian cells in vivo. Given this evidence it was concluded that methylene chloride may be a weak mutagen in mammalian systems (U.S. EPA, 1987).

4.4. WEIGHT OF EVIDENCE

Pertinent data regarding carcinogenicity of methylene chloride in humans were not located in the available literature. An NTP-sponsored gavage study in rats is currently underway, but results are not yet available (NTP, 1988). Burek et al. (1980, 1984) was unable to demonstrate carcinogenicity

in rats with chronic inhalation exposure to high levels 1383.4 mg/kg/day methylene chloride. Another NCI bioassay that involved inhalation exposure has recently been published (NTP, 1985, 1986). The results indicate that methylene chloride is may be carcinogenic to rats (mammary tumors) and mice (lung and liver tumors). However, questionable statistical assumptions used in deriving carcinogenic incidences makes the NTP (1985, 1986) conclusions equivocal. Applying the criteria for evaluating the overall weight of evidence of carcinogenicity to humans adopted by the Carcinogen Assessment Group of the U.S. EPA (1986a), methylene chloride is most appropriately classified a B2 - Probable Human Carcinogen. This classification is consistent with the current analysis of the U.S. EPA (1985a, 1986c).

5. REGULATORY STANDARDS AND CRITERIA

Pertinent regulatory standards and criteria for methylene chloride are summarized in Table 5-1. According to the ACGIH (1986) the TLV committee adopted a TLV-TWA of 100 ppm in the workplace. The committee recommends the elimination of the STEL until additional toxicological data and industrial hygiene experience become available.

The NIOSH (1976) occupational criteria for methylene chloride was set at a TWA of 75 ppm for a 10-hour workday, 40-hour workweek. Recognizing the additional relationship between methylene chloride and carbon monoxide, a formula has been derived to relate methylene chloride toxicity and carbon monoxide toxicity with concentrations that are >9 ppm.

$$[C(CO) \div L(CO)] + [C(DCM) \div L(DCM)] < 1$$

where

C(CO) = TWA concentration of carbon monoxide (ppm)
L(CO) = 35 ppm, the recommended TWA limit for carbon monoxide
C(DCM) = TWA concentration of methylene chloride (ppm)
L(DCM) = 75 ppm, the recommended TWA limit for methylene chloride

The carcinogenic response to methylene chloride has been documented in several studies of chronic effects in animals, (see Section 4.2.1.). Consequently, a recent report by NIOSH (1986) recommends that methylene chloride be regarded as a "potential occupational carcinogen". Therefore, NIOSH (1986) recommends that occupational exposure to methylene chloride be controlled to the lowest feasible limit.

The U.S. EPA (1986c) has verified an oral slope factor of 7.5×10^{-3} $(mg/kg/day)^{-1}$ and a drinking water unit risk of 2.1×10^{-7} $(\mu g/\ell)$. An inhalation slope factor of 1.4×10^{-2} $(mg/kg/day)^{-1}$ and an inhalation unit risk of 4.1×10^{-6} $(\mu g/m^3)^{-1}$. These values were derived using a linearized multistage procedure.

TABLE 5-1

Regulatory Standards or Criteria for Methylene Chloride[a]

Standard or Criteria	Value	Reference
TLV-TWA	100 ppm (~360 mg/m³)	ACGIH, 1986
Level in spice oleo-resins	30 mg/kg	NIOSH, 1976
Level in decaffeinated coffee	10 mg/kg	
8-hour PEL-TWA	500 ppm (1737 mg/m³)	OSHA, 1986
Acceptable ceiling	1000 ppm (3474 mg/m³)	
Maximum peak	2000 ppm (6948 mg/m³)	
Ambient water quality criterion		U.S. EPA, 1980a
Ingesting water and organisms	0.19 µg/ℓ	
Ingesting organisms only	15.7 µg/ℓ	
Health advisories (HAs)		U.S. EPA, 1985c
1-day (child)	13.3 mg/ℓ	
10-day (child)	1.5 mg/ℓ	
DWEL[b]	1.75 mg/ℓ	
Suggested no adverse response level (SNARL)		U.S. EPA, 1985c NAS, 1980
1-day	45.5 mg/ℓ	
7-day	6.5 mg/ℓ	

[a]See discussion in text for concurrent exposure to carbon monoxide.

