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Provisional Peer-Reviewed Toxicity Values for

Chloromethane
(CASRN 74-87-3)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

AUTHORS, CONTRIBUTORS, AND REVIEWERS

CHEMICAL MANAGER

Custodio V. Muianga, PhD, MPH
National Center for Environmental Assessment, Cincinnati, OH

DRAFT DOCUMENT PREPARED BY

SRC, Inc.
7502 Round Pond Road
North Syracuse, NY 13212

PRIMARY INTERNAL REVIEWERS

Ambuja Bale, PhD, DABT
National Center for Environmental Assessment, Washington, DC

Dan D. Petersen, PhD, DABT
National Center for Environmental Assessment, Cincinnati, OH

This document was externally peer reviewed under contract to
Eastern Research Group, Inc.
110 Hartwell Avenue
Lexington, MA 02421-3136

Questions regarding the contents of this document may be directed to the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

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COMMONLY USED ABBREVIATIONS

BMC	benchmark concentration
BMCL	benchmark concentration lower bound 95% confidence interval
BMD	benchmark dose
BMDL	benchmark dose lower bound 95% confidence interval
HEC	human equivalent concentration
HED	human equivalent dose
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
$LOAEL_{ADJ}$	LOAEL adjusted to continuous exposure duration
$LOAEL_{HEC}$	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
$NOAEL_{ADJ}$	NOAEL adjusted to continuous exposure duration
$NOAEL_{HEC}$	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
POD	point of departure
p-OSF	provisional oral slope factor
p-RfC	provisional reference concentration (inhalation)
p-RfD	provisional reference dose (oral)
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
UF	uncertainty factor
UF_A	animal-to-human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete-to-complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
WOE	weight of evidence

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR CHLOROMETHANE (CASRN 74-87-3)

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund Program. PPRTVs are derived after a review of the relevant scientific literature using established Agency guidance on human health toxicity value derivations. All PPRTV assessments receive internal review by a standing panel of National Center for Environment Assessment (NCEA) scientists and an independent external peer review by three scientific experts.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

The PPRTV review process provides needed toxicity values in a quick turnaround timeframe while maintaining scientific quality. PPRTV assessments are updated approximately on a 5-year cycle for new data or methodologies that might impact the toxicity values or characterization of potential for adverse human health effects and are revised as appropriate. It is important to utilize the PPRTV database (http://hhpprtv.ornl.gov) to obtain the current information available. When a final Integrated Risk Information System (IRIS) assessment is made publicly available on the Internet (http://www.epa.gov/iris), the respective PPRTVs are removed from the database.

DISCLAIMERS

The PPRTV document provides toxicity values and information about the adverse effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

Other U.S. Environmental Protection Agency (EPA) programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

QUESTIONS REGARDING PPRTVs

Questions regarding the contents and appropriate use of this PPRTV assessment should be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

INTRODUCTION

Chloromethane (also known as methyl chloride) is a colorless gas (ATSDR, 1998) with a faint, sweet smell noticeable only at levels which may be toxic. Chloromethane is produced in industry through reacting methanol and hydrogen chloride or chlorination of methane, but is also formed in oceans by natural processes (e.g., marine phytoplankton) and from biomass burning in grasslands and forest fires; it has been detected at low levels in air all over the world. Other sources of exposure to chloromethane include cigarette smoke, polystyrene insulation, and aerosol propellants; home burning of wood, coal, or certain plastics; and chlorinated swimming pools. Chloromethane is also present in some lakes and streams and has been found at low levels in drinking water.

Industrial uses of chloromethane include manufacturing of silicones, agrichemicals, synthetic rubber, methyl cellulose, tetramethyl lead, use as thermometric and thermostatic fluid in measurement equipment, use as a refrigerant, and use as an anesthetic (U.S. EPA, 2001).

The empirical formula for chloromethane is CH_3Cl (see Figure 1). Table 1 provides a table of physicochemical properties. In this document, "statistically significant" denotes a *p*-value of <0.05.

$CH_3—Cl$

Figure 1. Chloromethane Structure

Table 1. Physicochemical Properties Table (Chloromethane)[a]

Property (unit)	Value
Boiling point (ºC)	−23.7
Melting point (ºC)	−97.6
Density (0°C, 1 atm, air = 1)	1.74
Vapor pressure (mm Hg at 25ºC)	4310
pH (unitless)	Not available
Solubility in water (mg/L at 25ºC)	4800−5325
Vapor density (kg/m^3 at 0°C)	2.22
Molecular weight (g/mol)	50.49
Flash point (°C)	−46
Log octanol/water partition coefficient (unitless)	0.91

[a]Values from the U.S. EPA (2001), ATSDR (1998), and OECD (2003).

EPA's IRIS database (U.S. EPA, 2011) reports a noncancer chronic inhalation reference concentration (RfC) for chloromethane of 0.09 mg/m^3 based on cerebellar lesions in female C57BL/6 mice exposed continuously (22−22.5 hours/day) for 11 days. The IRIS report states that an oral reference dose (RfD) is not applicable because chloromethane exists primarily as a gas and because no adequate oral exposure studies exist from which an oral RfD may be derived. The IRIS data were last revised on July 17, 2001, and a review of more recent toxicological literature conducted in August 2003 did not identify any new critical studies. IRIS has not derived a quantitative estimate of carcinogenic risk from oral or inhalation exposure, and provided a weight-of-evidence descriptor of Group D ("*Not Classifiable as to its Human Carcinogenicity*") (U.S. EPA, 2001).

Chloromethane is not included in the National Toxicology Program's *12th Report on Carcinogens* (NTP, 2011). Also, chloromethane is considered "*Not Classifiable as a Human Carcinogen*" based on inadequate data in humans and/or animals and is, therefore, categorized as A4 by the American Conference of Governmental Industrial Hygienists (ACGIH, 2001) and in Group 3 by the International Agency for Research on Cancer (IARC, 1999). However, the National Institute of Occupational Safety and Health (NIOSH, 2005) considers chloromethane to be a potential occupational carcinogen. CalEPA (2008, 2009a,b) has not derived toxicity values for chloromethane.

The Drinking Water Standards and Health Advisories List (U.S. EPA, 2006) reports an RfD of 0.004 mg/kg-day, a Drinking Water Exposure Limit (DWEL) of 0.1 mg/L, and a life-time health advisory (HA) of 0.03 mg/L for chloromethane. Chloromethane has a time-weighted average threshold limit value (TLV-TWA) of 50 ppm (103 mg/m^3) and a short-term exposure limit (STEL) of 100 ppm for occupational exposures to chloromethane in workplace air (ACGIH, 2001; WHO, 2010). The Occupational Safety and Health Administration (OSHA, 2006) permissible exposure limit (PEL) values are a 100-ppm TWA and a 200-ppm acceptable ceiling concentration, with a 5-minute maximum peak of 300 ppm in any 3-hour period. The ATSDR (2010) reported an acute inhalation Minimal Risk Level (MRL) of 0.5 ppm derived from a NOAEL of 50 ppm for motor coordination and damage to the cerebellar granule cells in a study by Landry et al. (1983, 1985), and an intermediate MRL of 0.2 ppm derived from a LOAEL of 51 ppm for increased liver enzymes in male mice at the 6-month interval in the 2-year study by CIIT (1981), and a chronic MRL of 0.05 ppm derived from a LOAEL of 51 ppm for axonal swelling in male mice in the same study by CIIT (1981). The World Health Organization (WHO, 2010) published the Concise International Assessment Document 28 with a guidance value for indirect inhalation exposure to methyl chloride via the environment for the general population of 0.018 mg/m^3 (0.009 ppm) and a guidance value for occupational inhalation exposure of 1.0 mg/m^3 (0.5 ppm) (WHO, 2000).

Literature searches were conducted for studies from 1900 through May 2011 relevant to the derivation of provisional toxicity values for chloromethane, CAS No. 74-87-3. Searches were conducted using EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: AGRICOLA; American Chemical Society; BioOne; Cochrane Library; DOE: Energy Information Administration, Information Bridge, and Energy Citations Database; EBSCO: Academic Search Complete; GeoRef Preview; GPO: Government Printing Office; Informaworld; IngentaConnect; J-STAGE: Japan Science & Technology; JSTOR: Mathematics & Statistics and Life Sciences; NSCEP/NEPIS (EPA

publications available through the National Service Center for Environmental Publications [NSCEP] and National Environmental Publications Internet Site [NEPIS] database); PubMed: MEDLINE and CANCERLIT databases; SAGE; Science Direct; Scirus; Scitopia; SpringerLink; TOXNET (Toxicology Data Network): ANEUPL, CCRIS, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HEEP, HMTC, HSDB, IRIS, ITER, LactMed, Multi-Database Search, NIOSH, NTIS, PESTAB, PPBIB, RISKLINE, TRI; and TSCATS; Virtual Health Library; Web of Science (searches Current Content database among others); World Health Organization; and Worldwide Science. The following databases outside of HERO were searched for health-related values: ACGIH, ATSDR, CalEPA, EPA IRIS, EPA HEAST, EPA HEEP, EPA OW, EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

Table 2 provides information for all of the potentially relevant studies. Entries for the principal studies are bolded. Because a chronic RfC is available in IRIS, a subchronic p-RfC is developed here. The majority of the information in this PPRTV document is obtained from the *Toxicological Review of Methyl Chloride: in Support of Summary Information on the Integrated Risk Information System*, EPA/635/R01/003 (U.S. EPA, 2001). The studies included in the toxicological review for IRIS are listed in Table 2 but are not described in detail in the following section of this document. The study descriptions are limited only to those details necessary to demonstrate the selection of the principal study for the derivation of a provisional toxicity value. In contrast, the few studies not included in the toxicological review, and those published subsequent to the latest revision in IRIS, are detailed in the appropriate sections. Specifically, summaries of studies by Löf et al. (2000), Jonsson et al. (2001), and Asakura et al. (2008) are detailed in the section on "Other Data (Short-term Tests, Other Examination)," and a study by Kernan et al. (1999) is included in the sections discussing human inhalation toxicity and cancer weight of evidence. Additionally, these studies are summarized in an *Addendum to the Toxicological Profile for Chloromethane* (ATSDR, 2009).

Table 2. Summary of Potentially Relevant Data for Chloromethane (CASRN 74-87-3)[a]

Exposure Conditions or Toxicity Study Type	Species, Number of Male/Female, and Duration of Exposure	Dosimetry[b]	Conclusions and Major Findings	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b]	Reference (Comments)	Notes[c]
Human								
			1. Oral (mg/kg-day)[b]					
Subchronic	None							
Chronic	None							
Developmental	None							
Reproductive	None							
Carcinogenic	None							
			2. Inhalation (mg/m^3)[b]					
Short-term	9/9 workers (sector not specified), occupational epidemiological study 1−7.5 hr/d for 2 d or 7.5 hr/d for 5 d in a wk	0, 2, 9, 13 or 0, 13, 65, 97	No significant neurological or cognitive abnormalities were observed. Two to six times higher blood and breath chloromethane levels	97[d]	Not run	Not observed	Stewart et al. (1980)	U.S. NIOSH Report
	56 humans (39/17) divided in 8 or 12 per group, clinical study, 3 hr	0, 26 (behavioral effects not examined), 52 with or without concurrent ingestion of 10 mg of diazepam	Marginal (p = 0.053) decrease of 4% in performance tasks (visual vigilance and time discrimination)	Not established[e]	Not run	52[d]	Putz-Anderson et al. (1981)	PR

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Short-term	24 workers accidentally exposed to leaking refrigeration unit ranged from 2 to 4 d; mortality and cancer retrospective occupational epidemiological study, 32-yr follow-up	Concentration not measured; groups divided into the deckhands with direct, longer term exposure (15/17 displayed signs of toxicity within 2 d of exposure) compared to 11 other crewman with minimal exposure (officers and those with quarters further from leak)	Excess mortality more prominent among deckhands who had been subjected to higher exposure; risk ratios (RR) elevated for all causes of death (2.5), as well as for cardiovascular diseases (3.9). However, elevated RR for all cancers (1.5) and lung cancer (2.7) had wide confidence intervals, which included unity, and do not appear to be suggestive of an elevated cancer mortality risk	Not applicable	Not run	Not applicable	Rafnsson and Gudmundsson (1997)	PR
Subchronic	6 workers (4 male; 2 unspecified), exposed for at least 2−3 wk prior to the onset of symptoms); occupational case studies, duration not specified	Cases 1 and 2, 8 hr TWA ≤ 148 Cases 3 through 6, 8 hr TWA 130 Calculated from 8 hr/d, 5 d/wk, 2-wk exposure	Central nervous system (CNS) toxicity (confusion, blurry vision, short-term memory deficits, balance instability, hand tremor, slurring of speech, and loss of concentration)	Not established	Not run	130[d]	Dow Chemical Company (1992a)	NPR

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Chronic	114/8 exposed workers and 46/3 not exposed workers, occupational epidemiological study, duration of exposure ranged from 4 mo to 25 yr of employment	Range between 5−48 mg/m^3 with an average of 23 mg/m^3 (via conductivity analyses); 31 mg/m^3 via charcoal tube sampling during week of testing	Changes in performance on cognitive time-sharing tasks and increased magnitude of finger tremor	Not applicable	Not run	Not applicable	Repko et al. (1976) Concentration only measured during week of testing and not for entire potential exposure period (up to 25 yr); therefore precludes meaningful quantitative assessment	NPR NIOSH Report
	2610 white male workers working at Dow Chemical Company between 1956 and 1980; retrospective occupational study, mean of 8.3 yr of employment (range of 1 to 20+ yr). Mean number of years follow-up was 10.5 yr	Concentration not measured	Nonsignificant increases in cancers of brain and CNS; increased mortality due to leukemia and aleukemia (however, there were only 3 cases, and they were not of similar histology) (chronic granulocytic, acute lymphoblastic, and acute aleukemic myeloid), exposure duration (9.8, 1.2, and 2.8 yr), or job title (chemical analyst, chemical engineer, and mechanical engineer)	Not applicable	Not run	Not applicable	Olsen et al. (1989) Exposure to other chemicals (22 were listed) at Dow Chemical Company during this time frame confounded interpretation	PR

