Toxicological Profile for Chloromethane

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U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

DISCLAIMER

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FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR.

Each profile includes the following:

(A)   The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance due to associated acute, intermediate, and chronic exposures;

(B)   A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, intermediate, and chronic health effects; and

(C)   Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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*Legislative Background

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the NPL, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

VERSION HISTORY

Date	Description
September 2023	Final toxicological profile released
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June 2009	Addendum to the toxicological profile released
December 1998	Final toxicological profile released

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ATSDR scientists review peer reviewers' comments and determine whether changes will be made to the profile based on comments. The peer reviewers' comments and responses to these comments are part of the administrative record for this compound.

The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1   OVERVIEW AND U.S. EXPOSURES

Chloromethane (CH_3Cl; CAS 74-87-3) is a natural and ubiquitous constituent of the oceans and atmosphere (both the troposphere and the stratosphere). It is a product of biomass combustion and is also created from biogenic emissions by wood-rotting fungi. Chloromethane is an impurity in vinyl chloride, which is used to make polyvinylchloride (PVC), so it can be released to the environment during the production or use of vinyl chloride or from burning PVC (PubChem 2021; WHO 1999). Therefore, chloromethane can be introduced into National Priorities List (NPL) sites from vinyl chloride wastes. Chloromethane is also released from burning plastic, cigarette smoke, the process of dismantling e-waste, interior materials in vehicles, and laundry products. Historically (i.e., more than 50 years ago), there were reports of accidental exposures from leaking refrigerators that used chloromethane as a refrigerant. However, because of its toxic effects and the availability of chlorofluorocarbons (CFCs) for use as refrigerants, chloromethane was phased out from this use (UNEP 1999).

Chloromethane has been detected at low levels in air and water, and may be released into soil. Chloromethane is most frequently detected in outdoor air, as the chemical is highly volatile. In the United States, averages of all of the arithmetic means at 208 locations and 9,168 observations were approximately 0.60 ppbv in 2021 and 0.57 ppbv in 2022 (EPA 2022c). Chloromethane has been detected in surface water, groundwater, drinking water, municipal and hazardous waste landfill leachate, and industrial effluents. When detected in water, concentrations appear to be in the ppb to ppt range, possibly due to the rapid volatilization of chloromethane. Chloromethane may be formed during the chlorination of drinking water and subsequently chloromethane was monitored as part of the Third Unregulated Contaminant Monitoring Rule (UCMR 3) as a List 1 Contaminant (EPA 2016). Out of 36,845 samples taken, only 283 (i.e., less than 1%) had concentrations above the minimum reporting level of 0.2 µg/L (EPA 2017b). Plumb (1991) conducted a study of groundwater samples from 479 waste disposal sites and found that chloromethane was detected at 20 of these regulated sites. A national water quality study was done for contaminants including chloromethane over the period of 1991–2010 (USGS 2014). For 40 aquifers used for drinking water, the percentage of all samples containing chloromethane was 3.37%. For 17 shallow groundwater aquifers beneath agricultural land, 1.81% of samples contained chloromethane and in 22 shallow groundwater aquifers beneath urban land, 4.11% of samples contained chloromethane (USGS 2014). There is little reporting of actual concentration values or ranges for groundwater detections in the available literature. The presence of chloromethane in groundwater may

result from both natural and anthropogenic sources. Information on background levels in soils and sediments are limited in the available literature to levels reported at hazardous waste sites and landfill leachate. Chloromethane is regulated by the U.S. Environmental Protection Agency (EPA) under the Clean Air Act (CAA) as a hazardous air pollutant (HAP) (EPA 2017a) and is identified as a toxic waste under the Resource Conversation and Recovery Act (RCRA) (EPA 2018a).

Based on the high vapor pressure of chloromethane, volatilization to the atmosphere will be an important transport process if it is released to surface water and soils. The low octanol/water partition coefficient (K_{ow}) for chloromethane suggests that it is unlikely to bioconcentrate/biomagnify in aquatic organisms. In the atmosphere, chloromethane is broken down through reactions with sunlight-generated hydroxyl radicals. The estimated atmospheric half-life ranges from 0.6 to 3 years. In soils, surface water, and groundwater, chloromethane can undergo hydrolysis and biotransformation; however, volatilization is the dominant fate process.

General population exposure to chloromethane is expected to be low. The most likely route of exposure to chloromethane is through inhalation of contaminated ambient air. Additionally, dermal and inhalation exposure may occur during domestic water use (e.g., bathing or washing activities) if the water contains chloromethane. Vapor intrusion of chloromethane into structures from contaminated soil and groundwater may result in indoor air levels of chloromethane in buildings and residences. Historically ($\geq$50 years ago), leaking refrigerators were a potential source of high exposure; however, this exposure route is only relevant for individuals with very old refrigeration equipment in which chloromethane is used as a refrigerant. Since chloromethane has been detected at hazardous waste sites, populations living near contaminated sites may be exposed. Occupational exposure to chloromethane occurs via inhalation of contaminated workplace air and by dermal contact with chloromethane vapor or liquids and products containing the compound.

1.2   SUMMARY OF HEALTH EFFECTS

Information on chloromethane toxicity comes primarily from inhalation studies in laboratory animals, although some epidemiology and case studies have examined the toxicity in humans. Much of the data available for this chemical comes from comprehensive inhalation toxicological studies. Fifty-nine laboratory animal toxicity studies with health effects data have been identified: 58 inhalation, 1 oral, and 0 dermal studies.

1. RELEVANCE TO PUBLIC HEALTH

As illustrated in Figure 1-1, the neurological, hepatic, cardiovascular, developmental, and male reproductive systems appear to be sensitive to inhalation exposure to chloromethane. A systematic review of the available literature was conducted on these sensitive endpoints, including both human and animal data for cardiovascular and neurological endpoints and animal data for hepatic, male reproductive, and developmental endpoints. The following hazard identification conclusions were determined based on systematic review (see Appendix C for details):

- Neurological effects are a presumed health effect with inhalation exposure.

- Hepatic effects are a presumed health effect with inhalation exposure.

- Male reproductive effects are a presumed health effect with inhalation exposure.

- Cardiovascular effects are not classifiable with inhalation exposure.

- Developmental effects are not classifiable with inhalation exposure.

Cardiovascular Effects. Cardiovascular effects have been reported in humans following exposure to chloromethane via inhalation in several human case reports (Hansen et al. 1953; Kegel et al. 1929; McNally 1946; Spevak et al. 1976; Verriere and Vachez 1949; Scharnweber et al. 1974) and a group of Icelandic fishermen accidentally exposed to high levels associated with a refrigerant leak (Rafnsson and Gudmundsson 1997; Rafnsson and Kristbjornsdottir 2014). However, these data are limited by small subject numbers, lack of information on lifestyle factors for individuals being assessed (e.g., smoking and drinking water), and/or unknown exposure levels. In other human studies, the risk of death from circulatory disease was not increased in synthetic rubber workers exposed to chloromethane (Holmes et al. 1986) and no changes in cardiovascular function were noted following controlled acute-duration exposures to concentrations up to 150 ppm in human volunteers (Stewart et al. 1980). A study in dogs exposed to very high, lethal concentrations reported an initial increase in blood pressure followed by a precipitous decrease in blood pressure and heart rate; however, these effects were potentially secondary to central nervous system (CNS) depression (von Oettingen et al. 1949, 1950). No other identified animal studies evaluated functional cardiovascular endpoints (e.g., heart rate or blood pressure). A few inhalation studies reported elevated heart weights in rats and mice following intermediate- or chronic-duration exposure (CIIT 1981; McKenna et al. 1981b); however, no exposure-related changes in heart histology were observed following acute-, intermediate-, or chronic-duration exposure to chloromethane (CIIT 1981; McKenna et al. 1981a, 1981b; Mitchell et al. 1979).

Figure 1-1. Health Effects Found in Animals Following Inhalation Exposure to Chloromethane

Concentration$_{ADJ}$ (ppm)

Effects in Animals[a]

>500

138-178

107-132

71-101

40

27

9

Acute: Respiratory, gastrointestinal, hematological, renal, adrenal, and male reproductive effects

Acute: Decreased survival, inanition, decreased body weight, and thymus effects

Intermediate: Lung, renal, spleen, and thymus effects

Chronic: Decreased survival, decreased body weight; cancer; hepatic, renal, spleen, thymus, and male reproductive effects

Acute: Developmental effects

Intermediate: Decreased survival, decreased body weight

Acute: Hepatic and neurological effects

Intermediate: Hepatic effects, male reproductive effects

Chronic: Cardiovascular effects

Intermediate: Neurological effects

Chronic: Neurological effects

0.5 ppm ◯ **Acute MRL**

0.3 ppm ◯ **Intermediate MRL**

0.03 ppm ● **Chronic MRL**

[a]Exposure concentrations have been duration-adjusted for continuous exposure.

Hepatic Effects. Human data regarding hepatic effects are limited to case studies with findings suggestive of hepatic damage, including elevated urinary coproporphyrin II levels, jaundice, or liver disease (Jones 1942; Kegel et al. 1929; Mackie 1961; Spevak et al. 1976; Weinstein 1937; Wood 1951). However, damage to the liver has been consistently reported in animal studies following inhalation exposure, with elevated liver weights and/or histopathological changes (hepatocellular degeneration, fatty metamorphosis, necrosis, cytomegaly, etc.) observed in rats, mice, and guinea pigs at concentrations ranging from 100 to 2,000 ppm (Chellman et al. 1986b; CIIT 1981; Dunn and Smith 1947; Landry et al. 1985; McKenna et al. 1981b; Mitchell et al. 1979; Morgan et al. 1982). Mice appear to be the most susceptible species in these studies. Additionally, chloromethane exposure was associated with changes in liver enzyme levels in some studies (Chellman et al. 1986b; CIIT 1981).

Neurological Effects. Numerous case studies of individuals who were highly exposed to chloromethane resulting from refrigeration system leaks consistently reported neurological effects, including fatigue, progressive drowsiness, staggering, headache, nausea, slurred speech, blurred and double vision, mental confusion, tremor, vertigo, muscular weakness, muscular cramping and rigidity, sleep disturbances, ataxia, convulsions, and cyanosis alternating with coma, delirium, and restlessness (see Section 2.15 for citations). Similar effects were noted in a group of Icelandic fishermen acutely exposed via a refrigeration leak, with neurological effects persisting for years in some individuals (Gudmundsson 1977). In other human studies, neurological effects were not noted in fabricating workers exposed to chloromethane (NIOSH 1976) or following controlled acute-duration exposures to concentrations up to 200 ppm in volunteers (Putz-Anderson et al. 1981a, 1981b; Stewart et al. 1980). Experimental animal studies consistently show a range of neurological impacts in multiple species following acute-, intermediate-, and chronic-duration inhalation exposures. Effects in animals range from poor performance in sensorimotor tests and incoordination at ≥149 ppm (McKenna et al. 1981b) to severe clinical signs of toxicity at ≥200 ppm (e.g., ataxia, paralysis, prostration; see Section 2.15 for citations). Histopathological lesions on the cerebellum and spinal cord have also been observed at concentrations ≥51 ppm (Chellman et al. 1986a, 1986b; CIIT 1981; McKenna et al. 1981a; Morgan et al. 1982; Jiang et al. 1985; Landry et al. 1985).

Male Reproductive Effects. One case study was located that described a potential relationship between high chloromethane exposure and impotence (Mackie 1961). No other human studies were located evaluating the impact of chloromethane toxicity. Experimental studies in rats reported decreased fertility and increased pre- and post-implantation loss when males exposed to acute-duration exposures ≥3,000 ppm were mated with unexposed females (Chellman et al. 1986c; Working and Bus 1986;

Working et al. 1985a, 1985b). Decreased fertility was also observed in a 2-generation study in rats at exposures ≥472 ppm following mating with similarly exposed or unexposed females (Hamm et al. 1985). Additionally, sperm effects and/or testicular and epididymal lesions were consistently noted in rodents at acute-duration exposures ≥3,500 ppm (Chapin et al. 1984; Chellman et al. 1986a; 1987; Morgan et al. 1982) and ≥997 ppm for ≥6 months (CIIT 1981).

Developmental Effects. No studies were located regarding developmental effects in humans after exposure to chloromethane. In mice, there is some evidence of an increase in heart defects in fetuses following maternal exposure to concentrations ≥479 ppm during gestation (Wolkowski-Tyl et al. 1983a, 1983b). However, John-Greene et al. (1985) concluded that use of a longitudinal, rather than cross-sectional, sectioning technique utilized by Wolkowski-Tyl et al. (1983a) may have resulted in tissue damage that was misinterpreted as evidence of heart anomalies. While the sectioning technique used in Wolkowski-Tyl et al. (1983b) was considered appropriate by John-Greene et al. (1985), reported cardiovascular effects, particularly thrombosis, were attributed to fixation artifacts since fixed tissue, rather than fresh tissue, was used. In rats, decreased growth and delayed skeletal development were observed at maternally toxic concentrations (1,492 ppm) (Wolkowski-Tyl et al. 1983a). No such developmental effects were noted in rabbits following gestational exposure to concentrations up to 1,012 ppm (Theuns-van Vliet 2016).

Cancer Effects. Human data regarding carcinogenicity are limited. Increased risk of death from kidney cancer was reported in a 47-year follow-up of the Icelandic fisherman cohort acutely exposed to chloromethane from a refrigerant leak (Rafnsson and Kristbjornsdottir 2014); however, the risk of death from cancer was not elevated in a cohort of synthetic rubber workers exposed to chloromethane (Holmes et al. 1986). In most case-control studies, no associations were observed between estimated occupational exposure to chloromethane and non-Hodgkin's lymphoma (NHL), pancreatic cancer, or renal cell carcinoma (Barry et al. 2011; Dosemeci et al. 1999; Kernan et al. 1999). However, NHL (specifically the follicular lymphoma subtype) was associated with occupational exposure to chloromethane in women with a specific CYP2E1 rs2070673 polymorphism (Barry et al. 2011), and a small group of black men with a high probability of occupational chloromethane exposure had an increased risk of death from pancreatic cancer (Kernan et al. 1999). In animals, chronic inhalation exposure resulted in renal adenocarcinomas in male mice; no exposure-related neoplastic effects were observed in similarly exposed female mice or rats of either sex (CIIT 1981).

The International Agency for Research on Cancer (IARC) and the EPA have determined that chloromethane is not classifiable as to its carcinogenicity in humans (EPA 2001; IARC 2019). The National Toxicology Program (NTP) has not evaluated chloromethane's carcinogenicity potential.

1.3 MINIMAL RISK LEVELS (MRLs)

The inhalation database was considered adequate for derivation of acute-, intermediate-, and chronic-duration inhalation MRLs for chloromethane. As illustrated in Figure 1-2, the neurological system appears to be the most sensitive target of chloromethane toxicity following inhalation exposure. Cardiovascular, hepatic, male reproductive, and developmental effects also have relatively low LOAEL values. The MRL values are summarized in Table 1-1 and discussed in greater detail in Appendix A.

The oral database was not considered adequate for deriving oral MRLs. It is limited to a single study evaluating liver histology following acute-duration exposure; no adverse effects were observed.

Figure 1-2. Summary of Sensitive Targets of Chloromethane – Inhalation

Neurological endpoints are the most sensitive targets of chloromethane inhalation exposure.
Numbers in circles are the lowest LOAELs for all health effects in animals[a]; no human data were identified.

[a]Concentrations have been duration-adjusted for continuous exposure.

Table 1-1. Minimal Risk Levels (MRLs) for Chloromethane[a]

Exposure route	Exposure duration	MRL	Critical effect	POD type	POD value	Uncertainty/ modifying factor	Reference
Inhalation	Acute	**0.5 ppm** (1 mg/m^3)	Degeneration of cerebellar granule cells	NOAEL$_{HEC}$	46 ppm	UF: 90	Landry et al. 1985
	Intermediate	**0.3 ppm** (0.6 mg/m^3)	Impaired sensorimotor function	NOAEL$_{HEC}$	9 ppm	UF: 30	McKenna et al. 1981b
	Chronic	**0.03 ppm** (0.06 mg/m^3)	Swelling and slight degeneration of axons in the spinal cord	LOAEL$_{HEC}$	9 ppm	UF: 300	CIIT 1981
Oral	**No oral MRLs were derived for any duration.**						

[a]See Appendix A for additional information.

HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level POD = point of departure; UF = uncertainty factor

CHAPTER 2. HEALTH EFFECTS

2.1   INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of chloromethane. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to chloromethane, but may not be inclusive of the entire body of literature. A systematic review of the scientific evidence of the health effects associated with exposure to chloromethane was also conducted; the results of this review are presented in Appendix C.

Summaries of the human observational studies are presented in Table 2-1. Animal inhalation studies are presented in Table 2-2 and Figure 2-2, and animal oral studies are presented in Table 2-3 and Figure 2-3; no dermal data were identified for chloromethane.

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects (SLOAELs) are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute

respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health. Levels of exposure associated with cancer (Cancer Effect Levels, CELs) of chloromethane are indicated in Table 2-2 and Figure 2-2.

A User's Guide has been provided at the end of this profile (see Appendix D). This guide should aid in the interpretation of the tables and figures for LSEs and MRLs.

The health effects of chloromethane have been evaluated in epidemiological, human controlled trial and experimental animal studies. As illustrated in Figure 2-1, the vast majority of the health effects data come from inhalation exposure studies in animals. Animal data from inhalation studies are available for each health effect category and exposure duration category. Much of the data for chloromethane comes from toxicity studies which evaluated a suite of endpoints. The most reported effects on systems from the literature include reproductive, neurological, renal, and hepatic effects of chloromethane. Case reports and cohort studies also evaluated or summarized the impact chloromethane had on the nervous and cardiovascular systems and potential association with various cancers. Only a single oral exposure study in animals was identified, which evaluated potential hepatic effects following acute-duration exposure.

As outlined in Chapter 1, the neurological, hepatic, cardiovascular, developmental, and male reproductive systems appear to be sensitive targets of toxicity following inhalation exposure to chloromethane; the neurological endpoints appear to be the most sensitive (see Figure 1-2). A systematic review was conducted on the available human and animal inhalation studies for these endpoints. The information in these studies indicate the following on the potential targets of chloromethane toxicity:

- **Cardiovascular Endpoints.** Data are inadequate to conclude whether cardiovascular effects are associated with chloromethane exposure. Case reports and data from a cohort of accidentally exposed individuals suggest that chloromethane exposure may increase risk of death from cardiovascular disease or result in other cardiac abnormalities such as tachycardia, increased pulse rate, and sustained changes in blood pressure. One study in dogs reports elevated blood pressure followed by a precipitous decrease in blood pressure and heart rate prior to death following inhalation exposure to very high chloromethane levels; findings may be secondary to CNS depression. While a few studies report elevated heart weight following intermediate- or chronic-duration exposure, no exposure-related changes in heart histology were observed following inhalation exposure in experimental animal studies.

- **Hepatic Endpoints.** Hepatic effects are a presumed health effect for humans exposed to chloromethane via inhalation based on a high level of evidence in rodents following acute-, intermediate-, and chronic-duration inhalation exposure. Hepatic lesions and elevated liver weights have been observed in rodents following acute-, intermediate-, or chronic-duration inhalation exposure. Hepatic enzyme changes have also been observed in some studies. Mice appear to be more sensitive to hepatic effects than rats or guinea pigs.

- **Neurological Endpoints.** Neurological effects are a presumed health effect associated with chloromethane exposure via inhalation based on a low level of evidence in humans and a high level of evidence in animals. Case reports clearly indicate neurological effects associated with chloromethane exposure. Epidemiological studies provide limited evidence in humans, while animal inhalation studies consistently report effects including impaired performance on sensorimotor tests, mild-to-severe clinical signs of toxicity (e.g., incoordination, ataxia, paralysis), and histopathological lesions on the cerebellum and spinal cord.

- **Male Reproductive Endpoints.** Male reproductive effects are a presumed health effect associated with chloromethane exposure via inhalation based on a high level of evidence from rodent studies. Decreased fertility attributable to sperm effects and testicular lesions in male rats has been observed following acute- and intermediate-duration exposures. Additional studies report testicular damage in rats and mice following acute-, intermediate-, and chronic-duration exposure to chloromethane.

- **Developmental Endpoints.** Developmental effects are not a classifiable health effect for humans based on results of animal studies. Experimental animal studies provide low evidence of an association between chloromethane exposure via inhalation and adverse developmental outcomes based on interspecies differences. Reduced growth and delayed skeletal development were observed in rats, heart defects were observed in mice, and no developmental effects were noted in rabbits. The toxicological significance of the heart defects in mice has been questioned, and the defects may have been misdiagnosed and/or artifacts of the fixation and sectioning methods used.

2. HEALTH EFFECTS

Figure 2-1. Overview of the Number of Studies Examining Chloromethane Health Effects*

Most studies examined the potential neurological, hepatic, and renal effects of chloromethane
Fewer studies evaluated health effects in humans than animals (counts represent studies examining endpoint)

*Includes studies discussed in Chapter 2. A total of 96 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Table 2-1. Health Effects Evaluated in Humans Exposed to Chloromethane—Epidemiological Studies

Reference, study type, and population	Exposure	Outcome evaluated	Result

Barry et al. 2011
 	
Case-control; 518 women with NHL (classified by subtype) and 597 controls (Connecticut)
	Job-exposure matrix used to estimate subject's probability and intensity of occupational exposure to chloromethane	Total NHL
		  CYP2E1 polymorphism (TT)
		  CYP2E1 polymorphism (TA/AA)
			↔ (ever versus never exposed)
			↑ (ever versus never exposed)
			↔ (ever versus never exposed)

		Diffuse large B-cell lymphoma
		  CYP2E1 polymorphism (TT)
		  CYP2E1 polymorphism (TA/AA)
			↔ (ever versus never exposed)
			↔ (ever versus never exposed)
			↔ (ever versus never exposed)

		Follicular lymphoma
		  CYP2E1 polymorphism (TT)
		  CYP2E1 polymorphism (TA/AA)
			↑ (ever versus never exposed)
			↑ (ever versus never exposed)
			↔ (ever versus never exposed)

Delfino et al. 2003
 	
Panel study; 22 Hispanic children (10–16 years old) with asthma living in Los Angeles community with high traffic density (California)
	Daily mean (SD) in ppb:
	  0.58 (0.14)
		Asthma symptoms
		  Bothersome
		  Severe (interfere with daily activities)
			Association with daily air levels
			↔
			↔

Dosemeci et al. 1999
 	
Case-control study; 438 white subjects (273 men, 165 women) diagnosed with renal cell carcinoma and 687 controls (462 men, 225 women) (Minnesota)
	Job-exposure matrix used to estimate subject's probability of occupational exposure to chloromethane	Renal cell carcinoma
		  All
		  Men
		  Women
			
			↔ (ever versus never exposed)
			↔ (ever versus never exposed)
			↔ (ever versus never exposed)

Holmes et al. 1986
 	
Occupational cohort; 852 males employed ≥1 month at a synthetic rubber manufacturing plant; cohort mortality compared to U.S. averages (Louisiana)
	Job-exposure matrix used to estimate subject's probability and intensity of occupational exposure to chloromethane	Standard mortality ratio
		  All causes
		  All malignant neoplasms
		    Digestive
		    Respiratory
		    Lymphatic
		    Unspecified
		  Circulatory system diseases
			
			↓ (observed versus expected)
			↔ (observed versus expected)
			↔ (observed versus expected)
			↔ (observed versus expected)
			↔ (observed versus expected)
			↔ (observed versus expected)
			↔ (observed versus expected)

Table 2-1. Health Effects Evaluated in Humans Exposed to Chloromethane—Epidemiological Studies

Reference, study type, and population	Exposure	Outcome evaluated	Result

Kernan et al. 1999
 	
Case-control; 63,097 patients that died from pancreatic cancer and 252,386 controls that died from causes other than cancer (United States)
	Job-exposure matrix used to estimate subject's probability and intensity of occupational exposure to chloromethane	Pancreatic cancer
		  All
		  Men
		  Women
		  Black men
			↔ (exposed versus unexposed)
			↔ (exposed versus unexposed)
			↔ (exposed versus unexposed)
			↑ (high probability of exposure versus no exposure)

NIOSH 1976
 	
Cross-sectional; 122 workers exposed to chloromethane (144 male, 8 female) and 49 unexposed workers (46 male, 3 female) for seven different locations of the same company (United States)
	Mean (range) [range from facility means] air levels in ppm:
	  33.57 (1.8–70.0) [8.46–58.72]
	
	Mean (range) [range of facility means] worker breath levels in ppm:
	  13.32 (0.4–79.5) [10.81–24.19]
		Neurobehavioral and neurofunctional tasks
		
		EEG
			↔ (exposed versus unexposed)
			
			↔ (exposed versus unexposed)

Rafnsson and Gudmundsson 1997
 	
Occupational cohort (32-year follow-up); 24 male crew members from an Icelandic fishing boat that experienced accidental exposure; 120 referent Icelandic fishermen (Iceland)
	Estimates not available; acute-duration exposure occurred due to leaking refrigerant on fishing vessel.	Death (all causes)
		  Cancer
		  Cardiovascular diseases
			↑ (exposed versus referent)
			↔ (exposed versus referent)
			↑ (exposed versus referent)

Rafnsson and Kristbjornsdottir 2014
 	
Occupational cohort (47-year follow-up); 27 male crew members from an Icelandic fishing boat that experienced accidental exposure; 135 referent Icelandic fishermen (Iceland)
	Estimates not available; acute-duration exposure occurred due to leaking refrigerant on fishing vessel.	Death (all causes)
		  All cancers
		  Kidney cancer
		  All cardiovascular disease
		  Acute coronary heart disease
		  Cerebrovascular disease
		  Suicide
			↑ (exposed versus referent)
			↔ (exposed versus referent)
			↑ (exposed versus referent)
			↑ (exposed versus referent)
			↑ (exposed versus referent)
			↑ (exposed versus referent)
			↑ (exposed versus referent)

↑ = association with increase; ↓ = association with decrease; ↔ = no association; CYP2E1 = cytochrome P450 2E1; EEG = electroencephalogram; NHL = non-Hodgkin's lymphoma; SD = standard deviation

Table 2-2. Levels of Significant Exposure to Chloromethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Putz-Anderson et al. 1981a									
1	Human 4–12 B	3 hours	0, 100, 200	NX	Neuro	200			
Putz-Anderson et al. 1981b									
2	Human 12 B	3 hours	0, 199	NX	Neuro	199			
Stewart et al. 1980									
3	Human 4 M, 4 F	2–5 days; 1, 3, or 7.5 hours/day	0, 20, 100, 150, 50+100+150 average 100	CS, BC, HE, UR, NX	Resp	150			
					Cardio	150			
					Hemato	150			
					Neuro	150			
Smith and von Oettingen 1947a, 1947b									
4	Monkey (NS) 2–5 NS	2 weeks 6 days/week 6 hours/day	300, 500, 2,000	LE, CS	Death			2,000	5/5 died
					Neuro	500		2,000	Motor impairments, incoordination, seizures, loss of consciousness
Burek et al. 1981									
5	Rat (Sprague-Dawley) 20 M, 20 F	72 hours continuous	0, 198, 504, 976, 1,950	CS, BW, HE, BC, UR, GN, OW, HP	Death			976	6/10 males and 8/10 females died; 100% mortality at 1,950 ppm
					Bd wt	504 F 198 M	504 M	976	LOAEL: 15% decrease in body weight in males
									Serious LOAEL: 29–30% decrease in body weight
					Resp		1,950		Congestion and edema of the lungs in animals that died
					Hemato	504	976		Increased red blood cell count, hemoglobin, and hematocrit (secondary to dehydration)

2. HEALTH EFFECTS

	Table 2-2. Levels of Significant Exposure to Chloromethane – Inhalation (ppm)								
Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Hepatic		198		Males: Decreased absolute and relative liver weight and altered tinctorial appearance of hepatocytes (slight) Females: Increased lipid accumulation and slight extramedullary hematopoiesis
					Renal	198 M 504 F	504 M	976	LOAEL: multifocal renal tubules in males Serious LOAEL: renal failure and histopathological changes in the kidney in both sexes, alterations in urinalysis in both sexes, increased BUN in females
					Neuro	504	976		Lethargy
					Repro	198 M	504 M		Sperm granulomas, decreased sperm in the tubule lumen, interstitial edema, coagulated proteinaceous obstruction of lumen, inflammation, sperm granuloma formation, testicular atrophy secondary to alterations
Burek et al. 1981									
6	Rat (Sprague-Dawley) 20 M, 20 F	48 hours continuous	0, 196, 501, 972, 1,968	LE, CS, BW, HE, BC, UR, GN, OW, HP	Death			972 F 1,968 M	1/20 females at 972 ppm and 14/20 males and 10/20 females at 1,958 ppm died
					Bd wt	972 F	1,968 F		18% decrease in body weight
						501 M		972 M	20% decrease in body weight
					Resp	1,968			
					Hemato	972	1,968		Increased red blood cell count, hemoglobin, and hematocrit (secondary to dehydration)
					Hepatic	972 F	1,968 F		Dark, congested, or mottled liver

Table 2-2. Levels of Significant Exposure to Chloromethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
							196 M		Decreased liver weight
					Renal	501		972	Renal tubular necrosis, increased renal tubular cytoplasmic homogeneity, and increased lipid accumulation in renal tubular cells; alterations in urinalysis
					Neuro	501	972		Lethargy
					Repro	196 M	501 M		Sperm granulomas, decreased sperm in the tubule lumen, interstitial edema, coagulated proteinaceous obstruction of lumen
Chapin et al. 1984									
7	Rat (Fischer-344) 2–8 M	12 days 4-5 days/week 6 hours/day	0, 3,500	BC, HP	Repro		3,500		Decreased serum testosterone, delayed spermiation, seminiferous epithelium vacuolation, and bilateral epididymal granulomas
Chellman et al. 1986a									
8	Rat (Fischer-344) 5–12 M	2 days 6 hours/day	0, 7,500	LE, CS, BW, OW, HP	Death			7,500	8/12 died
					Repro	7,500			Bilateral epididymal granulomas
Chellman et al. 1986a									
9	Rat (Fischer-344) 5 M	5 days 6 hours/day	0, 5,004	LE, CS, BW, OW, HP	Death			5,004	1/5 died
					Bd wt			5,004	20% decreased body weight
					Hepatic	5,004			Hepatocellular degeneration - cloudy swelling of hepatocytes, obliteration of sinusoids
					Renal			5,004	Necrosis of proximal convoluted tubules
					Endocr	5,004			Vacuolation of cell cytoplasm in the adrenal cortex

Table 2-2. Levels of Significant Exposure to Chloromethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Neuro			5,004	Severe cerebellar degeneration (granule layer), tremors, ataxia, and limb paralysis
					Repro			5,004	Severe epididymis granulomas, pachytene spermatocytes and early stage spermatids in the tubular lumen, slight separation of early stage spermatids, and formation of multinucleated giant cells
Chellman et al. 1986c									
10	Rat (Fischer-344) 20-40 M	5 days 6 hours/day prior to breeding	0, 3009	HP, RX	Repro			3,009	Increased pre- and post-implantation loss in mated females, and increased infiltration of neutrophils and macrophages into interstitium of cauda epididymis
Chellman et al. 1987									
11	Rat (Fischer-344) 18 M	5 days 6 hours/day	0, 3056	BW, OW, HP	Bd wt	3,056			
					Repro			3,056	Decreased testes weight, delayed spermiation, decreased sperm production, and sperm motility and an increase in abnormal sperm
Dunn and Smith 1947; Smith and von Oettingen 1947a, 1947b									
12	Rat (NS) 10–59 NS	2 weeks 6 days/week 6 hours/day	0, 300, 500, 1,000, 2,000, 3,000, 4,000	LE, CS, HP	Death			2,000	50% mortality; 100% mortality at ≥3,000 ppm
					Resp	1,000		2,000	Lung congestion and slight edema
					Hepatic	1,000		2,000	Fat accumulation, centrilobular necrosis
					Renal	1,000		2,000	Renal tubule necrosis
					Neuro	1,000	2,000		Agitation, hunched posture

Table 2-2. Levels of Significant Exposure to Chloromethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Morgan et al. 1982									
13	Rat (Fischer-344) 10 M, 10 F	9 days 6 hours/day	0, 2,000, 3,500, 5,000	LE, CS, HP	Death			3,500 F 5,000 M	2/10 females at 3,500 ppm and 6/10 males and 5/10 females at 5,000 ppm sacrificed moribund
					Gastro	2,000	3,500		Diarrhea
					Hepatic	2,000 M	2,000 F 3,500 M		Minimal hepatocyte degeneration
					Renal	2,000 F		3,500 F 2,000 M	Degeneration and necrosis of proximal convoluted tubules
					Endocr	2,000	3,500		Clear droplets in endothelial cytoplasm assumed to be fatty degeneration of adrenals
					Neuro	3,500		5,000	Hindlimb paralysis, forelimb incoordination, minimal cerebellar degeneration (granule layer)
					Repro			2,000 M	Reduction in spermatids and sperm, separation of spermatocytes and early stage spermatids with sloughing of cells into the lumen and fusion into giant cells
Wolkowski-Tyl et al. 1981a, 1983a									
14	Rat (Fischer-344) 25 F	13 days 6 hours/day GDs 7–19	0, 102, 479, 1,492	LE, BW, FI, WI, RX, DX	Bd wt	102		479	21% reduction in body weight gain from GD 7 to 15
					Repro	1,492			
					Develop	479	1,492		Delayed skeletal development (reduced ossification and fewer caudal bones); 10% decrease in fetal body weight in both sexes, and 4% decrease in crown-rump length in females

Table 2-2. Levels of Significant Exposure to Chloromethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Working and Bus 1986									
15	Rat (Fischer-344) 10–30 M	5 days prior to mating, 6 hours/day	0, 1,000, 3,000	CS, RX	Repro	1,000		3,000	≥16% decrease in fertilization rate
Working et al. 1985a									
16	Rat (Fischer-344) 40 M	5 days prior to mating, 6 hours/day	0, 1,000, 3,000	CS, BW, RX	Bd wt	1,000	3,000		16% decrease in body weight
					Repro	1,000		3,000	Postimplantation loss in female rats mated with exposed males, and persistent decreased fertility
Working et al. 1985b									
17	Rat (Fischer-344) 40 M	5 days prior to mating, 6 hours/day	0, 1,000, 3,000	CS, GN, OW, HP, RX	Repro	1,000		3,000	Decreased number of live and total implants, increased post-implantation loss, reversible disruption of spermatogenesis, transient reduction in testes weights
Chellman et al. 1986b									
18	Mouse (B6C3F1) 5–15 M	6 hours	500, 1,000, 1,500, 2,000, 2,500	LE, CS	Death			2,200	LC$_{50}$
					Neuro			2,500	Tremors, ataxia, and forelimb/hindlimb paralysis
Chellman et al. 1986b									
19	Mouse (B6C3F1) 6 M	6 hours	0, 1,500	LE, CS, BC	Hepatic			1,500	Increased serum ALT and hepatocellular necrosis and cytoplasmic vacuolization
Chellman et al. 1986b									
20	Mouse B6C3F1 36-45 M	2 weeks 5 days/week 6 hours/day	0, 1,500	LE, CS, BC, BI, UR, HP, OF	Death			1,500	5/45 died
					Renal	1,500			
					Neuro			1,500	Multiple degenerative and necrotic foci in cerebellar granular cell layer

2. HEALTH EFFECTS

Table 2-2. Levels of Significant Exposure to Chloromethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Chellman et al. 1986b									
21	Mouse (B6C3F1) NS B	2 weeks 5 days/week 6 hours/day	0, 1,500	OF	Renal		1,500		Increased renal cell regeneration (3-fold increased thymidine incorporation)
Dunn and Smith 1947; Smith 1947; Smith and von Oettingen 1947a, 1947b									
22	Mouse (Swiss, Strain A, C3H) 20–61 NS	2 weeks 6 days/week 6 hours/day	0, 300, 500, 1,000, 2,000, 3,000	LE, CS, UR, HP	Death			1,000	50% mortality; 100% mortality at ≥2,000 ppm
					Resp			2,000	Lung congestion
					Hepatic			2,000	Centrilobular necrosis, fatty metamorphosis
					Renal	500	1,000	2,000	LOAEL: Hemoglobinuria Serious LOAEL: Renal necrosis, fatty metamorphosis, hemoglobin globules and casts
					Neuro	300		500	Neuromuscular abnormalities, impaired gait, hindlimb drag
[Histopathology assessed at 2,000 ppm only]									
Jiang et al. 1985									
23	Mouse (C57BL/6) 10 F	2 weeks 5 days/week 6 hours/day	0, 1,500	LE, CS, GN, HP	Death			1,500	2/10 died
					Renal		1,500		Slight degeneration of proximal tubules
					Neuro			1,500	Motor incoordination, severe cerebellar degeneration (granule layer)
Landry et al. 1985									
24	Mouse (C57BL/6) 12 F	11 days 5.5 hours/day	0, 150, 2,400	LE, CS, BW, GN, OW, HP, NX	Death			2,400	All sacrificed moribund after 8 or 9 days
					Bd wt	150	2,400		16% decrease in body weight on day 8
					Hemato	150	2,400		Enlarged spleen and hemoglobinuria (suggestive of extramedullary hematopoiesis)

Table 2-2. Levels of Significant Exposure to Chloromethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Hepatic	150	2,400		Decreased hepatocyte size; glycogen depletion
					Renal	150	2,400		Slight multifocal degeneration and regeneration of tubules
					Immuno	150	2,400		Thymus atrophy; decrease in absolute and relative thymus weight
					Neuro	150		2,400	Sedation, hindlimb rigidity, impaired motor coordination on day 8, slight cerebellar degeneration (granular layer)
					Other noncancer	150		2,400	Inanition (exhaustion caused by lack of nourishment), decreased food consumption
Landry et al. 1985									
25	Mouse (C57BL/6) 12 F	11 days 5.5 hours/day	0, 400, 800, 1,600	LE, CS, BW, GN, OW, HP, NX	Bd wt	1,600			
					Hepatic		400		Decreased hepatocyte size; glycogen depletion
					Renal	1,600			
					Immuno	800	1,600		Thymus atrophy; decreased absolute and relative thymus weight
					Neuro		400	1,600	LOAEL: slight cerebellar degeneration (granular layer) SLOAEL: sedation, hindlimb rigidity