[b]DWEL = drinking water equivalent level.

As an oil and fat solvent, methylene chloride is allowed in spice oleoresins at concentrations up to 30 mg/kg and in decaffeinated coffee at concentrations up to 10 mg/kg (NIOSH, 1976).

OSHA (1986) has established Permissible Exposure Limits (PELs) for occupational exposures to methylene chloride as follows: 8-hour TWA, 500 ppm; acceptable ceiling concentration, 1000 ppm; acceptable maximum peak > ceiling (5 minutes in any 2 hours), 2000 ppm.

The U.S. EPA (1980a) has set the ambient water quality criterion for ingesting water and organisms at 0.19 µg/ℓ and for ingesting organisms only at 15.7 µg/ℓ.

The U.S. EPA Office of Drinking Water (ODW) has prepared health advisories (HAs) for a number of drinking water contaminents. The HAs describe concentrations of contaminents in drinking water at which non-carcinogenic effects would not be anticipated to occur and would provide a margin of safety to protect sensitive members of the population. The 1-day and 10-day HAs are calculated for exposure of children; for methylene chloride these values are 13.3 and 1.5 mg/ℓ, respectively (U.S. EPA, 1985c). Adequate data for calculating a longer-term HA were not available, however, IRIS reports a modified DWEL value of 0.5 mg/ℓ as the longer-term HA. Since methylene chloride is classified by EPA is a B2 carcinogen, a lifetime HA value is not recommended. However, a drinking water equivalent level (DWEL) of 1.75 mg/ℓ is recommended.

The U.S. EPA (1985c) has recalculated previously published 1- and 7-day suggested-no-adverse-response level (SNARL) data (NAS, 1980). These values are 45.5 and 6.5 mg/ℓ, respectively. Because of a lack of suitable data, a chronic SNARL was not calculated.

The U.S. EPA (1985d) has verified a chronic RfD_0 of $6x10^{-2}$ mg/kg/day for methylene chloride based on NOAELs of 5.85 and 6.47 mg/kg/day for male and female rats, respectively. The data was derived from a 2-year drinking water bioassay (NCA, 1983; Serota et al., 1986a,b). However, since the supporting data base is limited, the confidence in the RfD_0 is only medium.

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S)

Methylene chloride has been demonstrated to probably be carcinogenic in both rats and mice. Data are sufficient for estimating carcinogenic potency.

6.2. REFERENCE DOSE (RfD)

Methylene chloride has been demonstrated to probably be carcinogenic in both rats and mice. Data are sufficient for estimating carcinogenic potency.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. In the 2-year NCA studies (NCA, 1982a,b, 1983; Serota et al., 1986a,b), F344 rats and B6C3F1 mice were administered methylene chloride in the drinking water. Female rats had an increased incidence of neoplastic nodules or hepatocellular carcinomas, which was significant when compared with matched but not historical controls. No increased incidence of liver tumors was reported in male rats. Male mice had increased incidences of combined neoplastic nodules and hepatocellular carcinomas; however, these increases were not statistically significant or dose-related.

U.S. EPA (1985b) derived a drinking water unit risk estimate of 2.1×10^{-7} $(\mu g/\ell)^{-1}$ based on extrapolation using the linearized multistage model. The slope factor is an arithmetic mean of slope factors derived from the NTP (1985) inhalation study and the NCA (1983) oral data. This value was verified by the U.S. EPA (1986c) and is available on IRIS. This analysis of the NTP inhalation study is discussed more fully in Section 6.3.2. According to the analysis presented by U.S. EPA (1986c), methylene chloride is absorbed rapidly following either inhalation or oral exposure. Therefore, use of inhalation data for calculation of risk from oral exposure is possible if lung tumor data are omitted. Further details of the assumptions and derivation of the oral unit risk for humans are presented in the

U.S. EPA (1986c) summary. Methylene chloride was considered to be a well absorbed vapor at low doses. The unit risk should not be used if the water concentration exceeds 5×10^{4} µg/ℓ, because above this concentration the slope factor may differ from that stated.