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Chronic	Follow-up case control study of respiratory cancers at one of Dow Corning Corporation's silicone production plants, an area specific for chloromethane exposure; no further information (e.g., sample size or study design) was provided in toxicology review (U.S. EPA, 2001)	Concentration not measured	No association between exposure and respiratory cancer risk was found	Not applicable	Not run	Not applicable	Dow Chemical Company (1992b). High prevalence of smoking noted as a confounding factor	NPR
	Retrospective occupational epidemiological study of 852 males employed in a synthetic rubber manufacturing plant from at least 1 mo to 35 yr during 1943−1978	Exposure levels (high, medium, low) based on process description, list of job titles and associated locations, duties, and activities associated with job titles, and information from workers and personal experience. No additional information was reported	No excess mortality from any specific cause of death found in the study population after analysis by level and duration of exposure; some groups actually showed lower incidences of cancer due to "healthy worker" effect	Not applicable	Not run	Not applicable	Holmes et al. (1986)	PR

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Chronic	Population-based case-control study on 63,097 persons who died from pancreatic cancers from 1984−1993 compared to 252,386 individuals who died from causes other than cancer during the same time period	Concentration was not measured. A job-exposure matrix (JEM) was developed for each individual solvent, and the risk for each was estimated by levels of probability of exposure (low, medium, and high vs never exposed to the solvent)	No association of pancreatic cancers with exposure to chloromethane	Not applicable	Not run	Not applicable	Kernan et al. (1999)	PR
Developmental	Mother exposed during pregnancy to chloromethane and ammonia	Concentration not measured	Single case of an infant born with sacral agenesis	Not applicable	Not run	Not applicable	John et al. (1984) citing Kucera (1968). Confounded by exposure to ammonia	PR
	5 pregnant females exposed to chloromethane and other industrial chemicals	Concentration not measured	Association of sacral agenesis in five infants born to mothers having close contact during pregnancy to "trichloroethylene and chloromethane, among other industrial chemicals…"	Not applicable	Not run	Not applicable	Schardein (1993) citing Kucera (1968) Confounded by exposure to other chemicals	PR
Reproductive	Former workers (female, number not specified) in a New Mexico microelectronics assembly plant; 90 worker-referent pairs	Concentration not measured	Increased risk of spontaneous abortion in former workers	Not applicable	Not run	Not applicable	Huel et al. (1990) Confounded by exposure to other chemicals	PR

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Exposure Conditions or Toxicity Study Type	**Species, Number of Male/Female, and Duration of Exposure**	**Dosimetry[b]**	**Conclusions and Major Findings**	**NOAEL[b]**	**BMDL/ BMCL[b]**	**LOAEL[b]**	**Reference (Comments)**	**Notes[c]**
Animal								
			1. Oral (mg/kg-day)[b]					
Subchronic	Rabbit (sex and strain not specified) 2 (one per dose group); dosed via gavage in olive oil with 60 doses over 83−85 d	28, 71 mg/kg-d	Spleen enlarged and dark-colored, microscopically displayed moderate congestion, phagocytosis, and slight hemosiderosis. No other effects were reported	28[d]	Not run	71[d]	Dow Chemical Company (1982) Too few animals for meaningful interpretation; no control group	NPR
Chronic	None							
Developmental	None							
Reproductive	None							
Carcinogenic	None							
			2. Inhalation (mg/m^3)[b]					
Short-term	**C57BL/6 mouse 0/12, whole body continuous (22−22.5 hr/d) exposure for 11 d**	**0, 28.4, 94.6, 189.3, 283.9, 378.6, or 757.2**	**Degenerative changes in granule cells of the cerebellum Decreased glycogen content in liver**	**94.6**	**Not run**	**189.3**	**Landry et al. (1983, 1985)**	**PS IRIS**
	0/12, whole body intermittent (5.5 hr/d) exposure for 11 d	0, 71.0, 189.3, 378.6, 757.2, or 1135.8	Cerebellar incidence of granule-cell pyknosis and karyorrhexis	189.3	Not run	378.6		

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Short-term	20/20 Sprague-Dawley rats, continuous exposure for 72 hr (3 d) with a follow-up period of 12 d. Another 20/20, continuous exposure for 48 hr (2 d) with a follow-up period of 12 d	0, 413, 1033, 2065, or 4130	Liver effects at 72 hr (decreased weight, altered tinctorial appearance, and increased amount of fat) Testicular effects at 72 hr (atrophy and epididymis degeneration, inflammation, sperm granuloma formation, scarring, and obstructive changes)	Not established 413	Not run	413 1033	Dow Chemical Company (1981)	NPR
	Beagle dog and cat (strain not specified) 3/0 each species 23.5 hr/d, for 3 d with a follow-up period of 26 d	0, 404, 1011	Clinical signs of neurotoxicity and histopathological lesions in the brain and spinal cord in dogs and cats	404	Not run	1011	McKenna et al. (1981a)	NPR
	10/10 F344 rat, 6 hr/d, for 5 d, and for another 4 d after a 2-d break	0, 845, 1478, and 2112	Renal, hepatic, and testicular-related degeneration Cerebellar degeneration	Not established 1478	Not run	845 2112	Morgan et al. (1982)	PR
	Mouse (three strains: C3H, C57BL/6, B6C3F$_1$) 5/5 6 hr/d, for 12 consecutive d	0, 258, 516, or 1033	Hepatocellular degeneration Cerebellar degeneration	Not established 258	Not run	258 516		
	C57BL/6 mouse 0/10 6 hr/d, 5 d/wk, for 2 wk	0, 553	Cerebellar lesions, including degeneration, coagulative necrosis, nuclear condensation, focal malacia, karyorrhexis, and edema	Not established	Not run	553[d]	Jiang et al. (1985)	PR

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Subchronic	CD-1 mouse 10/10 6 hr/d, 5 d/wk, during a 93−95 d period (a total of 64−66 exposures)	0, 18, 54, or 144	No unequivocal toxic effects observed. Decreased performance on wire-maneuver test at 54 mg/m^3 for Days 40−66 and at 144 mg/m^3 for Days 16−39 and 40−66. However, this was not corroborated by other neurological deficits; authors attributed effects to general muscle weakness and confounding due to increasing body weight with time	144	Not run	Not observed	McKenna et al. (1981b)	NPR
	Sprague-Dawley rat 10/10 6 hr/d, 5 d/wk, during a 93−95 d period (a total of 64−66 exposures	0, 18, 54, or 144	None observed	144	Not run	Not observed		
	Beagle dogs 4/0 6 hr/d, 5 d/wk, during a 93−95 d period (a total of 64−66 exposures)	0, 18, 54, or 144	None observed	144	Not run	Not observed		
	$B6C3F_1$ mouse 10/10 6 hr/d, 5 d/wk, for 13 wk	0, 138, 277, or 553	Increased relative liver weights	138	Not run	277	Mitchell et al. (1979a)	NPR
	F344 rat 10/10 6 hr/d, 5 d/wk, for 13 wk	0, 138, 277, or 553	Decreased body weights, vacuolar changes in hepatocytes	138	Not run	277		

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Chronic	$B6C3F_1$ mouse 120/120 6 hr/d, 5 d/wk, for 2 yr	0, 18, 83, or 368	Mortality; clinical signs of neurotoxicity (hunched posture, tremor, and paralysis); liver toxicity (hepatocellular vacuolization, karyomegaly, cytomegaly, and degeneration and increased ALT); kidney effects in males (renal tubuloepithelial hyperplasia, hypertrophy, and/or karyomegaly); cerebellar (degeneration and atrophy of the granular layer); seminiferous tubule atrophy and degeneration; splenic atrophy; and lymphoid depletion	83	Not run	368 Frank effect level (FEL) due to high treatment-related mortality	CIIT (1981), final report Mitchell et al. (1979b), interim report	NPR
Carcinogenicity			368-mg/m^3 males had renal benign and malignant tumors and renal cortical tubuloepithelial hyperplasia and karyomegaly At 83 mg/m^3, two renal adenomas in males, equivocal as to treatment-related status	83	Not run	368 FEL due to high treatment-related mortality		NPR
Chronic/ Carcinogenicity	F344 rat 120/120 6 hr/d, 5 d/wk, for 2 yr	0, 18, 83, or 368	Decreased overall body-weight gain; effects in testes (degeneration and atrophy of the seminiferous tubules, interstitial hyperplasia, sperm granulomas)	83	Not run	368	CIIT (1981), final report Mitchell et al. (1979b), interim report	NPR

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Developmental	F344 rat 0/25 6 hr/d, Gestation Day (GDs) 7−19	0, 52, 258, or 774	Decreased maternal and fetal body weights and delayed ossification	258	Not run	774	Wolkowski-Tyl et al. (1983a)	PR
	$B6C3F_1$ mouse 0/33 6 hrs/day from GDs 6−17	0, 52, 258, or 774	Heart malformations in fetuses Frank effect level at 774, early termination due to moribundity; necrosis in cerebellum	52	Not run	258		
	C57BL/6 mouse 0/74−77 females/exposure 6 hr/d from GDs 6−17	0, 129, 258, or 387	Developmental: heart malformations in fetuses Maternal: mortality, ataxia, convulsions, tremors, hypersensitivity to sound or touch, decreased body weights	Developmental: 129 Maternal: 258	Not run	Developmental: 258 Maternal: 387	Wolkowski-Tyl et al. (1983b)	PR
Reproductive two-generation reproduction	F344 rat 40/80 6 hr/d, 5 d/wk, for 10-wk premating, 6 hr/d, 7 d/wk for 2-wk mating period, and throughout gestation and lactation (except from GD 18 to Postnatal Day 4)	0, 59, 186, or 589	Decreased male fertility at 186 mg/m^3 Degeneration and atrophy of seminiferous tubules, epididymal granulomas, and decreased testes size	59 186	Not run	186 589	Hamm et al. (1985)	PR

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Reproductive	Rat (strain not specified) 40/0 6 hr/d, for 5 consecutive d, not exposed for 3 d, and exposed again for 4 d. Six or eight treated and two control animals were euthanized on Days 5, 7, 9, 11, 13, 15, 19, and 70 after starting exposures	0 or 1359	Bilateral epididymal granulomas	Not established	Not run	1359[d]	Chapin et al. (1984)	PR
	F344 rat 40/0 6 hr/d, for 5 consecutive d, then bred weekly for 8 wk with untreated females	0, 516, or 1549	Increased pre- and postimplantation loss	516	Not run	1549	Working et al. (1985a)	PR
	F344 rat 40/0 6 hr/d, for 5 consecutive d, then bred weekly for 4 wk with untreated females	0, 516, or 1549	Increased unilateral and bilateral sperm granulomas in epididymides; decreased testes weights; sperm cytotoxicity (delayed spermiation, chromatin margination in round spermatids, epithelial vacuolation, luminal exfoliation of spermatogenic cells, and multinucleated giant cells); decreased sperm motility, and increased incidence of sperm abnormalities	516	Not run	1549	Working et al. (1985b)	PR

Table 2. Summary of Potentially Relevant Data for Chloromethane (CASRN 74-87-3)[a]

Exposure Conditions or Toxicity Study Type	Species, Number of Male/Female, and Duration of Exposure	Dosimetry[b]	Conclusions and Major Findings	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b]	Reference (Comments)	Notes[c]
Reproductive	F344 rat 30/0, 10/0, and 20/0 per 0, 516, and 1549 mg/m^3, respectively, 6 hr/d, for 5 consecutive d, then bred weekly for 8 wk with untreated females. Females euthanized 12 hr postmating, and embryos and ova were scored as unfertilized or fertilized	0, 516, or 1549	Distinguished that increased preimplantation loss due to failure of fertilization (cytotoxicity) and not embryonic death due to genotoxicity	516	Not run	1549	Working and Bus (1986)	PR
	F344 rat 20/0 (controls), 40/0 (treated), 6 hr/d, for 5 consecutive d with or without cotreatment with anti-inflammatory agent (BW 755C)[f], a Burroughs Wellcome experimental compound, then bred weekly for 3 wk with untreated females	0 or 1549 with or without i.p. injection of BW 755C	Increased postimplantation loss in treated group; however, cotreatment with anti-inflammatory agent (BW 755C) prevented effects. Concluded that the cytotoxicity in epididymis was prevented by blocking inflammatory response	Not established	Not run	1549	Chellman et al. (1986a)	PR
	F344 rat 12/0 (chloromethane without BW 755C); 6 males (chloromethane with cotreatment with BW 755C) for 6 hr/d, for 2 d	0 or 3872	Mortality and epididymal granulomas; however, cotreatment with anti-inflammatory agent (BW 755C) prevented effects	Not established	Not run	3872[d]	Chellman et al. (1986b)	PR

Table 2. Summary of Potentially Relevant Data for Chloromethane (CASRN 74-87-3)[a]

Exposure Conditions or Toxicity Study Type	Species, Number of Male/Female, and Duration of Exposure	Dosimetry[b]	Conclusions and Major Findings	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b]	Reference (Comments)	Notes[c]
Reproductive	F344 rat 5/0 at 2581 mg/m^3, for 6 hr/d, for 5 d, with or without cotreatment with BW 755C	0 or 2581	Degenerative changes in testes and epididymides (including formation of epididymal sperm granulomas), necrosis of the inner granular layer of the cerebellum, hepatocellular cloudy swelling, degeneration of renal proximal convoluted tubules, vacuolar degeneration in the adrenal cortex Except for adrenal tissue, the above listed tissues showed virtually no evidence of lesions in animals cotreated with BW 755C	Not established	Not run	2581[d]	Chellman et al. (1986b)	PR

Table 2. Summary of Potentially Relevant Data for Chloromethane (CASRN 74-87-3)[a]

Exposure Conditions or Toxicity Study Type	Species, Number of Male/Female, and Duration of Exposure	Dosimetry[b]	Conclusions and Major Findings	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b]	Reference (Comments)	Notes[c]
Reproductive	F344 rat 18/0 per concentration, 6 hr/d, for 5 consecutive d with or without cotreatment with BW 755C 12 hr pre- and postexposure (6 euthanized weekly for 3 wk)	0 or 1549	Decreased relative testes weights, testicular histopathology, and decreased sperm production; these effects were not prevented by BW 755C Sperm transit times and epididymal sperm depletion indicated that effects on preimplantation loss noted in previous studies were likely due to cytotoxic effects on sperm in the testes at the time of exposure	Not established	Not run	1549[d]	Chellman et al. (1987)	PR

[a]With the exception of Kernan et al. (1999), all of the studies listed in Table 2 are included in the *Toxicological Review of Methyl Chloride: in Support of Summary Information on the Integrated Risk Information System* (U.S. EPA, 2001).