2. HEALTH EFFECTS

Table 2-2. Levels of Significant Exposure to Chloromethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Landry et al. 1985									
26	Mouse (C57BL/6) 12 F	11 days 22 hours/day	0, 15, 50, 150	LE, CS, BW, GN, OW, HP, NX	Death			150	All sacrificed moribund after 10.5 days
					Bd wt	50	150		12% decrease in body weight
					Hepatic	50	150		Decreased hepatocyte size; glycogen depletion
					Renal	150			
					Immuno	50	150		Decreased absolute and relative thymus weight
					Neuro	50[b]	150		Moderate cerebellar degeneration (granular layer); impaired motor coordination
					Other noncancer	50		150	Inanition (exhaustion caused by lack of nourishment), decreased food consumption
Landry et al. 1985									
27	Mouse (C57BL/6) 12 F	11 days 22 hours/day	0, 100, 200, 400	LE, CS, BW, GN, OW, HP, NX	Death			200	100% mortality by day 5
					Bd wt	100		200	32% decrease in body weight by day 4
					Hepatic	50	100		Decreased hepatocyte size; glycogen depletion
					Renal	100			
					Immuno	100			
					Neuro		100	200	LOAEL: slight cerebellar degeneration (granular layer) Serious LOAEL: ataxia, prostration, inability to perform motor assessment
					Other noncancer	100		200	Inanition (exhaustion caused by lack of nourishment), decreased food consumption, decreased feces amount

Table 2-2. Levels of Significant Exposure to Chloromethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Morgan et al. 1982									
28	Mouse (B6C3F1) 5 M, 5 F	12 days 6 hours/day	0, 500, 1,000, 2,000	LE, CS, HP	Death			2,000	100% mortality/moribundity
					Hepatic	1,000	2,000 F	2,000 M	Minimal-to-moderate hepatocellular degeneration in both sexes; hepatocellular necrosis in males
					Renal	500	1,000	2,000	LOAEL: minimal-to-moderate basophilic renal tubules in both sexes and hematuria in females Serious LOAEL: minimal-to-severe degeneration and necrosis of renal proximal convoluted tubules
					Neuro	1,000		2,000	Ataxia in both sexes; minimal cerebellar degeneration (granular layer) in females
Morgan et al. 1982									
29	Mouse (C57Bl/6) 5 M, 5 F	12 days 6 hours/day	0, 500, 1,000, 2,000	LE, CS, HP	Death			2,000	100% mortality
					Hepatic		500	2,000 M	LOAEL: minimal hepatocellular degeneration Serious LOAEL: severe hepatocellular degeneration and necrosis
					Renal	500	1,000	2,000	LOAEL: minimal basophilic renal tubules in males and hematuria in females Serious LOAEL: moderate degeneration and necrosis of renal proximal convoluted tubules
					Neuro	500	1,000 M	1,000 F	Cerebellar degeneration (granular layer; minimal in males, moderate-to-severe in females)

Table 2-2. Levels of Significant Exposure to Chloromethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Morgan et al. 1982									
30	Mouse (C3H) 5 M, 5 F	12 days 6 hours/day	0, 500, 1,000, 2,000	LE, CS, HP	Death			2,000 F	100% mortality
					Hepatic	2,000 F	500 M		Minimal hepatocellular degeneration
					Renal	500	1,000	2,000	LOAEL: minimal-to-moderate basophilic renal tubules in both sexes; hematuria in females Serious LOAEL: severe degeneration and necrosis of renal proximal convoluted tubules in both sexes; hematuria in males
					Neuro	1,000		2,000	Ataxia
von Oettingen et al. 1949, 1950									
31	Mouse (White) 20 NS	7 hours	2,900, 3,100, 3,400, 3,750, 5,100	LE, CS	Death			3,080	LC$_{50}$
					Neuro			2,900	Convulsions, decreased activity
Wolkowski-Tyl et al. 1981a, 1983a									
32	Mouse (C57BL/6); fetus (B6C3F1) 33 F	12 days 6 hours/day GDs 6–17	0, 102, 479, 1,492	LE, BW, FI, WI, RX, DX	Death			1,492	100% mortality/moribundity
					Neuro	479		1,492	Tremors, piloerection, difficulty righting, focal granule cell necrosis in cerebellum
					Repro	479			
					Develop	102		479	Increased heart defects (reduction or absence of valves and muscles)

Table 2-2. Levels of Significant Exposure to Chloromethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Wolkowski-Tyl et al. 1981b, 1983b									
33	Mouse (C57BL/6); fetus (B6C3F1) 74–77 F	12 days 6 hours/day GDs 6–17	0, 251, 502, 749	LE, BW, OW, RX, DX	Death			749	6/75 died, 1/75 moribund
					Bd wt	251		749	41% decrease in maternal body weight gain during gestation
					Hepatic	749			
					Neuro	251		502	Ataxia; tremors, convulsions, increased then reduced activity, hypersensitivity to touch and sound at 749 ppm
					Repro	502			
					Develop	251		502	Increased heart defects (reduction or absence of valves and muscles)
Dunn and Smith 1947; Smith and von Oettingen 1947a, 1947b									
34	Guinea Pig (NS) 22–62 NS	6 days 6 hours/day	0, 300, 500, 1,000, 2,000, 3,000	LE, CS, HP	Death			1,000	50% mortality by day 4; 100% mortality at ≥2,000 ppm
					Resp	1,000		2,000	Marked lung congestion and edema
					Hepatic	500	1,000		Fatty metamorphosis
					Renal	500	1,000		Fatty metamorphosis
					Neuro	500		1,000	Convulsions, lost righting reflex, backward arching of the head, neck, and spine
McKenna et al. 1981a									
35	Dog (Beagle) 3 M	3 days 23.5 hours/ day	0, 197, 496	CS, BC, HE, OP, GN, OW, HP, NX	Bd wt	496			
					Resp	496			
					Cardio	496			
					Gastro	496			
					Hemato	496			
					Hepatic	496			
					Renal	496			

Table 2-2. Levels of Significant Exposure to Chloromethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Dermal	496			
					Ocular	496			
					Endocr	496			
					Neuro	197		496	Clinical signs of neurotoxicity (incoordination, impaired gait, limb paresis and stiffness, tremors, ataxia); Slight, multifocal lesions in brain and spinal cord; vacuolization, swollen axons, and loss of axons
					Repro	496			
Smith and von Oettingen 1947a, 1947b									
36	Dog (NS) 6–12 NS	2 weeks 6 days/week 6 hours/day	0, 300, 500, 1,000, 2,000, 3,000	LE, CS	Death			1,000	5/10 died; 100% mortality at 3,000 ppm
					Resp	500		1,000	Dyspnea (prior to death)
					Neuro	300		500	Severe clinical signs of neurotoxicity (e.g., tremors, spasticity, impaired gait)
McKenna et al. 1981a									
37	Cat (NS) 3 M	3 days 23.5 hours/ day	0, 192, 501	CS, BW, HE, BC, OP, GN, OW, HP	Bd wt	501			
					Resp	501			
					Cardio	501			
					Gastro	501			
					Hemato	501			
					Hepatic	501			
					Renal	501			
					Dermal	501			
					Ocular	501			
					Endocr	501			
					Neuro	501			
					Repro	501			

Table 2-2. Levels of Significant Exposure to Chloromethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Smith and von Oettingen 1947a, 1947b									
38	Cat (NS) 4 NS	6 days 6 hours/day	2,000	LE, CS	Neuro			2,000	Weakness, ataxia, loss of righting reflex
Smith and von Oettingen 1947a, 1947b									
39	Rabbit (NS) 4–12 NS	2 weeks 6 days/week 6 hours/day	0, 300, 500, 1,000, 2,000, 3,000, 4,000	LE, CS	Death			2,000	Decreased survival; 100% mortality at 4,000 ppm
					Neuro			2,000	Neuromuscular dysfunction of hindlegs; spastic adduction
INTERMEDIATE EXPOSURE									
Smith and von Oettingen 1947a, 1947b									
40	Monkey (NS) 2 NS	120 days 6 days/week 6 hours/day	300, 500	LE, CS	Death			500	2/2 died
					Neuro	300		500	Progressive debility, prostration, loss of consciousness
CIIT 1981									
41	Rat (Fischer-344) 10 M, 10 F	6 months 5 days/week 6 hours/day	0, 51, 224, 997	LE, CS, BW, HE, BC, BI, UR, OP, OW, GN, HP	Bd wt	224	997		10–11% decreased body weight
					Resp	224 F 997 M		997 F	Interstitial pneumonia with peribronchiolitis and perivasculitis, alveolar hyperplasia, alveolar luminal infiltrates, subacute tracheitis
					Cardio	997			
					Gastro	997			
					Musc/skel	997			
					Hepatic	997			
					Renal	997			
					Dermal	997			
					Ocular	997			
					Endocr	997			
					Immuno	997			
					Neuro	997			

Table 2-2. Levels of Significant Exposure to Chloromethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Repro	224 M 997 F		997 M	Degeneration and atrophy of seminiferous tubules; sperm granulomas
Dunn and Smith 1947; Smith and von Oettingen 1947a, 1947b									
42	Rat (NS) 18–59 NS	175 days 6 days/week 6 hours/day	0, 300, 500, 1,000	LE, CS, HP	Death			1,000	100% mortality
					Resp	1,000			
					Hepatic	1,000			
					Renal	1,000			
					Neuro	1,000			
Hamm et al. 1985									
43	Rat (Fischer-344) 40 M, 80 F	2-generation study 12–19 weeks per generation 5–7 days/week 6 hours/day	0, 151, 472, 1,502	CS, BW, GN, OW, HP, RX, DX	Bd wt	472	1,502		10–20% decrease in F0 body weight gain
					Repro	151 M	472 M	1,502 M	LOAEL: decreased number of fertile F0 males, decreased number of litters per copulation plug in F0 rats Serious LOAEL: 100% F0 male sterility, atrophy of the seminiferous tubules, epididymal granulomas
					Develop	472			
McKenna et al. 1981b									
44	Rat (Sprague-Dawley) 10 M, 10 F	93 days 5 days/week 6 hours/day	0, 51, 149, 399	LE, BW, OW, GN, HP, BC, CS, UR, HE, NX	Bd wt	399			
					Resp	399			
					Cardio	399			
					Gastro	399			
					Hemato	399			
					Musc/skel	399			
					Hepatic	399 F 149 M	399 M		Increased relative liver weight
					Renal	399			

Table 2-2. Levels of Significant Exposure to Chloromethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Dermal	399			
					Immuno	399			
					Neuro	51[c]	149		Impaired sensorimotor function
					Repro	399 M			
Mitchell et al. 1979									
45	Rat (Fischer-344) 10 M, 10 F	90 days 5 days/week 6 hours/day	0, 368, 741, 1,473	BW, OW, FI, HP, BC, CS, UR, HE, OP	Bd wt	741 F 368 M	1,473 F 741 M	1,473 M	LOAEL: 10–11% decrease in body weight Serious LOAEL: 22% decrease in male body weight
					Resp	1,473			
					Cardio	1,473			
					Hemato	1,473			
					Musc/skel	1,473			
					Hepatic	1,473			
					Renal	1,473			
					Dermal	1,473			
					Ocular	1,473			
					Endocr	1,473			
					Immuno	1,473			
					Neuro	1,473			
					Repro	1,473			
CIIT 1981									
46	Mouse (B6C3F1) 9 M, 11 F	6 months 5 days/week 6 hours/day	0, 51, 224, 997	LE, BW, BI, OW, GN, HP, BC, CS, UR, HE, OP	Bd wt	224 F 997 M	997 F		16% decrease in body weight
					Resp	997			
					Cardio	997			
					Hemato	997			
					Musc/skel	997			

Table 2-2. Levels of Significant Exposure to Chloromethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Hepatic	224	997		Hepatocellular degeneration (males: diffuse that was midzonal; females: diffuse or multifocal centrilobular)
					Renal	997 F 224 M	997 M		Decreased absolute and relative kidney weight
					Dermal	997			
					Ocular	997			
					Endocr	997			
					Immuno	224	997		Lymphoid depletion of spleen in males and females; thymic lymphoid necrosis in females
					Repro	997			
					Neuro	997			
McKenna et al. 1981b									
47	Mouse (CD-1) 10 M, 10 F	94 days 5 days/week 6 hours/day	0, 51, 149, 399	LE, BW, OW, GN, HP, CS, NX	Resp	399			
					Cardio	399 F 149 M	399 M		Increased relative heart weight
					Gastro	399			
					Hemato	399			
					Musc/skel	399			
					Hepatic	399 M 149 F	399 F		Increased relative liver weight
					Renal	399			
					Dermal	399			
					Immuno	399			
					Neuro	399			
					Repro	399 M			

Table 2-2. Levels of Significant Exposure to Chloromethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Mitchell et al. 1979									
48	Mouse (B6C3F1) 10 M, 10 F	90 days 5 days/week 6 hours/day	0, 368, 741, 1,473	BW, OW, FI, HP, BC, CS, UR, HE, OP	Bd wt	1,473			
					Resp	1,473			
					Cardio	1,473			
					Gastro	1,473			
					Hemato	1,473			
					Musc/skel	1,473			
					Hepatic	368	741		Increased relative liver weight
					Renal	1,473			
					Dermal	1,473			
					Ocular	1,473			
					Endocr	1,473			
					Immuno	1,473			
					Neuro	1,473			
					Repro	1,473			
Smith and von Oettingen 1947a, 1947b									
49	Mouse (Swiss, Strain A, C3H) 22–34 NS	266 days 6 days/week 6 hours/day	0, 300, 500, 1,000	LE, CS	Death			500	82% mortality in adults, 27% mortality in "young" animals; 100% mortality at 1,000 ppm
					Neuro	300		500	Persistent neuromuscular abnormalities, impaired gait, hindlimb drag
Smith and von Oettingen 1947a, 1947b									
50	Guinea Pig (NS) 22–36 NS	266 days 6 days/week 6 hours/day	0, 300, 500, 1,000	LE, CS	Death			500	84% mortality in adult mice; 53% mortality in "young" mice; 100% mortality at 1,000 ppm
					Neuro	500		1,000	Progressive weakness, inability to walk, convulsions, loss of righting reflex

Table 2-2. Levels of Significant Exposure to Chloromethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
McKenna et al. 1981b									
51	Dog (Beagle) 4 M	93 days 5 days/week 6 hours/day	0, 51, 149, 399	LE, BW, OW, GN, HP, CS, UR, HE, BC	Resp	399			
					Cardio	399			
					Gastro	399			
					Hemato	399			
					Musc/skel	399			
					Hepatic	399			
					Renal	399			
					Dermal	399			
					Ocular	399			
					Immuno	399			
					Neuro	399			
					Repro	399			
Smith and von Oettingen 1947a, 1947b									
52	Dog (NS) 6–12 NS	211 days 6 days/week 6 hours/day	0, 300, 500, 1,000	LE, CS	Death			500	4/6 dogs died; 100% mortality at 1,000 ppm
					Resp	500		1,000	Dyspnea (prior to death)
					Neuro	300		500	Severe clinical signs of neurotoxicity (e.g., tremors, spasticity, impaired gait)
Dunn and Smith 1947; Smith and von Oettingen 1947a, 1947b									
53	Cat (NS) 4 NS	32 days 6 days/week 6 hours/day	2,000	LE, CS, HP	Death			2,000	4/4 died
					Resp			2,000	Gasping, pulmonary congestion
					Neuro			2,000	Inability to walk, extensor spasms, heightened reflexes
Smith and von Oettingen 1947a, 1947b									
54	Rabbit (NS) 4–12 NS	266 days 6 days/week 6 hours/day	0, 300, 500, 1,000, 2,000	LE, CS	Death			500	50% mortality; 100% mortality at 1,000 ppm

2. HEALTH EFFECTS

Table 2-2. Levels of Significant Exposure to Chloromethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Theuns-van Vliet 2016									
55	Rabbit (New Zealand) 22 F	23 days 6 hours/day GDs 6–28	0, 265, 511, 1012	CS, BW, FI, GN, OW, DX, RX	Bd wt	1,012			
					Repro	1,012			
					Develop	1,012			
CHRONIC EXPOSURE									
CIIT 1981									
56	Rat (Fischer-344) 10 M, 10 F	12 months 5 days/week 6 hours/day	0, 51, 224, 997	LE, BW, BI, OW, GN, HP, BC, CS, UR, HE, OP	Bd wt	997 M 224 F	997 F		10% decrease in body weight
					Resp	997			
					Cardio	997 F 224 M	997 M		Increased absolute and relative heart weight
					Gastro	997			
					Hemato	997			
					Musc/skel	997			
					Hepatic	997 F 224 M	997 M		Increased serum ALT levels
					Renal	997			
					Dermal	997			
					Endocr	997			
					Immuno	997			
					Neuro	997			
					Repro	224 M 997 F		997 M	Degeneration and atrophy of seminiferous tubules
CIIT 1981									
57	Rat (Fischer-344) 20 M, 20 F	18 months 5 days/week 6 hours/day	0, 51, 224, 997	LE, BW, BI, OW, GN, HP, BC, CS, UR, HE, OP, NX	Bd wt	997 F 224 M	997 M		12% decrease in body weight
					Resp	997			
					Cardio	997			
					Gastro	997			

Table 2-2. Levels of Significant Exposure to Chloromethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Hemato	997			
					Musc/skel	997			
					Hepatic	997			
					Renal	997			
					Dermal	997			
					Endocr	997			
					Immuno	997			
					Neuro	997			
					Repro	224 M 997 F		997 M	Degeneration and atrophy of seminiferous tubules; sperm granulomas

CIIT 1981

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
58	Rat (Fischer-344) 65–68 M; 57–61 F	21–24 months 5 days/week 6 hours/day	0, 51, 224, 997	LE, BW, BI, OW, GN, HP, BC, CS, UR, HE, OP, NX	Bd wt	224 F 997 M	997 F		10% decrease in body weight
					Resp	997			
					Cardio	997 F 224 M	997 M		Increased relative heart weight
					Gastro	997			
					Hemato	997			
					Musc/skel	997			
					Hepatic	997			
					Renal	997			
					Dermal	997			
					Ocular	997			
					Endocr	997			
					Immuno	997			
					Neuro	997			
					Repro	224 M 997 F		997 M	Degeneration and atrophy of seminiferous tubules; sperm granulomas

2. HEALTH EFFECTS

Table 2-2. Levels of Significant Exposure to Chloromethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
CIIT 1981									
59	Mouse (B6C3F1) 10 M, 10 F	12 months 5 days/week 6 hours/day	0, 51, 224, 997	LE, BW, BI, OW, GN, HP, BC, CS, UR, HE, OP	Death			997 F	10% decrease in survival
					Bd wt	224	997		15–18% decrease in body weight
					Resp	997			
					Cardio	224 F 997 M	997 F		Increased absolute and relative heart weight
					Hemato	997			
					Musc/skel	997			
					Hepatic	224	997		Increased absolute and relative liver weight in females; Increased serum ALT, necrosis, cytomegaly, karyomegaly, and polykaryocytes in males
					Renal	997 F 224 M	997 M		Renal tubule hyperplasia
					Dermal	997			
					Ocular	997			
					Endocr	997			
					Immuno	997			
					Neuro	997			
					Repro	997			

2. HEALTH EFFECTS

								Less serious	Serious	
Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL		LOAEL	LOAEL	Effects
CIIT 1981										
60	Mouse (B6C3F1) 7 M; 8–10 F	18 months 5 days/week 6 hours/day	0, 51, 224, 997	LE, BW, BI, OW, GN, HP, BC, CS, UR, HE, OP, NX	Death				997 F	17% decrease in survival
					Bd wt	224			997	20–25% decrease in body weight
					Resp	997				
					Cardio	997				
					Hemato	997				
					Musc/skel	997				
					Hepatic	224		997 F	997 M	LOAEL: increased absolute and relative liver weight
										Serious LOAEL: increased serum ALT, centrilobular degeneration, karyomegaly, and cytomegaly
					Renal	997 F 224 M		997 M		Renal tubule hyperplasia
					Dermal	997				
					Ocular	997				
					Endocr	997				
					Immuno	224		997		Diffuse splenic atrophy in mice that died
					Neuro			51[d]	997	LOAEL: swelling and degeneration of axons in spinal cord Serious LOAEL: tremor, paralysis, altered neurofunction (abnormal gait and reflexes), minimal-to-mild degeneration of cerebellar granule cell neurons
					Repro	224 M 997 F			997 M	Testicular seminiferous tubule degeneration and atrophy

Table 2-2. Levels of Significant Exposure to Chloromethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
CIIT 1981									
61	Mouse (B6C3F1) 20–32 M; 57–68 F	21–24 months 5 days/week 6 hours/day	0, 51, 224, 997	LE, BW, BI, OW, GN, HP, BC, CS, UR, HE, OP, NX	Death			997	100% mortality
					Bd wt	224		997	Body weight decreased by 31% in males and 36% in females in animals sacrificed moribund at 21–22 months
					Resp	997			
					Cardio	51 F 997 M	224 F		Increased relative heart weight
					Hemato	997			
					Musc/skel	997			
					Hepatic	224		997	Necrosis, cytomegaly, karyomegaly, and polykaryocytes (males sacrificed at 21 months, females at 22 months)
					Renal	224	997		Renal tubule hyperplasia
					Dermal	997			
					Ocular	997			
					Endocr	997			
					Immuno	224 F 997 M	997 F		Splenic atrophy and mild-to-moderate lymphoid depletion of the spleen and thymus
					Neuro		51[d]	997	LOAEL: swelling and degeneration of axons in spinal cord Serious LOAEL: tremor, paralysis, altered neurofunction (abnormal gait and reflexes), minimal-to-mild degeneration of cerebellar granule cell neurons
					Repro	224 M 997 F		997 M	Testicular degeneration and atrophy

Table 2-2. Levels of Significant Exposure to Chloromethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Cancer			997 M	CEL: renal cortex adenocarcinomas, metastatic fibrosarcoma in the lung

Green shading indicates critical study selected for MRL derivation.

[a]The number corresponds to the entries in Figure 2-2.
[b]This value was used to derive the acute-duration inhalation MRL. The NOAEL of 50 was converted to a NOAEL$_{HEC}$ of 46 ppm and then divided by a total uncertainty factor of 100 resulting in a MRL of 0.5 ppm. See Appendix A for more detailed information regarding the MRL.
[c]This value was used to derive the intermediate-duration inhalation MRL. The NOAEL of 31 was converted into a NOAEL$_{HEC}$ of 9 ppm and then divided by a total uncertainty factor of 30 resulting in a MRL of 0.3 ppm. See Appendix A for more detailed information regarding the MRL.
[d]This value was used to derive the chronic-duration inhalation MRL. The LOAEL of 51 was converted to a LOAEL$_{HEC}$ of 9 ppm and then divided by a total uncertainty factor of 300 resulting in a MRL of 0.03 ppm. See Appendix A for more detailed information regarding the MRL.

ALT = alanine aminotransferase; B = both males and females; BC = serum (blood) chemistry; BI = biochemical changes; BUN = blood urea nitrogen; BW or Bd wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; F = female(s); FI = food intake; Gastro = gastrointestinal; GD = gestational day; GN = gross necropsy; HE or Hemato = hematological; HEC = human equivalent concentration; HP = histopathology; Immuno = immunological; LC$_{50}$ = median lethal concentration; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = Minimal Risk Level; Musc/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; NX = neurological function; OF = organ function; OP = ophthalmology; OW = organ weight; Repro = reproductive; Resp = respiratory; RX = reproductive function; UR = urinalysis; WI = water intake
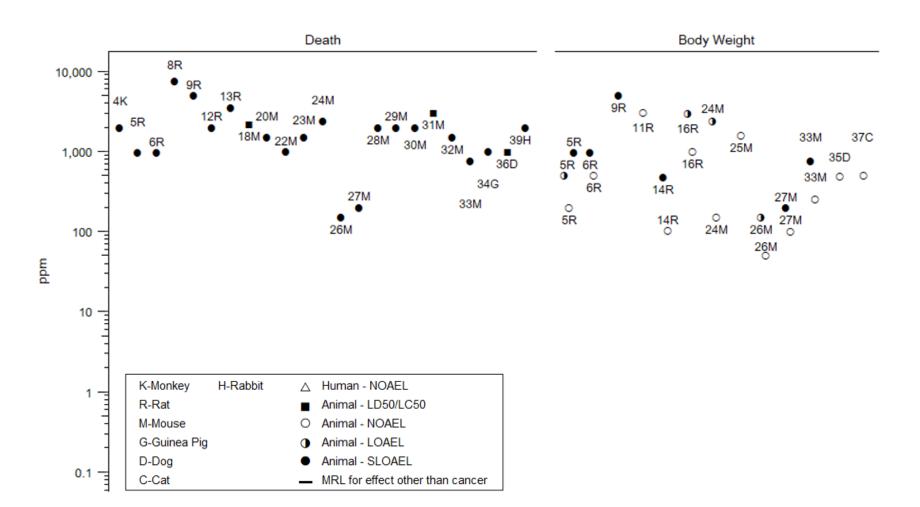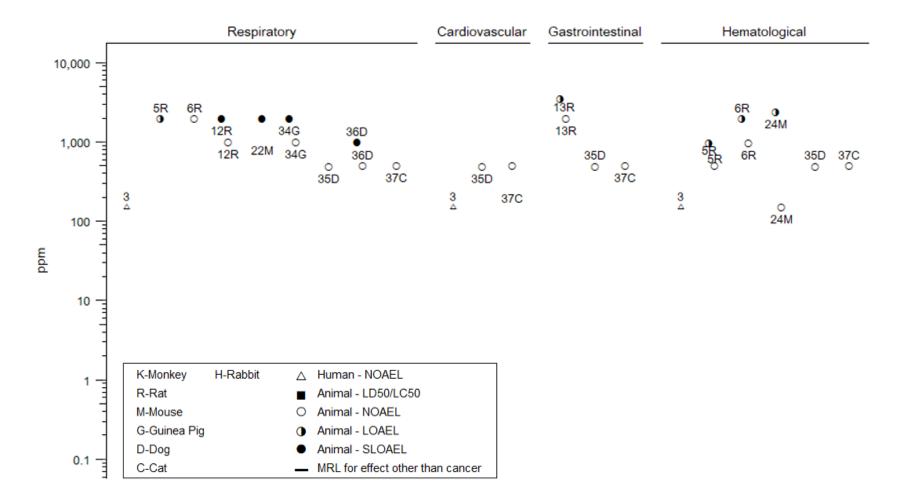
Figure 2-2. Levels of Significant Exposure to Chloromethane – Inhalation
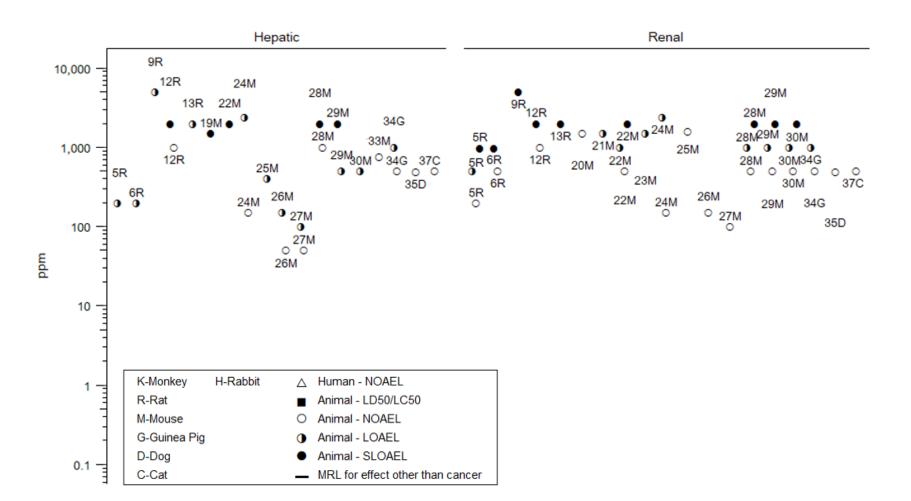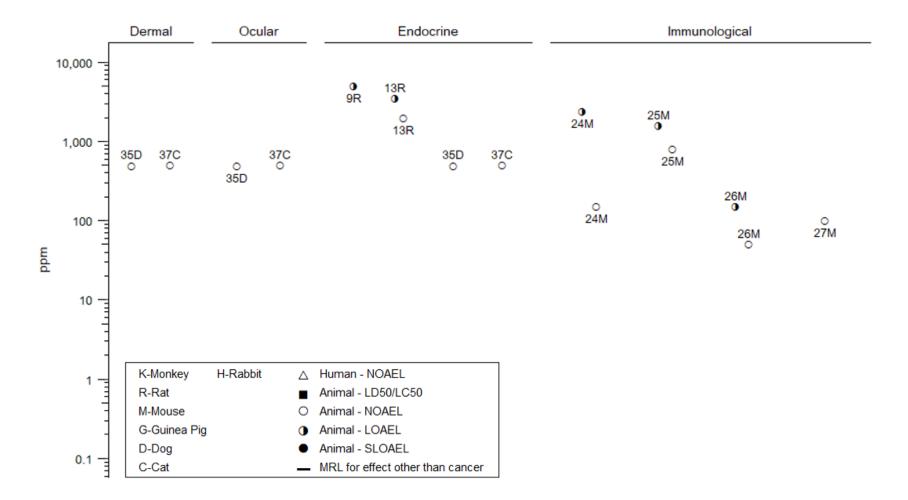## Acute (≤14 days)

2. HEALTH EFFECTS

Figure 2-2. Levels of Significant Exposure to Chloromethane – Inhalation
Acute (≤14 days)

2. HEALTH EFFECTS

Figure 2-2. Levels of Significant Exposure to Chloromethane – Inhalation
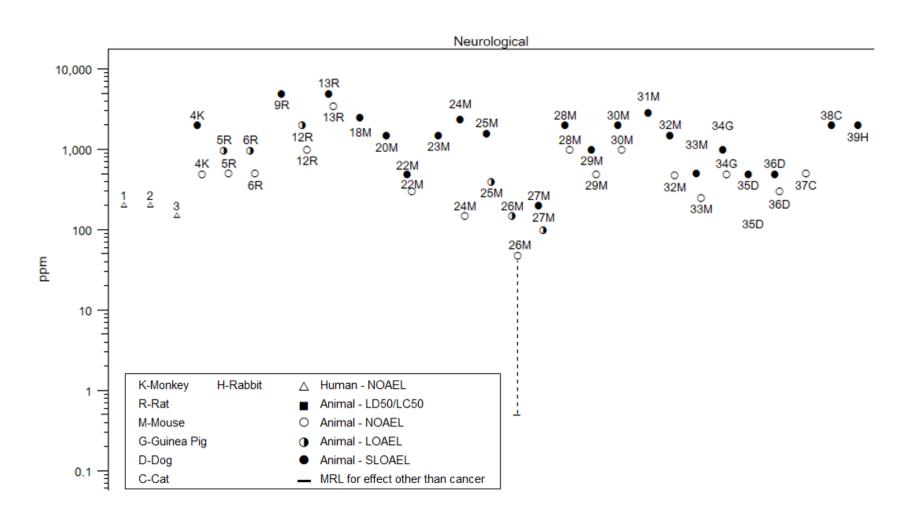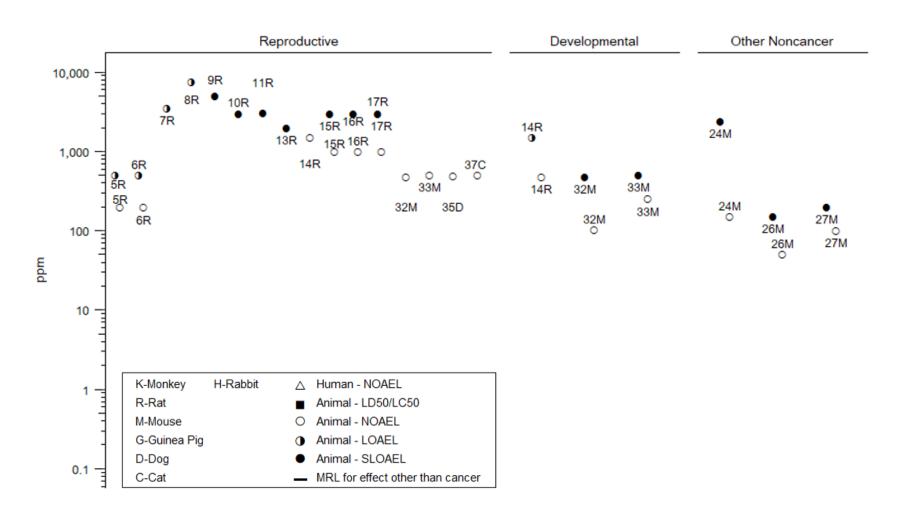Acute (≤14 days)

2. HEALTH EFFECTS

Figure 2-2. Levels of Significant Exposure to Chloromethane – Inhalation
Acute (≤14 days)

Figure 2-2. Levels of Significant Exposure to Chloromethane – Inhalation
Acute (≤14 days)

Figure 2-2. Levels of Significant Exposure to Chloromethane – Inhalation
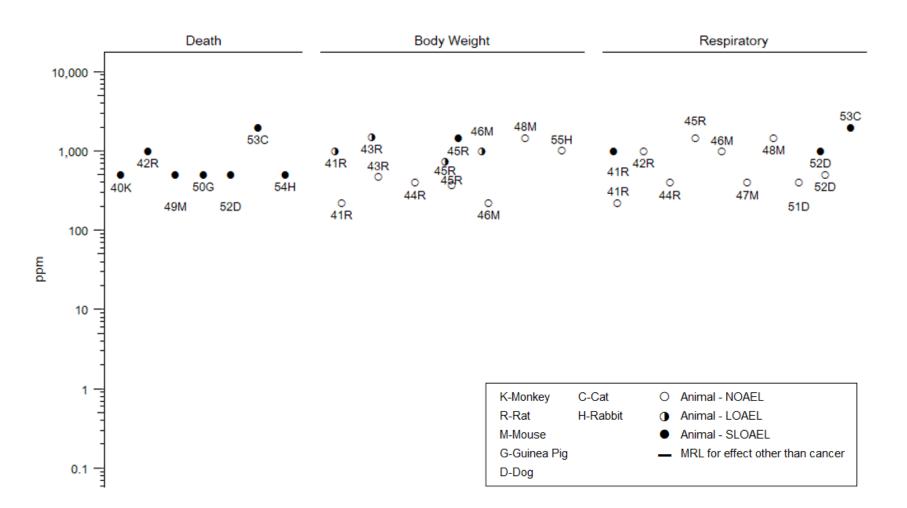## Acute (≤14 days)
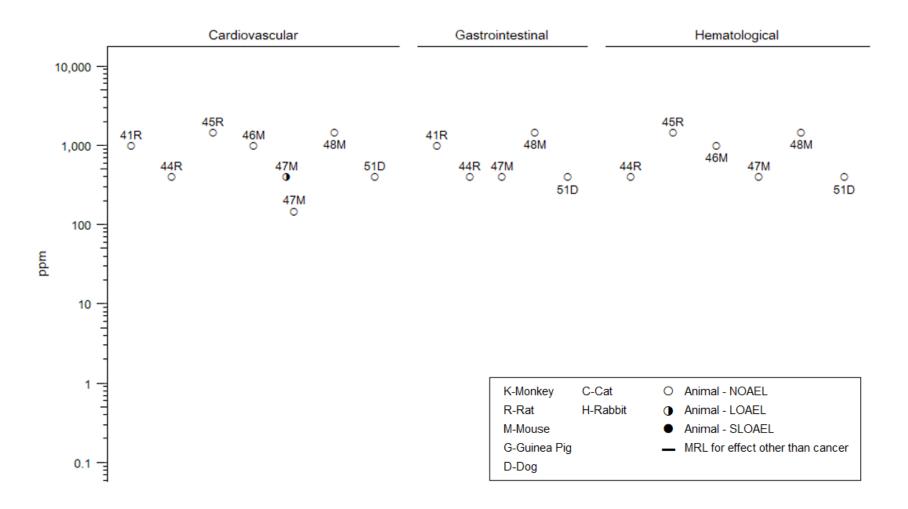
2. HEALTH EFFECTS

Figure 2-2. Levels of Significant Exposure to Chloromethane – Inhalation
Intermediate (15-364 days)

Figure 2-2. Levels of Significant Exposure to Chloromethane – Inhalation
Intermediate (15-364 days)

Figure 2-2. Levels of Significant Exposure to Chloromethane – Inhalation
Intermediate (15-364 days)
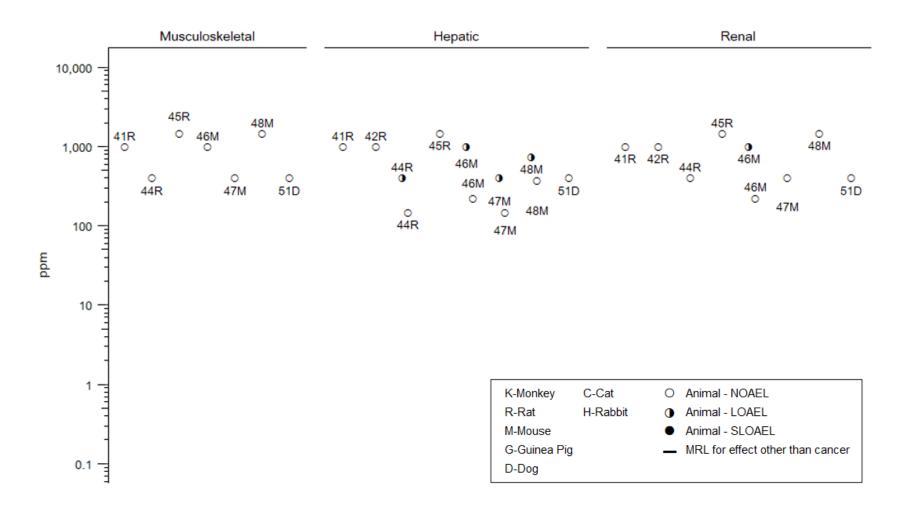
2. HEALTH EFFECTS