Subsequent to the derivation of the U.S. EPA (1985b) analysis, the NTP data became available in a final form (NTP, 1986). The NTP (1986) data did not differ from the 1985 version and there has been no modification of the risk assessment. The value of 2.1×10^{-7} $(\mu g/\ell)^{-1}$ is equivalent to 7.5×10^{-3} $(mg/kg/day)^{-1}$, which is adopted as the estimate of the carcinogenic potency to orally exposed humans for the purposes of this document.

6.3.2. Inhalation. The U.S. EPA (1985b) used the data from the 2-year inhalation study reported by NTP (1985) for combined carcinomas and adenomas of the lung or liver in B6C3F1 mice for derivation of the inhalation unit risk of 4.1×10^{-6} $(\mu g/m^{3})$. Details of the NTP (1985) study, as well as other inhalation studies are discussed in Section 3.2.2. of this document, and assumptions and derivation of the inhalation unit risk are presented in the U.S. EPA (1985b) document. As discussed in Section 6.3.1., the NTP data are available in a final form (NTP, 1986), which does not differ substantially from the 1985 version and there is no modification to this risk assessment based upon this final NTP report. The above value is equivalent to 1.4×10^{-2} $(mg/kg/day)^{-1}$ and is verified and available on IRIS (U.S. EPA, 1986c). The value of 1.4×10^{-2} $(mg/kg/day)^{-1}$ is adopted for the purposes of this document as the estimate of the carcinogenic potency of methylene chloride to humans exposed by inhalation. The unit risk should not be used if the air concentration exceeds 2×10^{3} $\mu g/m^{3}$ because above this concentration the slope factor may differ from that stated.

After critical analysis of the evidence, EPA has concluded that methylene chloride may be a weak genotoxicant in mammals (U.S. EPA, 1987). Current evidence is not sufficient to identify the mechanism of action or to indicate that this mechanism would not be expected in humans. Indeed, it seems reasonable to assume that humans metabolize methylene chloride via the glutathion-s-transferase pathway as do rats and mice, albeit at a much slower rate. U.S. EPA (1987) suggests that since some data exist on the pharmacokinetics and metabolic pathways of methylene chloride, it may be more appropriate to use a physiolgically based, pharmacokinetic model (Andersen et al., 1987). However, this model has not been fully validated.

Nevertheless, using the pharmacokinetic model with its original kinetic parameters to estimate the internal dose of the glutathion-s-transferase metabolite, and correcting internal dose for interspecies differences in sensitivity by using the surface area correction factor, leads to a unit risk estimate for continuous inhalation exposure to 1 $\mu g/m^3$ of 4.7×10^{-7}. This factor is ~8.7-fold lower than the inhalation unit risk of 4.1×10^{-6} derived from the 2-year NTP (1986) bioassay. This difference, in light of the uncertainties of the model mentioned above, are not, in practical terms, very distinct. In this case, pharmacokinetic considerations have not revealed a great error inherent in using applied dose as a surrogate for internal or delivered dose.

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APPENDIX

Summary Table for Methylene Chloride

Carcinogenic Potency	Species/Sex	Experimental Dose/Exposure	Effect	q_1^* or Unit Risk Slope $(mg/kg/day)^{-1}$	Reference
Inhalation	mouse/female	≤4000 ppm (13,894 mg/m^3), 6 hours/day, 5 days/week for 2 years	combined carcinomas and adenomas of the lung and liver	1.4×10^{-2}	NTP, 1985; U.S. EPA, 1985b, 1986c
Oral	mouse/male and female	inhalation ≤4000 ppm (13,894 mg/m^3), 6 hours/day, 5 days/week for 2 years and drinking water study: ≤250 mg/kg/day for 2 years	hepatocellular adenomas or carcinomas	7.5×10^{-3}†	NTP, 1985; NCA, 1983; U.S. EPA, 1985b, 1986c

†Arithmetic mean of slope factors derived from NTP (1986) and the NCA (1983) data.