[b]Dosimetry: NOAEL, BMDL/BMCL, and LOAEL values are converted to an adjusted daily dose (ADD in mg/kg-d) for oral noncancer effects and a human equivalent concentration (HEC in mg/m^3) for inhalation noncancer effects. Values are converted to a human equivalent dose (HED in mg/kg-d) for oral carcinogenic effects and a HEC for inhalation carcinogenic effects. All long-term exposure values (4 wk and longer) are converted from a discontinuous to a continuous (weekly) exposure. Values from animal developmental studies are not adjusted to a continuous exposure.

[c]IRIS = Utilized by IRIS, date of last update July 17, 2001; PS = principal study, NPR = not peer-reviewed, PR = peer-reviewed.

[d]Not reported by the study author but determined from data.

[e]The study subjects in the 26-mg/m^3 group were not subjected to behavioral tests; therefore, a NOAEL is not established in this study.

[f]BW755C = cyclooxygenase/lipoxygenase inhibitor 3-amino-1-[*m*-(trifluoromethyl)phenyl]-2-pyrazoline.

HUMAN STUDIES

Oral Exposure

No studies on the effects of oral exposure of humans to chloromethane were identified.

Inhalation Exposure

Chloromethane acts principally as a depressant of the central nervous system (CNS). Exposure situations typically have been related to accidental overexposure resulting from leaking refrigerators or refrigeration systems. Signs and symptoms typically appear within 2−3 hours of exposure and include headache, nausea, vomiting, painful neck, loss of appetite, diarrhea, dizziness, giddiness, blurred vision, ataxia, confusion, slurred speech, diplopia (double vision), tremors of the hands and lips, drooping eyelids and eye twitch, muscle spasms, convulsions and opisthotonus (body spasms), cold and clammy skin, loss of memory, hallucinations, respiratory depression, unconsciousness, coma, and death (U.S. EPA, 2001). Effects of longer-term, low-level exposure are thought to be generally, although not always, mild and reversible after a recovery period of days to months, and include fatigue or malaise, loss of appetite, headache, disequilibrium, blurred vision, confusion, anxiety, personality changes, short-term memory loss, vertigo, loss of coordination, weakness, pale skin, nausea, and vomiting. Evidence suggests that in persons exposed to doses of chloromethane sufficient to cause serious CNS effects, other organ systems including the heart, gastrointestinal tract, liver, kidneys, and lungs can be adversely affected, although the cardiovascular and gastrointestinal effects may largely be secondary to CNS toxicity (U.S. EPA, 2001).

The literature contains a number of other, mostly older, case reports and human studies that have been previously summarized (U.S. EPA, 2001). They provide descriptions of the CNS, cardiovascular, hepatic, and renal effects that can be caused in humans by exposure to chloromethane. Most exposures appear to have been acute and of unknown duration; chloromethane concentrations may have generally been known to be high or low but rarely were quantified. Although some effects were noticeable within hours or a day or two of exposure and resolved within days or several months of the cessation of exposure, in some cases, the effects appeared to persist for years, and rarely, for the lifetime of the individual.

An epidemiological study by Kernan et al. (1999)—not included in the IRIS toxicological review (U.S. EPA, 2001)—is summarized below. An extensive population-based case-control study to determine which industries may be related to an increased risk of pancreatic cancers was conducted. Death certificates of 63,097 persons who had died from pancreatic cancer in 24 U.S. states from 1984−1993 were obtained, and the occupations of these persons were determined. The control group was composed of 252,386 persons who died from causes other than cancer during the same time period. The National Cancer Institute, National Institute for Occupational Safety and Health, and the National Center for Health Statistics supported the coding of occupation and industry on death certificates from the 24 participating states. The coding of the occupation and industry on death certificates was performed according to the classification system designed for the 1980 U.S. census. Overall, 509 occupation codes and 231 industry codes were screened in these data. The International Classification of Disease (ICD, 9th Rev.) was used to code the underlying cause of death. To evaluate the effects of exposure to specific solvents, a job-exposure matrix (JEM) was applied. Industrial hygienists developed JEMs for formaldehyde and 11 chlorinated hydrocarbons, including chloromethane. Concentrations were not measured; however, the risk for each solvent was estimated by levels of

probability of exposure (low, medium, and high vs. never exposed to the solvent). Odds ratios (ORs), reported for each exposure intensity according to race and gender, ranged from 0.7−1.1, indicating no association of pancreatic cancer with exposure to chloromethane.

ANIMAL STUDIES

Oral Exposure

Subchronic-duration Studies

No subchronic-duration oral studies on chloromethane have been located, with the exception of a single gavage study using only two rabbits (one/dose group) and no control group (Dow Chemical Company, 1982). The Dow Chemical Company (1982) dosed two rabbits (sex and strain not specified) with cold olive oil solution by means of a stomach tube each work day until 60 doses. One animal received 60 doses of chloromethane (purity not specified) at 40 mg/kg in 85 days and showed no signs of toxic effects. Another rabbit received 60 doses at 100 mg/kg in 85 days. This animal showed a very slight pathology of the spleen as evidenced by congestion, phagocytosis, and hemosiderosis. The authors reported that it was not practical to feed larger doses because the volume of oil would become too large, and the rapid escape of the gas from the oil in the stomach would cause considerable blasting. Although effects were observed in the spleen, the deficiencies of the study design, sample size, and data reporting do not allow to draw conclusions regarding subchronic oral toxicity of chloromethane in rabbits.

Chronic-duration Studies

No chronic oral studies were identified.

Developmental and Reproduction Studies

No developmental or reproductive toxicity studies via oral exposure were identified.

Inhalation Exposure

Short-term Studies

Landry et al. (1983, 1985), Dow Chemical Company (1981), McKenna et al. (1981a), Morgan et al. (1982), and Jiang et al. (1985) conducted short-term inhalation toxicity studies of chloromethane in the mouse, rat, dog, and cat using exposure durations ranging from 48 hours to 12 days. A brief summary of each of these short-term inhalation studies, followed by the subchronic-duration inhalation studies, is included below in order to demonstrate the reasoning leading to the selection of the principal study for deriving the subchronic p-RfC. Further details of these studies are available in the *Toxicological Review of Methyl Chloride: in Support of Summary Information on the Integrated Risk Information System* (U.S. EPA, 2001).

The study by Landry et al. (1983, 1985) is selected as the principal study for deriving the subchronic p-RfC because it provides the most sensitive endpoint (lowest POD) compared with each of the other relevant short-term- and subchronic-duration studies. Landry et al. (1983, 1985) exposed female C57BL/6 mice (12/group; about 10 weeks old at time of exposure) "continuously" (22−22.5 hours/day) to 0, 15, 50, 100, 150, 200, or 400 ppm (0, 28.4, 94.6, 189.3, 283.9, 378.6, or 757.2 mg/m^3), or "intermittently" (5.5 hours/day) to 0, 150, 400, 800, 1600, or 2400 ppm (0, 71.0, 189.3, 378.6, 757.2, or 1135.8 mg/m^3) of chloromethane (purity = 99.5%) for whole body during 11 days. Exposures were interrupted once in the morning and once in the afternoon in order to move intermittently exposed mice in and out of the exposure chambers, observe all animals, and train or test animals.

Neurofunctional testing was conducted during the course of the study, which consisted of monitoring mice (previously trained for 2 weeks on the apparatus) for their abilities to stay on an accelerating rod (acceleration = 1 rpm/second, from 10 rpm up to 70 rpm) 2−2.5 hours postexposure after 4, 8, and 11 days of exposure. Upon termination, the nonfasted mice were subjected to gross and histopathological examination (i.e., brain, thymus, liver, and kidneys). Body and organ weights were obtained, as were samples of most major organs and tissues (including spinal cord). Tissue samples from the cerebella of three preselected mice from each of the 0- and 150-ppm continuously exposed groups were examined by electron microscopy after 1, 2, 4, 6, 8, or 10.5 days of exposure.

In the continuous exposure groups (Landry et al., 1983, 1985), no exposure-related mortality was observed at the lower concentrations (15 and 50 ppm), whereas exposure to 200 or 400 ppm was lethal after 5 or 4 days, respectively. Death was preceded by loss of appetite and ataxia with frequent falling. Mice exposed to 150 to 400 ppm developed poor motor coordination and deteriorated to a moribund condition with accompanying inanition (the exhausted condition that results from lack of food and water) (i.e., marked weakness) at a rate that was dose dependent. Mice in the 200-ppm group were sacrificed on Day 5 because one mouse died prior to scheduled necropsy, and most of those remaining were moribund. Mean body weights were significantly ($p \leq 0.05$) decreased by 12−34% at 150 and 200 ppm and slightly decreased by 4−7% at 100 ppm but were not affected at ≤50 ppm (see Table B.1). Body weights were not obtained for the 400-ppm mice. No significant decrements in rotating-rod test performance were noted for the control and 15- to 100-ppm groups; however, at 150 ppm, rotating-rod test performance was decreased ($p \leq 0.05$) by 59% on Day 4 and by 74% on Day 8, with animals moribund or dead by Day 11 (see Table B.2). All mice at 200 ppm, the majority of which were moribund, scored zero in this test.

No organ-weight data were reported for the 200- and 400-ppm groups (Landry et al., 1983, 1985). Mean relative (but not absolute) kidney weights were increased by 9% at 150 ppm compared to controls (no increase at Day 8) but not at 50 and 15 ppm (see Table B.3). Kidney-weight data were not obtained for the 100-ppm group. Absolute liver weights at 150 ppm were decreased by 13% ($p \leq 0.05$) compared to controls. Absolute and relative thymus weights were significantly ($p \leq 0.05$) decreased by 21−23% at 50 and 15 ppm, respectively, and by 69−71% at 150 ppm. However, the decreased thymus weights at 15 and 50 ppm were considered unrelated to treatment because they lacked corroborating histopathology data, and the values fell within the range of other control groups in this study (i.e., the control group run concurrently with the 100-ppm group). The decrease at 150 ppm was considered exposure related, with the only histopathological finding being thymic involution (7 out of 12 minimal and 5 out of 12 marked), reflecting decreased body weights and stress.

Gross pathology observations included significant inanition in the 200- and 400-ppm mice prior to death or sacrifice, and in some 150-ppm mice after ≥4 days of exposure. No treatment-related gross pathology was observed at 15, 50, or 100 ppm. Exposure to 100 ppm and above resulted in concentration- and duration-dependent degenerative changes to the cerebellum, principally in the granule cells, which were characterized by nuclear pyknosis and karyorrhexis, the latter referring to the rupture of the cell nucleus in which chromatin disintegrates (see Table B.4). These effects were observed most frequently in the dorso-medial cerebellar folia. Lesions were more severe at 200 and 400 ppm. Transient intra- and extracellular vacuolation in

the Purkinje and/or molecular cell layer, and in the white matter, was also noted. Electron microscope observations were consistent with those obtained through light microscopy. Duration-dependency of cerebellar lesions was examined by serial necropsy of 150-ppm animals on Days 1, 2, 4, 6, 8, and 11 (see Table B.5). At 150 ppm, there was a marked loss of granule cells, a decrease in Purkinje cells, and an increase in macrophages. Decreased glycogen content at 100−400 ppm was the principal significant change observed in the liver, although focal periportal hepatocellular degeneration and/or necrosis was also noted at 400 ppm (see Table B.4). No statistical test was performed with the data in Tables B.4 and B.5. No exposure-related histopathological effects were observed at 15 or 50 ppm.

In the intermittent exposure groups, (Landry et al., 1983, 1985), transient (i.e., at 0.5 hours, but not 3 hours, postexposure) sedation was observed in 1600- and 2400-ppm groups at 4−7 days of exposure but not after 8 days. Inanition was apparent in the 2400-ppm group (also slow movement and roughened haircoats), as was thin, watery blood from the heart, a finding supported by low hematocrit values. The spleens of this group were considerably enlarged. This was suggestive of extramedullary hematopoiesis, which was microscopically confirmed. The in-life observation of red urine at 2400 ppm was determined to result from hemoglobinuria consistent with intravascular hemolysis (hemoglobinemia) rather than from hematuria. These animals deteriorated (e.g., hind limb extensor rigidity) and were euthanized in moribund condition on Days 8−9. Decreased ingesta was noted at 1600 ppm. Severe clinical signs of toxicity were observed at 1600 ppm, including slightly rigid hind limbs, some tendency toward rearing on hind legs (2 out of 12), and greater excitability compared to controls; these effects tended to mitigate during overnight periods of nonexposure. Mean body weights were significantly ($p \leq 0.05$) decreased by 8−16% at 2400 ppm but were not affected at lower concentrations (see Table B.1). Compared to controls, rotating-rod test performance was significantly decreased by 15% at 800 and 1600 ppm on Day 4, by 36% at 2400 ppm on Day 4, and by 84% at 2400 ppm on Day 8 (see Table B.2). No significant decreases in rotating-rod test performance were noted after intermittent exposure to 150- or 400-ppm chloromethane.