Figure 2-2. Levels of Significant Exposure to Chloromethane – Inhalation
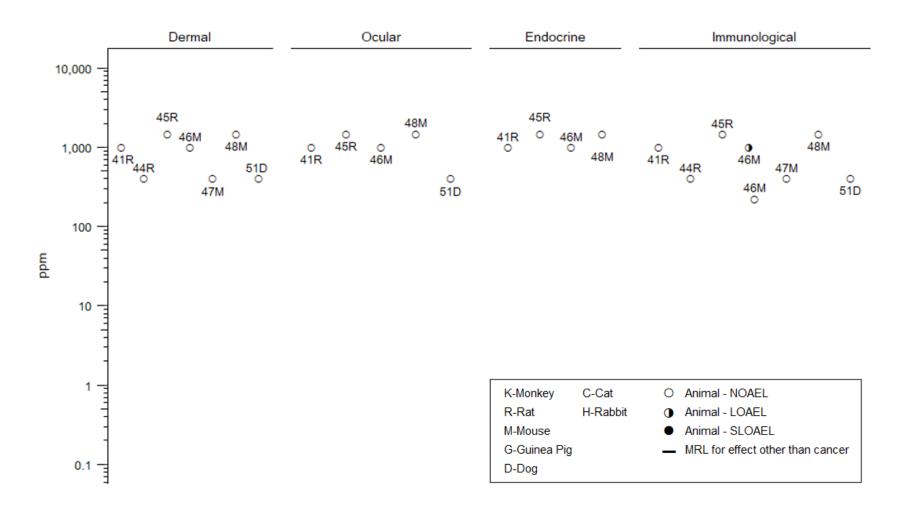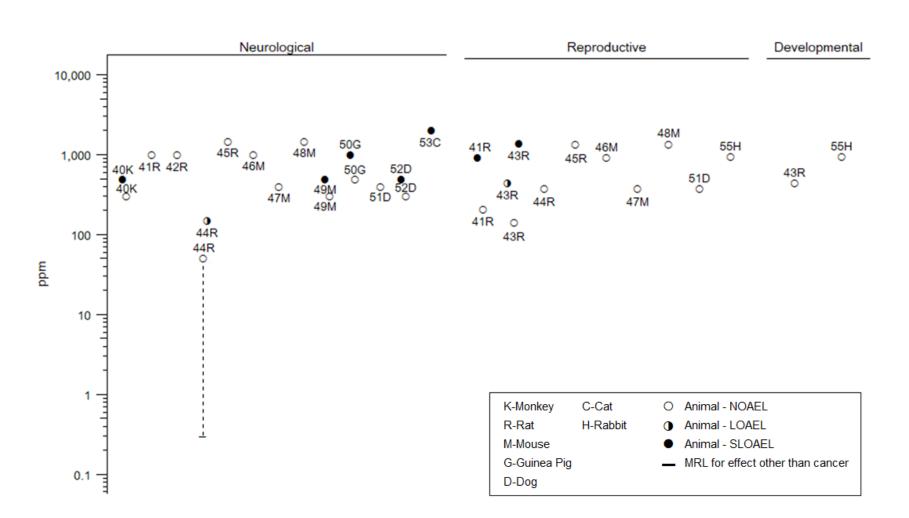Intermediate (15-364 days)

Figure 2-2. Levels of Significant Exposure to Chloromethane – Inhalation
Intermediate (15-364 days)

Figure 2-2. Levels of Significant Exposure to Chloromethane – Inhalation
Chronic (≥365 days)

2. HEALTH EFFECTS

Figure 2-2. Levels of Significant Exposure to Chloromethane – Inhalation
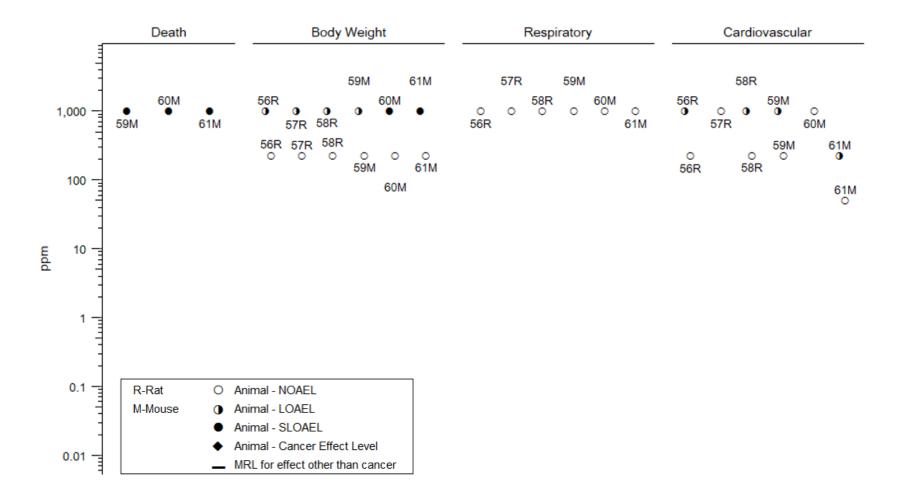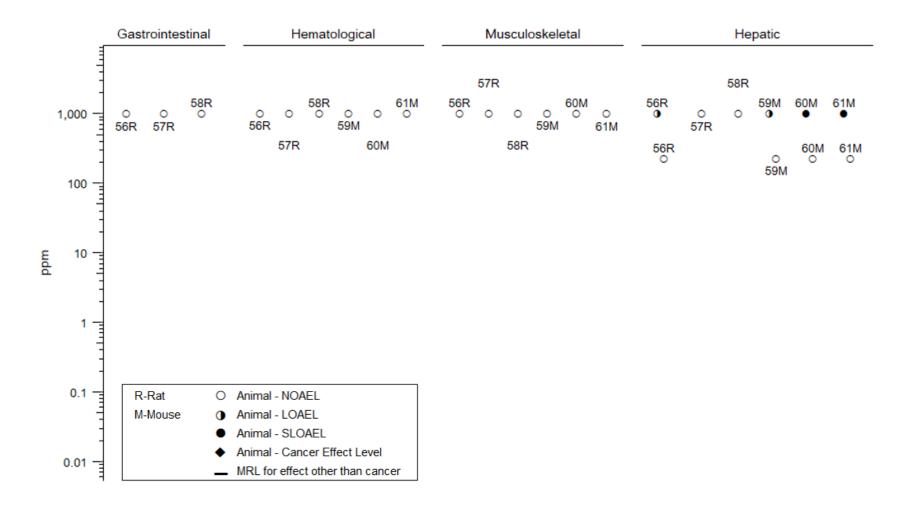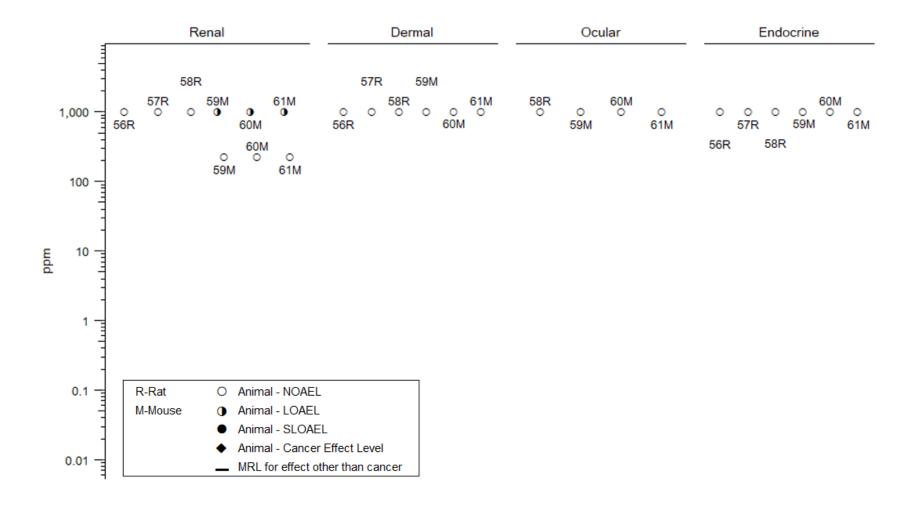Chronic (≥365 days)

2. HEALTH EFFECTS

Figure 2-2. Levels of Significant Exposure to Chloromethane – Inhalation
Chronic (≥365 days)

Figure 2-2. Levels of Significant Exposure to Chloromethane – Inhalation
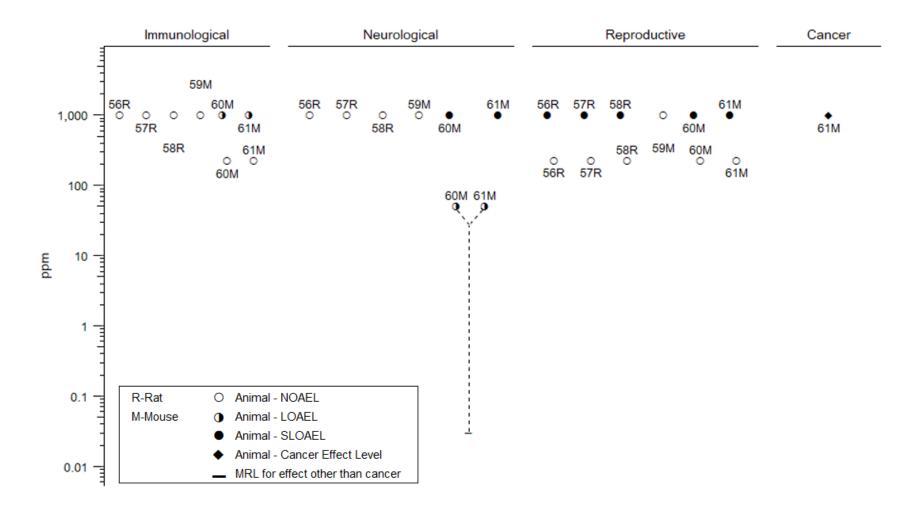Chronic (≥365 days)

2. HEALTH EFFECTS

Table 2-3. Levels of Significant Exposure of Animals to Chloromethane – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Reynolds and Yee 1967									
1	Rat (Charles River) NS M	Once (GO)	0, 420	HP	Hepatic	420			

[a]The number corresponds to the entries in Figure 2-3.

HP = histopathology; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; NS = not specified
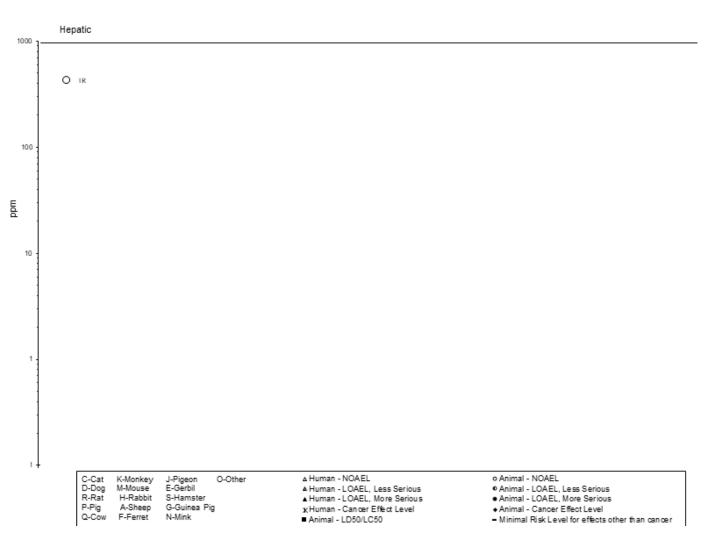
2. HEALTH EFFECTS

Figure 2-3. Level of Significant Exposure of Animals to Chloromethane – Oral
Acute (≤14 days)

C-Cat	K-Monkey	J-Pigeon	O-Other	
D-Dog	M-Mouse	E-Gerbil		
R-Rat	H-Rabbit	S-Hamster		
P-Pig	A-Sheep	G-Guinea Pig		
Q-Cow	F-Ferret	N-Mink		

Δ Human - NOAEL   o Animal - NOAEL
▲ Human - LOAEL, Less Serious   ◎ Animal - LOAEL, Less Serious
▲ Human - LOAEL, More Serious   ● Animal - LOAEL, More Serious
✗ Human - Cancer Effect Level   ◆ Animal - Cancer Effect Level
■ Animal - LD50/LC50   ─ Minimal Risk Level for effects other than cancer

2.2   DEATH

Exposure-related deaths have been reported in human and laboratory animals following inhalation exposure to high concentrations of chloromethane. No studies were located regarding death in humans or animals after oral or dermal exposure to chloromethane. Studies that examine the potential association of chloromethane exposure with death specifically from cancer are reviewed in Section 2.19.

In the late 1920s chloromethane began being used as a refrigerant (UNEP, 1999). Subsequently, there were several case reports of human deaths resulting from exposure to chloromethane vapors from leaks in home refrigerators and industrial cooling and refrigeration systems (Baird 1954; Borovska et al. 1976; Kegel et al. 1929; McNally 1946). Numerous neurological symptoms were reported prior to death in these cases, including headache, dizziness, nausea and vomiting, anorexia, visual disturbances, slurred speech, unstable gait, weakness, fatigue, tremors, and/or convulsions.

In 1963, an Icelandic fisherman died within 24 hours of an accidental exposure to high (unspecified) concentrations of chloromethane due to a refrigerator leak (Gudmundsson 1977). Follow-up studies of the remaining 27 exposed fishermen through 2010 showed an increased risk of death, compared to unexposed Icelandic fishermen, specifically deaths associated with kidney cancer, cardiovascular diseases, and suicide (Table 2-1) (Rafnsson and Gudmundsson 1997; Rafnsson and Kristbjornsdottir 2014). The increase in mortality was greater in the deckhands (n=20), who were estimated to have received the greatest exposure due to the location of their living quarters, compared to officers (n=7). While the reference and exposure group had similar occupations and thus likely similar socioeconomic status, the study authors did not directly control for lifestyle factors, such as smoking habits, intensity of work demands, or diet. Due to the small number of individuals in the exposure group (n=27) and the assumption that the exposed and referent groups had similar lifestyle factors, generalization of these results to the general population must be done with caution.

In another occupational cohort study, all-cause mortality was decreased in synthetic rubber workers exposed to chloromethane; which may reflect the healthy worker effect (Holmes et al. 1986). Specific analysis did not find increased risk of death from cancer or circulatory system diseases (Table 2-1). While no exposure estimates are available, exposure to rubber workers is likely lower than the acute-duration exposure experienced in the Icelandic fisherman cohort and case reports associated with refrigerant leaks.

In animals, reported acute inhalation LC_{50} values in mice were 2,220 ppm following a 6-hour exposure (Chellman et al. 1986b) and 3,080 ppm following a 7-hour exposure (von Oettingen et al. 1949, 1950). Several additional acute-duration exposure studies in experimental animals observed increased mortality or instances in which researchers "killed animals *in extremis*" (at the point of death). In the majority of cases, this occurred at chloromethane concentrations ≥972 ppm in rats and ≥150 ppm in mice via continuous exposure (22–24 hours/day) (Burek et al. 1981; Landry et al. 1985), or at concentrations ≥1,500 ppm in both rats and mice via intermittent exposure (5.5–6 hours/day) (Chellman et al. 1986a, 1986b; Jiang et al. 1985; Landry et al. 1985; Morgan et al. 1982; Wolkowski-Tyl et al. 1983b; Wolkowski-Tyl et al. 1983a). The study authors attributed death to kidney (Burek et al. 1981; Morgan et al. 1982) or liver toxicity (Morgan et al. 1982). In dogs exposed to extremely high air levels of chloromethane, the average survival time was 5.9 hours at 14,661 ppm and 4 hours at 40,560 ppm; death was preceded by CNS depression and a precipitous drop in blood pressure and respiratory rate (von Oettingen et al. 1949, 1950).

Smith and von Oettingen (1947a, 1947b) exposed a variety of species including monkeys, rats, mice, guinea pigs, rabbits, dogs, and cats to concentrations ranging from 300 to 4,000 ppm for 6 hours/day, 6 days/week for up to 64 weeks. Exposure continued until animals died, allowing study authors to determine mean survival time and time until 50% of animals died (LT_{50}). Findings showed differences in susceptibility between different species, and different ages within the same species. The lowest concentrations associated with 50% lethality following acute-duration exposure were 1,000 ppm in guinea pigs (LT_{50} of 4 days), dogs (LT_{50} of 6 days), and mice (LT_{50} of 10.5 days); 2,000 ppm in monkeys (LT_{50} of 10 days); 3,000 ppm in rats (LT_{50} of 5 days); and 4,000 ppm in rabbits (LT_{50} of 13 days). All four cats survived acute-duration exposure to 2,000 ppm (only concentration evaluated in cats). For intermediate-duration exposure, the lowest concentrations associated with 50% lethality were 500 ppm in dogs (LT_{50} of 23 days), guinea pigs (LT_{50} of 71 days), monkeys (LT_{50} of 115 days), mice (LT_{50} of 143 days), and rabbits (LT_{50} of 192 days); and 2,000 ppm in rats (LT_{50} of 15 days) and cats (LT_{50} of 23 days). No exposure-related changes in survival were observed in monkeys, rats, mice, guinea pigs, dogs, or rabbits exposed to 300 ppm for 64 weeks. In species that evaluated both adult and "young" animals (rat, mouse, guinea pig, dog, rabbit), adult animals were generally more susceptible compared to younger animals. Across all species, severe clinical signs of neurotoxicity were commonly observed prior to death (see Section 2.15 for more details). Dogs and cats also displayed dyspnea and gasping, respectively, prior to death. At necropsy, deaths were associated with lung congestion and liver and kidney toxicity in rats, mice, and guinea pigs (Dunn and Smith 1947).

In longer-duration studies, no exposure-related increases in mortality were observed in rats following exposure to concentrations up to 997 ppm for 24 months (CIIT 1981). However, increased mortality was observed in similarly exposed mice (CIIT 1981). In females, overall survival was significantly decreased at 997 ppm, compared to control. Decreased survival was first noted at 10 months, with a dramatic decrease at 20 months. In males exposed to 997 ppm, increased mortality was observed at 17 months with a precipitous drop in survival at 19 months; however, survival was not statistically different from control. Findings in male mice were confounded during the first year by several deaths attributed to dominance fighting across all exposure groups, predominantly in the first 6 months, resulting in decreased survival of the control group during the first year of the study, compared to exposure groups. The lack of a statistically significant, exposure-related effect on male mouse survival, despite a dramatic decrease in survival at the end of the exposure period, is attributed to an unusually low survival rate in male control mice. Due to high mortality, remaining mice from the 997-ppm group were terminated at 21 months (2 males) and 22 months (18 females) (CIIT 1981).

2.3 BODY WEIGHT

No studies were located regarding body weight effects in humans exposed to chloromethane. A consistent systemic effect of chloromethane exposure in rodents is reduced body weight and/or body weight gain, which was observed in rats and mice exposed to chloromethane via inhalation for acute-, intermediate-, and chronic-duration exposures. No studies were located regarding body weight in animals after oral or dermal exposure to chloromethane.

In acute-duration studies, continuous exposure (22–24 hours/day) was associated with decreased body weights in rats at ≥504 ppm (Burek et al. 1981) and in mice at ≥150 ppm (Landry et al. 1985). With intermittent exposure over an acute duration, decreased body weights were observed in rats at ≥3,000 ppm (Chellman et al. 1986a; Working et al. 1985a) and in mice at 2,400 ppm (Landry et al. 1985). Some of the observed body weight effects may be secondary to decreased food consumption and water intake associated with overall poor health of the animals at high exposure concentrations (Landry et a. 1985). In maternal rats and mice, decreased body weights following gestational exposure were observed at ≥479 ppm (Wolkowski-Tyl et al. 1981a, 1981b, 1983a, 1983b). In intermediate- and chronic-duration studies, reduced body weights were consistently observed in rats at concentrations ≥741 ppm (CIIT 1981; Hamm et al. 1985; Mitchell et al. 1979). In one study, the study authors attributed body weight effects to transient reductions in body weight gain during weeks 3–8 of a 13-week study; however, despite body

weight gains comparable to control from weeks 9 to 13, final body weights were still reduced by >10% in males at ≥741 ppm and females at 1,473 ppm (Mitchell et al. 1979). In mice, no body weight effects were noted after exposure to concentrations up to 1,473 ppm for 90 days (Mitchell et al. 1979). However, decreased body weights were observed at 997 ppm in males exposed for ≥6 months and in both sexes exposed for ≥12 months (CIIT 1981).

No effect on body weight was observed in dogs and cats exposed for 72 hours to 500 ppm chloromethane (McKenna et al. 1981a). Additionally, no impact on body weight was observed in New Zealand white rabbits exposed to chloromethane at concentrations up to 1,012 ppm 6 hours/day on gestation days (GDs) 6–28 (Theuns-van Vliet 2016). These findings may be due to species difference in response to exposure to chloromethane.

2.4   RESPIRATORY

Available human studies are too limited to determine if inhalation exposure to chloromethane affects respiratory health or function. Based on inhalation studies in animals, there is limited evidence that exposure to high concentrations of chloromethane may cause adverse respiratory effects. No studies were located regarding respiratory effects in humans or animals after oral or dermal exposure to chloromethane.

Case reports generally have described limited respiratory effects in humans exposed to chloromethane. In a case study of individuals who were exposed to chloromethane from refrigeration leaks in a refrigerator manufacturing plant or in kitchenette apartments in Chicago in 1928 and 1929, several survivors presented with increased respiration and an autopsy of one case showed diffuse dilation of the alveolar space. Many presented cases were noted as having breath that smelled musty and sweetish, and the odor of acetone surrounded them (Kegel et al. 1929); or the work area where exposure occurred smelled sweet like methyl alcohol (Baird 1954). In a neurological study with volunteers, no effects on pulmonary function were observed following acute-duration inhalation exposure of up to 150 ppm chloromethane (Stewart et al. 1980). This study, however, had several limitations such as small sample size and subjects lost to attrition.

One epidemiological paper evaluated how subjects' respiratory outcomes changed with changes in air pollutants, including chloromethane. No association between self-reported bothersome or more severe asthma symptoms (i.e., symptoms that were anticipated to interfere with daily activities) and daily

chloromethane air levels was seen in a cohort of Hispanic children from an East Los Angeles community with high traffic density (Table 2-1) (Delfino et al. 2003). However, given the very low levels of exposure (mean 0.58 ppb) and small subject number (n=22), this study is limited in its evaluation of chloromethane-associated respiratory effects.

As discussed in Section 2.2, lethal exposure to chloromethane at acute-duration concentrations ≥1,000 ppm is associated with lung congestion and/or edema in several species, including rats, mice, guinea pigs, and cats (Dunn and Smith 1947; Smith and von Oettingen 1947a). Burek et al. (1981) also reported lung congestion and edema in rats that died following exposure to 1,950 ppm for up to 72 hours (Burek et al. 1981). In dogs exposed to extremely high concentrations for 4–6 hours (14,661 or 40,560 ppm), reduced respiration rates were observed prior to death (von Oettingen et al. 1949, 1950). Additionally, dyspnea was observed in dogs prior to death following acute-duration exposure to ≥1,000 ppm or intermediate-duration exposure to 500 ppm (Smith and von Oettingen 1947a, 1947b). Effects observed in dogs may be secondary to CNS depression rather than a direct effect on the respiratory system.

Acute-duration studies evaluating nonlethal concentrations failed to find any exposure-related respiratory effects. No exposure-related histopathological lesions or clinical signs of respiratory distress were noted in the lungs of dogs and cats exposed continuously (23.5 hours/day) to concentrations up to 496 and 501 ppm, respectively (McKenna et al. 1981a) or rats exposed continuously for 48 hours to concentrations up to 1,968 ppm (Burek et al. 1981). Similar to the acute-duration studies, intermediate-duration exposure studies did not find any association between chloromethane and histopathologic lesions in the lungs in dogs at concentrations up to 399 ppm or in rats and mice at concentrations up to 1,473 ppm (McKenna et al. 1981b; Mitchell et al. 1979). CIIT (1981) reported a significant increase in absolute and/or relative lung weight at ≥51 ppm in male rats following exposure for 6 months; however, this was not associated with exposure-related histopathological lesions. In females, respiratory findings at 997 ppm included minimal-to-moderate interstitial pneumonia with lymphocytic peribronchiolitis and perivasculitis; alveolar cell hyperplasia; mild alveolar luminal infiltrates consisting of large macrophages, lymphocytes, and in some areas, a few neutrophils; and areas of minimal subacute tracheitis. However, at 12, 18, or 24 months after the initial exposure, no chloromethane-related lung effects were observed in rats at concentrations up to 997 ppm. No effects on lungs were observed at any time point in similarly exposed mice. These respiratory effects observed in this study were considered transient and unrelated to exposure by the study authors (CIIT 1981).

2.5   CARDIOVASCULAR

A systematic review of the literature (Appendix C) determined that chloromethane is not classifiable as it relates to cardiovascular outcomes based on inadequate evidence from inhalation studies in humans and laboratory animals. No studies were located regarding cardiovascular effects in humans or animals after oral or dermal exposure to chloromethane.

Several case reports of humans exposed to high acute levels of chloromethane associated with refrigerator leaks have reported cardiovascular effects. The effects of these exposures vary by case and include electrocardiogram abnormalities, tachycardia, increased pulse rate, elevated body temperature, and both hypertension and decreased blood pressure (Hansen et al. 1953; Kegel et al. 1929; McNally 1946; Scharnweber et al. 1974; Spevak et al. 1976; Verriere and Vachez 1949). The concentrations and durations of exposure in these studies are not known. Kegel et al. (1929) reported that body temperatures in one survivor reached 104°F prior to death. One reported adult survivor had a recorded pulse rate of 150 beats/minute, and one child had a pulse rate recorded as 164 beats/minute.

As discussed in Section 2.2 (Death), an increased risk of death from cardiovascular disease was observed in a cohort of Icelandic fishermen accidently exposed to high levels of chloromethane from a refrigeration leak (Rafnsson and Gudmundsson 1997; Rafnsson and Kristbjornsdottir 2014). This risk was increased in both the 32- and 47-year follow-up rates of cardiovascular related mortality, including both acute coronary heart disease and cerebrovascular disease, compared with a reference group of seamen from the Icelandic registries. This excess was only significant for the deckhands who were estimated to have received the highest exposure to chloromethane due to the proximity of their sleeping quarters to the leaking refrigerator. In contrast, the risk of death due to circulatory diseases was not increased in an occupational cohort of synthetic rubber workers exposed to chloromethane (Holmes et al. 1986). While neither cohort study reported exposure levels, it is expected that the accidental exposure concentration in Icelandic fishermen was higher (potentially much higher) than occupational levels in the rubber plant. The risk of bias in these studies is increased given that they did not explicitly control for smoking or diet and there were relatively small numbers of individuals with significant exposure.

In a human controlled exposure experiment, volunteers were exposed for 1, 3 or 7.5 hours/day for 2–5 days per exposure group and no abnormalities of cardiac function or electrocardiograms were found for any of the exposure durations at concentrations up to 150 ppm (Stewart et al. 1980). However, a man exposed to an unknown acute dose of chloromethane presented for medical examination the day of

exposure with a pale, ashen face complaining of a headache. The patient died the following day, and the necropsy demonstrated capillary engorgement and chloromethane throughout the tissues examined (Baird 1954).

Only one study evaluating cardiovascular function in animals following inhalation exposure to chloromethane was identified. In dogs acutely exposed to lethal concentrations ≥14,661 ppm for 4– 6 hours, an initial rise in blood pressure was followed by a precipitous drop in blood pressure after 2.5– 3 hours (von Oettingen et al. 1949, 1950). Blood pressure continued to fall and was accompanied by a marked decrease in heart rate until death, which occurred within 4–6 hours. Changes observed in blood pressure and respiration were closely related for most of the observation period. Just prior to death, there was a transient increase in heart rate. The initial increase in blood pressure may have been due to residual anesthesia from the surgical procedure to cannulate the artery and vein for monitoring of cardiovascular function, while drastic reductions in blood pressure and heart rate were attributed to vasodilation in response to CNS depression.

Several additional studies evaluated heart weight and/or histology in animals. No exposure-related changes in heart histology were observed at acute-duration concentrations up to approximately 500 ppm in dogs and cats (McKenna et al. 1981a), intermediate-duration concentrations up to 399 pm in dogs or 1,473 ppm in rats or mice (CIIT 1981; McKenna et al. 1981b; Mitchell et al. 1979), or chronic-duration concentrations up to 998 ppm in rats and mice (CIIT 1981). However, some studies reported exposure-related increases in heart weight after intermediate- or chronic-duration exposure. In mice, increased relative heart weights were reported in males exposed to 399 ppm for 94 days in one study (McKenna et al. 1981b), while no exposure-related changes in heart weight were observed in mice in other studies at concentrations up to 1,473 ppm for 90 days (Mitchell et al. 1979) or 997 ppm for 6 months (CIIT 1981). In chronic-duration studies, exposure-related increases in absolute and/or relative heart weights were observed in male rats exposed to 997 ppm for 12 or 24 months, female mice exposed to 997 for 12 months, and female mice exposed to ≥224 ppm for 24 months (CIIT 1981). Increases in relative heart weight were also observed in female rats exposed to 997 ppm at 12 and 24 months; however, these effects were considered to be secondary to decreases in body weights due to a lack of concurrent increase in absolute heart weight. No exposure-related changes in heart weight were observed in male mice exposed to concentrations up to 997 ppm for up to 24 months (CIIT 1981).

2.6   GASTROINTESTINAL

Available human studies indicate that reported gastrointestinal effects following inhalation exposure may be secondary to neurological effects. Based on inhalation studies in animals, chloromethane does not appear to have direct adverse effects on the gastrointestinal system. No studies were located regarding gastrointestinal effects in humans or animals after oral or dermal exposure to chloromethane.

Numerous case reports of humans exposed to chloromethane have described symptoms of pain in the abdomen, hiccups, nausea, and vomiting (Baird 1954; Baker 1927; Battigelli and Perini 1955; Borovska et al. 1976; Hansen et al. 1953; Jones 1942; Kegel et al. 1929; Mackie 1961; Spevak et al. 1976; Verriere and Vachez 1949; von Raalte and van Velzen 1945; Weinstein 1937). In all cases, these symptoms were accompanied by CNS toxicity, which was usually severe. It is not clear, therefore, if the abdominal pain, nausea, and vomiting were secondary to the neurotoxic effects of chloromethane. Two of the reports (Battigelli and Perini 1955; Jones 1942) provided refrigerator chloromethane capacity and room size from which exposures of 75–1,282 ppm could be calculated.

In animals, no exposure-related histopathological changes in the gastrointestinal tract were observed at acute-duration exposures up to approximately 500 ppm in dogs and cats (McKenna et al. 1981a) or 5,000 ppm in rats (Morgan et al. 1982); intermediate-duration exposures up to 399 ppm in dogs (McKenna et al. 1981b), 1997 ppm in rats (CIIT 1981; McKenna et al. 1981b) or 1,473 ppm in mice (CIIT 1981; McKenna et al. 1981b; Mitchell et al. 1979); or chronic-duration exposures up to 997 ppm in rats and mice (CIIT 1981; McKenna et al. 1981b). One acute-duration study reported foul-smelling diarrhea in male and female rats within 2-days of exposure to 5,000 ppm (Morgan et al. 1982). In another study, decreased ingesta were observed in the gastrointestinal tract of male rats exposed to 1,000 ppm chloromethane for 72 hours (Burek et al. 1981). As observed in human case reports, gastrointestinal distress was observed at an exposure level associated with severe neurotoxicity.

2.7   HEMATOLOGICAL

Available human studies are too limited to determine if inhalation exposure to chloromethane affects hematological endpoints. Based on inhalation studies in animals, the hematological system does not appear to be a sensitive target of chloromethane toxicity. No studies were located regarding hematological effects in humans or animals after oral or dermal exposure to chloromethane.

No hematological effects were found in volunteers who participated in a controlled human exposure study of neurological and neurobehavioral effects of acute-duration inhalation exposure of up to 150 ppm chloromethane (Stewart et al. 1980). This study, however, had several limitations such as small sample size and subjects lost to attrition. Additionally, measured blood and breath concentrations in several participants were much higher than for other participants.

In a series of case reports, Kegel et al. (1929) reported decreases in reticulocyte count, hemoglobin, red blood cell count, and white blood cell count among several cases of poisonings in Chicago in 1928 and 1929 associated with chloromethane leaks in a refrigerator manufacturing plant and in kitchenette apartments. However, other case reports of human exposure to chloromethane have generally not found an association between chloromethane exposure and hematological effects (Gudmundsson 1977; Jones 1942). For example, in a group of Icelandic fishermen exposed accidentally to chloromethane due to a refrigeration leak, no evidence of long-term impacts on the hematological system was seen in the 10 patients the researchers evaluated 13 years post-exposure (Gudmundsson 1977).

Increased red blood cell (RBC) parameters (RBC count, hematocrit, hemoglobin) that were observed in rats continuously exposed to chloromethane at 1,968 ppm for 2 days or 972 ppm for 3 days were considered secondary to dehydration (and subsequent hemoconcentration) in lethargic or moribund animals, rather than a direct effect on the hematological system (Burek et al. 1981). In other inhalation studies, no exposure-related effects on hematological parameters were found in acute-duration studies in dogs or cats at concentrations up to 496 or 501 ppm, respectively (McKenna et al. 1981a); intermediate-duration studies in dogs at concentrations up to 299 ppm (McKenna et al. 1981b) or in rats or mice at concentrations up to 1,473 ppm (CIIT 1981; McKenna et al. 1981b; Mitchell et al. 1979); or chronic-duration studies in rats or mice at concentrations up to 997 ppm (CIIT 1981).

Spleen enlargement, suggestive of extramedullary hematopoiesis, and hemoglobinuria without hematuria, suggestive of intravascular hemolysis, were found in female mice exposed intermittently to a high concentration (2,400 ppm) of chloromethane for 11 days (Landry et al. 1985). These effects were not seen when mice were exposed continuously to a lower concentration (200 ppm) (Landry et al. 1985). This study did not evaluate hematological parameters in blood or examine male mice.

2.8   MUSCULOSKELETAL

No studies were located regarding musculoskeletal effects in humans exposed to chloromethane. In inhalation studies in animals, no musculoskeletal effects were observed following intermediate-duration exposures to concentrations up to 399 ppm in dogs (McKenna et al. 1981b) or 1,473 ppm in rats or mice (CIIT 1981) McKenna et al. 1981b; Mitchell et al. 1979), or chronic-duration exposure to concentrations up to 997 ppm in rats or mice (CIIT 1981). No studies were located regarding musculoskeletal effects in animals after oral or dermal exposure to chloromethane.

2.9   HEPATIC

Available human studies are too limited to determine if inhalation exposure to chloromethane affects the liver; no oral or dermal studies in humans were identified. A systematic evaluation of the literature (Appendix C) determined that hepatic toxicity is a presumed health effect associated with inhalation exposure to chloromethane based on a high level of evidence from laboratory animals. Only one study evaluating hepatic effects in animals following oral exposure was identified; no studies were located regarding hepatic effects in animals after dermal exposure to chloromethane.

Evidence from human studies is limited to case reports of people exposed to chloromethane via inhalation (Jones 1942; Kegel et al. 1929; Mackie 1961; Spevak et al. 1976; Weinstein 1937; Wood 1951). Jones (1942) reported large amounts of coproporphyrin III in the urine (initially 6 times normal, increased to 30 times normal, and then slowly fell to normal) which was suggestive of liver damage. Spevak et al. (1976) reported jaundice in 3 women exposed to chloromethane from a commercial refrigerator leak. Other case reports found marked hyperemia, lipoid granules in Kupffer cells, thickened capsule, and Glisson septums with lymphocyte accumulations (Kegel et al. 1929), clinical jaundice (Weinstein 1937), and cirrhosis of the liver (Wood 1951). While these case reports lacked exact exposure data, it is likely that the liver effects were due to exposure to chloromethane rather than to alcohol, another chemical, a virus, or a parasite.

Hepatic effects have also been observed in animals exposed to chloromethane via inhalation, including liver weight effects, alterations in serum clinical chemistry parameters, and mild histopathological lesions. However, there is some inconsistency between studies and species. In general, mice appear to be the most susceptible species.

A transient decrease in absolute and/or relative liver weight was observed in male rats continuously exposed to ≥196 ppm for 48 or 72 hours; this effect was no longer observed after a 12-day recovery period (Burek et al. 1981). Liver weights were unaltered in female rats similarly exposed up to 1,968 ppm. In contrast to decreased liver weight observed in the rat study by Burek et al. (1981), an increase in relative liver weights was observed in male rats exposed intermittently to 399 ppm for 93 days (McKenna et al. 1981b). In other studies in rats, no exposure-related changes in liver weight were observed following intermittent exposure to chloromethane at acute-duration concentrations up to 5,004 ppm (Chellman et al. 1986a), intermediate-duration concentrations up to 1,473 ppm (CIIT 1981; Mitchell et al. 1979), or chronic-duration concentrations up to 997 ppm (CIIT 1981). In mice, inconsistent findings were observed following acute-duration exposure to chloromethane. In a study by Landry et al. (1985) that evaluated both intermittent (5.5 hours/day) and continuous (22 hours/day) exposures in four separate 11-day experiments, one intermittent study reported increased absolute and relative liver weight in female mice exposed to 1,600 ppm. However, the second intermittent study did not observe adverse changes in liver weight in female mice at concentrations up to 2,400 ppm. In continuous-exposure paradigms, no adverse changes in liver weight were observed in female mice at concentrations up to 150 ppm (Landry et al. 1985). In another acute-duration study, no changes in liver weight were observed in mice at concentrations up to 749 ppm for 2 days (Wolkowski-Tyl et al. 1981b, 1983b). In longer-duration mouse studies, intermittent exposure was associated with increased absolute and/or relative liver weights in several studies, including male and female mice exposed to ≥741 ppm for 90 days (Mitchell et al. 1979), female mice exposed to 399 ppm for 93 days (McKenna et al. 1981b), and female mice exposed to 997 ppm for 12 or 18 months (CIIT 1981). However, no exposure-related changes in liver weight were observed in mice following intermittent exposure to concentrations up to 997 ppm for up to 24 months (CIIT 1981). In other species, no exposure-related changes in liver weights were observed in dogs or cats exposed to concentrations of 496 or 501 ppm, respectively, for 3 days (McKenna et al. 1981a) or dogs exposed to concentrations up to 399 ppm for 93 days (McKenna et al. 1981b).

Evidence for altered hepatic clinical chemistry parameters following inhalation exposure to chloromethane are limited and inconsistent between studies and exposure durations. In an acute-duration study, rats exposed continuously to 1,950 ppm for up to 72 hours showed decreased alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin levels just prior to death (Burek et al. 1981). No changes in hepatic clinical chemistry were observed at nonlethal concentrations in this study. Increased serum ALT was also observed following nonlethal exposures in mice at 1,500 ppm for 6 hours (Chellman et al. 1986b) and in male rats and male and female mice at 997 ppm for

12 months (CIIT 1981). However, in chronic-duration studies, only male mice showed increased serum ALT after exposure to 997 ppm for 18 months; this effect was no longer observed at 24 months (CIIT 1981). In other animal inhalation studies, no exposure-related changes in hepatic clinical chemistry were noted at acute-duration exposures up to 1,968 ppm in rats (Burek et al. 1981) and approximately 500 ppm in dogs and cats (McKenna et al. 1981a), or intermediate-duration exposures up to 1,473 ppm in rats and mice (CIIT 1981; McKenna et al. 1981b; Mitchell et al. 1979).

In an acute lethality study, dark, congested, and mottled livers were observed in rats that died following continuous exposure to 1,950 ppm for up to 72 hours (Burek et al. 1981). At nonlethal doses, slight liver effects observed following exposure to ≥198 ppm for 48 or 72 hours included lipid accumulation, slight extramedullary hematopoiesis, and altered tinctorial appearance of hepatocytes. These effects resolved after 12 days of recovery (Burek et al. 1981). Hepatic effects (centrilobular necrosis and/or fatty accumulation) were also noted in several species following acute exposure to lethal concentrations, including ≥1,000 ppm in guinea pigs and ≥2,000 ppm in rats and mice (Dunn and Smith 1947).