Relative (but not absolute) kidney weights were increased by 19% (not significant) in the 2400-ppm group compared to controls but were not increased at 150 ppm (see Table B.3). Kidney-weight data were not obtained for the 400-, 800-, or 1600-ppm groups. Microscopically, evidence of kidney toxicity was found only at 2400 ppm, and consisted of slight multifocal tubular degeneration and regeneration and eosinophilic-staining tubular casts. Absolute and relative liver weights at 1600 ppm were significantly ($p \leq 0.05$) increased by 23% over the control group. Decreased hepatocyte size, without degeneration or necrosis, was variable in mice from the 400- through 2400-ppm groups (see Table B.6). Decreases in mean absolute and relative thymus weights were statistically significant and considered treatment related (reflecting decreased body weights and stress) at 1600 (39−40% decrease) and 2400 (87−89% decrease) ppm (see Table B.3.), with a decrease in the size of the thymus noted at 1600 ppm. No treatment-related macroscopic findings were noted at 400 or 800 ppm. A concentration-related increase in the incidence of pyknosis and karyorrhexis (slight) of the granule cells was observed at 400 ppm and above (see Table B.6).

Based upon cerebellar damage, the 11-day study (Landry et al., 1983, 1985) identifies a NOAEL of 50 ppm and a LOAEL of 100 ppm (equivalent to $NOAEL_{HEC}$ of 94.6 mg/m^3 and $LOAEL_{HEC}$ of 189.3 mg/m^3) for continuous exposure. For intermittent exposure, the NOAEL

and LOAEL are 150 and 400 ppm (equivalent to $NOAEL_{HEC}$ of 189.3 and $LOAEL_{HEC}$ of 378.6 mg/m^3), respectively. There was no evidence of damage to spinal or peripheral nerves in either exposure regimen. The authors noted that these NOAELs were nearly proportionate to the product of concentration and exposure duration, although the dose-response curve for continuous exposure was much steeper than that for intermittent exposure. It was also noted that cerebellar lesions were observed in 150-ppm mice exposed continuously, and these animals also demonstrated impaired rotating-rod test performance, suggesting a causal relationship. There was no effect of continuous exposure on rotating-rod test performance at 100 ppm, although all animals in this group had slight pyknosis and karyorrhexis in the cerebellum.

In a short-term inhalation study reported by Dow Chemical Company (1981), Sprague-Dawley rats (20/sex/concentration) were exposed to 0, 200, 500, 1000, or 2000 ppm (0, 413, 1033, 2065, or 4130 mg/m^3) of chloromethane (purity = 99.5%) for 48 hours, and another group of 20/sex/concentration were exposed to the same concentrations for 72 hours. Half of the rats in each group were euthanized at the end of the exposure period, and the remaining animals were sacrificed after a 12-day recovery period. Histopathology was performed on five rats/sex/concentration. The LOAEL is 200 ppm (413 mg/m^3), based on decreased body weight in both male and female rats and minimal liver effects in male rats exposed for 72 hours (see Tables B.7 and B.8). A NOAEL was not established. At ≥500 ppm, epididymal lesions were noted that progressed to sperm granulomas. At 1000 and 2000 ppm (HEC equivalent to 1033 and 3065 mg/m^3), kidney toxicity predominated, characterized by tubular necrosis and degeneration, resulting in renal failure.

In another Dow Chemical Company study (McKenna et al., 1981a), three groups of three male beagle dogs and three male cats (strain not specified) were exposed for approximately 23.5 hours/day, for 3 days (i.e., 72-hour treatment regimen) to chloromethane (purity = 99.5%) concentrations of 0, 200, or 500 ppm (0, 404, or 1011 mg/m^3) with a follow-up period of 26 days. The findings of this study indicate a NOAEL of 200 ppm (404 mg/m^3) and a LOAEL of 500 ppm (1011 mg/m^3) based upon a spectrum of neurotoxic findings noted in all three male dogs exposed to 500 ppm, evident as clinical signs of neurotoxicity (tremors, increased salivation, limb stiffness, incoordination, loss of balance, weakness, ataxia, and inability to stand) and microscopic lesions in the spinal cord and brain (vacuolization, swelling and loss of axons, demyelination and presence of gitter cells).

The histopathology of subacute chloromethane (purity = 99.95%) exposure in one strain of rat (F344) and three strains of mice (C3H, C57BL/6, B6C3F$_1$) was investigated by Morgan et al. (1982). Groups of rats (10/sex/concentration) were exposed 6 hours/day to 0, 2000, 3500, or 5000 ppm (0, 845, 1478, and 2112 mg/m^3) for 5 days, then for another 4 days after a 2-day break (i.e., on Days 1−5 and 8−11). Histopathology was conducted on five rats/sex/concentration. Groups of mice (five/sex/strain/concentration) were exposed 6 hours/day to 0, 500, 1000, or 2000 ppm (0, 258, 516, or 1033 mg/m^3) for 12 consecutive days. No tabular data were presented for the control groups. For Selected histopathology F344 rats following 5-days and another 4 days after a 2-days break to chloromethane via inhalation during a 12-days periods, the LOAEL in rats is 2000 ppm (845 mg/m^3), the lowest dose tested, based upon renal, hepatic, and testicular toxicity, whereas the LOAEL for neurotoxicity is 5000 ppm (2112 mg/m^3) (see Table B.9). In mice, the LOAEL for hepatotoxicity is 500 ppm (258 mg/m^3), the lowest concentration tested (see Table B.10). However, the dose response was not clearly apparent in

all the mouse strains/sexes. Cerebellar degeneration, which was most demonstrable in the female C57BL/6 mouse, supports a LOAEL of 1000 ppm (516 mg/m^3), with a NOAEL of 500 ppm (258 mg/m^3). This LOAEL is slightly higher than that for the intermittently exposed female C57BL/6 mice in the study by Landry et al. (1983, 1985), in which the LOAEL is 378.6 mg/m^3 (see Table B.6).

Jiang et al. (1985) conducted an ultrastructural study of lesions induced in the cerebella of C57BL/6 mice (10 females/concentration) exposed 6 hours/day, 5 days/week, for 2 weeks to 0- or 1500-ppm (0 or 553 mg/m^3) chloromethane (purity = 99.9%). Under light microscopy, two types of lesions were found in inner granular layer cells of the cerebellum: (1) a coagulative necrosis (also seen in controls, but in milder form and in substantially fewer cells) involving nuclear and cytoplasmic condensation; and (2) a focal malacia involving edema in groups or extensive areas of cells, with nuclear condensation, karyorrhexis, necrosis, separation of myelinated axons, and microvacuolation. Electron microscopy confirmed the type-one lesion, showing pyknotic nuclei without cytoplasmic edema, but with variable disruption of organelles. Areas of malacia exhibited characteristics, ranging from perikarya edema of granule cells to near-complete destruction of all tissue components, with the exception of blood vessels (nuclear pyknosis and condensation, karyorrhexis, organelle remnants). No incidence data were provided. Few abnormalities were observed in the kidneys of treated females (slight degeneration of proximal tubules with some proteinaceous material in tubular lumina was seen in only two animals), leading the study authors to conclude that the reported brain lesions were probably not a secondary effect of renal toxicity (these types of brain lesions had been associated with renal insufficiency in humans).

Subchronic-duration Studies

In a 90-day inhalation study for Dow Chemical Company, McKenna et al. (1981b) exposed groups of CD-1 mice (10/sex/concentration), Sprague-Dawley rats (10/sex/concentration), and male beagle dogs (4/concentration) for 6 hours/day, 5 days/week, during a 93−95 day period (a total of 64−66 exposures) to chloromethane (purity = 99.9%) at 0, 50, 150, or 400 ppm (0, 18, 54, or 144 mg/m^3). Only the results of the statistical analyses (i.e., significance) were reported in the data tables for sensory and motor function testing in the study report; no other quantitative data are available for review. Performance on the wire maneuver test in female rats at 400 ppm was significantly decreased ($p \leq 0.05$) compared to controls during the second (Days 16−39) and third (Days 40−66) testing intervals. Additionally, during the final one-third of the study (Days 40−66), performance on the wire maneuver test was decreased ($p \leq 0.05$) in the 150-ppm female rats compared to controls. However, because this finding was not associated with any discernible neuromuscular incoordination or other deficit, it was interpreted to be due to general muscular weakness. Additionally, the authors reported a general decline in performance of this test over time in all groups and postulated that this observation may be due to increasing body weight. The authors considered the toxicological significance of this finding to be suspect. The identification of an unequivocal NOAEL/LOAEL for neurotoxicity from this study is questionable. In the rats, equivocal findings of decreased urine specific gravity in the 400-ppm males were not corroborated by other findings of nephrotoxicity (see Table B.11). Subtle reversible changes (e.g., altered tinctorial properties) were noted in the appearance of some hepatocytes from the livers of 5 out of 10 male mice at 400 ppm. However, similar changes were also observed in some control mice and in 1 out of 7 male mice at 150 ppm. No summary data tables for histopathology were available; only individual pathology

data were included in the original study report. In conclusion, this study did not reveal any unequivocal evidence of toxicity related to chloromethane exposure in mice, rats, or dogs, and a NOAEL of 400 ppm (144 mg/m^3) for intermittent subchronic exposure is indicated.

A 90-day inhalation study was also conducted by Battelle for the CIIT in F344 rats and B6C3F$_1$ mice (U.S. EPA, 2001 citing Mitchell et al., 1979a). This study was conducted to select exposure levels for the 2-year chronic-duration study (detailed subsequently). Animals (10/sex/species/concentration) were exposed for 6 hours/day, 5 days/week, for 13 weeks to chloromethane (purity = 99%) at concentrations of 0, 375, 750, or 1500 ppm (0, 138, 277, or 553 mg/m^3). Decreased body weight in rats and increased relative liver weight in mice at 750 and 1500 ppm, as well as hepatic histology (cytoplasmic vacuolar change and hepatic infarction) in mice and rats at 1500 ppm, were considered likely or potentially related to chloromethane exposure, indicating a LOAEL of 750 ppm (277 mg/m^3) and a NOAEL of 375 ppm (138 mg/m^3) (U.S. EPA, 2001). No histopathological effects in the brain in either the mouse or rat were observed.

Chronic-duration Studies

Battelle conducted a 24-month, chronic-duration inhalation study in F344 rats and B6C3F$_1$ mice for the CIIT (1981). Groups of animals (120/sex/species/concentration) were exposed 6 hours/day, 5 days/week, for up to 24 months to concentrations of chloromethane (purity = at least 99%) at 0, 50, 225, or 1000 ppm (0, 18, 83, or 368 mg/m^3). Interim sacrifices and toxicological evaluations were scheduled for 6, 12, and 18 months after initiation of the study. However, due to high mortality in the 1000-ppm mice, this group was euthanized after 21 or 22 months of exposure. A 6-month interim report of this study was prepared by Mitchell et al. (1979b). The results of the chronic-duration study were presented in the unpublished final report by CIIT (1981). It was noted that exposures for the 50- and 1000-ppm mice were inadvertently switched on three consecutive days, so that they received each other's dose; however, the effect of this exposure mistake was considered negligible by the study authors.

In the CIIT study (1981), treatment-related findings in the rats were limited to the 1000-ppm group and were characterized by decreased overall body-weight gain, atrophy and diffuse degeneration of the seminiferous tubules, and the presence of sperm granulomas. The following noncancer effects of treatment were observed at 1000 ppm in the mice: decreased survival; clinical signs of neurotoxicity (hunched posture, tremor, and paralysis); hepatotoxicity (hepatocellular vacuolization, karyomegaly, cytomegaly, and degeneration and increased ALT); seminiferous tubule atrophy and degeneration; lymphoid depletion; and atrophy of the spleen. Additionally in mice in the CIIT study (1981), a principal finding was degeneration and atrophy of the granular layer of the cerebellum. The lesion was found in the 1000-ppm mice that died spontaneously between 0 and 17 months (15 out of 24 males, 9 out of 20 females) and between 18 and 22 months (45 out of 47 males, 35 out of 37 females). The lesion did not occur at 0, 50, or 225 ppm. In the 18−24 month spontaneous death category, 35 out of 37 females and 45 out of 47 males in the 1000-ppm group had cerebellar granular cell atrophy that was more extensive at 24 months than at 18 months (U.S. EPA, 2001).