In rats, nonlethal, acute-duration exposures to concentrations ≥2,000 ppm were generally associated with mild effects, such as minimal hepatocellular degeneration and cloudy swelling of hepatocytes (Chellman et al. 1986a; Morgan et al. 1982). In mice, a single 6-hour exposure to 1,500 ppm was associated with hepatocellular necrosis and cytoplasmic vacuolation (Chellman et al. 1986b). An 11-day study in mice reported decreased hepatocyte size and evidence of glycogen depletion following exposure to ≥400 ppm for 5.5 hours/day or ≥100 ppm for 22 hours/day; in mice exposed for 22 hours/day, "higher exposure levels" (unspecified) were associated with focal hepatic necrosis (Landry et al. 1985). While adverse effects were observed at a lower exposure concentration with continuous exposure, when exposures are adjusted for duration (5.5 hours or 22 hours/24 hours), the duration-adjusted concentrations are equivalent (92 ppm). Minimal hepatocellular degeneration progressed to severe hepatocellular degeneration and necrosis in mice exposed to concentrations ranging from 500 to 2,000 ppm for 12 days (Morgan et al. 1982).

No exposure-related hepatic lesions were observed in rats following intermediate-duration exposure to concentrations up to 1,473 ppm (CIIT 1981; Dunn and Smith 1947; McKenna et al. 1981a; Mitchell et al. 1979) or chronic-duration exposure concentrations up to 997 ppm (CIIT 1981). In mice, no exposure-related lesions were observed in mice exposed to concentrations up to 1,473 ppm for approximately 3 months (McKenna et al. 1981b; Mitchell et al. 1979). However, exposure to 997 ppm resulted in hepatocellular degeneration in mice after 6 months, which progressed to necrosis, cytomegaly,

karyomegaly, and polykaryocytes at ≥12 months (CIIT 1981). In dogs, exposure to 51, 149, or 399 ppm for 3 months resulted in swollen hepatocytes in 2/4, 1/4, and 2/4 dogs, respectively, compared to 0/4 controls (McKenna et al. 1981b). Since a clear dose-response was not observed, and no other liver effects were observed, the toxicological significance of these effects are unlikely to be treatment-related.

Only one animal study was located in which chloromethane was administered orally. In this study, the hepatotoxic effects of chloroform, carbon tetrachloride, dichloroethane, and chloromethane were compared (Reynolds and Yee 1967). Rats were given chloromethane in mineral oil by gavage at a single dose of 420 mg/kg and no centrilobular hepatic necrosis was found. Chloromethane neither suppressed glucose 6-phosphatase activity in the centrilobular portion of the liver lobule, nor increased cell sap ribonucleic acid content, indicating that oral exposure to chloromethane is unlikely to induce hepatic necrosis.

2.10 RENAL

Available human studies are too limited to determine if inhalation exposure to chloromethane affects the renal system; no oral or dermal studies in humans were identified. Animal data indicate that the renal system is a toxicity target following inhalation exposure to high concentrations. No studies were located regarding renal effects in animals after oral or dermal exposure to chloromethane.

Case reports of humans exposed to chloromethane have described indicators of renal toxicity such as albuminuria, red blood cells in the urine, increased serum creatinine and blood urea nitrogen (BUN), proteinuria, granular or hyaline casts, anuria, and the presence of acetone, diacetic acid, and occasionally formic acid in the urine (Jones 1942; Kegel et al. 1929; Mackie 1961; Spevak et al. 1976; Verriere and Vachez 1949). Exposure concentrations at which these effects occurred are not known. Microscopic examination of the kidney of an individual who died following chloromethane exposure revealed marked capillary hyperemia, dilated glomerular and interstitial capillaries packed with blood cells, swollen epithelial lining of the convoluted tubules, and narrowing of the lumen (Kegel et al. 1929). In individuals exposed to less chloromethane, symptoms of renal damage disappeared after 2 weeks after admission (Spevak et al. 1976).

Studies in rodents have consistently observed renal damage following acute-duration inhalation exposures to high concentrations of chloromethane. In acute-duration studies with continuous inhalation exposure, renal failure was cited as the cause of death in rats exposed to ≥972 ppm continuously for up to 78 hours

(Burek et al. 1981). Renal lesions observed in rats exposed to ≥972 ppm for ≥48 hours included renal tubule necrosis, increased renal tubular cytoplasmic homogeneity, and increased lipid accumulation in renal tubular cells; multifocal renal tubules were also observed in male rats exposed to 504 ppm for 72 hours (Burek et al. 1981). Clinical chemistry and urinalysis findings were also indicative of renal toxicity, including elevated serum BUN in females exposed to 972 ppm for 72 hours and in males and females exposed to 1,968 ppm for 48 hours and increased protein, ketones, glucose, and blood in the urine at ≥972 ppm for both durations (Burek et al. 1981). Dunn and Smith (1947) also report renal tubule necrosis and/or fatty metamorphosis in several species at acute concentrations associated with lethality, including guinea pigs at ≥1,000 ppm rats and mice at ≥2,000 ppm. Mice also displayed hemoglobinuria at ≥1,000 ppm (Dunn and Smith, 1947; Smith and von Oettingen 1947b).

Renal lesions have also been consistently observed in rats and mice following intermittent (6 hours/day), acute-duration exposures, with reports of necrosis and degeneration of the proximal convoluted tubules at concentrations ≥2,000 ppm (Chellman et al. 1986a; Landry et al. 1985; Morgan et al. 1982). A few acute-duration studies in mice reported effects at lower concentrations, including slight degeneration of the proximal tubules and increased renal cell regeneration at 1,500 ppm for 2 weeks (Chellman et al. 1986b; Jiang et al. 1985) and minimal-to-moderate basophilic renal tubules with hematuria at ≥1,000 ppm for 12 days (Morgan et al. 1982).

In longer-duration studies, no adverse renal effects were noted in rats or mice at concentrations up to 1,473 ppm for 3 months (McKenna et al. 1981b; Mitchell et al. 1979), in rats at concentrations up to 1,000 ppm for 175 days (Dunn and Smith 1947), or in rats at concentrations up to 997 ppm for 6–24 months (CIIT 1981). In mice, decreased absolute and relative kidney weights were seen in male mice (but not female mice) following exposure to 997 ppm for 6 months; these findings were not accompanied by any changes in clinical chemistry, urinalysis, or histology (CIIT 1981). However, renal tubule hyperplasia was observed in male mice (but not female mice) exposed to 997 ppm for ≥12 months (CIIT 1981).

In non-rodent species, no adverse renal effects were noted at acute-duration exposures up to approximately 500 pm in dogs or cats (McKenna et al. 1981a) or intermediate-duration exposures up to 399 ppm in dogs (McKenna et al. 1981b).

2.11 DERMAL

No studies were located regarding dermal effects in humans after exposure to chloromethane. Based on inhalation studies in laboratory animals, the skin is not a target of chloromethane toxicity. No studies were located regarding dermal effects in animals after oral or dermal exposure to chloromethane.

No dermal effects were observed from acute-duration inhalation exposure to chloromethane at concentrations up to approximately 500 ppm in dogs or cats (McKenna et al. 1981a), although one dog with approximately 200 ppm of exposure had multiple areas of alopecia. The study authors noted that this may have been "secondary to fighting with cage mates." In 3-month inhalation studies, no dermal effects were observed at concentrations up to 1,473 ppm in rats or mice (McKenna et al. 1981b; Mitchell et al. 1979) or 399 ppm in dogs (McKenna et al. 1981b). Similarly, no dermal effects were noted in rats or mice exposed to concentrations up to 997 ppm for 6–24 months (CIIT 1981).

2.12 OCULAR

Available human case reports indicate that reported ocular effects following inhalation exposure are likely secondary to neurological effects. Based on inhalation studies in animals, chloromethane does not appear to have adverse effects on the eyes. No studies were located regarding ocular effects in humans or animals after oral or dermal exposure to chloromethane.

Case reports of humans exposed to chloromethane via inhalation have described such symptoms as blurred and double vision and dilated and slowly reacting pupils (Baker 1927; Borovska et al. 1976; Kegel et al. 1929; Mackie 1961). These symptoms likely reflect effects on the nervous system rather than effects on the eye itself.

No exposure-related ocular effects were observed during ophthalmological or histopathological examinations of male cats and Beagle dogs exposed to concentrations up to approximately 500 ppm continuously for 3 days (McKenna et al. 1981a), dogs exposed to concentrations up to 399 ppm for 90 days (McKenna et al. 1981b), or rats or mice exposed to concentrations up to 1,473 ppm for 90 days (Mitchell et al. 1979) or 997 ppm for 6 months (CIIT 1981). In mice, mucopurulent conjunctivitis was observed at an increased incidence following exposure to 368 ppm for 90 days; however, incidences were not increased at 741 or 1,473 ppm, compared to control (Mitchell et al. 1979). Therefore, these findings are not considered toxicologically relevant.

In chronic-duration inhalation studies, no exposure-related ocular effects were noted in mice at
concentrations up to 997 ppm (CIIT 1981). Some effects were noted in rats; however, findings lacked a
clear duration-related response and may have been secondary to a sialodacryo-adenitis (SDA) infection in
the colony. Therefore, the adversity of these findings is unclear. After 12 months of exposure to
chloromethane vapor, a corneal lesion described as a haze elliptically patterned over a central portion of
the eye was seen in the majority of exposed rats at ≥51 ppm (CIIT 1981). This corneal haze may have
been the result of chemical effects upon the eyes in which the lacrimal function was compromised by the
undercurrent SDA infection, which was histopathologically diagnosed at 12 months. The study authors
hypothesized that this disease reduced lacrimal function, making the eye more vulnerable to irritation
from chloromethane. After exposure for 18 months, this haze was no longer apparent; however, an
increase in the incidence of corneal opacity was observed in female rats at ≥224 ppm (CIIT 1981). By
24 months, the incidence of corneal opacity was no longer different between rats in the control and
exposure groups. Minimal vacuolar degeneration of the anterior lens fibers was also observed in
7/10 male and 6/10 female rats exposed to 997 ppm for 18 months; however, this lesion was not observed
in excess at 24 months, so its relationship to chloromethane exposure is unclear.

2.13 ENDOCRINE

No studies were located regarding endocrine effects in humans after exposure to chloromethane.
Exposure-related endocrine effects (outside the reproductive system) were only observed in rats following
acute exposure to very high concentrations. Reproductive effects, including alterations in serum
reproductive hormone levels, are discussed in Section 2.16. No studies were located regarding endocrine
effects in animals after oral or dermal exposure to chloromethane.

Observed effects following inhalation exposure in rats included vacuolation of cell cytoplasm in the
adrenal cortex in rats exposed to 5,004 ppm for 5 days (Chellman et al. 1986a) and clear droplets in
endothelial cytoplasm indicative of fatty degeneration in rats exposed to ≥3,500 ppm for 9 days (Morgan et
al. 1982). In other studies, no exposure-related changes in the endocrine system were observed at acute-
duration exposures up to approximately 500 ppm in dogs and cats (McKenna et al. 1981a), intermediate-
duration exposures up to 1,473 ppm in rats and mice (CIIT 1981; Mitchell et al. 1979), or chronic-duration
exposures up to 997 ppm in rats and mice (CIIT 1981).

2.14 IMMUNOLOGICAL

No studies were located regarding immunological effects in humans after exposure to chloromethane. Evidence from animal inhalation studies is inconsistent but suggests that the thymus and spleen may be toxicity targets at high concentrations. No studies were located regarding immunological effects in animals after oral or dermal exposure to chloromethane.

No studies evaluating immunological function in animals following exposure to chloromethane were located; however, several studies evaluated immune organ weight and/or histology. In a series of 11-day inhalation studies in mice, thymus atrophy and decreased absolute and relative thymus weight were observed at ≥1,600 ppm when exposure was 5.5 hours/day (Landry et al. 1985). When exposure was nearly continuous (22 hours/day), one set of experiments reported decreased absolute and relative thymus weight at 15, 50, and 150 ppm, compared to control, while another did not observe exposure-related changes in thymus weight at concentrations up to 100 ppm (Landry et al. 1985). Observed changes in the spleen (enlarged spleen) in mice exposed to 2,400 ppm for 11 days were attributed to extramedullary hematopoiesis by the study authors (Landry et al. 1985).

In longer-duration studies, no exposure-related changes in immune organ weight or histology were observed in rats or mice exposed to concentrations up to 1,473 ppm for 3 months (McKenna et al. 1981b; Mitchell et al. 1979), dogs exposed to concentrations up to 399 ppm for 3 months (McKenna et al. 1981b), or rats exposed to 997 ppm for 6–24 months (CIIT 1981). Mice exposed to 997 ppm for 6 months showed lymphoid depletion of the spleen and thymic lymphoid necrosis (CIIT 1981). Splenic atrophy and splenic and thymic lymphoid depletion were also observed in mice after exposure to 997 ppm for 18–24 months; however, these effects were not observed at the 12-month interim sacrifice (CIIT 1981).

2.15 NEUROLOGICAL

A systematic evaluation of the literature (Appendix C) determined that neurological effects are a presumed outcome associated with inhalation exposure to chloromethane based on a low level of evidence from human studies and high level of evidence from inhalation studies in laboratory animals. No studies were located regarding neurological effects in humans or animals after oral or dermal exposure to chloromethane.

Numerous case reports of humans exposed to chloromethane vapors as a result of industrial, refrigeration leaks, or other household exposures have described neurological effects. In general, symptoms develop within a few hours after exposure and include fatigue, progressive drowsiness, staggering, headache, nausea and vomiting, abdominal pain, slurred speech, blurred and double vision, mental confusion, disorientation, combativeness, tremor, vertigo, muscular weakness, muscular cramping and rigidity, sleep disturbances, ataxia, convulsions, cyanosis alternating with coma, delirium, and restlessness (Baird 1954; Baker 1927; Battigelli and Perini 1955; Borovska et al. 1976; Hansen et al. 1953; Hartman et al. 1955; Jones 1942; Kegel et al. 1929; Lanham 1982; MacDonald 1964; McNally 1946; Minami 1998; Scharnweber et al. 1974; Spevak et al. 1976; von Raalte and van Velzen 1945; Wood 1951). In some cases, symptoms persisted for several hours after exposure ended but disappeared completely within a few days. In other cases, symptoms lasted for several months, and depression and personality changes developed. In cases of more severe poisoning, convulsion, coma, and death ensued; or neurological effects remained (Kegel et al. 1929; McNally 1946; MacDonald 1964). In one lethal case, a gradual onset of headache and nausea occurred the day of exposure and improved the following day, but the symptoms worsened to coma, convulsions, and death (Baird 1954). Microscopic examination of the brain of an individual who died following chloromethane exposure revealed accumulation of lipoid-filled histiocytes in the leptomeninges of the hemispheres, hyperemia of the cerebral cortex, and lipoid droplets in the adventitia cells of the capillaries throughout the brain (Kegel et al. 1929).

Additional evidence of the neurotoxic effects of chloromethane comes from the crew of an Icelandic fishing boat that were exposed for up to 4 days in 1963 to chloromethane that leaked from a refrigerator on board a fishing trawler (Gudmundsson 1977). Initial effects of exposure in the crew were signs of intoxication that continued after exposure ended (no estimates of exposure levels were reported). Four of the 15 crew members with symptoms of severe chloromethane poisoning died within 10 years of exposure; 1 died within 24 hours of the exposure. Two patients developed severe depression and committed suicide 11 and 18 months later. The fourth patient was assessed as 75% disabled due to severe neurological and psychiatric disturbances and died 10 years post exposure at the age of 34 years. Autopsy revealed a recent coronary occlusion, which was not necessarily connected with the primary illness. In a 13-year follow-up of this cohort (Gudmundsson 1977), 5 out of the 10 patients that were alive 13 years post-exposure still exhibited abnormal neurological signs upon examination. Ten survivors stated they had a reduced tolerance to alcohol (compared with 5 at 20 months post-exposure), while 4 admitted excessive alcohol intake. Regarding the progress or reversibility of the symptoms, one patient who had considerable muscle atrophy and fasciculations 20 months after the accident, had improved by 13 years

post-exposure, but still exhibited signs of anterior horn damage. In two survivors, the paralysis of accommodation remained unchanged, but in one there was a complete regression.

In another occupational cohort, there were no associations between chloromethane exposure in fabricating plants (mean 33.57 ppm) and neurological function (Table 2-1) (NIOSH 1976). Endpoints evaluated included electroencephalogram (EEG) recordings and numerous measures of neurological function or behavior. While no exposure estimates are available for the Icelandic fisherman cohort, exposure to fabricating workers is likely lower than the acute-duration exposure experienced in the fishing boat accident.

Three human controlled trials evaluated exposure to chloromethane and potential neurotoxic effects and did not find any association (Putz-Anderson et al. 1981a, 1981b; Stewart et al. 1980). In Putz-Anderson et al. (1981a, 1981b), exposure to concentrations up to 200 ppm for up to 3.5 hours did not impact hand-eye coordination or alertness, with the only finding being a slight time delay in an auditory time-discrimination test, which could be due to solvent effects on ear hairs rather than a neurological effect. In Stewart et al. (1980), exposure to concentrations up to 150 ppm for 1, 3, and 7.5 hours/day on 2 or 5 consecutive days resulted in no exposure-related neurological abnormalities, abnormal EEG observations, effects on cognitive test, or significant subjective responses were observed, other than a slight time delay in a light-stimulus time-discrimination test, which was determined by the authors to not be related to chemical exposure. These studies, however, had several limitations such as small sample size, subjects lost to attrition, and multiple exposure schemes.

Chloromethane exposure at sufficiently high levels also results in neurological effects in animals. Consistent findings across numerous studies include clinical signs of neurotoxicity, some severe, and histopathological changes in the brain (cerebellum) and spinal cord. In general, mice and dogs appear to be the most sensitive species, with similar, but more severe, responses at lower exposure concentrations. There are no mechanistic data to explain the marked difference in neurotoxicity between species and strains, see Section 2.21, Mechanisms of Toxicity for general mechanisms of toxicity.

As discussed in Section 2.2, deaths associated with exposure to chloromethane for acute or intermediate durations were preceded by clinical signs of neurotoxicity in several species, predominantly neuromuscular and sensorimotor effects (Smith and von Oettingen 1947a, 1947b; von Oettingen et al. 1949, 1950). These results demonstrate a universal response of animals to the neurotoxic effects of chloromethane. Effects observed following acute-duration exposures included neuromuscular

abnormalities, impaired gait, and hindlimb drag in mice at ≥500 ppm; tremors, spasticity, and impaired gait in dogs at ≥500 ppm; backward arching of the head, neck, and spine, lost righting reflex, and convulsions in guinea pigs at ≥1,000 ppm; incoordination, motor impairments, seizures, and/or loss of consciousness in monkeys at 2,000 ppm; agitation and hunched posture in rats at ≥2,000 ppm; and neuromuscular dysfunction of hind legs and spastic adduction. While all cats survived an acute-duration exposure to 2,000 ppm, weakness, ataxia, and loss of righting reflex were observed. Effects became more severe (e.g., inability to walk) and/or were observed at lower concentrations following intermediate-duration exposure in monkeys, mice, and dogs at ≥500 ppm, guinea pigs at 1,000 ppm, and cats at 2,000 ppm (Smith and von Oettingen 1947a, 1947b). However, no clinical signs were noted in rabbits exposed to ≥500 ppm or rats exposed to 1,000 ppm for up to 266 days (despite ≥50% mortality). In dogs exposed to extremely high concentrations for 4–6 hours (14,661 or 40,560 ppm), decreased corneal and pupillary reflexes and complete muscle relaxation were observed prior to death, indicating CNS depression (von Oettingen et al. 1949, 1950).

Additionally, studies have reported clinical signs of neurotoxicity and motor deficits in rats and mice following inhalation exposure, with mice more susceptible than rats. Studies with continuous exposure (22 hours/day), showed lethargy in rats at ≥972 ppm after 48 or 72 hours (Burek et al. 1981), motor incoordination in mice at ≥150 ppm within 11 days (Landry et al. 1985), and ataxia in mice at ≥200 ppm within 5 days (Landry et al. 1985). With intermittent exposure (6 hours/day) for 5–9 days, severe signs of neurotoxicity were observed in rats at ≥5,000 ppm, including incoordination, ataxia, hindlimb paralysis, and sedation (Chellman et al. 1986a; Morgan et al. 1982). In longer-duration intermittent exposure studies, no clinical signs of neurotoxicity were reported in rats at concentrations up to 1,473 ppm for 3 months (McKenna et al. 1981b; Mitchell et al. 1979) or 997 ppm for 6–24 months (CIIT 1981). In mice, intermittent (5.5–6 hours/day) exposure for up to 2 weeks was associated with motor incoordination, altered activity levels (increased, then decreased), hypersensitivity to touch and sound, piloerection, tremors, convulsions, ataxia, front and hindlimb paralysis or rigidity, and/or sedation at concentrations ≥502 ppm (Chellman et al. 1986b; Jiang et al. 1985; Landry et al. 1985; Wolkowski-Tyl et al. 1981a, 1981b, 1983a, 1983b). In mice, severe neurological signs and motor impairment were observed following intermittent exposure to 997 ppm for ≥18 months, including tremor, hindlimb rigidity, paralysis, altered gait, and impaired reflexes (CIIT 1981). However, no clinical signs of neurotoxicity were observed at intermittent concentrations up to 1,473 ppm for 3 months (McKenna et al. 1981b; Mitchell et al. 1979) or 997 ppm for 6 or 12 months (CIIT 1981).

Consistent with the observed motor impairments described above, the granular layer of the cerebellum, which controls posture and coordination, appears to be a target of chloromethane toxicity in rodents. As observed with clinical signs, mice appear to be markedly more sensitive than rats, and mouse strains showed differences in susceptibility. Degeneration of the cerebellum was observed in rats following acute-duration inhalation exposure to ≥5,000 ppm; severity of lesions ranged from minimal to severe (Chellman et al. 1986a; Morgan et al. 1982). However, no histopathological changes in the brain or spinal cord were noted in rats following continuous exposure to concentrations up to 1,968 ppm for 48 hours or 1,950 ppm for 72 hours (Burek et al. 1981), up to 1,473 ppm for 3 months (McKenna et al. 1981b; Mitchell et al. 1979), or up to 997 ppm for 6–24 months (CIIT 1981).

In mice, the most sensitive mouse strain appears to be C57BL/6. In this strain, continuous exposure (22 hours/day) for 11 days resulted in slight cerebellar degeneration at ≥150 ppm (Landry et al. 1985). Intermittent exposure (5.5–6 hours/day) for 11–14 days showed slight cerebellar degeneration at 400 ppm, minimal-to-severe cerebellar degeneration at 1,000 ppm, focal necrosis at 1,492 ppm, and severe cerebellar degeneration at 1,500 ppm (Jiang et al. 1985; Landry et al. 1985; Morgan et al. 1982; Wolkowski-Tyl et al. 1981a, 1983a). Landry et al. (1985) addressed an apparent greater sensitivity to continuous exposure and hypothesized that it might be related to the conversion of chloromethane to an active metabolite, and/or diurnal susceptibility. Diurnal susceptibility (i.e., in this case, lower sensitivity during the daytime intermittent exposure) could result from the lower activity of mice during the daytime and the lower respiratory minute volume. However, when neurological effects are compared on the basis of total chloromethane inhaled per day, they appear to be similar for intermittent and continuous exposures. No longer-duration studies in C57BL/6 mice were identified. In B6C3F1 mice, minimal cerebellar degeneration was observed after intermittent exposure to concentrations ≥1,500 ppm for 12–14 days (Chellman et al. 1986b; Morgan et al. 1982). No exposure-related lesions were observed in B6C3F1 mice after intermittent exposure to concentrations up to 1,473 ppm for 3 months (Mitchell et al. 1979) or 997 ppm for 6 or 12 months (CIIT 1981). However, after 18–24 months, axonal swelling and degeneration of axons in spinal cord were observed in B6C3F1 mice exposed to ≥51 ppm; minimal-to-mild cerebellar degeneration was observed at 997 ppm (CIIT 1981). In other mouse strains, no histopathological changes in the brain or spinal cord were observed in C3H mice intermittently exposed to concentrations up to 2,000 ppm for 12 days (Morgan et al. 1982) or CD-1 mice intermittently exposed to concentrations up to 399 ppm for 94 days (McKenna et al. 1981b).

While mice appear more susceptible than rats with respect to overt clinical signs of neurotoxicity and histopathological findings, sensorimotor response testing during a 93-day inhalation study revealed

sensorimotor impairments in female rats, including impairments in the wire maneuver task at ≥149 ppm (inability of the animals to raise their hindquarters to the top of the wire while grasping with forelimbs) and decreased hindlimb clasp at 399 ppm (McKenna et al. 1981b). These effects were not observed in mice at concentrations up to 399 ppm (McKenna et al. 1981b). No other studies evaluating sensorimotor responses were identified.

In dogs, clinical signs of neurotoxicity and various CNS lesions were observed following continuous (23.5 hours/day) exposure to 496 ppm for 3 days (McKenna et al. 1981a). Clinical signs included severe limb stiffness, tremors, salivation, and incoordination. Unlike rodents, the cerebellum was not a target of chloromethane toxicity in dogs. However, observed brain and spinal cord lesions included vacuolization, swollen eosinophilic axons, loss of axons, demyelination, and gitter cells. These changes were very slight and multifocal in the brain stem (medulla, pons, or both), and slight and multifocal in the lateral and ventral funiculi of the spinal cord. In a 93-day study, intermittent (6 hours/day) exposure to concentrations up to 399 ppm did not result in neurological effects in dogs.

In cats, no signs of neurotoxicity were observed after continuous exposure (23.5 hours/day) to concentrations up to 501 ppm for 3 days (McKenna et al. 1981a).

2.16 REPRODUCTIVE

Available human studies are too limited to determine if inhalation exposure to chloromethane affects the reproductive system; no oral or dermal studies in humans were identified. A systematic evaluation of the literature (Appendix C) determined that toxicity to the male reproductive system is a presumed health effect associated with inhalation exposure to chloromethane based on a high level of evidence from laboratory animals. No studies were located regarding reproductive effects in animals after oral or dermal exposure to chloromethane.

One case report of a human with a history of exposure to chloromethane described sexual impotence as a possible indicator of reproductive toxicity. The individual owned a refrigeration plant and reported high exposures to chloromethane along with signs and symptoms typically associated with acute overexposure. In addition, during a 1-year period, he began experiencing morning urethral discharge and sexual impotence that gradually increased to completeness in a 3–4-month period (Mackie 1961). No additional studies were located regarding reproductive effects in humans after exposure to chloromethane.

Impaired male fertility has been observed in rats following inhalation exposure. In acute-duration studies, exposure to concentrations ≥3,000 ppm for 5 days prior to breeding with unexposed female rats resulted in decreased fertilization rate, decreased number of live and total implants, and increased pre- and post-implantation loss (Chellman et al. 1986c; Working and Bus 1986; Working et al. 1985a, 1985b). Exposed males showed a reversible disruption of spermatogenesis, transient reduction in testes weights, and increased infiltration of neutrophils and macrophages into the interstitium of the cauda epididymis (Chellman et al. 1986c; Working et al. 1985b). In a 2-generation study in which males were exposed for 10 weeks prior to mating, the number of fertile males and the number of litters per copulation plug were reduced in F0 males at 472 ppm following mating with similarly exposed or unexposed females (Hamm et al. 1985). Complete male sterility, atrophy of the seminiferous tubules, and epididymal granulomas were observed in F0 rats at 1,502 ppm (Hamm et al. 1985). A nonsignificant decrease in F1 male fertility was observed at 472 ppm.

Several additional studies evaluated male reproductive organ weight and/or histology in rodents following inhalation exposure to chloromethane. Continuous exposure to >500 ppm for 48 hours was associated with numerous histopathological changes in the testes, including sperm granulomas, decreased sperm in the tubule lumen, interstitial edema, and coagulated proteinaceous obstruction of lumen in rats; testicular atrophy and inflammation was also observed after exposure for 72 hours (Burek et al. 1981). In acute-duration inhalation studies with intermittent exposure for 2–12 days, testicular changes were consistently observed at ≥3,500 ppm. Observed changes include reduced testes weight, sperm effects (delayed spermiation, reduction in spermatids and sperm, reduced sperm motility, altered sperm maturation), and/or various testicular lesions (seminiferous epithelium vacuolation, bilateral epididymal granulomas, multinucleated giant cells) (Chapin et al. 1984; Chellman et al. 1986a; 1987; Morgan et al. 1982). One acute study in rats also reported decreased serum testosterone after exposure to 3,500 ppm for 12 days (Chapin et al. 1984). In longer-duration studies in rats and mice, no adverse testicular effects were noted at concentrations exposed up to 1,473 ppm for 3 months (McKenna et al. 1981b; Mitchell et al. 1979). However, degeneration and atrophy of the seminiferous tubules and sperm granulomas were observed following exposure to 997 ppm for 6, 12, 18, or 24 months in rats and 18 or 24 months in mice (CIIT 1981).

No histopathological changes in male reproductive organs were noted in dogs or cats exposed continuously (23.5 hours/day) to concentrations up to approximately 500 ppm for 3 days (McKenna et al. 1981a) or dogs exposed intermittently (6 hours/day) for 3 months (McKenna et al. 1981b).

The female reproductive system does not appear to be a target of chloromethane toxicity. No exposure-related changes in female reproductive organ weight or histology were observed in F0 or F1 rats exposed to concentrations up to 1,502 ppm during a 2-generation study (Hamm et al. 1985). However, due to clear deficits in male fertility in this study (and lack of a mating study between unexposed males and exposed females), female reproductive function could not be adequately assessed. In gestational exposure studies, no adverse reproductive effects were observed in rats exposed to concentrations up to 1,492 ppm on GDs 7–19 (Wolkowski-Tyl et al. 1981a, 1983a), mice exposed to concentrations up to 502 ppm on GDs 6–17 (Wolkowski-Tyl et al. 1981a, 1981b, 1983b, 1983b), or rabbits exposed to concentrations up to 1,012 ppm on GDs 6–28 (Theuns-van Vliet 2016). In other studies, no changes in female reproductive organ weight or histology were observed in rats or mice exposed to concentrations up to 1,473 ppm for 3 months (McKenna et al. 1981b; Mitchell et al. 1979) or 997 ppm for 6–24 months (CIIT 1981).

2.17 DEVELOPMENTAL

No studies were located regarding developmental effects in humans after exposure to chloromethane. A systematic review of the literature (Appendix C) determined that chloromethane is not classifiable as it relates to developmental toxicity following inhalation exposure, based on a low level of evidence in laboratory studies. Potential developmental effects following gestational exposure have been examined in rats, mice, and rabbits; findings suggest differences in species susceptibility and developmental targets. No studies were located regarding developmental effects in animals after oral or dermal exposure to chloromethane.

In rats, decreased fetal body weight, decreased crown-rump length (females only), and delayed skeletal development were observed after maternal exposure to 1,492 ppm on GDs 7–19 (Wolkowski-Tyl et al. 1981a, 1983a). These findings may have been secondary to maternal toxicity (marked reduction in body weight gain), which was observed at ≥479 ppm. In a 2-generation study in rats, no adverse effects on survival, growth, or development were observed in F1 or F2 offspring at parental exposure concentrations up to 472 ppm (Hamm et al. 1985).

In mice, an exposure-related increase in heart defects was observed following maternal exposure to concentrations ≥479 ppm on GDs 6–17, characterized by small right ventricle, globular heart, white spots (assumed to be calcium deposits, in the left ventricular wall), and/or absent or abnormal atrioventricular valves, chordae tendinea, and papillary muscles (Wolkowski-Tyl et al. 1981a, 1981b, 1983a, 1983b). In the mouse studies, maternal toxicity (reduced survival and body weight) was not observed until

≥749 ppm. However, in a letter to the journal from the same research organization, John-Greene et al. (1985) suggested that the heart anomalies reported by Wolkowski-Tyl et al. (1983a) may have been an artifact of the sectioning technique, due to the examination of the fixed as opposed to unfixed fetal tissue, or a misdiagnosis. They also suggested that, though Wolkowski-Tyl et al. (1983b) used a more appropriate sectioning technique, the papillary muscle effects reported were rare and should not have occurred without other expected cardiovascular malformations. In pilot exposures of 250–300 ppm on GDs 11.5–12.5, John-Greene et al. (1985) observed inter-animal variability in the appearance of the papillary muscles in control mice and could not reproduce the results of Wolkowski-Tyl et al. (1983a, 1983b). However, in a response to the John-Greene et al. (1985) letter, Wolkowski-Tyl (1985) countered that the inability of John-Greene et al. (1985) to detect the abnormality was due to the lower exposure concentrations, shorter exposure durations, and difference in timing of exposure during gestation, arguing that the most critical day is GD 14.

No exposure-related changes in litter outcomes, fetal body weight, or malformations or anomalies were observed in rabbits exposed to concentrations up to 1,012 ppm on GDs 6–28 (Theuns-van Vliet 2016).

2.18 OTHER NONCANCER

No studies were located regarding other systemic effects in humans after exposure to chloromethane. The only other systemic effect reported in inhalation studies in animals was inanition (exhaustion caused by lack of nourishment) associated with a decrease in food consumption in mice exposed to ≥200 ppm for up to 11 days (22 hours/day) or 2,400 ppm for up to 9 days (5.5 hours/day) (Landry et al. 1985). No studies were located regarding other noncancer effects in animals after oral or dermal exposure to chloromethane.

2.19 CANCER

Available human data regarding carcinogenicity of chloromethane following inhalation exposure are limited and findings are mixed. Cancer bioassays in animals are available for rats and mice via inhalation exposure. Increased renal tumors were reported in male mice; no neoplastic changes were noted in female mice or male or female rats. No studies were located regarding carcinogenicity in animals after oral or dermal exposure to chloromethane.

Several epidemiological studies have evaluated the potential association between occupational exposure to chloromethane and risk of cancer (Table 2-1). Most available studies did not have direct measures of

chloromethane exposure and used job exposure matrices instead to estimate the probability and intensity of chloromethane exposure. Of these, the occupational cohort study with the highest probability and intensity of exposure is most likely the Icelandic fisherman cohort (discussed in Section 2.2) accidentally exposed to high levels of chloromethane due to a refrigerant leak. At the 32-year follow-up, the risk of death from cancer was not increased in this cohort, compared to a referent group of Icelandic fishermen (Rafnsson and Gudmundsson 1997). However, at the 47-year follow-up, the risk of death specifically from kidney cancer was increased in the exposed cohort, compared to the referent group (Rafnsson and Kristbjornsdottir 2014). It is noted that the Icelandic fisherman cohort is small (<30 men), had high but unmeasured exposure levels, and was not adjusted for other lifestyle factors such as smoking and diet. Therefore, the generalizability of these results is unclear. In another occupational cohort study, the risk of death due to cancer was not increased in synthetic rubber workers exposed to chloromethane (Holmes et al. 1986). While no exposure estimates are available, exposure to rubber workers is likely lower than the acute-duration exposure experienced in the Icelandic fisherman cohort.

In general, case-control studies did not observe associations between estimated occupational exposure to chloromethane and overall risk of cancer. Barry et al. (2011) did not observe an increased risk of NHL in women with occupational exposure to chloromethane, compared to unexposed women (Barry et al. 2011). However, the risk was increased specifically for follicular lymphoma in exposed women, and exposed women with a specific CYP2E1 rs2070673 polymorphism (TT but not TA genotype) had an increased risk of both total NHL and follicular lymphoma. No associations were observed for diffuse large B-cell lymphoma. Kernan et al. (1999) did not observe an increased risk of death from pancreatic cancer in patients with occupational exposure to chloromethane, compared to unexposed patients, when sexes and races were combined. Based on a small sample of black men, there was an increased risk of death from pancreatic cancer when there was a high probability of exposure to chloromethane. This association was not observed in white men, white women, or black women. Dosemeci et al. (1999) did not observe any associations between renal cell carcinoma and occupational exposure to chloromethane.

A high incidence of renal tumors was found in male mice that were exposed primarily to approximately 997 ppm chloromethane and died or were killed at 12 months or later (primarily between 18 and 24 months) in a 2-year oncogenicity study (CIIT 1981). Tumors consisted of renal cortex adenomas, adenocarcinomas, papillary cystadenomas, tubular cystadenomas, and a papillary cystadenocarcinoma. Renal cortex adenomas were also observed in two male mice at 225 ppm after 24 months; while this incidence did not differ significantly compared to controls, they were considered treatment-related by the study authors due to similarity with findings at 1,000 ppm. No evidence of carcinogenicity was found in

similarly exposed female mice or male or female rats exposed to concentrations up to 997 ppm (CIIT 1981).

IARC and EPA have both determined that chloromethane is not classifiable as to its carcinogenicity in humans (EPA 2001; IARC 2019). HHS (NTP 2016) has not evaluated the potential for chloromethane to cause carcinogenicity in humans.

2.20 GENOTOXICITY

Available evidence indicates that chloromethane is mutagenic and clastogenic and has the potential to directly interact with deoxyribonucleic acid (DNA). Results of *in vitro* and *in vivo* genetic testing are presented in Tables 2-4 and 2-5, respectively.

Table 2-4. Genotoxicity of Chloromethane *In Vitro*

Species (test system)	Endpoint	Results Activation With	Without	Reference
Prokaryotic organisms				
Salmonella typhimurium	Gene mutation	+	+	Simmon et al. 1977
S. typhimurium strain TA1535	Gene mutation	+	+	Andrews et al. 1976
S. typhimurium strains TA18, TA100, TA1535, TA1537	Gene mutation	+	+	DuPont 1977
S. typhimurium strain TA677	Gene mutation	NT	+	Fostel et al. 1985
S. typhimurium strains TA98, TA100	Gene mutation	+	+	NTP 2019
Mammalian cells				
Human lymphoblasts	Gene mutation	NT	+	Fostel et al. 1985
Human lymphoblasts	Sister-chromatid exchange	NT	+	Fostel et al. 1985
Chinese hamster lung cells	Chromosomal aberrations	+	+	Asakura et al. 2008
Human lymphoblasts	DNA strand breaks	NT	–	Fostel et al. 1985
Rat hepatocytes	Unscheduled DNA synthesis	NT	+	Working et al. 1986
Rat spermatocytes	Unscheduled DNA synthesis	NT	+	Working et al. 1986
Rat tracheal epithelial cells	Unscheduled DNA synthesis	NT	–	Working et al. 1986
Primary hamster embryo cells	Unscheduled DNA synthesis	NT	+	Hatch et al. 1982, 1983

+ = positive result; — = negative result; DNA = deoxyribonucleic acid; NT = not tested

Table 2-5. Genotoxicity of Chloromethane *In Vivo*

Species (test system)	Endpoint	Results	Reference
Rat (inhalation)	Dominant lethal	+	Working et al. 1985a
Rat (inhalation)	Dominant lethal	+	Chellman et al. 1986c
Rat (inhalation)	Dominant lethal	+	Rushbrook 1984
Rat (inhalation)	Unscheduled DNA synthesis in hepatocytes	(+)	Working et al. 1986
Rat (inhalation)	Unscheduled DNA synthesis in spermatocytes	–	Working et al. 1986
Rat (inhalation)	Unscheduled DNA synthesis in tracheal epithelial cells	–	Working et al. 1986
Mouse (inhalation)	DNA damage in kidney cells (single strand breaks)	+	Jager et al. 1988
Mouse (inhalation)	DNA damage in kidney cells (single strand breaks)	+	Ristau et al. 1990
Drosophila (inhalation)	Recessive lethal	+	University of Wisconsin 1986

– = negative results; + = positive results; (+) = marginally positive result; DNA = deoxyribonucleic acid

Chloromethane is mutagenic in *Salmonella typhimurium* both with and without metabolic activation (Andrews et al. 1976; DuPont 1977; Fostel et al. 1985; NTP 2019; Simmon et al. 1977) and human lymphoblasts without metabolic activation (not tested with metabolic activation) (Fostel et al. 1985). In *in vivo* studies, chloromethane induced recessive lethal mutations in *Drosophila melanogaster* (University of Wisconsin 1986) and dominant lethal mutations in rats (Chellman et al. 1986c; Rushbrook 1984) following inhalation exposure.

Chloromethane is also clastogenic, inducing sister chromatid exchanges and in human lymphoblast cells without metabolic activation (not tested with metabolic activation) (Fostel et al. 1985) and chromosomal aberrations in Chinese hamster lung cells both with and without metabolic activation (Asakura et al. 2008).

Findings regarding direct interactions with DNA are mixed. Chloromethane did not induce DNA strand breaks in human lymphoblasts following *in vitro* exposure without metabolic activation (Fostel et al. 1985); however, DNA strand breaks were observed in kidney cells of mice follow *in vivo* inhalation exposure (Jager et al. 1988; Ristau et al. 1990). Chloromethane also induced unscheduled DNA synthesis (UDS) in cultured primary hamster embryo cells without metabolic activation (Hatch et al. 1982, 1983). Working et al. (1986) evaluated the potential for chloromethane to induce UDS in rat hepatocytes, spermatocytes, and tracheal epithelial cells both *in vitro* and *in vivo*. UDS was induced in cultured rat

hepatocytes and spermatocytes without metabolic activation at near-cytotoxic concentrations; however, *in vivo* exposure only marginally induced UDS in hepatocytes (Working et al. 1986).

2.21 MECHANISMS OF TOXICITY

Lethal and toxic effects associated with chloromethane have been attributed to common mechanisms across organ systems. Chellman et al. (1986b) proposed that glutathione (GSH) conjugation of chloromethane into toxic metabolites underlies its effects, as evidenced by reduced lethality, hepatotoxicity, renal toxicity, and neurotoxicity in mice following pre-treatment with the GSH deplete, L-buthionine-S,R-sulfoximine (BSO). For example, the LC_{50} in the non-pretreated mice was 2,200 ppm, while the LC_{50} for the pretreated rats was 3,200 ppm. Additionally, a single, 8-hour exposure to 1,000 ppm chloromethane significantly reduced glutathione-S-transferase (GST) activity in the liver and kidney in female and male mice and in male rats, but when exposure was repeated 6 hours/day for 4 days, GST activity was only significantly reduced in the liver of male mice (Jager et al. 1988). Additionally, several studies have provided evidence of dose-related depletion of nonprotein sulfhydryls (NPSH) in the rat liver and/or kidney following exposure to chloromethane, which is likely the result of GSH conjugation of chloromethane (Chapin et al. 1984; Dodd et al. 1982; Landry et al. 1983a).

Pro-inflammatory changes may also contribute to systemic toxicity of chloromethane. Chellman et al. (1986a) showed that pre- and post-treatment with an anti-inflammatory agent (3-amino-l-[m-(trifluoromethyl)phenyl]-2-pyrazoline [BW775C]) reduced lethality, hepatotoxicity, neurotoxicity, and testicular toxicity. Both incidence and severity of chloromethane-induced lesions were reduced following treatment with BW775C. The study authors concluded that protection from toxic effects was not simply the result of altered metabolism because BW755C had no effect on tissue distribution or excretion of ^{14}C-chloromethane, and administration of BW755C did not decrease hepatic GSH content. The protection afforded by BW755C may have been related to an inhibition of leukotriene and prostaglandin synthesis.

However, decreased fertility in male rats exposed to chloromethane does not appear to be related to inflammatory changes. Multiple studies showed that BW755C did not protect against sperm damage or pre-implantation loss in females mated with exposed males (Chellman et al. 1986c, 1987). Instead, the study authors proposed that these outcomes were related to the cytotoxicity of chloromethane, not chloromethane-induced inflammation. Other studies speculated that while inflammation-derived reactive metabolites (e.g., superoxide anion) could damage DNA or sperm in epididymides, chloromethane may

not reach the testes in sufficient concentrations to produce detectable DNA damage (Working et al. 1985a). The study authors concluded that preimplantation losses observed in acute-duration inhalation studies in rats could be explained by a cytotoxic effect resulting in failure of fertilization, rather than a genotoxic effect resulting in early embryonic death (Working and Bus 1986).

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

Information on the toxicokinetics of chloromethane are available from limited human studies and several animal studies.

- Chloromethane is readily absorbed from the lungs and rapidly approaches equilibrium with the blood (Putz-Anderson et al. 1981a, 1981b).

- Animal studies demonstrate that chloromethane absorbed from the lungs is extensively distributed throughout the body with relatively little variation in the pattern of distribution with respect to dose (Chellman et al. 1986a; Kornbrust et al. 1982; von Oettingen et al. 1949, 1950).

- Rapid and biphasic blood clearance was found in humans, rats, and dogs (Landry et al. 1983a; Nolan et al. 1985; Putz-Anderson et al. 1981a).

- Conjugation of chloromethane via GSH transferase is the main form of metabolism in humans and animals. Cytochrome P450 may dehalogenate chloromethane to formaldehyde, but oxidation of GSH-chloromethane conjugation intermediates by cytochrome P450 may also be involved in the formation of formaldehyde (Heck et al. 1982; Kornbrust and Bus 1983).

- Very little chloromethane is excreted unchanged. The majority of the metabolites are excreted in the urine or expired as carbon dioxide (Morgan et al. 1970; Putz-Anderson et al. 1981a).

3.1.1 Absorption

Chloromethane is absorbed readily from the lungs of humans following inhalation exposure. Alveolar breath levels of chloromethane approached equilibrium within 1 hour during a 3- or 3.5-hour exposure of men and women (Putz-Anderson et al. 1981a, 1981b). Mean±SD alveolar expired breath levels were 63±23.6 ppm in 24 men and women exposed to 200 ppm, and 36±12 ppm in 8 men and women exposed to 100 ppm for 3 hours. Mean ± SD blood levels were 11.5±12.3 ppm for the 200-ppm exposed group, and 7.7±6.3 ppm for the 100-ppm exposed group. The results indicate that uptake was roughly proportional to exposure concentration, but individual levels were quite variable. A high correlation between alveolar air and blood levels (r=0.85, p<0.01) was found.

Blood and expired air levels of chloromethane also approached equilibrium during the first hour of exposure in 6 men exposed to 10 or 50 ppm for 6 hours (Nolan et al. 1985). The levels in blood and expired air were proportional to the exposure concentrations. Based on elimination data, the subjects

were divided into two groups: fast and slow metabolizers. The difference between inspired and expired chloromethane concentrations indicated that the fast metabolizers absorbed chloromethane at the rate of 3.7 µg/min/kg, and the slow metabolizers absorbed it at 1.4 µg/min/kg.

In experiments in rats, uptake of chloromethane approached equilibrium within 1 hour and was proportional or nearly proportional to exposure concentrations of 50–1,000 ppm for 3–6 hours (Landry et al. 1983a, 1983b). Absorbed doses (and absorption rates) for 6-hour exposures were calculated as 67 mg/kg (0.167 mg/minute/kg) for rats exposed to 1,000 ppm, and 3.8 mg/kg (0.01 mg/minute/kg) for rats exposed to 50 ppm (i.e., a ratio of 17.6). The ratio is nearly proportional to the actual exposure concentration ratio of 20. The difference was assumed to be a slightly lower uptake at the higher dose (perhaps due to a decrease in minute volume such as is observed when animals inhale formaldehyde or another irritant), or to lower metabolism at the higher concentration. Blood chloromethane concentrations reached approximately 90% of equilibrium within 1 hour for dogs exposed to 50 or 1,000 ppm (Landry et al. 1983a), or 15,000 or 40,000 ppm (von Oettingen et al. 1949, 1950) for 6 hours, and the concentration was proportional to the exposure concentration (Landry et al. 1983a; von Oettingen et al. 1949). This proportionality was confirmed at 15,000 and 40,000 ppm chloromethane for which the respective blood concentrations in dogs peaked at 0.12 mmol/100 cc at the lower dose, with proportional extrapolation to approximately 0.32 mmol/100 cc at the higher dose (von Oettingen et al. 1949).

Gaskin et al. (2018) evaluated *in vitro* skin permeability of gaseous chloromethane using human epidermis. Chloromethane gas was diluted to 20,000 and 2,000 ppm to reflect the lowest reported lethal concentration (LC) and an immediately dangerous to health (IDLH) concentration, respectively. Short-term exposures of less than one hour were used to reflect possible exposures in the workplace or HAZMAT situations. Skin penetration by chloromethane was reported after 15 minutes and increased by a factor of 10 after 1 hour of exposure at 20,000 ppm. As a result of this analysis, a skin notation was assigned by ACGIH (2012).

No studies were located regarding absorption in humans or animals after oral exposure to chloromethane.

3.1.2   Distribution

No studies were located regarding distribution in humans or animals after oral or dermal exposure to chloromethane.

Putz-Anderson et al. (1981a) exposed volunteers to 100 ppm (n=8) or 200 ppm (n=24) chloromethane for 3 hours and collected blood and periodic breath samples. Breath concentrations approached equilibrium within one hour and averaged 36±12 and 63±23.6 ppm for the respective doses. The respective blood concentrations were 7.7±6.3 and 11.5±12.3 ppm. There was a high degree of correlation between blood and breath concentrations (r = 0.85, N=29, p<0.01).

After absorption of chloromethane, distribution of chloromethane and/or its metabolites is extensive in animals. Total uptake of radioactivity (as μmol ^{14}C-chloromethane equivalents/g wet weight) in whole tissue homogenates following exposure of rats to 500 ppm for 6 hours was 1.21 for lungs, 4.13 for liver, 3.43 for kidneys, 2.29 for testes, 0.71 for muscles, 0.57 for brain, and 2.42 for intestines (Kornbrust et al. 1982). In rats exposed to 5,000 ppm for 2 hours and sacrificed 4 hours later, the comparable values were 1.46 for liver, 0.98 for kidneys, 1.02 for testes, 0.69 for epididymides, and 0.36 for brain (Chellman et al. 1986a). Little difference in the pattern of distribution was found at an exposure concentration of 1,500 ppm as compared with 500 ppm. Upon acid precipitation of protein, 80% of the radioactivity present in liver and testes was found in the acid soluble (unbound) fraction. The remainder was found to have been metabolically incorporated into lipid, ribonucleic acid (RNA), DNA, and protein, rather than bound to the macromolecules as a result of direct alkylation. Tissue levels of chloromethane (in mg%) in dogs exposed to chloromethane for 6 hours were 13 in liver, 15 in heart, and 16 in brain at 15,000 ppm and 9.3 in liver, 8.1 in heart, and 9.9 in brain at 40,000 ppm (von Oettingen et al. 1949, 1950).

3.1.3 Metabolism

Information regarding metabolism of chloromethane in humans is limited. Nolan et al. (1985) exposed human volunteers to either 10 or 50 ppm chloromethane and determined that 15 and 61% of the chloromethane was metabolized within 6 hours after exposure, respectively, by those who metabolized chloromethane slowly or more rapidly (termed slow and fast metabolizers). Unlike previously reported assessments, they found that the amounts of urinary S-methylcysteine excreted by each group was comparable to that during the preexposure period. Another finding was that blood levels were 10-fold higher than previously reported, purportedly due to a rapid loss of chloromethane from samples stored at room temperature. Overall, they concluded that measurement of urinary S-methylcysteine is inappropriate for assessing chloromethane exposure and that previously reported blood levels were likely inaccurate. This helped clarify previously reported assessments described below.

3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

In a group of six workers exposed to TWA 8-hour workroom concentrations of 30–90 ppm, the urinary excretion of S-methylcysteine showed wide variations, with little correlation to exposure levels (van Doorn et al. 1980). S-Methylcysteine is formed from conjugation of chloromethane with GSH (Kornbrust and Bus 1983). In four of the workers, all values were higher than in controls, and appeared to build up during the course of the week. Two of the workers had only minor amounts of S-methylcysteine in the urine, but these workers experienced the highest exposure concentrations. The author concluded that there are two distinct populations of individuals: fast metabolizers with lower body burdens and higher excretion, and slow metabolizers with higher body burdens and lower excretion (van Doorn et al. 1980). The author speculated that the difference may be due to a deficiency of the enzyme GST that catalyzes the conjugation of chloromethane with GSH. Other possible reasons for the differences in chloromethane elimination among subjects include differences in tissue GSH levels and differences in biliary excretion and fecal elimination of thiolated conjugates. As a working hypothesis, however, the two distinct populations are referred to as fast and slow eliminators.

Two distinct subpopulations were also found based on venous blood and expired concentrations of chloromethane in volunteers (Nolan et al. 1985). In addition, Nolan et al. (1985) observed a 5-fold difference in the first-order rate constant for elimination with slow metabolizers demonstrating a K_m of 0.039 to 0.069/minute and fast metabolizers demonstrated a K_m of 0.284 to 0.342/minute. The urinary excretion of S-methylcysteine in the volunteers exposed to chloromethane was variable and was not significantly different in pre- and post-exposure levels. No change was detected in the S-methylcysteine concentration or in the total sulfhydryl concentration in the urine of 4 workers before and after a 7-hour shift in a styrene production plant by DeKok and Anthenius (1981), who concluded that S-methylcysteine is not a human metabolite of chloromethane. It is possible, however, that the small number of workers examined by DeKok and Anthenius (1981) were slow eliminators.

Stewart et al. (1980) exposed male and female volunteers to 0–150 ppm chloromethane for periods up to 7.5 hours/day for 2 or 5 consecutive days, and then evaluated blood carboxyhemoglobin saturation before, just following, and 15 and 30 minutes post exposure, and urinary methyl alcohol from 24-hour composites collected twice weekly post exposure. Results indicated that chloromethane was not metabolically converted to either carbon dioxide or methyl alcohol. Measured breath and blood concentrations were much higher in several individuals, indicating some human differences in metabolic rate.

Peter et al. (1989a, 1989b) assayed erythrocyte cytoplasm of humans with chloromethane and monitored the decline of chloromethane and the production of S-methylglutathione. About 60% of the human blood samples showed a significant metabolic elimination of the substance (conjugators), whereas 40% did not (non-conjugators). The results suggested that a minor form of human erythrocyte GST is responsible for the unique metabolism of chloromethane in human erythrocytes. Hallier et al. (1990) demonstrated that other monohalogenated methanes (methyl iodide and methyl bromide) could undergo enzymatic conjugation with GSH, but that in contrast to chloromethane, methyl iodide and methyl bromide also showed significant non-enzymatic conjugation with GSH.

Warholm et al. (1994) studied the polymorphic distribution of the erythrocyte GSH transferases in a Swedish population and found three distinct sub-groups:11.1% lacked activity, 46.2% had intermediate activity, and 42.8% had high activity. The authors calculated two allelic frequencies: one for a functional allele with a gene frequency of 0.659 and one for a defect allele with a frequency of 0.341. This two-allele hypothesis is compatible with the observed distribution of the three phenotypes. A follow-up study on genotype indicated that approximately 10% of the Swedish population lacked the GSH transferase isoenzyme (Warholm et al. 1995). This 10% number is considerably smaller than a previously proposed proportion of non-conjugators of 30–40% for a German population (Peter et al. 1989a). A different study by Kempkes et al. (1996) found a frequency of 15% for non-conjugators in a German cohort of 40 people. Whether this lack of activity poses an increased risk of developing disease such as cancer is not known. Warholm et al. (1995) suggest that additional ethnic groups be evaluated for percentage of non-conjugators.

Because of this unique polymorphism, these populations have been further studied in the development of physiologically based pharmacokinetic (PBPK) models to assess the reliability of such models in general (Johanson et al. 1999; Jonsson et al. 2001), and to investigate how the genetic polymorphism affects the metabolism and disposition of chloromethane specifically *in vivo* (Lof et al. 2000).

Lof et al. (2000) exposed 24 volunteers (8 with high, 8 with medium, and 8 with no GSTT) activity) to 10 ppm chloromethane for 2 hours. The concentration of chloromethane was 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 were 243, 148, and 44 μmol in high, medium, and no GSTT1 activity groups, respectively. During the first 15 minutes of exposure, the concentration of chloromethane in blood 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 exposure, the blood

concentrations declined rapidly in the high and medium metabolizing groups but declined more slowly in the group lacking GSTT1 activity. The half-times were 1.7, 2.8, and 3.8 minutes, respectively for the first phase and 44, 48, and 60 minutes, respectively, for the second phase. Metabolic clearance was 4.6 and 2.4 L/minute in the high and medium GSTT1 groups, but nearly absent in the non-metabolizing group. The rate of exhalation clearance was similar among the three groups, but the non-metabolism group had much higher concentrations of chloromethane in exhaled air after exposure.

The metabolism of chloromethane has been studied in rats, mice, and dogs *in vivo* after inhalation exposure, and *in vitro*. Based on these studies, the metabolic pathway shown in Figure 3-1 was proposed (Kornbrust and Bus 1983). According to the proposed pathways, chloromethane metabolism involves conjugation with GSH to yield S-methylglutathione, S-methylcysteine, and other sulfur-containing compounds (Kornbrust and Bus 1984; Landry et al. 1983a, 1983b; Redford-Ellis and Gowenlock 1971a, 1971b). These compounds can be excreted in the urine (Landry et al. 1983a), or S-methylglutathione may be further metabolized to methanethiol. Cytochrome P450-dependent metabolism of methanethiol may yield formaldehyde and formic acid, whose carbon atoms are then available to the one-carbon pool for incorporation into macromolecules or for formation of CO_2 (Kornbrust and Bus 1983; Kornbrust et al. 1982). Formaldehyde may also be a direct product of chloromethane metabolism via oxidative dechlorination. Production of methanethiol and formaldehyde, and lipid peroxidation due to GSH depletion have been suggested as possible mechanisms for the toxicity of chloromethane, but the precise mechanisms are not known (Kornbrust and Bus 1983, 1984). Dekant et al. (1995) demonstrated oxidation of chloromethane to formaldehyde by cytochrome P450 (2El) in male mouse kidney microsomes, and that the amount of formaldehyde formed was dependent upon the hormonal status of the animal. Female mouse kidney microsomes produced considerably less formaldehyde than male kidney microsomes. Liver microsomal activity from both sexes was 2-fold higher than in kidney microsomes from the male. In contrast, rat kidney microsomes did not catalyze formaldehyde formation from chloromethane. In addition, Heck et al. (1982) observed a doubling of formaldehyde in the liver and testes of male F344 rats after 4 days of 6-hour exposure to 3,000 ppm of chloromethane compared to the control rats. In this same study, there was a 7-fold increase in formaldehyde in the brain of exposed rats compared to controls.

Peter et al. (1989a) assayed erythrocyte cytoplasm of a variety of test animals with chloromethane and monitored the decline of chloromethane and the production of S-methylglutathione. Rats, mice, bovine, pigs, sheep, and rhesus monkeys showed no conversion of chloromethane in erythrocyte cytoplasm.

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Species differences in the GSTT1 activity for chloromethane in liver and kidney tissues from mice, rats, hamsters, and all three phenotypes of humans were studied *in vitro* (Thier et al. 1998). No GSTT1 activity was found in either tissue of the non-metabolizing phenotypic human subjects. The GSTT1 activities in the liver and kidney tissue from the high GSTT1 humans were twice as high as in the low metabolizing group, and 2–7 times higher in the liver tissues than in the kidney tissues of either group. The GSTT1 activities in decreasing order were mice > high GSTT1 humans > rat > low GSTT1 humans > hamster > GSTT1-deficient humans. A proposed scheme of metabolism is illustrated in Figure 3-1.

Figure 3-1. Proposed Scheme for Metabolism of Chloromethane

*Indicates the position of the radioactive label.

Source: Kornbrust and Bus 1983

3.1.4 Excretion

Very little unchanged chloromethane is excreted in the urine. In volunteers exposed to chloromethane, urinary excretion was <0.01 %/minute (Morgan A et al. 1970). Putz-Anderson et al. (1981a) exposed volunteers to 100 or 200 ppm chloromethane for 3 hours, and breath concentrations approached equilibrium within 1 hour at 36 ppm (SD 12 ppm) and 63 ppm (SD 23.6 ppm), respectively. The excretion patterns of chloromethane following prolonged exposure may be similar to those observed in short term (>1 hour) experiments due to rapid air-blood equilibrium. Therefore, any sampling of blood or serum for occupational exposure assessment should occur during or promptly after exposure ends. Volunteers exposed to 10 or 50 ppm eliminated chloromethane from blood and the expired air in a biphasic manner when exposure ceased (Nolan et al. 1985). Based upon data presented in the report, the half-life for the β-phase was estimated at 50 minutes for fast metabolizers and 90 minutes for slow metabolizers. These fast elimination rates suggest that chloromethane is unlikely to accumulate in tissues, even if exposure is prolonged or repeated.

In rats exposed to [^{14}C] chloromethane for 6 hours and dogs exposed for 3 hours at concentrations of 50 or 1,000 ppm, blood levels rose rapidly and approached equilibrium proportionate, or nearly proportionate to exposure levels (Landry et al. 1983a). Blood concentrations declined rapidly in a biphasic, non-concentration-dependent manner when exposure was stopped. The disappearance from blood was consistent with a linear two-compartment open model. Half-lives for the a-phase were 4–5 minutes in rats, and 6–10 minutes in dogs; half-lives for the β-phase were 15 minutes in rats, and 35–50 minutes in dogs. The disappearance of chloromethane from blood probably represents excretion of metabolites rather than the parent compound. As discussed above in Section 3.1.3 on metabolism, chloromethane is conjugated with GSH and cysteine, leading to urinary excretion of sulfur-containing compounds. Further metabolism of the cysteine conjugate by one-carbon metabolic pathways leads to incorporation of the carbon atom into macromolecules, and the production of carbon dioxide.

Information pertaining to the ability of chloromethane or its metabolites to cross the placenta or be excreted into breast milk is limited. There is some evidence from animals that chloromethane can cross the placenta into developing fetuses. Wolkowski-Tyl et al. (1983a) noted from unpublished observations that mouse dams exposed to 100, 500, or 1,500 ppm chloromethane for 6 hours on GD 17 had significant NPSH concentration reductions in both dams (livers and kidneys) and fetuses (livers and carcasses), indicative of potential transplacental passage of chloromethane or its metabolites during late gestation,

though no chloromethane was observed in the placenta. One study in humans detected chloromethane in two of eight breast milk samples; however, the concentration was not quantified, and potential exposure sources were not determined (Pellizzari et al. 1982).

No studies were located regarding excretion in humans or animals following oral or dermal exposure to chloromethane.

3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

PBPK models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints.

Jonsson et al. (2001) used the data from the GSTT1 deficient group from the Lof et al. (2000) study (see Section 3.1.3) to develop a standard PBPK model for chloromethane with six tissue 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 was fit to the experimental data using a Bayesian approach and assumptions regarding parameters related to metabolism. Although the model provided a good general model, the concentrations in exhaled air and blood were slightly overpredicted. The authors noted that the use of non-metabolizing subjects allowed them to assess the kinetics of a volatile chemical without interference from metabolism and to obtain greater knowledge on physiological parameters, but using chloromethane as a model compound had limitations, such as low solubility of chloromethane in blood, low blood:air partition coefficient, and rapid decay during the first minutes after exposure.

3.1.6   Animal-to-Human Extrapolations

Acute- and chronic-duration inhalation studies indicate that mice are more sensitive than rats to the lethal effects of chloromethane (Chellman et al. 1986b; CIIT 1981; Morgan et al. 1982). Smith and von Oettingen (1947a) provided acute mortality data indicating that species susceptibility follows the general order of mice > guinea pig > dog > goat > monkey > rat > rabbit, with a 4-fold difference between mice and rabbits. The greater susceptibility of mice may be due to different metabolic rates involving GSH or different oxidative rates that increase production of formaldehyde. Chloromethane conjugates with GSH to a much greater extent in mouse liver, kidney, and brain compared with rats (Kornbrust and Bus 1984). Pretreatment (intraperitoneal) of mice with BSO, a GSH depleter, protected mice from the chloromethane-induced lethal effects (Chellman et al. 1986b). Thus, the reaction of chloromethane with GSH to produce S-methylglutathione appears to be a toxifying rather than a detoxifying reaction (Chellman et al. 1986b).

Alternatively, chloromethane can elicit lipid peroxidation due to GSH depletion (Kornbrust and Bus 1984). In humans, S-methylcysteine appears as a metabolite of chloromethane, so conjugation with GSH probably also occurs in humans.

Different P450 activities between species, sexes, and tissues within the body (i.e., liver versus kidney) affect the dehalogenation of chloromethane to formaldehyde and can thus influence the level of formaldehyde-induced DNA or tissue damage (Dekant et al. 1995; Jager et al. 1988; Ristau et al. 1989, 1990).

3.2   CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic

makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke).
These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to chloromethane are discussed in
Section 5.7, Populations with Potentially High Exposures.

There have been no human studies to determine the health effects of exposure to chloromethane in
children, or whether children are more or less susceptible to the potential health effects of chloromethane at
a given exposure level and duration of exposure. There is no information on whether the effects reported
in adults following either accidental short-term exposures or longer-term, lower-level exposures would be
similarly observed in children. There is a lack of human data on whether chloromethane affects the
developing fetus or the development of young children.

Since there are limited data on the toxicity of chloromethane in children, it is assumed that the toxicity of
chloromethane in children is similar to the toxicity observed in adults. However, in guinea pigs, Smith
and von Oettingen (1947b) reported that older guinea pigs developed symptoms more rapidly compared
to a younger guinea pig, although both young and older animals lost the ability to turn over from a supine
position. Also, the older animals were more likely to develop severe effects or die from high exposure
(Smith and von Oettingen 1947a, 1947b); young mice, rats, guinea pigs, and dogs were found to have less
severe effects compared to older animals exposed to the same amount of chloromethane, and in some
cases, survived exposure to high levels of chloromethane, while older animals died.

Only limited information is available from animal studies on potential effects in the developing young. In
one animal study, pregnant rats were exposed to 1,500 ppm chloromethane by inhalation during gestation.
Maternal toxicity, evidenced by decreased body weight gain and retarded development of fetuses, was
observed in rats exposed to 1,500 ppm chloromethane for 6 hours/day during GDs 7–19 (Wolkowski-Tyl
et al. 1983a). The fetal effects consisted of reduced fetal body weight and crown-rump length, and reduced
ossification in the metatarsals and phalanges, centra of the thoracic vertebrae, pubis of the pelvic girdle,
and metatarsals of the hindlimbs.

In a mouse study, dams were exposed by inhalation to chloromethane during GDs 6–17 (Wolkowski-Tyl
et al. 1983a). The investigators found increased incidences of heart malformations in the fetuses of mouse
dams exposed to 500 ppm chloromethane during GDs 6–17. The heart malformations consisted of
absence or reduction of atrioventricular valves, chordae tendineae, and papillary muscles. Heart

malformations, however, were not found in fetuses of mouse dams exposed to higher concentrations of chloromethane during GDs 11–12.5, which they considered to be the critical period for development of the embryonal heart (John-Greene et al. 1985). John-Greene et al. (1985) suggested that the heart anomaly reported by Wolkowski-Tyl et al. (1983a, 1983b) may have been an artifact of the sectioning technique, due to the examination of the fixed as opposed to unfixed fetal tissue, or a misdiagnosis. They also found much inter-animal variability in the appearance of the papillary muscles in control mice. However, Wolkowski-Tyl (1985) countered that the inability of John-Greene et al. (1985) to detect the abnormality was due to the different exposure protocol, and that the critical period is more appropriately GD 14. The developmental toxicity of chloromethane in mice is, therefore, controversial; it is not known whether chloromethane could produce developmental effects in humans.

Acute-, intermediate-, and chronic-duration inhalation exposures of male rats to chloromethane have resulted in such reproductive effects as inflammation of the epididymides, sperm granuloma formation in epididymides, disruption of spermatogenesis, decreased fertility at about 500 ppm, and sterility at higher concentrations of 1,000 or 3,000 ppm (Burek et al. 1981; Chapin et al. 1984; Chellman et al. 1986a, 1986b, 1987; CIIT 1981; Hamm et al. 1985; Morgan et al. 1982; Working and Bus 1986; Working et al. 1985a, 1985b). Testicular effects of chloromethane have manifested as preimplantation loss in unexposed female rats mated with males exposed to chloromethane (Working et al. 1985a). Testicular lesions were also observed in mice after 18 months of exposure to chloromethane (CIIT 1981). Studies on the mechanism of chloromethane-induced testicular effects suggested that preimplantation loss was potentially due to cytotoxicity of chloromethane to sperm in the testes at the time of exposure (Chellman et al. 1986c, 1987; Working and Bus 1986; Working et al. 1985a, 1985b). However, these findings do not negate the possibility of a dominant lethal mutation leading to post-implantation loss. Both mechanisms are plausible.

Chloromethane exposure consistently produced dominant lethal mutations in the sperm of rats, as measured by post implantation loss in females mated to exposed males (Chellman et al. 1986c; Rushbrook 1984; Working et al. 1985a). Because of the known transit times for sperm in the epididymis and the resulting observed times of the post implantation losses, Working et al. (1985a) observed that the timing of the genetic damage to the sperm coincided with their location in the chloromethane-induced inflammation of the epididymis. Since concurrent exposure of male rats to chloromethane and BW755C, an anti-inflammatory agent, greatly reduced the amount of post implantation loss, it is possible both dominant lethal mutations and an epididymal inflammatory response (Chellman et al. 1986c; Working and Chellman 1989) can lead to post implantation loss. The activation of phagocytic cells during the inflammatory

process may result in the production of potentially genotoxic chemical species including the superoxide anion radical, hydrogen peroxide, and lipid peroxide decomposition products (Fridovich 1978; Goldstein et al. 1979, 1981; Working et al. 1985a).

Chloromethane has been tested for genotoxicity in several *in vitro* and *in vivo* studies. Chloromethane gave positive results for gene mutation, sister chromatid exchange, and transformation in cultured mammalian cells, including human lymphoblast cells (Asakura et al. 2008; Fostel et al. 1985; Hatch et al. 1982, 1983; Working et al. 1986); and appears to be a direct-acting genotoxicant *in vitro*. The ability of inflammatory cells (human phagocytes) to produce superoxides capable of genetic damage has been demonstrated (Weitzman and Stossel 1981). Although chloromethane produced genotoxic effects in human lymphocytes in culture, it is not known whether chloromethane could produce dominant lethal mutations or other genotoxic effects in humans exposed by any route. No information was available on the distribution of chloromethane or metabolites to parental reproductive organs or germ cells in humans that could lead to genetic or epigenetic damage to germ cells. It is also not known whether chloromethane produces a sublethal level of genetic or epigenetic damage to sperm that would, in turn, be sufficiently viable to form an embryo and subsequently be detrimental (at clinical or subclinical levels) to the developing young. Further, chloromethane was found to be a potent mutagen in *D. melanogaster* (University of Wisconsin 1986).

In humans, there appear to be two distinct populations regarding metabolism and elimination of chloromethane. One population has higher amounts of the metabolizing enzyme, GST, and thus a higher rate of elimination of chloromethane from the body. The toxicity of chloromethane, however, is thought to result from toxic metabolites formed following the conjugation with GSH or from the depletion of GSH (Chellman et al. 1986b; Kornbrust and Bus 1983, 1984; Landry et al. 1985). Individuals with higher amounts of the metabolizing enzyme (GSTT1-high) may have increased susceptibility to toxic effects of chloromethane. Conversely, individuals with GSTT1-deficiency may have decreased susceptibility to toxic effects of chloromethane. There is one PBPK model for chloromethane exposure based on data for GSTT1 deficient individuals (Jonsson et al. 2001).

3.3   BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to chloromethane are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/ exposurereport/). If available, biomonitoring data for chloromethane from this report are discussed in Section 5.6, General Population Exposure.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by chloromethane are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1   Biomarkers of Exposure

There are no reliable biomarkers of exposure for children or adults, although clinical symptoms of drunkenness or food poisoning, a smell of acetone around the individual, and a musty and sweet odor of the breath may alert a physician to potential chloromethane exposure. Previous studies have unsuccessfully attempted to correlate exposure levels of chloromethane in air with urinary excretion of S-methylcysteine. In a group of six workers exposed to TWA 8-hour workroom concentrations of 30– 90 ppm, the excretion of S-methylcysteine in urine showed wide variations, with little correlation with

exposure levels (van Doorn et al. 1980). Based on variable excretion of S-methylcysteine in six male volunteers exposed to 10 or 50 ppm chloromethane for 6 hours, Nolan et al. (1985) found no relationship between inhalation exposure and urinary S-methylcysteine; blood levels of NPSH assessed in previous research was low due to failure to recognize chloromethane loss from the sample during equilibration at room temperature. They concluded that measurement of S-methylcysteine in urine is not a valid method for monitoring exposure to chloromethane.

In an evaluation of the use of blood and breath analysis of chloromethane to monitor acute exposure in volunteers, it was concluded that breath sampling is not useful for quantitatively assessing chloromethane exposure. However, breath analysis can identify elevated exposures if promptly sampled and determine which individuals retain higher than normal body burdens such that they are potentially more sensitive. Stewart et al. (1980) exposed male and female volunteers to 0–150 ppm chloromethane for periods up to 7.5 hours/day for 2 or 5 consecutive days. Breath and blood samples were collected starting immediately after to 3 hours after exposure, and early samples for 20 or 100 ppm correlated well each other and with exposure; however, they decreased 5-fold or more in 15 minutes, and by 2 hours, samples were difficult to interpret. Exposure to 100 ppm could not be distinguished from exposure to 150 ppm after 1 minute postexposure (Stewart et al. 1980).

Xu et al. (1990) evaluated whether covalent binding of chloromethane to hemoglobin would be a viable measure for monitoring exposure to chloromethane in air. In comparison to the other monohalomethanes tested (i.e., methyl bromide and methyl iodide), chloromethane had the lowest reactivity with hemoglobin, limiting its usefulness. The authors supported further assay development for methyl bromide but made no mention of the usefulness of a covalent binding assay for chloromethane, presumably because its reactivity was too low.

3.3.2 Biomarkers of Effect

Biomarkers of effect from chloromethane over-exposure can be difficult to evaluate in borderline and even higher exposure cases. One reason is that symptoms from acute and intermediate duration exposures are not completely consistent; they are similar to those from common viral and bacterial diseases, e.g., headache, dizziness, nausea, and vomiting; and none are specific to chloromethane (MacDonald 1964; Scharnweber et al. 1974). Another reason is large interindividual variability based on neurobehavioral testing (Putz-Anderson et al. 1981b). Attempts to correlate blood levels and expired air concentrations of chloromethane with health effects of occupational and experimental inhalation exposure have been

unsuccessful. In a study of 73 behavioral measures of task performance, 4 indices of exposure, and 8 indicators of neurological function in workers exposed to a mean concentration of 34 ppm chloromethane, effects on cognitive time-sharing and finger tremor were found, but correlation coefficients indicated that chloromethane in breath was not a sensitive indicator of performance (NIOSH 1976). Although volunteers exposed to 200 ppm chloromethane for 3 hours had a 4% decrement in their performance on behavioral tests, individual blood and alveolar air levels of chloromethane were too variable to be of practical use, but group average blood and breath samples were highly correlated (Putz-Anderson et al. 1981a). The decrement in performance was also small and not statistically significant.

3.4   INTERACTIONS WITH OTHER CHEMICALS

Chloromethane may interact with other solvents and its metabolism [genetic polymorphisms of xenobiotic enzymes (Phase I and II)] could be altered by exposure to other chemicals such as the use of alcohol, caffeine, smoking, etc.

Putz-Anderson et al. (1981a, 1981b) assessed whether neurobehavioral changes associated with chloromethane exposure would be modified by co-exposure with diazepam, alcohol, or caffeine. Inhalation exposure of volunteers to 200 ppm chloromethane along with oral dosing with 10 mg diazepam produced an additive impairment in performance on behavioral tests (Putz-Anderson et al. 1981a). Diazepam alone produced a significant 10% decrease in task performance, whereas exposure to chloromethane produced a nonsignificant average decrease of 4%, and diazepam and chloromethane together produced a combined 13.5% decrease. The authors suggested that there is no interaction between diazepam and chloromethane exposure, but instead that effects are additive. Similar additive effects were observed if exposure occurred in combination with alcohol or caffeine (Putz-Anderson et al. 1981b).

Minami et al. (1992) report a patient in Japan exposed simultaneously to chloromethane and chloramine gas. The exposure resulted from the patient first cleaning a porcelain toilet with sodium hypochlorite (NaOCl) in an alkaline solution then, without first rinsing off the hypochlorite, spraying a hydrochloric acid (HCl) solution to remove hard salt adhesions. The toilet was connected directly to a sewage storage tank. The resulting fumes produced a toxic response in the patient 30 minutes after cleaning. The patient recovered from the acidosis after bicarbonate transfusion, plasmapheresis, and plasma exchange; but permanent blindness ensued 3 days postexposure. In a follow-up study, Minami et al. (1993) demonstrated an increase in formate excretion in mice dosed via intraperitoneal injection with chloramine

after exposure to chloromethane. The authors ascribed this increase to an inhibitory effect of chloramine on formyl tetrahydrofolate dehydrogenase and FDH. Wang and Minami (1996) extended their proposed mechanism to include a potentiation of formaldehyde on chloramine inhibition of acetylcholinesterase activity. In their study, they stated that formaldehyde may potentiate the inhibitory action of chloramine on acetylcholinesterase activity. If formaldehyde is a metabolite of chloromethane, as proposed by Kornbrust and Bus (1983), there may be reason to conclude that these two chemicals may have an interactive neurological effect. However, as demonstrated by Jager et al. (1988), but disputed by Heck et al. (1982), there is some debate regarding whether formaldehyde is a metabolite of chloromethane metabolism *in vivo*. Additionally, consideration of how exposure occurs and how each chemical is distributed throughout the body may contribute to hypotheses for potential interactions.