Cancer findings (and findings likely indicating progression to cancer) were limited to the kidney in males (renal tubuloepithelial hyperplasia, hypertrophy, and/or karyomegaly, and renal cortical adenomas, adenocarcinomas, papillary cyst/adenocarcinomas). A detailed summary

table of the number and types of benign and malignant renal lesions (see Table B.12), obtained from the *Concise International Chemical Assessment Document (CICAD) 28, Methyl Chloride* (WHO, 2000), is included in Table B.12. The following data were obtained from the *Toxicological Review of Methyl Chloride in Support of IRIS* (U.S. EPA, 2001):

> *Cancer findings in the CIIT (1981) study were limited to the kidneys in the 1000-ppm male mice. Renal tumors were significantly increased ($p \leq 0.05$) in these animals during Months 12−21; due to early termination, no data from this group at 24 months was available: 17 renal neoplasms were found in 13 animals (8 renal cortical adenomas, 4 adenocarcinomas, 2 papillary cystadenomas, 2 tubular cystadenomas, and 1 papillary cystadenocarcinoma). These were considered induced by chloromethane exposure, as were two adenomas (not statistically significant) in 225-ppm males at 24 months. A statistically significant increase in renal cortical cysts was seen at 18−22 months in 7 males and 1 female from the 1000 ppm group, as well as in 1 male and 1 female from the 225 ppm group at 24 months. Also at 24 months, microcysts were observed in 6 males from the 50 ppm group, and 1 control male had a cyst. Although their precise relationship to each other and to the other renal lesions was not clear, renal cyst and microcyst formation was considered by the investigators to be possibly chloromethane-related. However, the low incidence in the 225-ppm group suggests that it may be a spontaneous lesion. Unpublished data (Johnson, 1988) for controls from eight 2-year mouse studies indicate that the incidence values for renal microcysts from the CIIT (1981) study fall within the Dow Chemical Company's historical control incidence for this strain. In addition, examination of nonneoplastic lesions in the B6C3F$_1$ from 122 chronic studies (drinking water, gavage, and inhalation) indicated that in no case was there a dose-response relationship between chemical exposure and cyst formation. In fact, control animals in inhalation studies (e.g., butadiene, acetonitrile, toluene) often evidenced a higher incidence of renal cysts than exposed mice. Additionally, if one considers the incidence of kidney cysts (no microcysts) in the NTP chronic inhalation study (TR 385) for methyl bromide (NTP, 1992), structurally very closely related to chloromethane, there also is no clear dose-response in male B6C3F$_1$ mice.*

Developmental and Reproduction Studies

In a developmental toxicity study, 25 female F344 rats and 33 female B6C3F$_1$ mice were exposed to 0-, 100-, 500-, or 1500-ppm (0, 52, 258, or 774 mg/m^3) chloromethane (purity = 99.98%) for 6 hours/day from Gestation Days (GDs) 7−19 for rats or GDs 6−17 for mice (Wolkowski-Tyl et al., 1983a). The authors did not provide a LOAEL; however, the following LOAELs are available from the data. In the rats, the LOAEL for maternal and developmental toxicity is 1500 ppm (774 mg/m^3) based on decreased ($p \leq 0.05$) maternal body-weight gain, body weight, and food consumption and reduced ($p \leq 0.05$) fetal body weight and crown-rump length and a NOAEL of 500 ppm (258 mg/m^3). However, there were no treatment-related external, visceral, or skeletal abnormalities. In the mice, the entire 1500-ppm group was euthanized in extremis during GDs 10−14, indicating a frank effect level. In all of the dams at 1500 ppm, microscopic examination of the brain revealed selective necrosis of neurons in the internal granular layer of the cerebellum, ranging from individual cell involvement to focal areas

comprising large numbers of neurons. The developmental LOAEL for the mice is 500 ppm (258 mg/m^3), based on a small but statistically significant increase in the incidence of heart defects at this concentration. The anomaly, a reduction or absence of the atrioventricular valve, chordae tendineae, and papillary muscle, was observed on the left side (bicuspid valve) in three mouse fetuses (B6C3F$_1$) and the right (tricuspid valve) in six fetuses. The developmental NOAEL in mice is 100 ppm (52 mg/m^3).

In a further extension of this work, 74−77 female C57BL/6 mice bred to C3H males were exposed to 0-, 250-, 500-, or 750-ppm (0, 129, 258, or 387 mg/m^3) chloromethane (purity = 99.97%) for 6 hours/day, from GDs 6−17 (Wolkowski-Tyl et al., 1983b). At 750 ppm, maternal toxicity was observed, as evidenced by clinical signs of toxicity (ataxia, hypersensitivity to touch and/or sound, tremors, and convulsions) and significantly ($p \leq 0.01$) decreased body weight and body weight gain. Six dams died at this concentration, and one was euthanized in extremis, indicating a frank effect level. The authors did not provide a LOAEL; however, the following LOAELs are available from the data. The developmental LOAEL is 500 ppm (258 mg/m^3) based on heart malformations found in 7 out of 444 fetuses (1.6%) at 500 ppm, and in 14 out of 400 (3.5%) fetuses at 750 ppm compared to 2 out of 433 fetuses in the control group. The developmental NOAEL is 250 ppm (129 mg/m^3). This second study confirmed the anomaly in the tricuspid valve. However, these anomalies were not observed in another laboratory (John-Greene et al., 1985) in which dams were exposed for 24 hours to 300 ppm (620 mg/m^3), the highest concentration compatible with survival, during the stated critical time interval for development of these heart structures (GDs 11.5−12.5). Several attempts at replicating the malformation indicated that its detection may be dependent upon histology preparation and examination techniques. It was also stated that limited historical control data with this hybrid strain of mice were available, further complicating its implications for human risk assessment. In response to the study by John-Greene et al. (1985), one of the original researchers (Tyl, 1985) conducting the study in which the malformations were found, stated that the attempt to duplicate these malformations may have failed for two reasons: (1) the exposure time frame (during GDs 11−12) may have actually preceded the development of the heart structures, and (2) the exposure duration of 24 hours versus 6 hours/day may have implications on the metabolism of chloromethane via glutathione. Tyl (1985) recommended repeating the study using the longer exposure duration in the same strain of mice, in addition to testing rats and rabbits to determine if heart malformations were observed. Thus, some uncertainty exists regarding the exposure conditions under which this anomaly occurs, although it is considered prudent to regard chloromethane as a developmental toxicant in the mouse.

In a two-generation reproduction study, F344 rats (40 males, 80 females) were exposed to chloromethane (purity = 99.98%) at concentrations of 0, 150, 475, or 1500 ppm (0, 59, 186, or 589 mg/m^3), for 6 hours/day, 5 days/week, for 10 weeks prior to mating (1 male:2 females) and then for 6 hours/day, 7 days/week, throughout a 2-week mating period (Hamm et al., 1985). At the end of the mating period, 10 males per group were necropsied, and the females continued exposure throughout gestation and lactation (except from GD 18 to Postnatal Day 4). Degeneration and atrophy of the seminiferous tubules were observed in all 1500-ppm F0 males (10 out of 10), in addition to increased incidences of epididymal sperm granulomas and decreased testes size in 3 out of 10 animals at this concentration. The remaining 30 males per group were then removed from exposure and mated during a 2-week period to unexposed females (1 male:2 females) to determine if decreased fertility was due to effects on the males. This study identified a reproductive LOAEL at 475 ppm (186 mg/m^3) based on statistically

significant decreased male fertility, with a corresponding NOAEL of 150 ppm (59 mg/m^3). Similar findings were observed whether or not the females were exposed, indicating that reduced fertility was due to treatment-related effects on the seminiferous tubules and epididymides. The total number of males proven fertile was significantly ($p \leq 0.05$) lower at 475 ppm (17 out of 28) and 1500 ppm (0 out of 26) compared to controls (25 out of 28). There were no clear effects of exposure on fertility of the F1 generation (no histopathology was performed). A lower percentage of male offspring was noted in the 475-ppm F2 litters (41 ± 16%) compared to controls (51 ± 18%), and a trend toward decreased fertility was observed at 150 ppm (65%) and 475 ppm (61%) compared to controls (78%) in the F1 generation. However, these decreases were not statistically significant.

Numerous other short-term reproduction toxicity studies have been performed to further investigate the effects of chloromethane on the epididymides and testes in rats (Chapin et al., 1984; Working et al. 1985a,b; Working and Bus, 1986; Chellman et al., 1986a,b, 1987; Working and Chellman, 1989). Table 2 presents a brief summary of the critical effects of these study summaries; a detailed assessment of these studies is available in the *Toxicological Review of Methyl Chloride: in Support of Summary Information on the Integrated Risk Information System* (U.S. EPA, 2001) and in the *Concise International Chemical Assessment Document (CICAD) 28, Methyl Chloride* (WHO, 2000). In general, exposure to chloromethane at concentrations of 1359−3872 mg/m^3, for 6 hours/day, for durations of 2−5 days, resulted in unilateral and bilateral sperm granulomas in the epididymis, decreased fertility (increased preimplantation loss) determined to be due to increased sperm cytotoxicity (delayed spermiation, chromatin margination in round spermatids, epithelial vacuolation, luminal exfoliation of spermatogenic cells, and multinucleated giant cells), decreased sperm motility, and increased incidence of sperm abnormalities. The postimplantation loss caused by chloromethane in the dominant lethal assays is considered to be due to inflammation because it was prevented by cotreatment with 3-amino-1-[*m*-(trifluoromethyl)phenyl]-2-pyrazoline, the Burroughs Wellcome experimental compound BW755C, an anti-inflammatory inhibitor of cyclooxygenase and lipoxygenase enzymes.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

The information included in this section describes the relevant metabolism and genotoxicity studies that have been reported since the publication of IRIS (U.S. EPA, 2001, 2011). Additionally, a study by Chellman et al. (1986c), which was included in the *Toxicological Review of Methyl Chloride: in Support of Summary Information on the Integrated Risk Information System* (U.S. EPA, 2001), is included to assist in describing the potential metabolism considerations and their relationship to the toxicity of chloromethane (see Table 3).

The following information regarding the comparative kinetics and metabolism of chloromethane in humans and animals is obtained from the *CICAD 28: Methyl Chloride* (WHO, 2000). In rats exposed to ^{14}C-labeled chloromethane by inhalation, the greatest amount of radioactivity was found in the liver, kidneys, and testes, and, to a smaller extent, in the brain and lungs. However, the presence of these residues was attributed to the metabolism of chloromethane to formaldehyde and formate, and their subsequent incorporation into macromolecules via anabolic pathways. Chloromethane may also bind to macromolecules—especially protein—and perhaps DNA to a minimal extent. The main route of metabolism of chloromethane in humans and animals is via conjugation with glutathione. To a lesser extent,

chloromethane is metabolized via cytochrome P-450 in rat liver, resulting in the formation of formaldehyde and formate. Formaldehyde and formate may also be formed via the glutathione pathway. Inhalation of chloromethane by male $B6C3F_1$ mice resulted in a concentration-dependent depletion of glutathione in the liver, kidney, and brain.

Chloromethane exposure in rats results in time- and concentration-dependent depletions on tissue (e.g., liver, kidney, testes) levels of nonprotein sulfhydryl (NPSH). The potentially toxic consequences of NPSH (principally GSH) depletion have not been fully characterized but may include conversion of chloromethane-GSH conjugates to toxic intermediates (e.g., methanethiol and formaldehyde), enhancement of the toxicity of other chemicals that are normally detoxified by conjugation with GSH, reduction in the capacity of GSH to buffer against excessive lipid peroxidation, free radical generation, and thiol oxidation; to transport amino acids; and to serve as a cofactor in enzymatic reactions (e.g., with formaldehyde dehydrogenase) (U.S. EPA, 2001).

Chellman et al. (1986c) used male $B6C3F_1$ mice to examine the role of GSH (measured as NPSH) in mitigating the toxicity of chloromethane exposure in brain, liver, and kidney target tissues. They found that when groups of mice were pretreated with buthionine-S,R-sulfoximine (BSO), a potent and specific inhibitor of γ-glutamylcysteine synthetase—the rate-limiting enzyme for de novo synthesis of GSH—and then exposed for 6 hours to 2500-ppm chloromethane (purity = 99%), chloromethane toxicity was prevented. Male mice were also exposed to 1500-ppm chloromethane (purity = 99%), 6 hours/day, 5 days/week, for 2 weeks, ± daily pretreatment with BSO. BSO pretreatment protected against both chloromethane-induced lethality and the induction of lesions in the brain (multiple degenerative/necrotic foci in the granular cell layer). Hepatic toxicity in male mice exposed for 6 hours to 1500-ppm chloromethane was reflected in hepatocellular necrosis and cytoplasmic vacuolation, as well as nearly a 50-fold increase in serum ALT activity. Pretreatment of the animals with 8-mmol BSO, 0.25-mL/kg DEM, or fasting for 18 hours was found to substantially deplete hepatic NPSH and virtually eliminate hepatotoxicity as measured by serum ALT levels. With respect to kidney toxicity in animals treated 6 hours/day, 5 days/week, for 2 weeks to 1500-ppm chloromethane, incorporation of tritiated thymidine into kidney DNA was elevated 3-fold in male mice and 8.5-fold in female mice by the exposure, presumably reflecting compensatory cell regeneration. In males, pretreatment with BSO completely eliminated this increase, while having no effect on label incorporation when administered alone (the effect of BSO pretreatment in females was not determined). This study demonstrates that chloromethane's lethality and target organ toxicity can largely be prevented by conditions that lower tissue NPSH levels, thus preventing the formation of chloromethane-GSH conjugates that would result in the metabolic conversion to toxic intermediates.

In several studies in humans, chloromethane concentrations in breath and blood and amounts of excreted urinary metabolites have differed greatly among volunteers (WHO, 2000). One explanation for the large interindividual differences in metabolism and excretion of chloromethane in humans is the presence or absence of the glutathione-*S*-transferase T1 (GSTT1) gene. The presence of the GSTT1 gene leads to conjugation of chloromethane with glutathione (GSTT1+), and the absence of this gene results in no conjugation (GSTT1-).

Löf et al. (2000) demonstrated the toxicokinetics of the GSTT1 polymorphisms in a study in which 24 volunteers (13 males and 11 females) previously characterized as having high, medium, or no conjugating activity (8 per group) were exposed to 10-ppm chloromethane (purity = 97.4%) for 2 hours. The concentrations of chloromethane were measured in inhaled air, exhaled air, and blood. The experimental data were used in a two-compartment model with pathways for exhalation and metabolism. Respiratory uptake averages decreased with decreasing GSTT1 activity. During the first 15 minutes of exposure, the blood concentration of chloromethane rose rapidly and then plateaued. The blood concentrations of chloromethane were similar in all three groups during the 2-hour exposure. At the end of the exposure, the blood concentrations declined rapidly in the high and medium metabolizing groups but declined more slowly in the group lacking GSTT1 activity. Metabolic clearance was nearly absent in the nonmetabolizing group. The rate of exhalation clearance was similar among the three groups, but the nonmetabolizing group had much higher concentrations of chloromethane in exhaled air after exposure.