The only other studies that show an effect of other compounds on the toxicity of chloromethane are those in which the effects of BW755C, an anti-inflammatory agent, and BSO, a depleter of GSH, are administered intraperitoneally to rats or mice prior to chloromethane exposure via inhalation (Chellman et al. 1986a, 1986b). BW755C co-exposure with chloromethane provided protection to several organs (brain, kidneys, liver, and testes). However, it is unlikely that these compounds would be found with chloromethane at hazardous waste sites.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1   CHEMICAL IDENTITY

Industrial chloromethane is a colorless compressed gas or liquid, commonly stored and shipped as a liquified compressed gas. Chloromethane in the environment is mainly from natural sources and is a trace component of the atmosphere. Chloromethane is composed of a single carbon atom bound to three hydrogen atoms and one chlorine atom. Chloromethane was previously used as a refrigerant; however, this use has been replaced by other chemicals such as hydrofluorocarbons. Although chloromethane has a faint sweet odor, at some time after a series of chloromethane-related deaths in 1928 and 1929, acrolein was added to chloromethane refrigerants as a nasal irritating tracer to help warn those who might be exposed (McNally 1946). Chloromethane is currently used as an industrial solvent; in the production of adhesives, sealants, silicones, agricultural chemicals, plastic, and rubber products; as a chemical intermediate; in paints and coatings; and in personal care products. It is also an impurity in vinyl chloride and may be present in polyvinyl chloride (PVC) products. Chloromethane is produced from methanol and hydrogen chloride using an aluminum oxide catalyst (PubChem 2022).

Table 4-1 lists common synonyms, trade names, and other pertinent identification information for chloromethane.

Table 4-1. Chemical Identity of Chloromethane

Characteristic	Information
Synonym(s) and registered trade name(s)	Chloromethane; methyl chloride; methane, chloro-; monochloromethane; methylchlorid; MeCl; chloride, methyl; R 40; Artic; Freon 40; Refrigerant R40; UNII A6R43525YO; EPA (RCRA) hazardous waste number U045
Chemical formula	CH_3Cl
Chemical structure	$H_3C - Cl$
CAS Registry Number	74-87-3

CAS = Chemical Abstracts Service

Source: PubChem 2022

4. CHEMICAL AND PHYSICAL INFORMATION

4.2   PHYSICAL AND CHEMICAL PROPERTIES

Chloromethane exists as a gas at room temperature and atmospheric pressure. It is highly soluble in water and several other organic solvents such as benzene, carbon tetrachloride, acetic acid, and ethanol. It is miscible in chloroform and ether. Chloromethane has a high vapor pressure and is extremely flammable. In addition to being highly water soluble, chloromethane has a low K_{ow} value, suggesting that it is unlikely to bioaccumulate. Chloromethane's low K_{oc} indicates a high mobility in soil. The Henry's Law constant for chloromethane suggests that it will rapidly volatilize from the surface of water and that it may volatilize from moist soil; the high vapor pressure of chloromethane indicates that it will volatilize from dry soil surfaces. Table 4-2 lists important physical and chemical properties of chloromethane.

Table 4-2. Physical and Chemical Properties of Chloromethane

Property	Information	Reference
Molecular weight	50.488 g/mol	Tsai 2017
Color	Colorless	PubChem 2022
Physical state	Gas (can leak as a liquid or vapor)	PubChem 2022
Melting point(s)	-97°C; -97.6°C; -97.7°C	PubChem 2022
Boiling point(s)	-23.7°C; -24.0°C	PubChem 2022
Critical temperature and pressure	416.25 K and 6.679 MPa	PubChem 2022
Density	0.911 g/cm^3 at 25°C; 0.997 g/cm^3 at -24°C	PubChem 2022; Tsai 2017
Viscosity	0.106 mPas (gas at 20°C)	Tsai 2017
Taste	Sweet taste	PubChem 2022
Odor	Faint sweet ethereal odor; mild odor[a]	PubChem 2022
Odor threshold:		PubChem 2022
Water	No data	
Air	21 mg/m^3 [a]	
Solubility:		PubChem 2022
Water	5,040 mg/L at 25°C	
Organic solvent(s) at 20°C	Benzene 4,723 mg/L, carbon tetrachloride 3,756 mg/L, glacial acetic acid 3,679 mg/L, ethanol 3,740 mg/L; miscible with ethyl ether, acetone, benzene, and chloroform	
Partition coefficients:		
Log K_{oa}	1.565	Vallero 2014
Log K_{ow}	0.91	PubChem 2022
Log K_{oc}	13 (estimated)	EPA 2012a; PubChem 2022
Relative vapor density	1.8 (air=1)	PubChem 2022; Tsai 2017

Table 4-2. Physical and Chemical Properties of Chloromethane

Property	Information	Reference
Vapor pressure at 25°C	4300 mmHg	PubChem 2022
Henry's law constant at 24°C	8.82×10^{-3} atm-m^3/mol	PubChem 2022
Degradation half-life in air via reaction with OH radicals	445 days (based on an OH radical rate constant of 3.6×10^{-14} cm^3/molecule-second at 25°C)	PubChem 2022
Dissociation constants:	Not applicable	
Heat of combustion	-5,290 Btu/lb; -2,939 cal/g; $-123.1 \times 10^{+5}$ J/kg	PubChem 2022
Heat of vaporization	18.92 kJ/mol at 25°C 21.40 kJ/mol at boiling point	PubChem 2022
Autoignition temperature	632°C	PubChem 2022
Flashpoint	-50°F (closed cup); -45.6°C	PubChem 2022
Flammability limits in air	8.1% (lower explosive limit); 17.4% (upper explosive limit)	PubChem 2022; Tsai 2017
Conversion factors:	1 mg/L = 484 ppm; 1 ppm = 2.06 mg/m^3 at 25°C and 760 torr	PubChem 2022
Explosive limits	Moderate explosion hazard when exposed to flames and sparks	PubChem 2022
Incompatibilities and reactivity	Chloromethane will attack some forms of plastics, rubber, and coatings; also attacks aluminum, magnesium and zinc; Incompatible with strong oxidizing agents and iron	PubChem 2022

[a]Chloromethane odor is not noticeable at dangerous concentrations.

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Chloromethane has been identified in at least 236 of the 1,868 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2022). However, the number of sites in which chloromethane has been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 235 are located within the United States and 1 is located in Puerto Rico (not shown).

Figure 5-1. Number of NPL Sites with Chloromethane Contamination

Source: ATSDR 2022

- The most likely route of exposure for the general population to chloromethane is through inhalation; the general population is not expected to be exposed to concentrations of chloromethane much above 1–3 ppbv in urban locations.

- The population with the highest potential exposures would include those people who work in chloromethane manufacturing or use industries.

- Chloromethane is mostly found in the air due to releases from processing facilities, and in the air and ocean from natural processes.

Chloromethane is a natural and ubiquitous constituent of the oceans and atmosphere (both the troposphere and the stratosphere). It is a product of biomass combustion and is also a product of biogenic emissions of wood-rotting fungi. Chloromethane has been detected in surface waters, drinking water, groundwater, and soil. Chloromethane is a constituent of municipal and industrial solid waste leachate; it is a component of industrial waste discharges and is also present in the effluents of publicly owned treatment works (POTWs). It is a component in vinyl chloride (WHO 1999), so chloromethane could be released to the environment during the manufacture of vinyl chloride or introduced into NPL sites from vinyl chloride wastes. Chloromethane in air has a half-life of about 1 year with estimated half-lives ranging from 0.6–3 years (see Section 5.4). Chloromethane is the dominant organochlorine species in the atmosphere. In the upper atmosphere, chloromethane is involved in the chemical reactions that remove ozone from the upper troposphere and stratosphere (Crutzen and Gidel 1983; Gidel et al. 1983; Singh et al. 1983). Since these processes are believed to be largely part of natural background cycles, chloromethane has not been the focus of ozone depletion control efforts under the CAA and the Montreal Protocol, which are targeted at such anthropogenic halogenated compounds as chlorofluorocarbons (EPA 2019; IPCC 1995).

In water, chloromethane is expected to volatilize rapidly (Mabey and Mill 1978). It is not expected to sorb to sediments or to bioaccumulate. Chemical hydrolysis and biodegradation are not expected to be significant processes. Chloromethane is expected to volatilize from soil surfaces; however, when present in a landfill, it has the potential to leach into groundwater. In groundwater, hydrolysis may be the only removal mechanism available to chloromethane, with an estimated half-life of ~4 years based on available data (Elliot and Rowland 1995; Mabey and Mill 1978). Air concentrations of chloromethane are generally in the low pbb range, but urban locations appear to have elevated concentrations compared to background concentrations. Although detailed information is lacking, water concentrations are likely to vary considerably depending on the season and the geographic location. Very little information is available concerning chloromethane concentrations in soil. The general population is not expected to be exposed to concentrations of chloromethane much above 1.22 ppbv in urban locations (Mohamed et al. 2002). In rural locations, the exposure concentration is expected to be approximately 0.7–0.9 ppb.

The database for occupational exposure is outdated (late 1980s or earlier). The Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) allows for a TWA 100 ppm, a ceiling exposure of 200 ppm and a peak exposure of 300 ppm (5-minute maximum peak in any 3 hours) (OSHA 2018). Also, no sufficiently comprehensive data on current applications of the substance are known,

precluding reliable predictions of average or probable occupational exposure levels. The population with the highest potential for exposure would likely include people who work in chloromethane manufacturing or use industries, such as those that produce chloromethane as an intermediary product.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

Chloromethane is both an anthropogenic and naturally occurring chemical. Chloromethane is a volatile organic compound (VOC) and is a halocarbon. Anthropogenic sources include industrial production, polyvinyl chloride burning, and wood burning; natural sources include the oceans (biogenic emissions from phytoplankton), normal human exhalation, microbial fermentation, and biomass fires (e.g., forest fires, grass fires). Chloromethane is produced industrially by reaction of methanol and HCl or by chlorination of methane (Edwards et al. 1982a; EPA 1980). While the reaction of methanol with HCl is the most common method, the choice of process depends, in part, on the HCl balance at the site (the methane route produces HCl, the methanol route uses it) (Edwards et al. 1982a). Typically, manufacturing plants that produce chloromethane also produce higher chlorinated methanes (methylene chloride, chloroform, and carbon tetrachloride).

The methanol-HCl process involves combining vapor-phase methanol and HCl at 180–200°C, followed by passage over a catalyst where the reaction occurs (EPA 1980). Catalysts include alumina gel, gamma alumina, and cuprous or zinc chloride on pumice or activated carbon. The exit gases from the reactor are quenched with water to remove unreacted HCl and methanol. The quench water is stripped of the dissolved methanol and chloromethane, and the remaining dilute HCl solution is used in-house or treated and discharged (EPA 1980). The chloromethane is then dried by treatment with concentrated sulfuric acid, compressed, cooled, and stored.

In the methane chlorination process, a molar excess of methane is mixed with chlorine, and the mixture is then fed to a reactor, which is operated at 400°C and 200 kPa pressure (EPA 1980). The exit gases can then be scrubbed with chilled chloromethanes (mono- to tetrachloromethane) to remove most of the reaction chloromethanes from unreacted methane and HCl. The byproduct HCl is removed by water wash, stripped of any chloromethanes, and either used in-house or sold; the unreacted methane is recycled through the process. The condensed chloromethanes are scrubbed with dilute NaOH to remove any HCl, dried, compressed, cooled, and then fractionally distilled to separate the four chloromethanes.

It is difficult to estimate the total production levels for chloromethane at specific industrial plants because many of the producers consume their output internally as a feedstock for other chemicals, including silicones and higher chlorinated methanes. The nine sites reported in Chemical Data Reporting (CDR) manufacturing information are: (1) Occidental Chemical Corp Geismar Plant in Geismar, Louisiana; (2) Occidental Chemical Corporation in Wichita, Kansas; (3) Momentive Performance Materials in Waterford, New York, with a 2015 production volume of 815,774,608 pounds; (4) Praxair Distribution, Inc. in Toledo, Ohio, with a 2015 production volume of 293,216 pounds; (5) Formosa Plastics Corp. in Point Comfort, Texas, with a 2015 production volume of 86,327 pounds; (6) Dow Corning Corp in Carrollton, Kentucky; (7) Olin Blue Cube in Freeport, Texas; (8) Solvay USA Inc. in Princeton, New Jersey; and (9) Blue Cube Operations LLC in Plaquemine, Louisiana (EPA 2022a). The production volume at the sites without values listed here is withheld as it is considered confidential business information (CBI). The on-site quantities of chloromethane reported by facilities to the EPA are shown in Table 5-1. In 2015, national aggregate production volume of chloromethane was between 1,000,000,000 and 5,000,000,000 pounds (EPA 2022a). National aggregate production volumes of chloromethane from 2012 to 2014 were also between 1,000,000,000 and 5,000,000,000 pounds (EPA 2022a). National aggregate production volumes in 2011 were 1,396,155,238 pounds (EPA 2022a).

Table 5-1. Facilities that Produce, Process, or Use Chloromethane

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	2	100	9,999	1, 5, 13
AR	2	0	99,999	1, 5
FL	1	10,000	99,999	6
GA	1	1,000,000	9,999,999	2, 3, 6
IA	1	100	999	1, 13, 14
IL	4	1,000	999,999	6
KS	2	1,000,000	9,999,999	1, 4, 6
KY	2	100,000	9,999,999	1, 3, 6
LA	11	100	99,999,999	1, 3, 4, 5, 6, 7, 9, 10, 12, 13, 14
MI	5	10,000	49,999,999	1, 3, 4, 5, 6, 10, 12, 13
MS	2	0	99	1, 5
NC	2	0	99	1, 5
NJ	1	100	999	14
NY	1	1,000,000	9,999,999	1, 3, 6
OH	4	1,000	999,999	6, 9, 12, 14
PA	1	100,000	999,999	6

5. POTENTIAL FOR HUMAN EXPOSURE

Table 5-1. Facilities that Produce, Process, or Use Chloromethane

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
SC	4	0	99,999	1, 5, 6, 10
TX	9	0	9,999,999	1, 3, 4, 5, 6, 10, 11, 12, 13, 14
WI	2	100,000	999,999	6
WV	1	10,000	99,999	1, 5, 6

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/uses:

1. Produce	6. Reactant	11. Manufacture Aid
2. Import	7. Formulation Component	12. Ancillary
3. Used Processing	8. Article Component	13. Manufacture Impurity
4. Sale/Distribution	9. Repackaging	14. Process Impurity
5. Byproduct	10. Chemical Processing Aid	

Source: TRI21 2022 (Data are from 2021)

5.2.2 Import/Export

Exports of chloromethane from the United States are considerably larger than imports. In the period from 2014 to 2018, general imports and imports for consumption of chloromethane were equal. General imports are total physical arrivals of chloromethane to the United States from other countries that either enter consumption channels immediately or enter bonded warehouses or Foreign Trade Zones (FTZs) (U.S. Census Bureau 2018). A bonded warehouse is an approved private warehouse used to store imports until duties or taxes are paid. FTZs are specially licensed commercial and industrial areas in or near ports of entry where goods may be brought in without paying customs duties. Imports brought to FTZs can be manipulated (i.e., sold, stored, exhibited, repacked, cleaned, manufactured, etc.) prior to re-export or entry (U.S. Census Bureau 2018). U.S. imports of chloromethane increased from 228,303 kg in 2014 to 3,246,844 kg in 2018 (USITC 2019). Between 2016 and 2017, imports more than doubled from 1,157,708 kg to 2,598,670 kg (USITC 2019). U.S. domestic exports of chloromethane fluctuated from 2014 to 2018, ranging from 22,042,539 kg in 2015 to 10,430,816 kg in 2017 (USITC 2019). Domestic exports are goods that are grown, produced, or manufactured in the United States, or goods of foreign origin that have been changed, enhanced in value, or improved in condition in the United States (U.S. Census Bureau 2018). U.S. total exports of chloromethane also fluctuated from 2014 to 2018. Total exports are the sum of domestic exports and foreign exports, which are goods of foreign origin that are in the same condition at the time of export as they were in when imported (U.S. Census Bureau 2018). Total

exports range from 22,048,825 kg in 2015 to 11,115,446 kg in 2017 (USITC 2019). In 2018, there were 13,332,060 kg of chloromethane domestic exports and 14,640,606 kg of total exports (USITC 2019).

5.2.3   Use

Chloromethane is used mainly (89%) in the production of silicones (PubChem 2022; Tsai 2017). Chloromethane has also been used in the production of methyl cellulose ethers (3%), quaternary ammonium compounds (3%), herbicides (3%), butyl rubber (1%), and miscellaneous uses (2%) (PubChem 2022). It has also been used in the past as a foam blowing agent (e.g., in producing polystyrene foams), as a refrigerant, and as aerosol propellant (PubChem 2022). At some time after a series of chloromethane related deaths in 1928 and 1929, acrolein was added to chloromethane refrigerants as a nasal irritating tracer to help warn individuals who were being exposed (McNally 1946). At the present time, virtually all commercial uses for chloromethane are consumptive in that the chloromethane is reacted to form another product during use. Thus, almost all chloromethane will be consumed when used and will no longer be available for release, disposal, or reuse.

Chloromethane is reported in the most recent CDR data for both industrial and consumer uses. Sectors that use chloromethane in industrial processing include plastic material and resin manufacturing, all other basic organic chemical manufacturing, and paint and coating manufacturing (EPA 2022a). Industry function categories include laboratory chemicals, intermediates, adhesives and sealant chemicals, paint additives, and coating additives not described by other categories (EPA 2022a).

According to CDR data for 12 sites, 4 report chloromethane use for commercial and 3 report for both commercial and consumer use (EPA 2022a). Product categories for consumer and commercial use include adhesives and sealants; fabric, textile, and leather products not covered elsewhere; paints and coatings; personal care products; and plastic and rubber products not covered elsewhere (EPA 2022a). Of these 12 sites, 6 reported that chloromethane is not intended for use in children's products (EPA 2022a).

5.2.4   Disposal

Of 22 sites that reported industrial processing and use of chloromethane in 2016, 4 reported that the chemical was recycled and 4 reported that it was not (EPA 2022a). In 2012, 1 of 22 sites reported that chloromethane was recycled while 5 of 22 reported that it was not (EPA 2022a).

Of 12 sites that reported consumer and commercial use of chloromethane in 2016, 1 reported that the
chemical was recycled while 7 reported that it was not (EPA 2022a). In 2012, one of nine sites reported
that chloromethane was recycled while five of nine reported that it was not (EPA 2022a).

Limited information was identified in the literature concerning the disposal of chloromethane. Since most
chloromethane is used consumptively, little remains to be disposed. Nonetheless, some chloromethane is
present in waste, and chloromethane has been detected in hazardous waste landfills. Its presence in
hazardous waste sites may result from the landfilling of still bottoms (accumulated solvent wastes) or
other residues from the manufacture and use of chloromethane. Its presence in municipal waste landfills
suggests that consumer products containing chloromethane were landfilled (e.g., propellants for aerosol
cans, old refrigerators). Since chloromethane is an impurity in vinyl chloride, the disposal of vinyl
chloride may also lead to chloromethane contamination. Like other chlorinated hydrocarbons,
chloromethane can inhibit the combustion of such fuels as methane. Chloromethane has a considerable
inhibitory effect on combustion when mixed with methane, the principal component of natural gas
(Philbrick et al. 1993). Changes in the amounts of chloromethane added to the methane fuel stock did not
affect combustion in a concentration-dependent or consistent manner. Such phenomena would
complicate the disposal of chloromethane using incineration technologies. When incineration was
attempted under oxygen-starved conditions (Taylor and Dellinger 1988), chloromethane was shown to
combine with other components of the combustion mixture to form, among other compounds, chlorinated
ethanes, hexachlorobenzene, and octachlorostyrene.

Chloromethane is listed as a toxic substance under Section 313 of the Emergency Planning and
Community Right to Know Act (EPCRA) under Title III of the Superfund Amendments and
Reauthorization Act (SARA). Disposal of wastes containing chloromethane is controlled by a number of
federal regulations (see Chapter 7).

5.3   RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of
facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing
facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if
their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and
1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of
generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or

oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that

combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953

(limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and

7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in

solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes

≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar

year (EPA 2005).

Table 5-2 lists the amounts of chloromethane released to the environment in each state (TRI21 2022).

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use Chloromethane[a]

| | | Reported amounts released in pounds per year[b] | | | | | | | |
| | | | | | | | Total release | | |
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AL	2	470	0	0	0	0	470	0	470
AR	2	47,095	0	0	10	0	47,105	0	47,105
FL	1	50	1	0	0	0	50	1	51
GA	1	5,500	4	0	0	0	5,504	0	5,504
IL	4	54,336	7	0	4	0	54,337	10	54,347
IA	1	151	0	0	0	0	151	0	151
KS	2	8,759	0	259,040	0	0	267,799	0	267,799
KY	2	19,080	56	0	0	0	19,136	0	19,136
LA	11	33,224	1,029	62,000	0	0	96,253	0	96,253
MI	5	37,901	110	0	0	0	38,011	0	38,011
MS	2	68,621	0	0	0	0	68,621	0	68,621
NJ	1	1	0	0	0	0	1	0	1
NY	1	4,150	21	0	0	0	4,171	0	4,171
NC	2	81,214	2	0	1	0	81,216	0	81,216
OH	4	20,754	0	0	0	0	20,754	0	20,754
PA	1	376	0	0	0	0	376	0	376
SC	4	63,911	0	0	0	0	63,911	0	63,911
TX	9	218,709	28	9,773	8,285	0	228,514	8,281	236,795
WV	1	7,309	30	0	0	0	7,339	0	7,339

5. POTENTIAL FOR HUMAN EXPOSURE

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use Chloromethane[a]

State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	Total release		
							On-site[j]	Off-site[k]	On- and off-site
WI	2	7,315	15	0	0	0	7,315	15	7,330
Total	58	678,926	1,302	330,813	8,300	0	1,011,035	8,306	1,019,341

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, wastewater treatment (metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown.
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI21 2022 (Data are from 2021)

5.3.1   Air

Estimated releases of 678,926 pounds (~307.96 metric tons) of chloromethane to the atmosphere from 58 domestic manufacturing and processing facilities in 2021, accounted for about 67% of the estimated total environmental releases from facilities required to report to the TRI (TRI21 2022). These releases are summarized in Table 5-2.

The reportable air discharges reported in the TRI 2021 data have dropped from the estimated releases of 757,156 pounds reported for 2020 (TRI20 2021). Chloromethane has been identified in air at 23 of the 236 NPL hazardous waste sites at which it was detected in one or more environmental media (ATSDR 2022). The geometric mean of maximum concentrations at these sites was approximately 0.033 mg/L (3.29 ppbv).

Most releases of chloromethane will be to air, since it is a gas at ambient temperatures, and manufacturing practices suggest that little will be discharged by any other route. Chloromethane will be released from

manufacturing and use (fugitive emissions) as well as from production resulting from human and natural activities. Anthropogenic sources include burning plastic (Lestari et al. 2011), cigarette smoke (Filipiak et al. 2012; Novak et al. 2008; Sleiman et al. 2014), biomass burning (Keppler et al. 2005), the manual process of dismantling television printed circuit boards using electric heating furnaces during e-waste recycling (Liu et al. 2017), and interior materials in vehicles (Xing et al. 2018). Recently, chloromethane has been found in VOC emissions from laundry products (Steinemann 2015). Chloromethane present in wastewaters also may be released to air during aeration (Pincince 1988). Chloromethane has also been detected in atmospheric emissions from municipal solid waste landfills (Manca et al. 1997) and from artificial waterfalls using reclaimed water (Ma et al. 2008).

An anthropogenic source of chloromethane may be cigarette smoke as estimated by (Novak et al. 2008). Novak et al. (2008) collected smoke samples from burning cigarettes in special smoking adaptors into 2-L canisters and analyzed the smoke for chloromethane using gas chromatography. The chloromethane concentrations were about 30–500 ppmv (1.5–5.3 mg/cigarette) compared with about 500 pptv in typical urban air. The chloromethane levels from some brands of cigarettes exceeded the EPA's maximum exposure limit of 200 ppmv (Novak et al. 2008).

Natural sources include the oceans, forest fires, burning wood, burning coal, volcanoes (Keppler et al. 2005; Moore 2008), biomass burning (Rudolph et al. 1995), fungi (Saxena et al. 1998), coastal salt marshes (Cox et al. 2004; Rhew et al. 2000), wetlands (Keppler et al. 2005), dead or senescent plant material (Derendorp et al. 2012) and tropical vegetation (Yokouchi et al. 2000, 2002, 2007). Emissions of chloromethane were previously known to come from animals such as cattle, and recent studies have shown that humans also exhale chloromethane in the range of 2.5–33 ppbv or <0.03% of the total annual global atmospheric source strength (Keppler et al. 2017).

Various estimates of average global annual production rates and estimates of the contributions from different natural production sources have been made. Estimates from terrestrial ecologists tend to emphasize the role of such sources as biomass burning, while oceanographers may emphasize the role of biogenic emissions from marine phytoplankton. The global budget figures presented below are based on a study by Keppler et al. (2005) and are used primarily to emphasize the overwhelming contributions from nonindustrial production.

Chloromethane is the most abundant halocarbon in the atmosphere, and its total atmospheric burden is between 4,000 and 5,000 Gg (8,818,490,487–11,023,113,109 pounds) (Keppler et al. 2005). Greater than

99% of ambient air concentrations of chloromethane on a global scale appear to come from releases from natural sources rather than from manufacturing or other emissions from anthropogenic processes or uses. Releases associated with manufacturing and production processes in the United States would constitute <1% of the global budget. Gases contributed by industrial and other anthropogenic sources tend to result in higher concentrations in middle northern latitudes (Khalil and Rasmussen 1999). Khalil and Rasmussen (1999) estimated that there is more chloromethane in the atmosphere in the tropical latitudes than at higher latitudes, which may be a result of more chloromethane being emitted from natural sources. McCulloch et al. (1999) estimated the global distribution of chloromethane from coal and waste combustion and industrial processes. In the United States, it appears that these emissions were higher in the east, with emissions nearing 0.022 g of equivalent chlorine emissions per square meter per year in the Northeast and Midwest.

Typical estimates for the natural background concentrations of chloromethane in ambient air are 0.58 ppm (1.2 $\mu g/m^3$) (Woodruff et al. 1998) to 0.87 ppm (1.8 $\mu g/m^3$) (Logue et al. 2012). Other than data from the TRI or rough estimates based on global budgets, no studies were identified that attempt to make quantitative estimates for natural or anthropogenic releases of chloromethane to the air in the United States.

EPA's National Emission Inventory (NEI) database contains information regarding sources that emit criteria air pollutants (CAPs) and their precursors, and hazardous air pollutants (HAPs) for the 50 United States, Washington DC, Puerto Rico, and the U.S. Virgin Islands. Emissions are estimated from multiple sources, including state and local environmental agencies; the TRI database; computer models for on- and off-road emissions; and databases related to EPA's Maximum Achievable Control Technology (MACT) programs to reduce emissions of HAPs. Chloromethane emissions estimated from the 2017 inventory are summarized in Table 5-3.

Table 5-3. Estimated Annual Chloromethane Emissions in the United States[a]

Emission sector	Pounds of chloromethane emitted
Fires, wildfires	18,950,991.39
Fires, prescribed fires	10,299,194.09
Waste disposal	15,377,95.697
Industrial processes, chemical manufacturing	484,200.14
Industrial processes, pulp and paper	425,652.70
Fuel combustion, electric generation, coal	127,064.91

Table 5-3. Estimated Annual Chloromethane Emissions in the United States[a]

Emission sector	Pounds of chloromethane emitted
Industrial processes, not elsewhere classified	70,708.94
Fuel combustion, industrial boilers, internal combustion engines, other	39,733.34
Fuel combustion, industrial boilers, internal combustion engines, biomass	16,166.54
Solvent, degreasing	10,831.38

[a]Emissions are estimated from the 2017 inventory.

Source: EPA 2022b

5.3.2   Water

Estimated releases of 1,302 pounds (~0.59 metric tons) of chloromethane to surface water from 58 domestic manufacturing and processing facilities in 2021, accounted for about < 1% of the estimated total environmental releases from facilities required to report to the TRI (TRI21 2022). This estimate includes releases to wastewater treatment and publicly owned treatment works (POTWs) (TRI21 2022). These releases are summarized in Table 5-2.

The reportable surface water discharges reported in the TRI 2021 data have increased from the estimated releases of 258 pounds reported for 2020 (TRI20 2021). Most of the amount released in 2021 was reported from Louisiana accounting for 1,029 pounds released to waters. Chloromethane has been identified in water at 38 of the 236 NPL hazardous waste sites at which it was detected in one or more environmental media (ATSDR 2022). The geometric mean of maximum concentrations at these sites was approximately 0.013 mg/L (12.9 ppb).

Chloromethane discharged to water will volatilize rapidly, based on the Henry's law constant; however, the amount volatilized will vary depending on a number of factors, including the temperature, turbulence, and depth of the receiving water.

Chloromethane is released into the water from several sources, including industrial discharges and effluents from municipal waste treatment plants, but insufficient information is available to quantify the releases. During the manufacture of chloromethane, process water contacts the reaction mixtures (Edwards et al. 1982a; Key et al. 1980). This water is stripped during manufacture and treatment to

remove most of the dissolved chloromethane and then discharged (some chloromethane manufacturing plants use the process water on-site as a source of dilute HCl rather than discharging it). Data regarding the use, application, and fate of process water were not found in the available literature; however, spent process water is likely treated (including aeration) prior to discharge. Chloromethane has also been detected in recycled water (Rodriguez et al. 2007). In a study to determine the concentration of volatile organic compounds in secondary treatment effluent (STE) and post-reverse osmosis (RO) treatment, chloromethane was found in 57.6% of STE samples and 62.9% of RO samples (Rodriguez et al. 2012). It is possible that chloramination may play a role in the detection of chloromethane in RO permeate, given that chloromethane has shown increases in concentration during MF/RO (micro filtration/reverse osmosis) (Linge et al. 2012).

Chloromethane has been found in wastewater effluents, possibly as a result of its formation (EPA 1975) or incomplete removal during industrial wastewater treatment (Snider and Manning 1982). Chloromethane has been detected in the leachate of both municipal (Sabel and Clark 1984) and hazardous waste landfills (Brown and Donnelly 1988; Kosson et al. 1985; Venkataramani et al. 1984).

5.3.3   Soil

Estimated releases of 8,300 pounds (~3.76 metric tons) of chloromethane to soil from 61 domestic manufacturing and processing facilities in 2021, accounted for about < 1% of the estimated total environmental releases from facilities required to report to the TRI (TRI21 2022). An additional 330,813 pounds (~150 metric tons), accounting for about 33% of the total environmental emissions, were released via underground injection (TRI21 2022). These releases are summarized in Table 5-2.

The reportable soil discharges reported in the TRI 2021 data have decreased from the estimated release of 9,596 pounds reported for 2020 (TRI20 2021). Chloromethane has been identified in soil at 11 of the 236 NPL hazardous waste sites at which it was detected in one or more environmental media (ATSDR 2022). The geometric mean of maximum concentrations at these sites was approximately 0.058 mg/L (58.3 ppb).

Chloromethane may be released into the soil during the landfilling of sludge and other wastes (e.g., still bottoms) generated from industrial processes and municipal sewage treatment. Chloromethane has been detected in the leachate of both municipal (Sabel and Clark 1984; Manca et al. 1997) and hazardous waste

landfills (Brown and Donnelly 1988; Kosson et al. 1985; Venkataramani et al. 1984), indicating that disposal of these materials apparently results in contamination of soils.

Chloromethane may be released to the environment due to abiotic and biotic formation of chloromethane in soils and sediments, which may occur at both ambient and higher temperatures (Keppler et al. 2020; Moore et al. 2005). A source of release of chloromethane to soils comes from abiotic and enzymatic production in certain plants (e.g., *Osmunda regalis; Salicornia europaea)* and wood-rotting fungi (Bringel et al. 2019; Jaeger et al. 2018; Keppler et al. 2020; Kröber et al. 2022; Moore et al. 2005). *O. regalis* has been reported to produce chloromethane at rates of 0.6–128 µg/g/day and *S. europaea* can produce chloromethane at rates of 0.2±0.04 ng/g/hour at 20°C and 2.1±0.8 ng/g/h at 40°C (Jaeger et al. 2018; Keppler et al. 2020). However, it has been shown that some lignin-degrading fungi (*Coriolus versicolor, Phanerochaete chrysosporium, Phlebia radiata*), plants and their associated microbiomes, and phyllospheric and other bacteria (*Arabidopsis thaliana, Cyathea australis, Cyathea cooperi, Methylobacterium extorquens*) also can degrade chloromethane, limiting its release to the environment (Bringel et al. 2019; Farhan Ul Haque et al. 2017; Kröber et al. 2021).

5.4   ENVIRONMENTAL FATE

5.4.1   Transport and Partitioning

Air. Most chloromethane discharged into the environment will be released into the air, where it will be subjected to transport and diffusion into the stratosphere (Tsai 2017). The relatively uniform concentration of chloromethane in the northern and southern hemispheres (Singh et al. 1979, 1982, 1983) indicates its widespread distribution and the importance of transport processes in its distribution. The water solubility of chloromethane is high enough that small amounts may be removed from the atmosphere by precipitation; however, no information confirming this environmental pathway was identified in the literature.

Water. The dominant transport process from water will be volatilization. The results of two model runs of the Exposure Analysis Modeling System (EXAMS) and the value of the Henry's law constant (calculated from the solubility and the vapor pressure) suggest that volatilization will be significant in surface waters. EXAMS is an environmental model that predicts the behavior of a chemical in surface waters. Using the embedded scenarios for a typical pond and lake developed by the Athens Environmental Research Laboratory of the EPA, half-lives for volatilization were calculated to be

2.5 hours and 18 days, respectively. The rate of disappearance of chemicals in the model is assumed to be driven by transformation and transport processes and by hydraulic and hydrological processes in the water bodies (Smith et al. 1977). For different water bodies, data on physical, chemical, and biological processes are integrated by the model, resulting in different half-lives for volatilization. The volatilization rates predicted by the EXAMS model appear to be in agreement with the observation of Lurker et al. (1983) who reported chloromethane concentrations in wastewater and in the air above the wastewater at the Memphis North Wastewater Treatment Plant in Memphis, Tennessee. Based on chloromethane's log K_{ow} and its estimated bioconcentration factor (BCF) (see Table 4-2), chloromethane is not expected to bioconcentrate in aquatic species.

Sediment and Soil. In soil, the dominant transport mechanism for chloromethane present near the surface will be volatilization (based on its Henry's law constant, water solubility, and vapor pressure), but no experimental information was identified in the literature to confirm this. The actual volatilization rate for a chemical in soil is influenced by several factors, including surface roughness, soil type, rainfall, leaching, depth of incorporation, temperature, and ground cover (Jury et al. 1987). Based on its estimated K_{oc} (see Table 4-2), chloromethane is not expected to sorb to soils or sediments. Chloromethane present in lower layers of the soil will be expected to leach to lower horizons as well as to diffuse to the surface and volatilize. The presence of chloromethane in groundwater confirms the importance of leaching as a transport route (Greenberg et al. 1982; Jury et al. 1987; Page 1981).

5.4.2   Transformation and Degradation

Air. The chemical and physical properties of chloromethane indicate that when it is released to the environment, it will partition predominantly to the atmosphere (Tsai 2017). The atmospheric degradation reaction of chloromethane is initiated by a hydroxyl radical attack (Tsai 2017). The main degradation products of chloromethane include HCl, CO, CO_2, HCOCl (formyl chloride), and H_2O_2 (Tsai 2017).

Using the measured rate constants for the chloromethane reaction with hydroxyl radicals, several researchers have made estimates of tropospheric total lifetimes or half-lives (Crutzen and Gidel 1983; Dilling 1982; Fabian 1986; Khalil and Rasmussen 1999; Singh et al. 1979). These studies estimate the half-life to range from 0.6 to 3 years. The differences in the estimated half-lives are associated mainly with differences in assumptions on the levels of hydroxyl free radical concentrations in the upper troposphere. Tsai (2017) estimates that chloromethane has an atmospheric lifetime of 1 year. In a laboratory study where degradation of chloromethane was evaluated at 20°C using photolitically

generated hydroxyl and chloride radicals, over 70% degradation was observed within 6–10 hours
(Keppler et al. 2020). These data suggest that although abiotic degradation may occur, there is potential
for atmospheric transport.

Water. In water, chloromethane can degrade via hydrolysis or biodegradation. Available data on the
abiotic and biotic degradation of chloromethane in water suggest that neither hydrolysis nor
biodegradation is a dominant fate process when compared with volatilization. Chloromethane hydrolysis
proceeds via an S_N2 mechanism (involving the nucleophilic substitution of chlorine with water) in which
no intermediate ions are formed, where methanol and HCl are the two degradation products. The kinetics
of chloromethane hydrolysis have been measured by Heppolette et al. (1959) and Laughton and
Robertson (1956) by bubbling chloromethane into water and following the reaction by measuring the
conductance of the water. The rate constant for hydrolysis of chloromethane at 50°C was reported to be
7.6×10^{-7} second^{-1}, with a half-life of 10.6 days. When extrapolated to 20°C and neutral conditions using
the thermodynamic constants calculated by Heppolette et al. (1959), a rate constant was calculated of
1.04×10^{-8} second^{-1} with a half-life of approximately 2.1 years. Other hydrolysis data from Elliot and
Rowland (1995) are in good agreement with the estimates of Mabey and Mill (1978) and the
measurements of Zafiriou (1975). Actual measurements conducted at 22 and 9°C in pure water, sea
water, and salt solution yield the same values of k (not listed), from which the Arrhenius relation was
derived: $k(\text{in second}^{-1}) = 9.5 \times 10^{10} e^{-12,800/T}$. This relation was used to estimate the values at 25 and 15°C
given in Table 4-2. These rates are expected to be unaffected by pH ranges normally encountered in the
environment (Mabey and Mill 1978). In a test conducted in a manner similar to EPA Office of Toxic
Substances (OTS) 796.3500 (hydrolysis as a function of pH) in compliance with Good Laboratory
Practices (GLP), the half-life in water at pH 7 and 25.5°C was determined to be 62 days (EPA 2022a;
ECHA 2022). A laboratory study evaluating the hydrolysis of chloromethane in distilled water at 23°C
resulted in a rate constant of 0.0015 day^{-1}, corresponding to a half-life of approximately 577 days (Horst
et al. 2019). Based on these data, the rate of hydrolysis is slow and is not considered to be of
environmental significance in surface waters, considering the rapid volatilization of chloromethane from
surface water (Mabey and Mill 1978).