Jonsson et al. (2001) subsequently used the data from the GSTT1-deficient group in the Löf et al. (2000) study to develop a standard physiologically based pharmacokinetic (PBPK) model for chloromethane (purity not specified) with six tissue compartments: lung, working muscle, resting muscle, well-perfused tissues, liver, and fat. The model also included uptake of chloromethane via inhalation, and all elimination was accounted for by exhalation, because these individuals lacked the ability to metabolize chloromethane. The PBPK model was fit to the experimental data in a Bayesian framework using Markov chain Monte Carlo simulation. Although the model provided good general forecasts, the concentrations in exhaled air and blood were slightly overpredicted. The authors noted that the use of nonmetabolizing subjects allowed them to assess the kinetics of a volatile chemical without interference from metabolism and to obtain greater knowledge of physiological parameters, but using chloromethane as a model compound had limitations, such as its low solubility in blood, low blood:air partition coefficient, and rapid decay during the first minutes after exposure.

In a study by Asakura et al. (2008) a gas exposure system using rotating vessels was improved for exposure of cultured mammalian cells to gaseous compounds in the chromosomal aberration assay using Chinese hamster lung cells (CHL/IU). This improved system allowed concurrent testing of three different concentrations, with and without metabolic activation, and duplicate cultures at each concentration, with positive and negative controls. Chloromethane (purity = >95%; one of seven chemicals tested) was positive for chromosome aberrations in cultured Chinese hamster lung cells with and without the presence of microsomal homogenate (S9) mix.

Table 3. Other Studies

Tests	Materials and Methods	Results	Conclusions	References
Metabolism Human Acute Inhalation	24 human volunteers (13 males/11 females) with GSTT1 activity characterized as high, medium, or no conjugating activity (8 per group) were exposed to 10-ppm chloromethane for 2 hrs. Chloromethane (purity = 97.4%) concentrations were determined in inhaled air, exhaled air, and blood. The experimental data were used in a two-compartment model with pathways for exhalation and metabolism.	Respiratory uptake averages were 243, 158, and 44 µmol for the high, medium, and no GSTT1 activity groups, respectively. Metabolic clearance was high (4.6 L/min) in the high activity group, intermediate (2.4 L/min) in the medium conjugating group, and close to zero in the nonconjugating group. The rate of exhalation clearance was similar among the groups.	The authors concluded that GSTT1 appears to be the sole determinant for chloromethane metabolism in humans.	Löf et al. (2000)
PBPK Modeling	Data from the GSTT1-deficient group in Löf et al. (2000) were used to develop a standard PBPK model for chloromethane (purity not specified) with six compartments: lung, working muscle, resting muscle, well-perfused tissues, liver, and fat. The model also included uptake of chloromethane via ventilation, and all elimination was accounted for by exhalation because these individuals lacked the ability to metabolize chloromethane.	The model provides a good description of the concentrations of chloromethane in arterial blood and exhaled air, although the final concentrations in exhaled air and blood were slightly overpredicted.	The use of nonmetabolizing subjects allowed the authors to assess the kinetics of a volatile chemical without interference from metabolism and to obtain additional knowledge on the physiological parameters involved. However, using chloromethane as a model compound had limitations, such as low solubility in blood, low blood:air partition coefficient, and rapid decay during the first minutes after exposure.	Jonsson et al. (2001)

Table 3. Other Studies

Tests	Materials and Methods	Results	Conclusions	References
Acute Metabolism	Male B6C3F$_1$ mice were pretreated (-1.5 hr before treatment) with buthionine-S,R-sulfoximine (BSO), an inhibitor of glutamylcysteine synthetase (rate-limiting step in de novo synthesis of GSH) and then exposed to 2500-ppm chloromethane (purity = 99.9%) for 6 hr.	Compared to controls (-BSO), GSH in the +BSO mice at 0, 3, and 6 hr was decreased in the kidney (to 25, 28, and 32%) and liver (to 19, 35, and 65%), and in the brain (to 90, 70, and 58%). BSO treatment reduced mortality at 18 hours from 93% (14/15) to 0% (0/10) and increased the LC50 from 2200 to 3200 ppm.	Chloromethane's lethality and target organ toxicity can largely be prevented by conditions that lower tissue NPSH levels, thus decreasing the formation of chloromethane-GSH conjugates that would result in the metabolic conversion to toxic intermediates.	Chellman et al. (1986c)
Subacute Metabolism	Male B6C3F$_1$ mice exposed to 1500-ppm chloromethane (purity = 99.9%) for 6 hr/d, 5 d/wk, for 2 wk, ± daily pretreatment with 2-mmol BSO.	BSO pretreated animals were protected against mortality (0% mortality vs. 11−28% in the controls), microscopic lesions in the brain (multiple degenerative/necrotic foci in the granular cell layer), increases in ALT levels, and incorporation of tritiated thymidine into kidney DNA.		
Genotoxicity	Chinese hamster lung cells were exposed to chloromethane (purity = >95%) in the presence and absence of S9 mix using an improved gas exposure system of rotating vessels.	Chloromethane was positive for chromosome aberrations in Chinese hamster lung cells in the presence and absence of S9 mix.		Asakura et al. (2008)

DERIVATION OF PROVISIONAL VALUES

Tables 4 and 5 below present a summary of noncancer and cancer reference values, respectively.

Table 4. Summary of Noncancer Reference Values for Chloromethane (CASRN 74-87-3)

Toxicity Type (Units)[a]	Species/Sex	Critical Effect	p-Reference Value	POD Method	POD	UF_C	Principal Study
Subchronic p-RfD (mg/kg-day)	None						
Chronic p-RfD (mg/kg-day)	None						
Subchronic p-RfC (mg/m^3)	Mouse/F	Cerebellar lesions	3×10^0	$NOAEL_{HEC}$	94.6	30	Landry et al. (1983, 1985)
Chronic RfC (mg/m^3; IRIS 2011)[a]	Mouse/F	Cerebellar lesions	9×10^{-2}	$NOAEL_{HEC}$	94.6	1000	Landry et al. (1983, 1985)

[a]All the reference values obtained from IRIS are indicated with latest review date.

Table 5. Summary of Cancer Reference Values for Chloromethane (CASRN 74-87-3)

Toxicity Type	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF	None			
p-IUR	None			

DERIVATION OF ORAL REFERENCE DOSES

Chloromethane exists primarily as a gas, and no adequate oral exposure studies are available. Therefore, no subchronic or chronic p-RfD values can be derived

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

IRIS (U.S. EPA, 2011) provides the following information regarding the rationale for the selection of the principal study for the derivation of the chronic RfC. This description informs the selection of the short-term study conducted by Landry et al. (1983, 1985) as the principal study for the derivation of the subchronic p-RfC.

> *Dysfunction of the central nervous system (CNS) is a hallmark for toxicity due to methyl chloride both in human case reports and in short- and long-term studies in laboratory animals. The 2-year CIIT study (1981), which is the only long-term intermittent (6 hours/day, 5 days/week) inhalation study currently available, would typically have been chosen for identification of the critical effect (e.g., cerebellar lesions) because it satisfies the criteria set forth in U.S. EPA (1994) in spite of several procedural errors (e.g., some misidentification of mice, pregnancy of some mice, and an exposure error early in the study). However, the continuous (22−22.5 hr/day) 11-day exposure of the female C57BL/6 mouse (Landry et al., 1983, 1985) is considered more appropriate in the context of protecting public health for the following reasons: (1) the study was well conducted; (2) cerebellar lesions (considered the most critical effect in the context of known CNS deficits from human case reports) occurred at continuous exposure levels (100 ppm) and at intermittent levels (400 ppm) far below those in the $B6C3F_1$ strain exposed chronically (1000 ppm) in the 1981 CIIT study; (3) no cerebellar lesions were observed in the 90-day pilot study in the $B6C3F_1$ mouse (Mitchell et al., 1979[a]) at levels up to 1500 ppm; and (4) continuous exposure of C57BL/6 mice resulted in mortality at 200 ppm, whereas intermittent 2-year exposure of the $B6C3F_1$ mouse did not cause mortality below 1000 ppm.*

Derivation of Subchronic p-RfC

The study by Landry et al. (1983, 1985) is selected as the principal study for derivation of the subchronic p-RfC. This study, conducted by Dow Chemical Company, was conducted prior to implementation of Good Laboratory Practice (GLP) standards and was initially submitted to the EPA under TSCA Section 8(e) (Landry et al., 1983). Subsequently published in a peer-reviewed journal (Landry et al., 1985), this study meets the standards of study design and performance, regarding the numbers of animals, examination of potential toxicity endpoints, and presentation of information. The critical endpoint is cerebellar lesions in female C57BL/6 mice, with a LOAEL of 189 mg/m^3. Cerebellar lesions were observed at higher concentrations in other short-term studies in dogs and cats (McKenna et al., 1981a) and rats and mice (Morgan et al., 1982; Jiang et al., 1985); in the chronic-duration toxicity study in mice (CIIT, 1981); and in the developmental toxicity study in mice (Wolkowski-Tyl et al., 1983a). In addition to being the predominant toxicological endpoint across species, exposure durations, and concentrations, the cerebellar lesions are considered to be the most relevant toxicological endpoint because they corroborate the CNS toxicity observed in humans. Although the LOAEL of 186 mg/m^3 in the reproduction study by Hamm et al. (1985), which is based on decreased male fertility in the F2 generation, is slightly lower than the LOAEL in the study by Landry et al.

(1983, 1985), there were no clear effects on fertility in the F1 generation. Additionally, CNS effects were observed across species and across studies as a target organ, the cerebellar lesions in female C57BL/6 mice ($LOAEL_{HEC}$ of 189 mg/m^3) are the most sensitive endpoint in the most sensitive species, strain, and sex (Morgan et al., 1982). Therefore, among the available, acceptable studies, this study provides the lowest POD for deriving a subchronic p-RfC. Benchmark dose (BMD) analysis is not performed due to the steep dose-response in the observed cerebellar lesions. The first two exposure levels (28.3 mg/m^{3}and 94.6 mg/m^3) showed no effect for cerebellar lesions but the next four exposure levels showed 100% cerebellar lesions with different severity, and no statistical analysis was performed. A NOAEL of 50 ppm is selected as the POD for deriving the subchronic p-RfC.

Adjusted points for daily exposure:

The following dosimetric adjustments were made for each dose in the principal study for inhalation treatment.

$$\begin{aligned} NOAEL_{ADJ} &= NOAEL_{\text{Landry et al., 1983, 1985}} \times [\text{conversion from ppm to mg/m}^3] \times [\text{Continuous exposure concentration}] \\ &= 50 \text{ ppm} \times (MW \div 24.45) \times (22 \text{ hours} \div 24 \text{ hours}) \\ &= 50 \text{ ppm} \times (50.49 \div 24.45) \times 0.9167 \\ &= 94.6 \text{ mg/m}^3 \end{aligned}$$

Because the treatment-related effects of chloromethane occur systemically without any local respiratory effects, the conversion to HEC requires multiplying the adjusted average daily dose by the animal to human blood:gas partition coefficient (U.S. EPA, 1994). Periodicity is assumed to be attained for systemic effects, and the blood:gas partition coefficients for humans (i.e., Nolan et al., 1985) and rats (i.e., Gargas et al., 1989) yield an approximate 1:1 ratio. The assumption that the partition coefficient for the mouse is similar to that for the rat is based on the tabulation of Gargas et al. (1989), who reported that blood:gas partition coefficients for six out of seven chemicals are similar for both the rat and the mouse. Additionally, according to current modeling practice, a maximum of 1 is used for the animal to human blood:gas partition coefficient. Thus, using a blood:gas partition coefficient of 1 and the $NOAEL_{ADJ}$ results in an $NOAEL_{HEC}$ of 94.6 mg/m^3.

$$NOAEL_{HEC} = 94.6 \text{ mg/m}^3 \times 1 = 94.6 \text{ mg/m}^3$$

The subchronic p-RfC for chloromethane, based on the $NOAEL_{HEC}$ of 94.6 mg/m^3 in female mice (Landry et al., 1983, 1985), is derived as follows:

$$\begin{aligned} \textbf{Subchronic p-RfC} &= NOAEL_{HEC} \div UF_C \\ &= 94.6 \text{ mg/m}^3 \div 30 \\ &= \mathbf{3 \times 10^0 \text{ mg/m}^3 \text{ or } 3 \text{ mg/m}^3} \end{aligned}$$

Tables 6 and 7, respectively, summarize the uncertainty factors (UFs) and the confidence descriptor for the subchronic p-RfC for chloromethane.

Table 6. Uncertainty Factors for Subchronic p-RfC of Chloromethane

UF	Value	Justification
UF_A	3 ($10^{0.5}$)	A UF_A of 3 is applied for animal:human extrapolation to account for the toxicodynamic portion of the UF_A because the toxicokinetic portion ($10^{0.5}$) has been addressed in dosimetric conversions.
UF_D	1	A UF_D of 1 is applied because the database has acceptable inhalation developmental toxicity studies (Wolkowski-Tyl et al., 1983a,b) and a two-generation reproduction study (Hamm et al., 1985).
UF_H	10	A UF_H of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of definitive information on the variability of response to humans.
UF_L	1	A UF_L of 1 is applied because the POD was developed using a NOAEL.
UF_S	1	A UF_S of 1 is applied because a short-term-duration study with 11-day continuous exposure is utilized as the principal study to derive a subchronic p-RfC.
$UF_C \leq 3000$	30	

Table 7. Confidence Descriptor for Subchronic p-RfC for Chloromethane

Confidence Categories	Designation[a]	Discussion
Confidence in Study	H	Confidence in the principal and supporting studies is high.
Confidence in Database	M	Overall confidence in the database is medium because of a lack of brain histopathology on F1 generation mice, particularly female C57BL/6, a strain that may be particularly sensitive to the effects of chloromethane.
Confidence in Subchronic p-RfC[b]	M	The overall confidence in the subchronic p-RfC is medium.

[a]L = Low, M = Medium, H = High.
[b]The overall confidence cannot be greater than the lowest entry in table.

Derivation of Chronic RfC

A chronic RfC of 0.09 mg/m^3 is available in IRIS (U.S. EPA, 2011), based on cerebellar lesions in female C57BL/6 mice exposed to 0, 15, 50, 100, 150, 200, or 400 ppm (0, 28.4, 94.6, 189.2, 283.9, 378.5, or 757.1 mg/m^3) by whole body inhalation exposure for 11 days for 22 hours per day (Landry et al., 1983, 1985). The IRIS database should be checked to determine if any changes have been made.

CANCER WEIGHT-OF-EVIDENCE (WOE) DESCRIPTOR

IRIS (U.S. EPA, 2011) applied the criteria for evaluating the overall weight-of-evidence (WOE) for carcinogenicity to humans using the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986) and designated chloromethane under the category of Group D, "*Not Classifiable as to its Human Carcinogenicity.*" The IRIS toxicological review further stated that

the *Proposed Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1996) suggested that chloromethane would be classified as an agent for which carcinogenic potential "cannot be determined." Using the current *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), the available data suggest that the cancer WOE descriptor for chloromethane is "*Inadequate Information to Assess Carcinogenic Potential*" (see Table 8). This determination is based upon the evidence available from the studies supporting the IRIS carcinogenicity assessment, in addition to all relevant studies that have been available since the publication of the IRIS toxicological review.

Human carcinogenicity data are inadequate. The following information is provided from IRIS (U.S. EPA, 2001):

> *The few studies that have examined methyl chloride's potential carcinogenicity in humans have failed to convincingly demonstrate any association, and in one instance even indicated a lower cancer incidence than expected in workers chronically exposed to methyl chloride in a butyl rubber manufacturing plant (Holmes et al., 1986). There was no conclusive evidence for an effect of acute, severe exposure to methyl chloride on mortality from all cancers or from lung cancer in a small cohort accidentally exposed to methyl chloride from a leaking refrigeration unit (Rafnsson and Gudmundsson, 1997); because of the wide confidence intervals that included unity, the data cannot be construed as suggestive of an elevated cancer mortality risk. Other occupational studies involved exposure to multiple chemicals in addition to methyl chloride, making it difficult to attribute any effects specifically to methyl chloride (Dow Corning Corporation, 1992b; Olsen et al., 1989).*

The epidemiological study by Kernan et al. (1999)—not included in IRIS (U.S. EPA, 2001)—examined death certificates of 63,097 persons who had died from pancreatic cancer in 24 U.S. states from 1984−1993 compared to 252,386 persons who died from causes other than cancer during the same time period. Results from this study indicate that the deaths from pancreatic cancer were not associated with exposure to chloromethane.

Animal carcinogenicity data are limited to a single study in which rats and mice were exposed to 0-, 50-, 225-, or 1000-ppm chloromethane for 6 hours/day, 5 days/week, for up to 2 years (CIIT, 1981). The incidences of benign and malignant renal tumors were significantly increased ($p \leq 0.05$) in male $B6C3F_1$ mice at 1000 ppm. Two renal adenomas were noted in the males at 225 ppm and were considered possibly treatment related. No tumors were found at lower concentrations or at any other site in the male mouse, nor at any site or concentration in female mice or F344 rats of either sex. Renal cortical tubuloepithelial hyperplasia and karyomegaly were also found only in the male mice at 1000 ppm.

Table 8. Cancer WOE Descriptor for Chloromethane (CASRN 74-87-3)			
Possible WOE Descriptor	**Designation**	**Route of Entry (Oral, Inhalation, or Both)**	**Comments**
"Carcinogenic to Humans"	N/A	N/A	
"Likely to be Carcinogenic to Humans"	N/A	N/A	
"Suggestive Evidence of Carcinogenic Potential"	N/A	N/A	
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Inhalation**	**Under the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), it is considered that there is inadequate information to assess carcinogenic potential because there is little pertinent information and/or conflicting evidence. In animals, only a single 2-year study (CIIT, 1981) was conducted, resulting in tumors in the kidneys of male mice but no tumors at any other site or in female mice or rats of either sex. Human studies were limited to an epidemiological study in which pancreatic cancer was not associated with chloromethane exposure (Kernan et al., 1999), along with other studies either confounded by exposure to other chemicals (Dow Corning Corporation, 1992; Olsen et al., 1989), by demonstrating a "healthy worker" effect (Holmes et al., 1986), or by having wide variability (Rafnsson and Gudmundsson, 1997), thus precluding meaningful conclusions.**
"Not Likely to be Carcinogenic to Humans"	N/A	N/A	

MODE-OF-ACTION (MOA) DISCUSSION

It has been proposed that the finding of increased incidence of renal tumors in male mice may be explained by biotransformation of chloromethane to the toxic intermediate, formaldehyde, via cytochrome P4502E1 (CYP2E1), an androgen-dependent isozyme present in male mouse kidneys (see IRIS, U.S. EPA, 2011). Concentrations of CYP2E1 are present at considerably higher concentrations in microsomal preparations from the male mouse kidney compared to female mice or rats of either sex; however, no CYP2E1 activity was detected in human kidney microsomal samples. The following discussion of this mechanism of tumorigenicity in mice and its implications for human carcinogenicity are available from IRIS (U.S. EPA, 2011):

> *The lack of detectable CYP2E1 protein in human kidney (in contrast to mice, which have high levels) suggests that the metabolism of methyl chloride by P450 (presumably leading to elevated formaldehyde concentrations) that could be responsible for the induction of male mouse kidney tumors may not be relevant to humans. However, the role of hepatic (and/or kidney) metabolism (leading to potential genotoxic metabolites) via the predominant GSH pathway (or even by P450 isozymes other than CYP2E1) in this regard cannot be discounted; in vivo metabolism of methyl chloride to formate in liver is GSH-dependent, via the GSH-requiring formaldehyde dehydrogenase that oxidizes formaldehyde to formate. Inasmuch as methyl chloride exposure can lower tissue nonprotein sulfhydryl concentrations, it thus has the potential to inhibit formaldehyde dehydrogenase and increase formaldehyde levels.*

Mutagenicity Information

Numerous mutagenicity and other possible mechanistic studies have been reviewed in support of IRIS, and "these data collectively indicate that methyl chloride is a relatively weak, direct-acting in vitro genotoxicant at high concentrations, and that its weak DNA-damaging effects in vivo either are or are likely to be primarily the result of various cytotoxicity-mediated mechanisms" (U.S. EPA, 2001). This assertion is supported by the studies by Working et al. (1985a,b), Working and Bus (1986), Chellman et al. (1986a,b, 1987), and Working and Chellman (1989), which determined that preimplantation losses induced by chloromethane are due to cytotoxic instead of genotoxic effects (i.e., failure of fertilization), and the postimplantation loss caused by chloromethane is due to inflammation in the epididymis. Weak-to-moderate mutagenicity has been demonstrated in *Salmonella typhimurium* at high concentrations of chloromethane. Induction of sister chromatid exchanges (SCEs) has been observed in human lymphoblasts by chloromethane and by a congener, methyl bromide, in lymphocytes from a human subgroup categorized as "slow metabolizers." This group is known to be genetically predisposed (polymorphisms in glutathione transferase) to have a lower rate of metabolism compared with the majority of human populations studied.

Since the evaluation of chloromethane under IRIS (U.S. EPA, 2011), only a single study was located relevant to the potential genotoxicity of chloromethane (Asakura et al., 2008). A gas exposure system using rotating vessels was improved for exposure of cultured mammalian cells to gaseous compounds in the chromosomal aberration assay using CHL/IU. This improved system allowed concurrent testing of three different concentrations, with and without metabolic activation, and duplicate cultures at each concentration, with positive and negative controls. Chloromethane (one of seven chemicals tested) induced structural chromosome aberrations in cultured Chinese hamster lung cells with and without the presence of S9 mix. Polyploidy was not observed.

The evidence from the mechanistic, mutagenicity, and genotoxicity studies on chloromethane indicate that, although it may have mutagenic capability at high concentrations, any findings observed in vivo are more accurately attributed to cytotoxicity due to inflammation and not mutagenicity.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

The evaluation of chloromethane for IRIS determined that the human data are inadequate to judge the carcinogenic potential of methyl chloride and that the findings in the single animal study on carcinogenicity (CIIT, 1981) are equivocal. The lack of data on the carcinogenicity of chloromethane precludes the derivation of quantitative estimates for either oral (p-OSF) or inhalation (p-IUR) exposure.

APPENDIX A. PROVISIONAL SCREENING VALUES

No screening values are presented.

APPENDIX B. DATA TABLES

Table B.1. Body Weights (g) in Female C57BL/6 Mice Exposed to Chloromethane via Inhalation Continuously (22 Hours/Day) or Intermittently (5.5 Hours/Day) for 11 Days[a]

Concentration (ppm) (HEC, mg/m^3)	Day 0	Day 4	Day 8	Day 11
Continuous exposure				
0 (0)	14.8 ± 1.4	16.1 ± 1.1	16.3 ± 1.3	17.9 ± 1.2[b]
100 (189.3)	14.9 ± 1.3	15.3 ± 1.4 (↓5)	15.7 ± 1.1 (↓4)	16.7 ± 1.1 (↓7)[b]
200 (378.6)	15.7 ± 2.1	10.7 ± 1.5* (↓34)	---	---
400 (757.2)	14.6 ± 1.7	---	---	---
0 (0)	16.5 ± 1.2	17.1 ± 0.9	17.1 ± 0.9	18.1 ± 0.9
15 (28.4)	16.1 ± 1.2	16.5 ± 1.6	16.5 ± 1.8	17.8 ± 1.5
50 (94.6)	16.7 ± 1.0	17.0 ± 0.8	17.1 ± 1.0	18.2 ± 1.0
150 (283.9)	17.1 ± 1.2	14.4 ± 1.1* (↓16)	15.0 ± 1.7* (↓12)	15.9 ± 1.9* (↓12)
Intermittent exposure				
0 (0)	15.8 ± 1.8	15.5 ± 1.3	15.3 ± 1.5	16.1 ± 0.7[b]
400 (189.3)	14.8 ± 1.1	15.3 ± 0.8	14.7 ± 1.2	16.2 ± 0.8[b]
800 (378.6)	14.8 ± 1.6	14.2 ± 1.8	14.7 ± 1.5	14.9 ± 2.5[b]
1600 (757.2)	14.7 ± 1.8	14.3 ± 1.6	14.3 ± 1.6	15. ± 0.8[b]
0 (0)	16.2 ± 1.4	17.3 ± 1.4	17.4 ± 1.3	18.2 ± 1.3
150 (71.0)	16.7 ± 1.4	17.3 ± 1.5	17.3 ± 1.5	17.8 ± 1.4
2400 (1135.8)	17.0 ± 1.2	15.9 ± 1.1* (↓8)	14.6 ± 1.2* (↓16)	---

[a]Landry et al. (1983, 1985). Data (mean ± SD) were obtained from Table 2 on page 91; $n = 12$, except as noted.
[b]$n = 6$ (only mice that underwent gross pathology were weighed).
*Statistically different from the controls at $p \leq 0.05$.

Table B.2. Rotating-rod Test Performance of Female C57BL/6 Mice Exposed to Chloromethane via Inhalation Continuously (22 Hours/Day) or Intermittently (5.5 Hours/Day) for 11 Days[a]

Concentration (ppm) (HEC, mg/m^3)	Terminal Rod Speed (rpm)		
	Day 4	Day 8	Day 11
Continuous exposure			
0 (0)	37 ± 7	34 ± 5	36 ± 5
100 (189.3)	36 ± 5	36 ± 7	33 ± 5
200 (378.6)	0.0[b]	---[c]	---
400 (757.2)	---[c]	---	---
0 (0)	41 ± 8	46 ± 12	39 ± 11
15 (28.4)	45 ± 9	49 ± 11	51 ± 12
50 (94.6)	39 ± 10	50 ± 14	51 ± 10
150 (283.9)	17 ± 10 (↓59)	12 ± 9* (↓74)	---[c]
Intermittent exposure			
0 (0)	34 ± 6	36 ± 6	35 ± 7
400 (189.3)	30 ± 4	39 ± 9	37 ± 3
800 (378.6)	29 ± 4* (↓15)	36 ± 7	34 ± 6
1600 (757.2)	26 ± 4* (↓15)	36 ± 7	33 ± 11
0 (0)	42 ± 7	45 ± 7[d]	40 ± 8
150 (71.0)	38 ± 6	40 ± 10	46 ± 7
2400 (1135.8)	27 ± 6* (↓36)	7 ± 15*[b] (↓84)	---

[a]Landry et al. (1983, 1985). Data (mean ± SD) were obtained from Table 4 on page 93; n = 10−12, except as noted. In cases when a mouse would repeatedly jump off the rod, the value was excluded from analysis.
[b]Moribund mice were scored as 0 rpm. Several mice were not considered moribund but scored zero on the test.
[c]Moribund or dead.
[d]n = 9.
*Statistically different from the controls at $p \leq 0.05$.