Several chloromethane-degrading bacteria have been isolated from various marine and freshwater
sources, and pure culture experiments have indicated the potential for aerobic biotransformation of
chloromethane (Bringel et al. 2019). In studies using the bacteria, *Methylococcus capsulatus,*
formaldehyde was a product of chloromethane biodegradation (Stirling and Dalton 1979).
Acetobacterium dehalogenans has been shown to use chloromethane as a sole source of carbon under

anoxic conditions (Bringel et al. 2019). Hartmans et al. (1986) reported that pure cultures of a
Hyphomicrobium sp. isolated from a sewage treatment plant were obtained with a chloromethane-
minima1 medium and demonstrated the ability to use chloromethane as a sole source of carbon under
aerobic conditions. Abiotic hydrolytic dehalogenation was not significant, while the observed microbial
cell growth and chloride formation confirmed biodegradation as the predominant transformation process
(Hartmans et al. 1986). These species may not degrade chloromethane in the environment to any
significant degree; however, there is potential for biodegradation of chloromethane under some
environmental conditions based on the available information. In a closed bottle test according to
Organisation of Economic Co-operation and Development (OECD) guideline 301D, chloromethane
reached 77% biodegradation after 28 days (ECHA 2022).

Based on carbon isotope analysis during aerobic chloromethane degradation using bacterial strains from
both marine and terrestrial environments, microbial degradation is likely by S_N2 type reactions resulting
in dehalogenation and 51–86% loss of chloromethane after 29 hours of bacterial growth (Keppler et al.
2020), and degradation rates of approximately 0.2–1.4 µg/g dry weight/day in various soils at pH values
of 4.7–7.1 (Jaeger et al. 2018).

Sediment and Soil. Limited information on transformation and degradation of chloromethane in soil
was identified in the literature. In lower soil horizons, hydrolysis may be the only relevant abiotic process
since no other non-biological removal mechanisms have been identified. Biological processes, especially
from some fungi, can release chloromethane (Fabian 1986; Harper 1985; Harper and Hamilton 1988;
Harper et al. 1988). Research also indicates that certain white rot fungi and lignin-degrading fungi, such
as *P. chrysosporium*, *P. radiata*, and *C. versicolor* can degrade (metabolize) chloromethane (Bringel et al.
2019; Harper et al. 1990). These fungi (especially *P. chrysosporium*) can also dehalogenate aliphatic
halocarbons such as chloroform, dichloromethane, and carbon tetrachloride (Khindaria et al. 1995)
possibly forming chloromethane as an intermediate product that, in turn, could be further dehalogenated.

Several chloromethane-degrading bacteria have been isolated from various soils and sediments, and pure
culture experiments have indicated the potential for anaerobic and aerobic biotransformation of
chloromethane (Bringel et al. 2019). Doronina et al. (1996) isolated eight strains of non-methane-
utilizing bacteria that can utilize chloromethane as the carbon and energy source. The new isolates were
classified as *Hyphomicrobium* spp. (strains CMl, CM2, CM9, CM29, CM35) and *Methylbacterium* spp.
(strains CM4, CM30, CM34). All strains possessed an inducible but unknown enzyme that catalyzed the
conversion of chloromethane to HCI and formaldehyde. The formaldehyde was oxidized via formate to

CO2 or assimilated through icl+ or icl-variants of the serine pathway. Vannelli et al. (1998) found that
Methylobacterium sp. (strain CM4) metabolized chloromethane quantitatively with a molar yield of 2.8 g
of whole-cell protein/mol of C, suggesting that under the experimental conditions of the test,
chloromethane was readily biodegradable (ECHA 2022). Based on the protein yield data and the
properties of the transposon mutants, they proposed a pathway for chloromethane metabolism that
depends on methyltransferase and dehydrogenase activities.

Biodegradation of chloromethane, with and without addition of methanol, was observed in forest topsoil
microcosms under aerobic conditions where mineralization to CO_2 occurred at rates of 0–0.3 mmol/g_{dry}
$_{soil}$/day (Chaignaud et al. 2018). Addition of chloromethane to microcosms representing forest
compartments resulted in first-order degradation rates constants of 0.19–2.35 hour^{-1} in leaf litter, 2.00–
6.96 hour^{-1} in various soil horizons, and 0.06–2.76 hour^{-1} in fresh beech leaves. *Alphaproteobacteria sp.*,
and *Actinobacteria sp.* were identified as the prominent degraders in the soil and the addition of
methanol-enhanced biodegradation suggests that co-metabolism may be preferred for methanotrophs.

Under anaerobic conditions as encountered in deeper soil profiles or in many sediments, a bacterial strain
called MC isolated from municipal anaerobic digester sludge flora seems capable of metabolizing
chloromethane into acetate (Meßmer et al. 1993; Zitomer and Speece 1995). It is not clear, however, that
such anaerobic biodegradation processes are common around waste sites with chloromethane site
contamination. Enzymatic dehalogenation of chloromethane was demonstrated using a bacterial strain
(*Acetobacterium dehalogens*) from a river sediment mixed culture that could use chloromethane as a sole
carbon source under anaerobic conditions (Chen et al. 2017).

Other Media. Several microbial strains including *Hyphomicrobium* sp., *Aminobacter* sp., a Gram-
positive isolate related to *Nocardiodides* sp., *Alphaproteobacteria sp.*, *Methylorubrum extorquens*, and
Leisingera methylohalidivorans from a variety of terrestrial, freshwater, estuarine, and marine
environments were determined as chloromethane-utilizing bacteria (Keppler et al. 2020; Kröber et al.
2022; McAnulla et al. 2001). Degradation rates of 0.3–17 µg/g/day have been determined for
chloromethane degradation in certain ferns (Jaeger et al. 2018). *C. australis* and its associated
microbiome have demonstrated the ability to consume (degrade) chloromethane at rates of 7–15 ppm/day
(µg/g/day) (Kröber et al. 2021).

5. POTENTIAL FOR HUMAN EXPOSURE

5.5   LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to chloromethane depends, in part, on the
reliability of supporting analytical data from environmental samples and biological specimens.
Concentrations of chloromethane in unpolluted atmospheres and in pristine surface waters are often so
low as to be near the limits of current analytical methods. In reviewing data on chloromethane levels
monitored or estimated in the environment, it should also be noted that the amount of chemical identified
analytically is not necessarily equivalent to the amount that is bioavailable.

Table 5-4 shows the limit of detections typically achieved by analytical analysis in environmental media.
Presented in Table 5-5 is a summary of the range of concentrations detected in environmental media of
NPL Sites.

Table 5-4. Lowest Limit of Detection Based on Standards[a]

Media	Detection limit	Reference
Outdoor air	0.01 µg/sample	NIOSH 1994
	0.02 ppb	Hsu et al. 2018
	<0.5 ppbv	Mohamed et al. 2002
Indoor air	~1 µg/m^3	Weisel et al. 2008
Surface water and groundwater	52 pg/L	USGS 2015
Drinking water	0.03 µg/L	EPA 1995
Water, soil, solid waste	0.03 µg/L	EPA 1986
Secondary treated effluent	0.066 µg/L	Rodriguez et al. 2012
Exhaled Air	243 pptv/200 mL	Keppler et al. 2017
E-waste	2.42 µg/M^3	Liu et al. 2017
Vehicle interior	0.042 µg/m^3	Xing et al. 2018
Urine	1 mg/L	DeKok and Anthenius 1981

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all
situations.

Table 5-5. Chloromethane Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean	Geometric standard deviation	Number of quantitative measurements	NPL sites
Water (µg/L)	13.0	12.9	8.19	54	38
Soil (ppb)	52.0	58.3	9.09	12	11

Table 5-5. Chloromethane Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean	Geometric standard deviation	Number of quantitative measurements	NPL sites
Air (ppbv)	1.04	3.29	24.0	32	23

[a]Concentrations found in ATSDR site documents from 1981 to 2022 for 1,868 NPL sites (ATSDR 2022). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

Chloromethane is a pollutant monitored for in the national Air Quality System (AQS) database which contains ambient air pollution data collected by EPA, state, local, and tribal air pollution control agencies from monitors throughout the country. Table 5-6 shows the yearly mean 24-hour percentile distributions of chloromethane at monitoring stations across the United States.

Table 5-6. Summary of Annual Concentration of Chloromethane Measured in Ambient Air at Locations Across the United States[a,b]

Year	Number of samples	Average of the arithmetic mean at all locations	Maximum concentration (ppbv)
2018	198	0.5180	2.6
2019	145	0.5699	9.0
2020	154	0.6018	9.9
2021	208	0.6036	52.6
2022	34	0.5712	1.5

[a]24-hour sampling period.
[b]As of August 26, 2022.

Source: EPA Air Quality System (AQS) annual summaries (EPA 2022c)

Several studies have also been conducted to measure chloromethane concentrations in outdoor air at specific locations across the United States since 2000. The results of these studies are summarized in Table 5-7.

Table 5-7. Outdoor Air Monitoring Data for Chloromethane

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Reference
Del Norte, Albuquerque, New Mexico	Not specified	Not specified	0.1–15.3 ppbv	1.1 ppbv	Kavouras et al. 2015
North Valley, Albuquerque, New Mexico	Not specified	Not specified	0.4–5.1 ppbv	1.1 ppbv	Kavouras et al. 2015
South Valley, Albuquerque, New Mexico	Not specified	Not specified	0.1–2.7 ppbv	0.7 ppbv	Kavouras et al. 2015
Baton Rouge, Louisiana	Urban	9/96–8/97	Not specified	0.537 ppbv	Mohamed et al. 2002
Brownsville, Texas	Urban	9/96–8/97	Not specified	1.222 ppbv	Mohamed et al. 2002
Brattleboro, Vermont	Urban	9/96–8/97	Not specified	0.511 ppbv	Mohamed et al. 2002
Burlington, Vermont	Urban	9/96–8/97	Not specified	0.495 ppbv	Mohamed et al. 2002
Camden, New Jersey	Urban	9/96–8/97	Not specified	0.542 ppbv	Mohamed et al. 2002
El Paso, Texas	Urban	9/96–8/97	Not specified	0.676 ppbv	Mohamed et al. 2002
Garyville, Louisiana	Urban	9/96–8/97	Not specified	0.641 ppbv	Mohamed et al. 2002
Galveston, Texas	Urban	9/96–8/97	Not specified	0.952 ppbv	Mohamed et al. 2002
Hahnville, Louisiana	Urban	9/96–8/97	Not specified	0.576 ppbv	Mohamed et al. 2002
Port Neches, Texas	Urban	9/96–8/97	Not specified	1.093 ppbv	Mohamed et al. 2002
Rutland, Vermont	Urban	9/96–8/97	Not specified	0.483 ppbv	Mohamed et al. 2002
Underhill, Vermont	Urban	9/96–8/97	Not specified	0.481 ppbv	Mohamed et al. 2002
Winooski, Vermont	Urban	9/96–8/97	Not specified	0.526 ppbv	Mohamed et al. 2002
Flag Plaza, Pittsburgh, Pennsylvania	Not specified	2/4/06–1/19/08	1.14–1.57 $\mu g/m^3$	0.00065 ppm (1.34 $\mu g/m^3$)	Logue et al. 2012
South Fayette, Pittsburgh, Pennsylvania	Not specified	2/4/06–1/19/08	1.03–1.47 $\mu g/m^3$	0.0006 ppm (1.23 $\mu g/m^3$)	Logue et al. 2012
Avalon, Pittsburgh, Pennsylvania	Not specified	2/4/06–1/19/08	1.03–1.40 $\mu g/m^3$	0.00059 ppm (1.22 $\mu g/m^{3)}$	Logue et al. 2012
Stowe, Pittsburgh, Pennsylvania	Not specified	2/4/06–1/19/08	1.04–1.44 $\mu g/m^3$	0.00061 ppm (1.25 $\mu g/m^3$)	Logue et al. 2012

Table 5-7. Outdoor Air Monitoring Data for Chloromethane

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Reference
Houston, Texas	Urban/suburban	5/15/80–5/24/80	531–1,015 ppt	955 ppt	Singh et al. 1982
St. Louis, Missouri	Urban/suburban	5/30/80–6/8/80	519–1,157 ppt	732 ppt	Singh et al. 1982
Denver, Colorado	Urban/suburban	6/16/80–6/26/80	437–1,593 ppt	763 ppt	Singh et al. 1982
Riverside, California	Urban/suburban	7/2/80–7/12/80	437–1,593 ppt	703 ppt	Singh et al. 1982
Staten Island, New York	Urban/suburban	3/27/80–4/5/80	466–1,280 ppt	701 ppt	Singh et al. 1982
Pittsburgh, Pennsylvania	Urban/suburban	4/8/80–4/16/80	450–852 ppt	665 ppt	Singh et al. 1982
Chicago, Illinois	Urban/suburban	4/21/80–4/30/80	575–1,311 ppt	856 ppt	Singh et al. 1982
Los Angeles, California	Urban/suburban	4/29/76–5/4/76	708–944 ppt	834 ppt	Singh 1977
Stanford Hills, California	Urban/suburban	11/24/75–11/30/75	700–1,700 ppt	1,022 ppt	Singh 1977
Pullman, Washington	Rural/remote	12/74–2/75	503–566 ppt	530 ppt	Grimsrud and Rasmussen 1975
Alaska	Rural/remote	5/24/75–5/30/75	505–970 ppt	Not specified	Robinson et al. 1977
Point Barrow, Alaska	Rural/remote	5/7/82 and 5/13/82	634–660 ppt	647 ppt	Rasmussen and Khalil 1983
Pacific Northwest	Rural/remote	3/11/76	428–611 ppt	569 ppt	Cronn et al. 1977
Point Reyes, California	Rural/remote	12/2/75–12/12/75	680–1,700 ppt	1,260 ppt	Singh et al. 1977
Yosemite Park, California	Rural/remote	5/12/75–5/17/75	654–999 ppt	713 ppt	Singh et al. 1977
Palm Springs, California	Rural/remote	5/24/76–5/27/76	645–2,128 ppt	1,058 ppt	Singh et al. 1977

Chloromethane is also present in indoor air. In a study to quantify and compare health impacts from indoor air pollutants, the population-average concentration of chloromethane in the United States was assumed to be 0.00087 ppm (1.8 µg/m^3), and chloromethane was estimated to result in 10,000 disability-adjusted life-years (DALYs) lost due to indoor inhalation (Logue et al. 2012). Weisel et al. (2008) measured indoor VOC air concentrations in 100 suburban and rural homes in New Jersey and found that the average concentration of chloromethane was 0.00072 ppm (1.49 µg/m^3). Van Winkle and Scheff

(2001) found that the average concentration of chloromethane in 10 urban homes in Southeast Chicago was 0.00097 ppm (2,000 ng/m^3).

5.5.2   Water

Chloromethane has been detected in surface water, groundwater, drinking water, municipal and hazardous waste landfill leachate, and industrial effluents. When detected, concentrations appear to be in the ppb to ppt range, possibly due to the rapid volatilization of chloromethane. Chloromethane is apparently formed during the chlorination of drinking water. Chloromethane is a List 1 contaminant and was monitored by EPA as part of UCMR3. In samples taken from 2013 to 2015, chloromethane was found at concentrations above the minimum reporting level of 0.2 µg/L in <1 percent of the 36,845 samples (EPA 2017b). In a study of tap water at residential and workplace sites, Bradley et al. (2018) found chloromethane at 6 of the 26 sites sampled. Concentrations ranged from not detected to 0.269 µg/L (Bradley et al. 2018). In a study at the Kwinana Water Reclamation Plant, recycled water was tested at four points during the reclamation process. Chloromethane was detected in all samples after reverse osmosis (Rodriguez et al. 2007).

In a study of groundwater samples collected prior to 1991 from 479 active waste disposal sites, representing 178 Superfund sites, 173 RCRA sites, and 128 sanitary/municipal landfill sites, chloromethane was detected at 20 sites in 9 EPA Regions with 30 detectable events where concentration exceeded the detection limits in groundwater (Plumb 1991). Since chloromethane has been detected in the groundwater near municipal waste sites containing the chemical (Sabel and Clark 1984), waste deposits of chloromethane on land may lead to groundwater contamination. In landfills, volatilization may be hindered and leaching to groundwater could become a transport pathway. Chloromethane may also be a product from the anaerobic metabolism of higher chlorinated methane present in the soil (Vogel et al. 1987).

A national water quality study was done for contaminants including chloromethane over the period of 1991–2010 (USGS 2014). The study evaluated frequency of chloromethane detected at any concentration in principal aquifers in the United States. For the 40 aquifers used for drinking water and sampled for chloromethane, the percentage of all samples containing chloromethane was 3.37% (range 0–27.59%). For the 17 shallow groundwater aquifers beneath agricultural land, 1.81% of samples contained chloromethane (range 0–56.25%), and for the 22 shallow groundwater aquifers beneath urban land, 4.11% of samples contained chloromethane (range 0–20.0 %) (USGS 2014).

No specific information concerning sources of chloromethane in fresh surface water was located in the
literature. Chloromethane concentrations in surface water may be the result of rain as well as human
activity (e.g., industrial effluents, chlorinated secondary effluent from POTWs). Industrial effluents may
be a significant source. Additionally, 34 species of fungi can produce chloromethane biosynthetically
(Harper et al. 1988). The presence of these fungi near lakes and streams may be a source of
chloromethane. The significance of this natural source to surface water, however, cannot currently be
estimated.

Since recent water monitoring data are available, both recent and historical data water monitoring data are
presented below. Table 5-8 shows surface water monitoring data for chloromethane, Table 5-9 represents
groundwater monitoring data for chloromethane, Table 5-10 represents drinking water monitoring data
for chloromethane, and Table 5-11 contains landfill leachate and effluent monitoring data for
chloromethane.

Table 5-8. Surface Water Monitoring Data for Chloromethane

Location(s)	Type	Date(s)	Range (µg/L)	Mean concentration (µg/L)	Notes	Reference
Monitoring sites in 19 U.S. states	Surface water	Jan 2019– August 2022	<LOD–0.6	Not specified	78 samples were analyzed	WQP 2022
38 streams in 24 states and Puerto Rico	34 urban/ agricultural impacted sites 4 undeveloped sites	November 2012–June 2014	<LOD	<LOD		Bradley et al. 2017a, 2017b
Delaware River and Raritan Canal	Surface water	August 1979– January 1980	<LOD	<LOD	Samples collected at 12 sites and during several storms	Granstrom et al. 1984
Lake Ontario	Not specified	Late 1970s– early 1980s	Detected	Not specified		Great Lakes Water Quality Board 1983
New Jersey	Surface water	1977–1979	<LOD–222	<LOD	Detected in 24 of 605 samples	Page 1981

LOD = level of detection

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Table 5-9. Groundwater Monitoring Data for Chloromethane

Location(s)	Type	Date(s)	Range (µg/L)	Mean concentration (µg/L)	Notes	Reference
Monitoring sites in 32 U.S. states	Groundwater	Jan 2019–August 2022	<LOD–360	16.6 (mean of samples with concentrations >LOD)	5527 samples were analyzed	WQP 2022
New Jersey	Groundwater	1977–1979	<LOD–6	Not specified	Detected in 3/1,058 samples	Page 1981
Minnesota	Groundwater (under municipal solid waste landfills)	Early 1980s	Detected	Not specified	Detected (but not quantified) in 11/20 samples	Sabel and Clark 1984

LOD = level of detection

Table 5-10. Drinking Water Monitoring Data for Chloromethane

Location(s)	Type	Date(s)	Range (µg/L)	Mean concentration (µg/L)	Notes	Reference
Tap water sites in California, Colorado, Florida, Iowa, Kansas, Michigan, New Jersey, Oklahoma, Oregon, South Carolina, and Virginia	Tap water	May–September 2016	<LOD–0.269	0.194	LOD=0.100 µg/L; chloromethane was detected in 6 of 26 sites	Bradley et al. 2018
Cincinnati, Ohio	Not specified	Not specified	Detected	Not specified		Kopfler et al. 1977

LOD = level of detection

Table 5-11. Landfill Leachate and Effluent Monitoring Data for Chloromethane

Location(s)	Type	Date(s)	Range (µg/L)	Mean concentration (µg/L)	Notes	Reference
Monitoring sites in three U.S. states	Leachate; Municipal wastewater; industrial effluent	Jan 2019– August 2022	<LOD–2.5	All samples below reporting limits	24 samples were analyzed	WQP 2022
Minnesota	Leachate; under municipal solid waste landfills	Early 1980s	Detected	Not specified	Detected in 4/6 samples	Sabel and Clark 1984
Wisconsin	Leachate; under municipal solid waste landfills	Early 1980s	170	170	Detected (but not quantified) in 1/5 samples	Sabel and Clark 1984
Love Canal, New York	Leachate; industrial landfill	1970s	180	180		Shuckrow et al. 1982
Kin-Buc Landfill, New Jersey	Leachate; industrial landfill	1970s	3.1	3.1		Shuckrow et al. 1982
Petroleum refinery effluents	Wastewater feeds to biotreatment effluents	1970s	<100–>100	Not specified	Samples from 17 refineries were analyzed	Snider and Manning 1982
Petroleum refinery effluents	Final effluents	1970s	<10	Not specified	Samples from 17 refineries were analyzed	Snider and Manning 1982

LOD = level of detection

5.5.3 Sediment and Soil

Information on background levels in soils and sediments is very limited in the available literature. Information located in the literature concerning the presence of chloromethane in soil refers to the natural formation of chloromethane by several species of fungi (Harper 1985), and to its presence in both landfill leachate and groundwater.

Soils from coastal Antarctica were incubated to evaluate their potential as a source or sink of chloromethane. Experiments suggested that chloromethane consumption was predominantly microbial, while production was through abiotic processes. Results indicated that tundra soil acted as a chemical sink for chloromethane with chemical fluxes ranging from -18.1 to -2.8 pmol/g/day (Zhang et al. 2020).

5.5.4   Other Media

As presented in Section 5.3.1, chloromethane is released from burning plastic, cigarette smoke, biomass burning, the process of dismantling e-waste, interior materials in vehicles, and laundry products (Lestari et al. 2011; Filipiak et al. 2012; Keppler et al. 2005; Liu et al. 2017; Novak et al. 2008; Sleiman et al. 2014; Steinemann 2015; Xing et al. 2018). When chlorine compounds are heated in contact with cellulose, gaseous chlorine compounds are produced by reactions involving the hydroxyl groups or the water formed *in situ* by dehydration (Palmer 1976). Chloromethane has been detected at a concentration of 860 µg/L as a pyrolysis product in simulated combustion experiments using plastic PVC pipes (Draper et al. 2022). Wood pulp and other cellulosic materials can release methane when burned that is converted to chloromethane by the chlorine in the material, producing 1 cm^3 of chloromethane gas (2.2 mg) for each gram of cellulose burned in glowing combustion (Palmer 1976). Concentrations of chloromethane in smoke from combustion processes, however, are highly variable and depend on both the fuel (i.e., the amount of inorganic chlorine present in the fuel) and the temperature of the burn. Thus, quantification of chloromethane in these media will be representative of the specific source and the exact conditions of the burn rather than of general emission levels. Chloromethane has not been detected in auto exhaust (detection limit of 1 ppm) (Häsänen et al. 1979).

In a 2018 study, VOC emissions from two memory foam mattresses were evaluated over a 32-day period using passive 12- and 24-hour samples; chloromethane was detected at concentrations ranging from 1.0 to 2.0 µg/m^3. It was not detected in background samples (Beckett et al. 2022). Although not quantified, chloromethane has been identified as a chemical present or emitted from crumb rubber used in synthetic turf athletic fields (Perkins et al. 2019).

Chloromethane was present in the expired air of all three tested groups of 62 nonsmoking adults, including a control, a prediabetic, and a diabetic group (Krotoszynski and O'Neill 1982). Since chloromethane is a ubiquitous constituent of air, it is reasonable that it would be found in the expired air of virtually all humans. Recent studies confirm that chloromethane is expired in both nonsmokers and smokers, and suggest that concentrations are influenced by environmental pollutants, food and beverages, and smoking-related compounds (Filipiak et al. 2012). Keppler et al. (2017) estimates that based on testing of 31 human subjects ages 3–87 years, all subjects exhaled between 2.5 and 33 ppbv of chloromethane, which significantly exceeds the amount of chloromethane in the inhaled air.

5.6   GENERAL POPULATION EXPOSURE

According to one report, persons living in Los Angeles, California; Phoenix, Arizona; and Oakland, California; would have daily chloromethane intakes of approximately 140.4, 108.6, and 59.7 µg/day, respectively (Singh et al. 1981), based on a total respirable air volume of 23 m^3/day at 25°C and 1 atm pressure. Using the data of Shah and Singh (1988) for remote, rural, suburban, and urban air masses, daily intakes were estimated to be 31, 40, 28, and 35 µg/day, respectively.

Chloromethane is a ubiquitous low-level constituent of air and is likely found at very low concentrations as a disinfection byproduct in many drinking water supplies that have used chlorine treatment for disinfection. As such, the general population may generally be exposed to low background levels at any time, while those living in urban centers may be exposed to slightly higher levels.

The intakes for rural and remote air masses are based on very small sample sizes and may be inaccurate. Dermal exposure and exposures from drinking water containing chloromethane are more difficult to estimate from the available information. Drinking water concentrations are not well described in the literature and may vary considerably both seasonally and geographically.

Chloromethane in water volatilizes fairly rapidly; thus, there is potential for inhalation exposure during showering and bathing. ATSDR's three-compartment Shower and Household-Use Exposure (SHOWER) model predicts air concentrations in the shower stall, bathroom, and main house throughout the day by estimating the contribution from showering or bathing and the contribution from other water sources in the house, such as the dishwasher, clothes washer, and faucets. This information along with human activity patterns are used to calculate a daily time-weighted average exposure concentration via inhalation exposure and from dermal uptake from skin contact. ATSDR's SHOWER model is available by sending a request to showermodel@cdc.gov.

Vapor intrusion may also be a potential source of chloromethane exposure, as vapor intrusion has been observed for several VOCs with similar properties. EPA's compilation of five studies of background indoor air concentrations found a 54–100% detection rate for chloromethane in 975 U.S. resident samples between 1994 and 2004 (EPA 2011). The background medians ranged from 0.5 to 1.69 µg/m^3, 95th percentiles ranged from 2.1 to 5 µg/m^3, and maximum values ranged from 4.2 to 260 µg/m^3.

Historically (50 years ago or longer), large exposures could have been associated with leaking refrigerators that used chloromethane as a refrigerant. While refrigeration-grade chloromethane may still be available, it is not known whether it is currently used to any significant degree in refrigeration equipment. Without this information, potential exposures cannot be estimated.

Chloromethane is a trace component of vinyl chloride present at concentrations in the range of 10–100 mg/kg and is a degradation product (PubChem 2021; WHO 1999). Exposures to chloromethane could take place during the manufacture of vinyl chloride or when vinyl chloride wastes have been released to the environment or to waste sites. Information is lacking to make any firm estimates of such potential exposures.

No data were found on the measurement of chloromethane or its metabolites in amniotic fluid, meconium, cord blood, or neonatal blood in humans that would indicate prenatal exposure. It is not known whether chloromethane in the body can cross the placenta and enter into the developing young. However, Wolkowski-Tyl et al. (1983a) noted from unpublished observations that rat dams exposed to 500 or 1,500 ppm, but not 100 ppm, chloromethane for 6 hours on GD 17 had significant NPSH concentration reductions in both dams and fetuses, indicative of transplacental passage of chloromethane or its metabolites. The case for placental transfer is also supported by their unpublished work (1983a) in which maternal animals were exposed for 6 hours on GD 19 to 1,500 ppm ^{14}C radiolabeled chloromethane. Both maternal and fetal tissues (lungs, heart, and brain) were found to contain ^{14}C, with fetal concentrations twice those of the dams. Since chloromethane is broken down and eliminated from the body quickly in adults, it is unlikely that chloromethane would be stored in maternal tissues or mobilized during pregnancy or lactation. Chloromethane was detected in two of eight samples of mothers' milk from Bayonne and Jersey City, New Jersey; Bridgeville, Pennsylvania; and Baton Rouge, Louisiana (Pellizzari et al. 1982). No concentrations were reported, and no information was given concerning potential source(s) of the chloromethane in the milk.

Parents can inadvertently carry certain hazardous materials home from work on their clothes, shoes, skin, hair, and tools, and in their vehicles. However, since chloromethane is highly volatile, it is unlikely that children would be exposed by this route. No incidents of home contamination by chloromethane were reported in the Workers' Home Contamination Study conducted under the Workers' Family Protection Act (29 U.S.C. 671a) (DHHS 1995).

5.7   POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

People with very old refrigeration equipment in which chloromethane is used as a refrigerant are a
population with potentially very high exposures. These refrigerators can leak and result in very high local
air concentrations of chloromethane. This population is, however, likely to be small since the number of
refrigerators using chloromethane has been decreasing for several decades (UNEP 1999). People who
smoke cigarettes and those exposed passively to the smoke have a higher exposure to chloromethane than
the general population as noted by Novak et al. (2008) and Sleiman et al. (2014).

All humans have the potential to be exposed to low concentrations of chloromethane. Those with
potentially higher than average exposures include workers employed in the manufacturing and use (by
analogy) industries. In addition to individuals occupationally exposed to chloromethane, there are several
groups within the general population that could have exposures higher than background levels. These
populations include individuals living in proximity to sites where chloromethane was produced or
disposed, and individuals living near one of the NPL hazardous waste sites where chloromethane has been
detected in environmental media (ATSDR 2022). The geometric mean of maximum concentrations in air
at the sites where chloromethane was detected was 0.006 mg/m^3, or 0.0029 ppm. This is higher than
estimates of background concentrations in ambient air, which are between 0.00058 and 0.00087 ppm
(Logue et al. 2012; Woodruff et al. 1998). Chloromethane may also be a constituent in other materials
such as vinyl chloride. Chloromethane exposure risks may be of concern to individuals working or living
in the vicinity of sites where vinyl chloride was produced or where there is evidence vinyl chloride has
been disposed.

Some insights can be gleaned from the NIOSH National Occupational Hazard Survey (NOHS) database
(the NOHS database is also called the National Occupational Exposure Survey or NOES database), which
estimates the number of potentially exposed workers in a variety of manufacturing jobs (Sieber et al.
1991). An estimated 10,003 employees in 10 industries were potentially exposed to chloromethane
according to survey results from 1981 to 1983 (NIOSH 1991). Most of these potential exposures
involved occupations where chloromethane could have been used as a cleaner or pest control fumigant.
There is virtually no mention in NOHS of current applications such as use as a process chemical in the
manufacture of silicone rubbers. While the NOHS data are of some historical value, it is doubtful
whether they accurately reflect the potential number of workers subject to current occupational exposures.
Several regulations, however, are in place to protect workers from exposure to levels of chloromethane
that are considered harmful.

CHAPTER 6. ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of chloromethane is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of chloromethane.

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.1 EXISTING INFORMATION ON HEALTH EFFECTS

Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to chloromethane that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of chloromethane. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

As shown in Figure 6-1, information on the health effects in humans exposed to chloromethane is available only for exposure via inhalation. Accidental leaks of chloromethane from refrigeration units primarily involves the inhalation exposure route. The organs or systems adversely affected in humans after exposure to chloromethane include the liver, kidney, neurological system (including behavioral alterations) and potentially the cardiovascular system. Death may occur at sufficiently high doses. Information on the adverse health effects of chloromethane has been presented for occupational exposures of acute, intermediate, and chronic durations. The evidence on chloromethane's carcinogenicity is mixed in epidemiological studies (Barry et al. 2011; Dosemeci et al. 1999; Holmes et al. 1986; Kernan et al. 1999; Rafnsson and Gudmundsson 1997; Rafnsson and Kristbjornsdottir 2014). One found an association with increased risk of death from renal cancer (Rafnsson and Kristbjornsdottir 2014), while another found an increased risk with non-Hodgkin's lymphoma for those individuals with one genetic phenotype whose functional significance is unclear (Barry et al. 2011). Other studies either did not find

Figure 6-1. Summary of Existing Health Effects Studies on Chloromethane by Route and Endpoint*

Potential reproductive, neurological, renal, hepatic, gastrointestinal and cardiovascular effects were the most studied endpoints
The majority of studies examined inhalation exposure in animals (versus humans)

Inhalation Studies

Endpoint	Value(s)
Death	49
Body weight	26
Respiratory	3, 25
Cardiovascular	11, 16
Gastrointestinal	11, 18
Hematological	3, 17
Musculoskeletal	13
Hepatic	6, 32
Renal	5, 33
Dermal	15
Ocular	3, 13
Endocrine	14
Immunological	18
Neurological	20, 46
Reproductive	1, 30
Developmental	5
Other Noncancer	1, 3
Cancer	6, 2

Oral Studies

Endpoint	Value
Hepatic	1

Inhalation Route Duration

- Chronic 18%
- Intermediate 25%
- Acute 57%

Oral Route Duration

- Acute 100%

*Includes studies discussed in Chapter 2. The number of studies includes those finding no effect; most inhalation studies examined multiple endpoints. No dermal studies in humans or animals were located.

an association with death from renal, lung, bladder, lymphatic, or other types of cancer (Dosemeci et al. 1999; Holmes et al. 1986), or the association was not dose, race, or gender related (Kernan et al. 1999).

No information was available regarding immunological, developmental, or genotoxic effects in humans exposed to chloromethane by inhalation, oral, or dermal exposure routes. There are *in vivo* and *in vitro* studies on human tissues. Reproductive effects were limited to one case study that did not provide exposure data.

Several studies have evaluated the health effects of chloromethane exposure in animals for the inhalation route, although only a single comprehensive chronic-duration study in rats and mice has been performed (CIIT 1981). Health effects of acute-, intermediate-, and chronic-duration inhalation exposures in animals include increased mortality, liver damage, kidney damage and tumors, neurological damage; and adverse reproductive, genotoxic, and possibly developmental effects. In the only oral study in animals, an attempt was made to compare the hepatotoxicity of chloromethane with that of carbon tetrachloride and chloroform. The administered dose of chloromethane, however, was too low to produce hepatic effects, and the use of a higher dose was precluded due to neurotoxicity.

6.2 IDENTIFICATION OF DATA NEEDS

Missing information in Figure 6-1 should not be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Acute-Duration MRLs. The inhalation database is adequate to derive an acute-duration inhalation MRL. The oral database is inadequate to derive an acute-duration oral MRL. Available oral data are limited to a single acute-duration gavage study reporting no adverse hepatic effects. Additional acute-duration oral studies examining a wide range of potential effects are needed to identify the most sensitive targets of toxicity and establish dose-response relationships. However, since the predominant route expected for human exposure is via inhalation, oral data may be less relevant to ongoing exposure scenarios in humans.

Intermediate-Duration MRLs. The inhalation database is adequate to derive an intermediate-duration inhalation MRL. The oral database is inadequate to derive an intermediate-duration oral MRL due to a complete lack of data. Intermediate-duration oral studies examining a wide range of potential effects are needed to identify the most sensitive targets of toxicity and establish dose-response relationships. However, since the predominant route expected for human exposure is via inhalation, oral data may be less relevant to ongoing exposure scenarios in humans.

Chronic-Duration MRLs. The inhalation database is adequate to derive a chronic-duration inhalation MRL. No chronic-duration studies were located for other routes. Additional low-concentration studies designed to identify a NOAEL for the critical effect (neurotoxicity) could decrease uncertainty in the chronic-duration inhalation MRL. The oral database is inadequate to derive a chronic-duration oral MRL due to a complete lack of data. Chronic-duration oral studies examining a wide range of potential effects are needed to identify the most sensitive targets of toxicity and establish dose-response relationships. However, since the predominant route expected for human exposure is via inhalation, oral data may be less relevant to ongoing exposure scenarios in humans.

Health Effects. Chloromethane is a volatile chemical. Subsequently, the primary concern regarding toxicity relates to exposure via inhalation. However, chloromethane is ubiquitous in the environment. No studies evaluated dermal exposure to chloromethane and only one animal study looked at oral exposure and hepatic effects. Therefore, a data need for all endpoints includes information on health effects resulting from oral and dermal exposure. For inhalation studies, identification of data needs for health effects in animal studies is limited to targets included in the systematic review.

> *Cardiovascular.* While human case studies and one (presumably) highly exposed occupational cohort indicate that the cardiovascular system may be a target of chloromethane toxicity, supporting animal data are inconsistent or lacking. Human epidemiological studies and/or additional animal studies designed to evaluate cardiovascular toxicity following exposure, particularly cardiovascular function, may be useful. Data showing mechanisms of cardiovascular toxicity distinct from CNS depression would also be useful.

> *Hepatic.* The liver has been identified as a sensitive target following acute-, intermediate-, and chronic-duration inhalation exposure in animals, particularly in mice. Studies designed to determine the mechanism of hepatotoxicity could be useful for evaluating the apparent species sensitivity and determining potential human relevance of these findings.

Neurological. The nervous system, particularly the motor areas of the cerebellum and spinal cord, have been identified as sensitive targets of chloromethane exposure in animals. Additionally, neurotoxic effects in humans from inhalation exposure to chloromethane are described in numerous case studies and one (presumably) highly exposed occupational cohort study. The acute-duration inhalation database is considered adequate. However, additional animal studies evaluating neurological function following intermediate-duration inhalation exposure at low exposure concentrations would be useful to strengthen the confidence and provide dose-response data. Additional repeat-exposure, low-concentration studies designed to identify a NOAEL for neurological effects following chronic-duration exposure, particularly neurological function, are needed. Studies designed to determine the mechanism of neurotoxicity may also be useful.

Male Reproductive. One case study described potential reproductive effects (i.e., impotence) in an occupationally exposed individual; however, no data on exposure levels were provided. The male reproductive tract has been identified as a target of toxicity following acute-, intermediate-, and chronic-duration inhalation exposure in animals, particularly rats. Human epidemiological studies and/or additional animal studies designed to evaluate male reproductive toxicity, particularly reproductive function, following inhalation exposure may be useful. Evaluation of male reproductive function in a second species (e.g., mice) and studies designed to determine the mechanism of male reproductive toxicity may be useful.

Developmental. Developmental toxicity data from inhalation studies in animals report species differences in fetal toxicity as well as questions regarding the validity of reported heart defects in mice. Additional studies evaluating specialized developmental effects (e.g., cardiotoxicity, neurotoxicity) following developmental exposure, including immediate effects in neonates as well as potential adverse effects at later life stages (delayed effects from developmental exposure) may be useful. Studies designed to determine the mechanism(s) of developmental toxicity could be useful for evaluating the apparent species differences and determining potential human relevance of these findings.

Epidemiology and Human Dosimetry Studies. A small number of epidemiology studies evaluated the toxicity of chloromethane in populations exposed to chloromethane most often due to occupational or accidental releases. One study evaluated the impact of chloromethane exposure in high

traffic areas in subsets of the general population and found no association between asthma symptoms and chloromethane exposure (Delfino et al. 2003); however, the exposures were very low and were not expected to cause health effects. A common limitation of occupational studies is the lack of exposure information (Rafnsson and Kristbjornsdottir 2014) and the need to use job-exposure matrices to either estimate the exposure or assess whether exposure is or is not likely to have occurred in the populations with unknown or no direct individual exposure data (Barry et al. 2011; Dosemeci et al. 1999; Kernan et al. 1999). Several human controlled trials were conducted with chloromethane; however, in several studies, the protocols used were confusing and limited the interpretation of the results. Further, some human controlled trials had trouble with volunteer attrition. Therefore, additional studies in occupational populations that include individual exposure data across a range of industries and a range of exposure levels relevant to community exposure would be useful.