Table B.3. Terminal Absolute and Relative Organ Weights of Female C57BL/6 Mice Exposed to Chloromethane via Inhalation Continuously (22 Hours/Day) or Intermittently (5.5 Hours/Day) for 11 Days[a]

Concentration (ppm) (HEC, mg/m^3)	Liver		Kidney		Thymus	
	g	g/100 g	g	g/100 g	g	g/100 g
Continuous exposure						
0 (0)	1.03 ± 0.13	5.73 ± 0.46	---	---	0.073 ± 0.014	0.410 ± 0.072
100 (189.3)	0.93 ± 0.15	5.57 ± 0.71	---	---	0.072 ± 0.010	0.434 ± 0.049
0 (0)	0.99 ± 0.08	5.43 ± 0.30	0.23 ± 0.01	1.29 ± 0.06	0.070 ± 0.010	0.386 ± 0.050
15 (28.4)	0.95 ± 0.07	5.34 ± 0.32	0.23 ± 0.02	1.31 ± 0.06	0.054 ± 0.018* (↓23)	0.303 ± 0.085* (↓22)
50 (94.6)	1.01 ± 0.08	5.57 ± 0.38	0.23 ± 0.02	1.26 ± 0.08	0.055 ± 0.015* (↓21)	0.306 ± 0.084*(↓21)
150 (283.9)	0.86 ± 0.13* (↓13)	5.43 ± 0.32	0.22 ± 0.02	1.40 ± 0.10* (↑9)	0.020 ± 0.011* (↓71)	0.120 ± 0.057* (↓69)
Intermittent exposure						
0 (0)	0.80 ± 0.07	5.00 ± 0.36	---	---	0.068 ± 0.011	0.422 ± 0.048
400 (189.3)	0.80 ± 0.06	4.95 ± 0.34	---	---	0.061 ± 0.019	0.378 ± 0.117
800 (378.6)	0.80 ± 0.13	5.36 ± 0.20	---	---	0.065 ± 0.018	0.432 ± 0.073
1600 (757.2)	0.98 ± 0.06* (↑23)	6.14 ± 0.28* (↑23)	---	---	0.041 ± 0.007* (↓40)	0.258 ± 0.041* (↓39)
0 (0)	0.96 ± 0.10	5.29 ± 0.37	0.23 ± 0.02	1.34 ± 0.10	0.072 ± 0.012	0.397 ± 0.062
150 (71.0)	0.96 ± 0.12	5.38 ± 0.47	0.24 ± 0.02	1.30 ± 0.05	0.068 ± 0.020	0.381 ± 0.114
2400 (1135.8)	0.88 ± 0.20	5.76 ± 0.88	0.23 ± 0.02	1.60 ± 0.07 (↑19)	0.008 ± 0.003* (↓89)	0.051 ± 0.021* (↓87)

[a]Landry et al. (1983, 1985). Data (mean ± SD) were obtained from Table 3 on page 92; $n = 12$, except as noted. Kidneys were not weighed at the termination of the first exposure series.
*Statistically different from the controls at $p \leq 0.05$.

Table B.4. Principal Microscopic Findings in Female C57BL/6 Mice Exposed to Chloromethane via Inhalation Continuously for 11 Days[a]

Lesion	Exposure Group (ppm) (HEC, mg/m^3)						
	0 (0)	**15 (28.4)**	**50 (94.6)**	**100 (189.3)**	**150 (283.9)**	**200 (378.6)**	**400 (757.2)**
Number examined	28	12	12	6	12	12	22
Pyknosis/karyorrhexis of granule cells in the cerebellum							
Slight	0	0	0	6	0	0	2
Moderate	0	0	0	0	12	0	4
Severe	0	0	0	0	0	12	16
Total	0(0)[b]	0 (0)	0 (0)	6 (100)	12 (100)	12 (100)	22 (100)
Decreased size of hepatocytes due to decreased glycogen							
Slight	1	0	0	0	1	0	0
Moderate	0	0	0	1	1	1	7
Severe	0	0	0	1	7	11	14
Total	1 (4)	0 (0)	0 (0)	2 (33)	9 (75)	12 (100)	21 (95)
Hepatocyte degeneration or necrosis	0	0	0	0	0	1 (8)	18 (82)

[a]Data were obtained from Table 2 on page 30 of the Toxicological Review (U.S. EPA, 2001), referencing Landry et al. (1983, 1985).
[b]Number (percent) affected.

Table B.5. Duration Dependence of Principal Microscopic Findings in the 150-ppm Female C57BL/6 Mice Exposed to Chloromethane via Inhalation Continuously for 11 Days[a]

	ppm (HEC, mg/m^3)	Day 1	Day 2	Day 4	Day 6	Day 8	Day 11
Number necropsied	0 (0)	5	5	5	5	5	12
	150 (283.9)	5	5	5	5	5	12
Cerebellum							
Vacuolation of white matter (slight)	0 (0)	0	0	0	0	0	0
	150 (283.9)	0	0	0	1	0	12 (100)
Increased pyknosis/karyorrhexis of granule cells (multifocal)	0 (0)	0	0	0	0	0	0
	150 (283.9)	0	0	5 (100)[b]	2 (40)	5 (100)	12 (100)
Loss of cells in granule layer with focal severe areas containing macrophages	0 (0)	0	0	0	0	0	0
	150 (283.9)	0	0	0	0	4 (80)	12 (100)

[a]Data were obtained from Table 4 on page 47 of the Toxicological Review (U.S. EPA, 2001), referencing Landry et al. (1983, 1985).
[b]Number (percent) affected.

Table B.6. Principal Microscopic Findings in Female C57BL/6 Mice Exposed to Chloromethane via Inhalation Intermittently for 11 Days[a]

	Exposure Group (ppm) (HEC, mg/m^3)					
Lesion	**0 (0)**	**150 (71.0)**	**400 (189.3)**	**800 (378.6)**	**1600 (757.2)**	**2400 (1135.8)**
Number examined	28	12	6	6	17	12
Increased pyknosis and karyorrhexis of granule cells						
Slight	0	0	2 (33)	4 (67)	11 (65)	12 (100)
Decreased size of hepatocytes due to decreased glycogen						
Slight	8	0	1	0	0	0
Moderate	2	0	2	0	4	2
Severe	0	0	0	3	0	3
Total	10 (36)[b]	0	3 (50)	3 (50)	4 (24)	5 (42)

[a]Data were obtained from Table 5 on page 48 of the Toxicological Review (U.S. EPA, 2001), referencing Landry et al. (1983, 1985).
[b]Number (percent) affected.

Table B.7. Body Weights (g) of Sprague-Dawley Rats Exposed to Chloromethane via Inhalation for 72 Hours Followed by 12 Days of Recovery[a]

Postexposure Day	Concentration (ppm) (HEC, mg/m^3)					
	0 (0)[b]	200 (413)	500 (1033)	0[b]	1000 (2065)	2000 (4130)
Males						
0	295 ± 11	282 ± 9*	251 ± 12*	214 ± 9	149 ± 9*	---
1	296 ± 13	---	267 ± 9*	---	---	---
4 [3][c]	319 ± 13	312 ± 11	300 ± 10*	235 ± 10	128 ± 27*	---
6 [5][c]	327 ± 10	329 ± 12	307 ± 12*	251 ± 12	145 ± 43*	---
7 [7][c]	338 ± 12	341 ± 15	323 ± 12*	270 ± 10	190 ± 20*	---
11 [10][c]	351 ± 14	351 ± 18	336 ± 14	292 ± 12	218 ± 27*	---
Females						
0	180 ± 8	159 ± 20*	163 ± 12*	175 ± 10	125 ± 7*	---
1	180 ± 9	---	172 ± 11	---	---	---
4 [3][c]	193 ± 8	180 ± 10*	188 ± 10	180 ± 12	127 ± 26*	---
6 [5][c]	198 ± 9	185 ± 15*	192 ± 12	189 ± 10	139 ± 44*	---
7 [7][c]	205 ± 10	196 ± 10	199 ± 11	195 ± 11	179 ± 2*	---
11 [10][c]	209 ± 10	197 ± 16	203 ± 14	204 ± 1	190 ± 5	---

[a]Dow Chemical Company (1981). Data (mean ± SD) were obtained from Table 3 on page 37 and Table 5 on page 39; $n = 10$, except for the 1000-ppm group, where $n = 4-6$ in the males and 2−3 in the females beginning on Postexposure Day 3. Percent differences from controls are included in parentheses.

[b]The study was divided into two exposure groups, one group in which animals were exposed to 0, 200, and 500 ppm and the other in which rats were exposed to 0, 1000, and 2000 ppm. Therefore, the concurrent control group is presented with each concentration.

[c]Exposure for the 200-ppm group began 1 day later than the remaining groups; therefore, body weights of the 200-ppm animals were not reported for Day 1 postexposure, and the subsequent measurements for this group occurred 1 day earlier (actual day included in brackets).

*Statistically different from the controls at $p \leq 0.05$.

Table B.8. Selected Histopathological Findings in F344 Rats Following 72 Hours of Exposure to Chloromethane via Inhalation[a]

Microscopic Lesion	Concentration (ppm) (HEC, mg/m^3)					
	0 (0)[b]	200 (413)	500 (1033)	0 (0)[b]	1000 (2065)	2000 (4130)
Males						
Altered tinctorial properties of the hepatocytes	0	4	3	0	2	4
Females						
Altered tinctorial properties of the hepatocytes	0	0	0	0	5	2

[a]Dow Chemical Company (1981). Data (number affected) were obtained from Tables 20, 33, and 44 on pages 60, 79, and 94, respectively; $n = 5$.
[b]The study was divided into two exposure groups, one group in which animals were exposed to 0, 200, and 500 ppm and the other in which rats were exposed to 0, 1000, and 2000 ppm. Therefore, the concurrent control group is presented with each concentration.

Table B.9. Selected Histopathology in F344 Rats Following 9 Days of Exposure to Chloromethane via Inhalation During a 11-Day Period[a]

Microscopic Lesion	Concentration (ppm) (HEC, mg/m^3)		
	2000 (845)	3500 (1478)	5000 (2112)
Males			
Kidney—degeneration and necrosis of renal proximal convoluted tubules	8	10	10
Liver—hepatocellular degeneration	0	9	10
Testes—degeneration	10	10	10
Cerebellum—degeneration	0	0	3
Females			
Kidney—degeneration and necrosis of renal proximal convoluted tubules	0	5	10
Liver—hepatocellular degeneration	8	9	9
Cerebellum—degeneration	0	0	2

[a]Morgan et al. (1982). Data (number affected) were obtained from Table 1 on page 294; $n = 10$. Data for control groups were not presented.

Table B.10. Selected Histopathology in Mice Following 12 Days of Exposure to Chloromethane via Inhalation[a]

Microscopic Lesion	Strain of Mouse	Concentration (ppm) (HEC, mg/m^3)		
		500 (258)	1000 (516)	2000 (1033)
Males				
Liver—hepatocellular degeneration	C3H	2/5	0/4	4/5
	C57BL/6	3/5	3/5	5/5
	$B6C3F_1$	0/5	0/5	5/5
Cerebellum—degeneration	C3H	0/5	0/4	0/5
	C57BL/6	0/5	3/5	0/5
	$B6C3F_1$	0/5	0/5	0/5
Females				
Liver—hepatocellular degeneration	C3H	0/5	0/5	0/5
	C57BL/6	2/5	3/5	0/5
	$B6C3F_1$	0/5	0/5	4/5
Cerebellum—degeneration	C3H	0/5	0/5	0/5
	C57BL/6	0/5	5/5	4/4
	$B6C3F_1$	0/5	0/5	2/5

[a]Morgan et al. (1982). Data (number affected/number examined) were obtained from Table 1 on page 294. Data for control groups were not presented.

Table B.11. Specific Gravity Values for Rats Following 90 Days of Exposure to Chloromethane via Inhalation[a]

Time	Concentration (ppm)			
	0	50	150	400
Males				
Preexposure	1.045 ± 0.013	1.045 ± 0.007	1.042 ± 0.009	1.045 ± 0.007
Preterminal	1.043 ± 0.009	1.038 ± 0.010	1.036 ± 0.007	1.029 ± 0.010
Females				
Preexposure	1.037 ± 0.009	1.033 ± 0.011	1.031 ± 0.009	1.036 ± 0.010
Preterminal	1.027 ± 0.007	1.026 ± 0.008	1.017 ± 0.009	1.023 ± 0.006

[a]McKenna et al. (1981b). Data were obtained from Table 7 on page 33; $n = 10$.

Table B.12. Incidences of Lesions in Renal Cortex of Male B6C3F$_1$ Mice Exposed to Chloromethane via Inhalation for 24 Months[a]

Lesion	Exposure Group (ppm)			
	0	**50**	**225**	**1000**
Adenocarcinoma	0/120 (0)[b]	0/118 (0)	0/117 (0)	5/120 (4.2)
Papillary cyst, adenocarcinomas	0/120 (0)	0/118 (0)	0/117 (0)	1/120 (0.8)
Adenoma	0/120 (0)	0/118 (0)	2/117 (1.7)	12/120 (10)
Papillary cyst, adenomas	0/120 (0)	0/118 (0)	0/117 (0)	2/120 (1.7)
Tubuloepithelium hypertrophy, hyperplasia, and/or karyomegaly	0/120 (0)	0/118 (0)	0/117 (0)	44/120 (36.7)

[a]Data were obtained from Table 3 on page 17 of *Concise International Chemical Assessment Document (CICAD) 28, Methyl Chloride* (WHO, 2000), citing CIIT (1981).
[b]Number affected/number examined (percent affected).

APPENDIX C. BMD MODELING OUTPUTS FOR CHLOROMETHANE

There are no BMD modeling outputs for chloromethane.

APPENDIX D. REFERENCES

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