Biomarkers of Exposure and Effect.

Exposure. No biomarker that can be associated quantitatively with exposure to chloromethane has been identified (see Section 3.3.1). While methods are available for the analysis of chloromethane in blood, expired air, and breast milk and the metabolite S-methylcysteine in urine, quantitative relationships have not been established between exposure and measurement of chloromethane or S-methylcysteine in these biological media. Several studies have unsuccessfully tried to relate blood and alveolar air levels of chloromethane and urinary levels of S-methylcysteine with exposure (DeKok and Anthenius 1981; Nolan et al. 1985; Stewart et al. 1980; van Doorn et al. 1980). However, the blood and alveolar air levels of chloromethane and the urinary levels of S-methylcysteine are highly variable. The observed variability of metabolism (see the discussion of the metabolism of chloromethane in Section 3.1.3) suggests that a correlation of chloromethane levels in tissues with levels of chloromethane exposure is not likely to be found. It may be possible to use levels of yet unidentified metabolites in blood or urine as biomarkers of exposure. If reliable biomarkers of exposure were available, it would allow both investigators and reviewers to assess the accuracy and uncertainty of the methods used in toxicological studies. Furthermore, the ready availability of tested analytical methods for biomarkers, including sample preservation, would permit a standardized approach to the analysis of biological materials to assist in measuring human exposure and monitoring effects in humans.

Although Xu et al. (1990) reported low chloromethane reactivity with hemoglobin, protein adducts may still hold promise as potential biomarkers for chloromethane exposure. In view of

chloromethane's genotoxicity in short-term assays, an assay for a DNA adduct or indicator of oxidative damage to DNA from chloromethane exposure might also be pursued. Further studies are therefore needed to identify a metabolite or biomarker that can be used to monitor chloromethane exposure.

Effect. No biomarkers specific for the health effects of chloromethane are available. The predominant health effects associated with chloromethane exposure in humans are clinical signs of neurotoxicity; however, none of these signs are unique to chloromethane exposure. In the absence of reliable biomarkers or exposure to chloromethane, known or suspected exposure is needed to attribute signs and symptoms to chloromethane rather than another neurotoxicant.

Absorption, Distribution, Metabolism, and Excretion. Experimental inhalation studies in animals and humans indicate that chloromethane is rapidly taken up from the lungs into the blood, exhaled with rapid equilibrium, widely distributed throughout the body, extensively metabolized, incorporated into macromolecules, and either excreted as CO_2 or as metabolites in the urine (Dekant et al. 1995; Heck et al. 1982; Jager et al. 1988; Kornbrust and Bus 1983, 1984; Kornbrust et al. 1982; Landry et al. 1983a, 1983b; Putz-Anderson et al. 1981a, 1981b; Redford-Ellis and Gowenlock 1971a, 1971b; van Doorn et al. 1980; von Oettingen et al. 1949, 1950). Differences in the rate and extent of absorption, metabolic pathways, and disposition will have a profound effect on the toxicity of chloromethane. There are limited data on oral and dermal routes so it is unknown how chloromethane may distribute with these routes of exposure. However, the most likely exposure route for chloromethane is inhalation. Additional human and animal pharmacokinetic studies are needed to evaluate the potential for delivery of toxic levels of chloromethane to human target tissues from different routes of exposure and durations of exposure.

Comparative Toxicokinetics. Studies on the pharmacokinetics of chloromethane following inhalation exposure have been conducted in rats, mice, dogs, and humans (Dekant et al. 1995; Dodd et al. 1982; Heck et al. 1982; Jager et al. 1988; Kornbrust and Bus 1983, 1984; Kornbrust et al. 1982; Landry et al. 1983a, 1983b; NIOSH 1976; Putz-Anderson et al. 1981a, 1981b; Redford-Ellis and Gowenlock 1971a, 1971b; van Doorn et al. 1980; von Oettingen et al. 1949, 1950). The kinetics of chloromethane in humans were similar to those in rats and dogs, with data for each species consistent with a two-compartment model. Some species differences can be explained by differences in respiratory minute volumes and basal metabolic rates (rat >dog >human). Additional pharmacokinetic studies in different species and with different routes of exposure are needed to further evaluate the target tissues and the

differences in potential toxic metabolites. Additional studies are especially needed to resolve the relative importance of GSH conjugation and P450 oxidation to the toxicity of chloromethane. These studies should be performed in different tissues, species, sexes, and life stages to resolve potential differences. Additional studies are needed to evaluate the importance of varying levels of human endogenous erythrocyte GSH transferase to the toxicity of chloromethane (Warholm et al. 1994), and to the identification of potentially susceptible populations.

Children's Susceptibility. Data needs related to both prenatal and childhood exposures, and developmental effects expressed whether (prenatally or during childhood), are discussed in the Developmental Toxicity subsection above.

There have been no studies on whether children are differentially susceptible than adults to adverse health effects from a given amount or duration of exposure to chloromethane, or how chloromethane may affect the developing human fetus or the development of young children.

Only limited information is available from rat and mouse studies on potential effects in the developing young (see above in Data Needs for Developmental Toxicity). In one rat study (Wolkowski-Tyl et al. 1983a), at levels that also produced maternal toxicity, fetal effects consisted of reduced fetal body weight (10.1% in males, 10.4% in females), reduced crown rump length (4% in females), and reduced ossification in the metatarsals and phalanges, the centra of thoracic vertebrae, the pubis of the pelvic girdle, and the metatarsals of the hindlimbs. Wolkowski-Tyl et al. (1983a, 1983a, 1981b, 1983b) also found increased incidences of heart malformations in the fetuses of mouse dams exposed to 500 ppm chloromethane during GDs 6–17. In a letter to an editor, John-Greene et al. (1985) summarized results of an experiment where heart malformations were not found in fetuses of mouse dams exposed to lower concentrations of chloromethane during GDs 11.5–12.5 (John-Greene et al. 1985). Theuns-van Vliet (2016) exposed rabbits to up to 1,000 ppm of chloromethane and did not observe heart malformations. The developmental toxicity of chloromethane is therefore not classifiable and may be only relevant in mice, with species differences in susceptibility. Further studies are needed to determine potential adverse effects on development from maternal and fetal exposure to chloromethane.

There is limited information on the movement of chloromethane or its metabolites across the placenta, into the developing young, or into breast milk. Information on potential transplacental transfer is limited to studies in animals. Wolkowski-Tyl et al. (1983a, 1983b) noted from unpublished observations that mouse dams exposed to 100, 500, or 1,500 ppm chloromethane for 6 hours on GD 17 had significant

NPSH concentration reductions in both dams and fetuses, indicative of transplacental passage of chloromethane or its metabolites. Regarding nursing mothers, one study detected chloromethane in two of eight sample of human breast milk, but the potential source(s) of chloromethane exposure were not discussed (Pellizzari et al. 1982). Further studies are needed that examine the presence of chloromethane in breast milk samples that both quantify levels in breast milk as well as potential exposure sources and exposure levels. Since chloromethane is broken down and eliminated from the body very quickly in adults (Nolan et al. 1985) and animals (Landry et al. 1983a; von Oettingen et al. 1949), it is unlikely that chloromethane would be stored in maternal tissues and subsequently mobilized (i.e., released from stores) during pregnancy or lactation.

In adults, there appear to be two distinct populations with regard to metabolism and elimination of chloromethane. One population has higher amounts of the metabolizing enzyme, GST, and thus a higher rate of elimination of chloromethane from the body. The toxicity of chloromethane, however, is thought to result from toxic metabolites formed following the conjugation with GSH or from the depletion of GSH (Chellman et al. 1986b; Kornbrust and Bus 1983, 1984; Landry et al. 1985). It is anticipated that children would have a polymorphism similar to the adult population, although no specific data have been collected to test this hypothesis. If a polymorphism is present in children, then some children (i.e., those with higher levels of GST) would potentially be more susceptible to the toxic effects of chloromethane. Moreover, cytochrome P450 dependent metabolism of methanethiol may yield formaldehyde and formic acid whose carbon atoms can then enter the one-carbon pool for incorporation into macromolecules or formation of CO_2 (Heck et al. 1982; Kornbrust and Bus 1983). However, Jager et al. (1988) disputed this conclusion. Guengerich and Shimada (1991) suggested that the human cytochrome P450 enzyme 2El is a major catalyst in the oxidation of chloromethane. Formaldehyde may also be a direct product of chloromethane via oxidative dechlorination. Studies are therefore needed to evaluate the differences among and between children and adults for P450 and transferase levels and isoforms, and for differences in chloromethane metabolism.

There is only one PBPK model for chloromethane exposure based on data for GSTT1-deficient individuals. There are no reliable biomarkers of exposure for children (or adults), although clinical symptoms of drunkenness or food poisoning and a sweet odor of the breath may alert a physician to possible chloromethane exposure. Attempts to use urinary levels of S-methylcysteine as an indicator of chloromethane exposure have not been successful. Further studies are needed to evaluate the toxicokinetics of chloromethane and its metabolites in children and to develop reliable biomarkers of exposure and effects.

Physical and Chemical Properties. Data regarding physical and chemical properties are essential for assessing the partitioning of a chemical and its fate in the environment. Experimental data on physical and chemical properties are available for chloromethane, and many of these have methodology descriptions accompanying them so that accuracy of the data can be evaluated. The data on known physical and chemical properties form the basis of many of the input requirements for environmental models that predict the behavior of a chemical under specific conditions including hazardous waste landfills. There are no data needs relating to the information of chloromethane's physical and chemical properties.

Production, Import/Export, Use, Release, and Disposal. Production methods for chloromethane are well-described in the literature (including the patent literature) and there does not appear to be a need for further information.

Uses of chloromethane have been documented, although a detailed description of all uses in industry may be difficult to obtain. This information is useful for estimating the potential for environmental releases from manufacturing and use industries as well as the potential environmental burden; however, it is difficult to obtain this information in the detail desired since generally, it is CBI for those industries that manufacture chloromethane.

Data on chloromethane releases to air, water, and landfills, which can be used to estimate environmental burdens and potentially exposed populations, are obtained from EPA's TRI. Data from industries that are not required to report to the TRI are difficult to obtain and is a data need.

Limited data are available in the literature on disposal of chloromethane. Data on the disposal of chloromethane would be valuable in determining whether industrial activities pose an important source of human exposure to chloromethane.

As a hazardous air pollutant (HAP), chloromethane is regulated by the Clean Air Act (CAA). Chloromethane is also regulated under RCRA, CERCLA, and by OSHA.

Environmental Fate. The fate of chloromethane in air is well-described because extensive air photolysis and photo-oxidation studies are available that characterize these processes. Biodegradation studies in surface water and groundwater are not as complete. These kinds of studies are important

because they would provide information about fundamental removal mechanisms for chloromethane in the environment and might aid in understanding the behavior of chloromethane at hazardous waste sites or municipal landfills. The vapor pressure of chloromethane and its presence in groundwater suggest that these processes are important, particularly at hazardous waste sites, and may account for some of the losses of chloromethane from the site. Limited research suggests that common soil fungi may be able to generate chloromethane as well as to dehalogenate it, and thus degrade it. Since these wood rot fungi can also break down other halogenated aliphatic compounds, there is the possibility that some of the chloromethane found at waste sites could have been produced through the action of such fungi on other waste compounds. More research is needed to document the importance of these biodegradation mechanisms, and to determine whether the net effects tend toward a progressive reduction in the levels of chloromethane found in contaminated soils and sediments at waste sites.

Inferences based on modeling indicate that chloromethane is not expected to accumulate in sediment or biota. Measured values are needed to confirm (or refute) these predictions.

Bioavailability from Environmental Media. Experimental inhalation studies in animals and humans indicate that chloromethane is bioavailable from the atmosphere. Studies examining inhalation pathways and the bioavailability of chloromethane from water, soil, and other environmental media would be useful.

Food Chain Bioaccumulation. The log K_{ow} for chloromethane is in the range of 0.91–1.086 (see Table 4-2). Such low values generally mean that the BCF will be low, suggesting that chloromethane will not tend to concentrate in aquatic organisms. However, no information was identified on experimental determinations of BCF levels for chloromethane. Determinations of BCF values for organisms at various trophic levels are needed to estimate human dietary intake of chloromethane.

Exposure Levels in Environmental Media. Extensive environmental monitoring data are available for chloromethane in air, while the available data are very limited for drinking water, surface water, and groundwater. The air monitoring data describe the concentrations that populations are exposed to through inhalation of ambient air. The data for water are not sufficient to accurately characterize the concentrations of chloromethane present in drinking water, surface water, or groundwater. Almost no data are available for soils. These data are needed to determine the ambient concentrations of chloromethane so that exposure of the general population as well as of terrestrial and aquatic organisms can be estimated.

Reliable monitoring data for the levels of chloromethane in contaminated media at hazardous waste sites are needed to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. No recent exposure level data are available for the general population. A complete database is needed to determine the current exposure levels and to estimate the average daily dose associated with various scenarios (e.g., living near a hazardous waste site). The available NOES database of potential occupational exposures was assembled in the late 1980s and is outdated. Updated information in the format of this statistically-based database of potential occupational exposures would be helpful. An environmental media monitoring program may provide the necessary information for estimating environmental exposures, while workplace monitoring at use sites, using personal dosimeters and remote sensing devices, would probably provide useful workplace exposure information.

Exposures of Children. Chloromethane was detected in two of eight samples of mothers' milk from Bayonne and Jersey City, New Jersey; Bridgeville, Pennsylvania; and Baton Rouge, Louisiana (Pellizzari et al. 1982). No concentrations were reported, and no information was given concerning the potential source(s) of the chloromethane in the breast milk. Studies to determine current chloromethane residues and sources in breast milk of women in the general population and in the workforce are needed. Drinking water sources should be surveyed in areas near landfills where chloromethane has been detected at significant levels in recent years. Ingestion of chloromethane contaminated drinking water could be an important route of exposure in children since it may be used to prepare baby formula or baby food.

Current information on whether children are different in their weight-adjusted intake of chloromethane via oral and dermal exposures was not available. A study to determine this information is needed. Additionally, it is not known if children's exposure is impacted by pica behavior. Genetic polymorphisms have been seen in adults that affect chloromethane metabolism in adults. A study to examine the effect of this polymorphism in children would be useful.

6.3   ONGOING STUDIES

No ongoing studies were found that address the health effects of chloromethane (RePORTER 2022).

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding chloromethane in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs, which are substance-specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1.3 and Appendix A for detailed information on the MRLs for chloromethane.

Table 7-1. Regulations and Guidelines Applicable to Chloromethane

Agency	Description	Information	Reference
Air			
EPA	RfC	0.09 mg/m^3 (0.04 ppm)	EPA 2001
	Provisional peer reviewed toxicity values		EPA 2012b
	Subchronic provisional RfC	3 mg/m^3 (1 ppm)	
WHO	Air quality guidelines	0.018 mg/m^3 (0.009 ppm)	WHO 2000
Water & Food			
EPA	Drinking water standards		EPA 2018a
	1-day health advisory for a 10-kg child	9 mg/L	
	10-day health advisory for a 10-kg child	0.4 mg/L	
	Lifetime health advisory	No data	
	National primary drinking water regulations	No data	EPA 2009
	RfD	No data	EPA 2001
WHO	Drinking water quality guidelines	No data	WHO 2022
FDA	Substances Added to Food[a]	No data	FDA 2022
Cancer			
HHS	Carcinogenicity classification	No data	NTP 2021
EPA	Carcinogenicity classification	Group D[b]	EPA 2001
IARC	Carcinogenicity classification	Group 3[c]	IARC 1999
NIOSH	Carcinogenicity classification	Potential occupational carcinogen[d]	NIOSH 2019
Occupational			
OSHA	PEL (8-hour TWA) for general industry and shipyards	100 ppm	OSHA 2021a, 2021b
	Ceiling PEL for general industry	200 ppm; 300 ppm maximum peak (5 minutes in any 3 hours)	OSHA 2021a

Table 7-1. Regulations and Guidelines Applicable to Chloromethane

Agency	Description	Information	Reference
NIOSH	REL (up to 10-hour TWA)	Lowest feasible concentration[d]	NIOSH 2018, 2019
Emergency Criteria			
EPA	AEGLs-air		EPA 2018b
	AEGL 1[e]		
	10-minute	NR[f]	
	30-minute	NR	
	60-minute	NR	
	4-hour	NR	
	8-hour	NR	
	AEGL 2[e]		
	10-minute	1,100 ppm	
	30-minute	1,100 ppm	
	60-minute	910 ppm	
	4-hour	570 ppm	
	8-hour	380 ppm	
	AEGL 3[e]		
	10-minute	3,800 ppm	
	30-minute	3,800 ppm	
	60-minute	3,000 ppm	
	4-hour	1,900 ppm	
	8-hour	1,300 ppm	
DOE	PACs		DOE 2018a
	PAC-1[g]	150 ppm	
	PAC-2[g]	910 ppm	
	PAC-3[g]	3,000 ppm	

[a]The Substances Added to Food inventory replaces EAFUS and contains the following types of ingredients: food and color additives listed in FDA regulations, flavoring substances evaluated by FEMA or JECFA, GRAS substances listed in FDA regulations, substances approved for specific uses in food prior to September 6, 1958, substances that are listed in FDA regulations as prohibited from use in food, delisted color additives, and some substances "no longer FEMA GRAS."
[b]Group D: Not classifiable as to its human carcinogenicity.
[c]Group 3: Not classifiable as to its carcinogenicity to humans.
[d]NIOSH recommends wearing the most protective respirators for chloromethane at any detectable concentration.
[e]Definitions of AEGL terminology are available from U.S. EPA (2018c).
[f]NR: not recommended due to insufficient data.
[g]Definitions of PAC terminology are available from U.S. Department of Energy (DOE 2018b).

AEGL = acute exposure guideline levels; HHS = Department of Health and Human Services; DOE = Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FEMA = Flavor and Extract Manufacturers Association of the United States; GRAS = Generally Recognized As Safe; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; JECFA = Joint FAO/WHO Expert Committee on Food Additives; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = Protective Action Criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

ACGIH. 2012. TLVs and BEIs based on the documentation of the threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

Andrews AW, Zawistowski ES, Valentine CR. 1976. A comparison of the mutagenic properties of vinyl chloride and methyl chloride. Mutat Res 40(3):273-276. http://doi.org/10.1016/0165-1218(76)90054-9.

Asakura M, Sasaki T, Sugiyama T, et al. 2008. An improved system for exposure of cultured mammalian cells to gaseous compounds in the chromosomal aberration assay. Mutat Res 652(2):122-130. http://doi.org/10.1016/j.mrgentox.2008.01.004.

ATSDR. 1989. Decision guide for identifying substance-specific data needs related to toxicological profiles. Agency for Toxic Substances and Disease Registry. Fed Regist 54(174):37618-37634. https://www.govinfo.gov/content/pkg/FR-1989-09-11/pdf/FR-1989-09-11.pdf. September 14, 2022.

ATSDR. 2022. Chloromethane. SPL data. Agency for Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/SPL/resources. June 15, 2023.

Baird TT. 1954. Methyl chloride poisoning. Br Med J 2(4900):1353. http://doi.org/10.1136/bmj.2.4900.1353.

Baker HM. 1927. Intoxication with commercial methyl chloride: Report of a series of cases. JAMA 88(15):1137-1138. http://doi.org/10.1001/jama.1927.02680410013005.

Barnes DG, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessments. Regul Toxicol Pharmacol 8(4):471-486.

Barry KH, Zhang Y, Lan Q, et al. 2011. Genetic variation in metabolic genes, occupational solvent exposure, and risk of non-Hodgkin lymphoma. Am J Epidemiol 173(4):404-413. http://doi.org/10.1093/2Faje/2Fkwq360.

Battigelli MC, Perini A. 1955. [Two cases of acute poisoning with methyl chloride]. Med Lav 46(11):646-652. (Italian)

Beckett EM, Miller E, Unice K, et al. 2022. Evaluation of volatile organic compound (VOC) emissions from memory foam mattresses and potential implications for consumer health risk. Chemosphere 303(Pt 1):134945. http://doi.org/10.1016/j.chemosphere.2022.134945.

Borovska D, Jindrichova J, Klima M. 1976. [Methyl chloride poisoning in the country of East Bohemia]. Z Gesamte Hyg 22:241-245. (German)

Bradley PM, Journey CA, Romanok KM, et al. 2017a. Expanded target-chemical analysis reveals extensive mixed-organic-contaminant exposure in U.S. streams. Environ Sci Technol 51(9):4792-4802. http://doi.org/10.1021/acs.est.7b00012.

Bradley PM, Journey CA, Romanok KM, et al. 2017b. Supplemental material: Expanded target-chemical analysis reveals extensive mixed-organic-contaminant exposure in U.S. streams. Environ Sci Technol 51(9) http://doi.org/10.1021/acs.est.7b00012.

Bradley PM, Kolpin DW, Romanok KM, et al. 2018. Reconnaissance of mixed organic and inorganic chemicals in private and public supply tapwaters at selected residential and workplace sites in the United States. Environ Sci Technol 52(23):13972-13985. http://doi.org/10.1021/acs.est.8b04622.

Bringel F, Besaury L, Amato P, et al. 2019. Methylotrophs and methylotroph populations for chloromethane degradation. Curr Issues Mol Biol 33:149-172. http://doi.org/10.21775/cimb.033.149.

Brown KW, Donnelly KC. 1988. An estimation of the risk associated with the organic constituents of hazardous and municipal waste landfill leachates. Haz Waste Haz Mater 5(1):1-30. http://doi.org/10.1089/hwm.1988.5.1.

Burek JD, Potts WJ, Gushow TS, et al. 1981. Initial submission: Methyl chloride: 48 and 72 hour continuous inhalation exposure in rats followed by up to 12 days of recovery (final report) with letter dated 102591 (sanitized). Dow Chemical Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8E. OTS0534632. 889200001828. 8EHQ109115369.

https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0534632.xhtml. September 14, 2022.

Chaignaud P, Morawe M, Besaury L, et al. 2018. Methanol consumption drives the bacterial chloromethane sink in a forest soil. ISME J 12(11):2681-2693. http://doi.org/10.1038/s41396-018-0228-4.

Chapin RE, White RD, Morgan KT, et al. 1984. Studies of lesions induced in the testis and epididymis of F-344 rats by inhaled methyl chloride. Toxicol Appl Pharmacol 76(2):328-343. http://doi.org/10.1016/0041-008x(84)90014-0.

Chellman GJ, Morgan KT, Bus JS, et al. 1986a. Inhibition of methyl chloride toxicity in male F-344 rats by the anti-inflammatory agent BW755C. Toxicol Appl Pharmacol 85(3):367-379. http://doi.org/10.1016/0041-008x(86)90344-3.

Chellman GJ, White RD, Norton RM, et al. 1986b. Inhibition of the acute toxicity of methyl chloride in male B6C3F1 mice by glutathione depletion. Toxicol Appl Pharmacol 86(1):93-104. http://doi.org/10.1016/0041-008x(86)90402-3.

Chellman GJ, Bus JS, Working PK. 1986c. Role of epididymal inflammation in the induction of dominant lethal mutations in Fischer 344 rat sperm by methyl chloride. Proc Natl Acad Sci U S A 83(21):8087-8091. http://doi.org/10.1073/pnas.83.21.8087.

Chellman GJ, Hurtt ME, Bus JS, et al. 1987. Role of testicular versus epididymal toxicity in the induction of cytotoxic damage in Fischer-344 rat sperm by methyl chloride. Reprod Toxicol 1(1):25-35. http://doi.org/10.1016/0890-6238(87)90068-2.

Chen G, Kleindienst S, Griffiths DR, et al. 2017. Mutualistic interaction between dichloromethane- and chloromethane-degrading bacteria in an anaerobic mixed culture. Environ Microbiol 19(11):4784-4796. http://doi.org/10.1111/1462-2920.13945.

CIIT. 1981. Final report on a chronic inhalation toxicology study in rats and mice exposed to methyl chloride. Battelle-Columbus Laboratories. Submitted to the U.S. Environmental Protection Agency under section 4. 40-8120717. OTS0511310.

Clewell HJ, Andersen ME. 1985. Risk assessment extrapolations and physiological modeling. Toxicol Ind Health 1(4):111-131. http://doi.org/10.1177/2F074823378500100408.

Cox ML, Fraser PJ, Sturrock GA, et al. 2004. Terrestrial sources and sinks of halomethanes near Cape Grim, Tasmania. Atmos Environ 38(23):3839-3852. http://doi.org/10.1016/j.atmosenv.2004.03.050.

Crutzen PJ, Gidel LT. 1983. A two-dimensional photochemical model of the atmosphere. 2: The tropospheric budgets of the anthropogenic chlorocarbons, carbon monoxide, methane, chloromethane and the effect of various nitrogen oxides sources on the tropospheric ozone. J Geophys Res 88(C11):6641-6661. http://doi.org/10.1029/JC088iC11p06641.

Dekant W, Frischmann C, Speerschneider P. 1995. Sex, organ and species specific bioactivation of chloromethane by cytochrome P4502E1. Xenobiotica 25(11):1259-1265. http://doi.org/10.3109/00498259509046681.

DeKok AC, Anthenius WS. 1981. S-Methylcysteine no human metabolite of methylchloride. Dow Chemical Company. Submitted to the U.S. Environmental Protection Agency under TSCA section 8. OTS0215176. 878221209.

Delfino RJ, Gong H, Linn WS, et al. 2003. Asthma symptoms in Hispanic children and daily ambient exposures to toxic and criteria air pollutants. Environ Health Perspect 111(4):647-656. http://doi.org/10.1289/ehp.5992.

Derendorp L, Wishkerman A, Keppler F, et al. 2012. Methyl chloride emissions from halophyte leaf litter: dependence on temperature and chloride content Chemosphere 87(5):483-489. http://doi.org/10.1016/j.chemosphere.2011.12.035.

DHHS. 1995. Report to Congress on workers' home contamination study conducted under the Workers' Family Protection Act (29 U.S.C. 671a). Cincinnati, OH: U.S. Department of Health and Human Services. DHHS(NIOSH) Publication No. 95-123. https://www.cdc.gov/niosh/docs/95-123/default.html. September 14, 2022.

Dilling WL. 1982. Atmospheric environment. In: Conway RA, ed. Environmental risk analysis for chemicals. New York, NY: Van Nostrand Reinhold Co., 154-197.

Dodd DE, Bus JS, Barrow CS. 1982. Nonprotein sulfhydryl alterations in F-344 rats following acute methyl chloride inhalation. Toxicol Appl Pharmacol 62(2):228-236. http://doi.org/10.1016/0041-008x(82)90121-1.

DOE. 2018a. Table 3: Protective action criteria (PAC) rev. 29a based on applicable 60-minute AEGLs, ERPGs, or TEELs. The chemicals are listed by CASRN. June 2018. U.S. Department of Energy. https://edms3.energy.gov/pac/docs/Revision_29A_Table3.pdf. July 6, 2022.

DOE. 2018b. Protective action criteria (PAC) with AEGLs, ERPGs, & TEELs: Rev. 29A, June 2018. U.S. Department of Energy. https://edms3.energy.gov/pac/. July 6, 2022.

Doronina NV, Sokolov AP, Trotsenko YA. 1996. Isolation and initial characterization of aerobic chloromethane-utilizing bacteria. FEMS Microbiol Lett 142(2-3):179-183. http://doi.org/10.1111/j.1574-6968.1996.tb08427.x.

Dosemeci M, Cocco P, Chow WH. 1999. Gender differences in risk of renal cell carcinoma and occupational exposures to chlorinated aliphatic hydrocarbons. Am J Ind Med 36(1):54-59. http://doi.org/10.1002/(sici)1097-0274(199907)36:1%3C54::aid-ajim8%3E3.0.co;2-0.

Draper WM, Li N, Solomon GM, et al. 2022. Organic chemical contaminants in water system infrastructure following wildfire. ACS ES T Water 2(2):357-366. http://doi.org/10.1021/acsestwater.1c00401.

Dunn RC, Smith WW. 1947. Acute and chronic toxicity of methyl chloride. IV. Histopathologic observations. Arch Pathol 43(3):296-300.

DuPont. 1977. Mutagenic activity of methane, chloro- in the Salmonella/microsome assay with cover letter. E.I. Du Pont de Nemours and Co., Inc. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8DS. OTS0215036. 878220403. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0215036.xhtml. September 14, 2022.

ECHA. 2022. Registration dossier: Chloromethane; methyl chloride. European Chemicals Agency. https://echa.europa.eu/de/registration-dossier/-/registered-dossier/15768. September 16, 2022.

Edwards PR, Campbell I, Milne GS. 1982a. The impact of chloromethanes on the environment. Part 1. The atmospheric chlorine cycle. Chem Ind 16:574-578.

Elliot S, Rowland FS. 1995. Methyl halide hydrolysis rates in natural waters. J Atmos Chem 20(3):229-236. http://doi.org/10.1007/BF00694495.

EPA. 1975. Identification of organic compounds in effluents from industrial sources. Washington, DC: Environmental Protection Agency. EPA560375002. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=2000YZQK.txt. September 14, 2022.

EPA. 1980. Organic chemical manufacturing. Vol. 6: Selected processes. Research Triangle Park, NC: U.S. Environmental Protection Agency. EPA450380028a. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=9101OOB1.txt. September 14, 2022.

EPA. 1986. Method 8021B: Aromatic and halogenated volatiles by gas chromatography using photoionization and/or electrolytic conductivity detectors. U.S. Environmental Protection Agency.

EPA. 1995. Reportable quantity adjustments. U.S. Environmental Protection Agency. Fed Regist 60(112):30926-30962. https://www.govinfo.gov/content/pkg/FR-1995-06-12/html/X95-10612.htm. September 14, 2022.

EPA. 2001. Toxicological review of methyl chloride. Washington, DC: U.S. Environmental Protection Agency. EPA635R01003. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/1003tr.pdf. August 2, 2019.

EPA. 2005. Toxic chemical release inventory reporting forms and instructions: Revised 2004 version. Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986). U.S. Environmental Protection Agency. EPA260B05001. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P100EI4V.txt. September 14, 2022.

EPA. 2009. National primary drinking water regulations. Washington, DC: U.S. Environmental Protection Agency. EPA816F09004. https://www.epa.gov/sites/production/files/2016-06/documents/npwdr_complete_table.pdf. August 2, 2019.

EPA. 2011. Background indoor air concentrations of volatile organic compounds in North American residences (1990–2005): A compilation of statistics for assessing vapor intrusion. Washington, DC: U.S. Environmental Protection Agency. EPA530R10001. https://www.epa.gov/sites/production/files/2015-09/documents/oswer-vapor-intrusion-background-report-062411.pdf. August 2, 2019.

EPA. 2012a. EPI Suite™ - Estimation Programs Interface v4.11. U.S. Environmental Protection Agency. https://www.epa.gov/tsca-screening-tools/download-epi-suitetm-estimation-program-interface-v411. September 15, 2022.

EPA. 2012b. Provisional peer-reviewed toxicity values for chloromethane (CASRN 74-87-3). Cincinnati, OH: U.S. Environmental Protection Agency. EPA690R12008F. https://cfpub.epa.gov/ncea/pprtv/documents/Chloromethane.pdf. August 2, 2019.

EPA. 2016. The third unregulated contaminant monitoring rule (UCMR 3): Fact sheet for assessment monitoring (List 1 contaminants). U.S. Environmental Protection Agency. EPA815F16003. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P100OFUT.txt. September 14, 2022.

EPA. 2017a. Section 7412. Hazardous air pollutants. U.S. Environmental Protection Agency. United States Code. 42 U.S.C. § 7412. https://www.govinfo.gov/content/pkg/USCODE-2016-title42/pdf/USCODE-2016-title42-chap85-subchapI-partA-sec7412.pdf. September 14, 2022.

EPA. 2017b. The third unregulated contaminant monitoring rule (UCMR 3): Data summary, January 2017. Environmental Protection Agency. EPA815S17001. https://www.epa.gov/sites/production/files/2017-02/documents/ucmr3-data-summary-january-2017.pdf. August 2, 2019.

EPA. 2018a. 2018 Edition of the drinking water standards and health advisories. U.S. Environmental Protection Agency. EPA822F18001. https://www.epa.gov/system/files/documents/2022-01/dwtable2018.pdf. September 14, 2022.

EPA. 2018b. Compiled AEGL values. U.S. Environmental Protection Agency. https://www.epa.gov/sites/production/files/2018-08/documents/compiled_aegls_update_27jul2018.pdf. April 12, 2020.

EPA. 2018c. About acute exposure guideline levels (AEGLs). U.S. Environmental Protection Agency. https://www.epa.gov/aegl/about-acute-exposure-guideline-levels-aegls. July 26, 2018.

EPA. 2019. The ozone-depleting substances phaseout: 2020-2030. U.S. Environmental Protection Agency. https://www.epa.gov/sites/production/files/2019-12/documents/fact_sheet_0.pdf. August 2, 2019.

EPA. 2022a. Chemical data reporting. U.S. Environmental Protection Agency. https://www.epa.gov/chemical-data-reporting/access-cdr-data. September 15, 2022.

EPA. 2022b. 2017 National Emissions Inventory (NEI) data. U.S. Environmental Protection Agency. https://www.epa.gov/air-emissions-inventories/2017-national-emissions-inventory-nei-data. September 14, 2022.

EPA. 2022c. AQS data. U.S. Environmental Protection Agency. https://aqs.epa.gov/aqsweb/airdata/download_files.html. September 14, 2022.

Fabian P. 1986. Halogenated hydrocarbons in the atmosphere. In: Hutzinger O, ed. The handbook of environmental chemistry. Vol. 4. Berlin, Germany: Springer-Verlag, 23-51.

Farhan Ul Haque M, Besaury L, Nadalig T, et al. 2017. Correlated production and consumption of chloromethane in the Arabidopsis thaliana phyllosphere. Scientific Reports 7(1):17589. http://doi.org/10.1038/s41598-017-17421-y.

FDA. 2019. Substances added to food (formerly EAFUS). Washington, DC: U.S. Food and Drug Administration. https://www.accessdata.fda.gov/scripts/fdcc/?set=FoodSubstances&sort=Sortterm&order=ASC&startrow=1&type=basic&search=74-87-3. May 8, 2019.

8. REFERENCES

FDA. 2022. Substances added to food. U.S. Food and Drug Administration. https://www.cfsanappsexternal.fda.gov/scripts/fdcc/?set=FoodSubstances. January 24, 2022.

Filipiak W, Ruzsanyi V, Mochalski P, et al. 2012. Dependence of exhaled breath composition on exogenous factors, smoking habits and exposure to air pollutants. J Breath Res 6(3):036008. http://doi.org/10.1088/1752-7155/6/3/036008.

Fostel J, Allen PF, Bermudez E, et al. 1985. Assessment of the genotoxic effects of methyl chloride in human lymphoblasts. Mutat Res 155(1-2):75-81. http://doi.org/10.1016/0165-1218(85)90028-x.

Fridovich I. 1978. The biology of oxygen radicals. Science 201(4359):875-880. http://doi.org/10.1126/science.210504.

Gaskin S, Thredgold L, Heath L, et al. 2018. Empirical data in support of a skin notation for methyl chloride. J Occup Environ Hyg 15(8):569-572. http://doi.org/10.1080/15459624.2018.1470636.

Gidel LT, Crutzoen PJ, Fishman J. 1983. A two-dimensional photochemical model of the atmosphere. 1: Chlorocarbon emissions and their effect on stratospheric ozone. J Geophys Res 88(C11):6622-6640. http://doi.org/10.1029/JC088iC11p06622.

Goldstein BD, Witz G, Amoruso M, et al. 1979. Protease inhibitors antagonize the activation of polymorphonuclear leukocyte oxygen consumption. Biochem Biophys Res Commun 88(3):854-860. http://doi.org/10.1016/0006-291X(79)91487-6.

Goldstein BD, Witz G, Amoruso M, et al. 1981. Stimulation of human polymorphonuclear leukocyte superoxide anion radical production by tumor promoters. Cancer Lett 11(3):257-262. http://doi.org/10.1016/0304-3835(81)90117-8.

Granstrom ML, Ahlert RC, Wiesenfeld J. 1984. The relationships between the pollutants in the sediments and in the water of the Delaware and Raritan Canal. Water Sci Technol 16(5-7):375-380. http://doi.org/10.2166/wst.1984.0144.

Great Lakes Water Quality Board. 1983. Status report on the development of an inventory of chemical substances identified in the Great Lakes ecosystem. Appendix E: Draft. November 9, 1983. Great Lakes Water Quality Board Implementation Committee. https://scholar.uwindsor.ca/cgi/viewcontent.cgi?article=1316&context=ijcarchive. September 14, 2022.

Greenberg M, Anderson R, Keene J, et al. 1982. Empirical test of the association between gross contamination of wells with toxic substances and surrounding land use. Environ Sci Technol 16(1):14-19. http://doi.org/10.1021/es00095a007.

Gudmundsson G. 1977. Methyl chloride poisoning 13 years later. Arch Environ Health 32(5):236-237. http://doi.org/10.1080/00039896.1977.10667287.

Guengerich FP, Shimada T. 1991. Oxidation of toxic and carcinogenic chemicals by human cytochrome P-450 enzymes. Chem Res Toxicol 4(4):391-407. http://doi.org/10.1021/tx00022a001.

Hallier E, Deutschmann S, Reichel C, et al. 1990. A comparative investigation of the metabolism of methyl bromide and methyl iodide in human erythrocytes. Int Arch Occup Environ Health 62(3):221-225. http://doi.org/10.1007/bf00379437.

Hamm TE, Raynor TH, Phelps MC, et al. 1985. Reproduction in Fischer-344 rats exposed to methyl chloride by inhalation for two generations. Fundam Appl Toxicol 5(3):568-577. http://doi.org/10.1016/0272-0590(85)90104-6.

Hansen H, Weaver NK, Venable FS. 1953. Methyl chloride intoxication; report of fifteen cases. AMA Arch Ind Hyg Occup Med 8(4):328-334.

Harper DB. 1985. Halomethane from halide ion - a highly efficient fungal conversion of environmental significance. Nature 315(6014):55-57. http://doi.org/10.1038/315055a0.

Harper DB, Hamilton JTG. 1988. Biosynthesis of chloromethane in Phellinus pomaceus. J Gen Microbiol 134(10):2831-2839. http://doi.org/10.1099/00221287-134-10-2831.

Harper DB, Kennedy JT, Hamilton JTG. 1988. Chloromethane biosynthesis in poroid fungi. Phytochemistry 27(10):3147-3153. http://doi.org/10.1016/0031-9422(88)80017-7.

8. REFERENCES

Harper DB, Buswell JA, Kennedy JT, et al. 1990. Chloromethane, methyl donor in veratryl alcohol biosynthesis in Phanerochaete chrysosporium and other lignin-degrading fungi. Appl Environ Microbiol 56(11):3450-3457. http://doi.org/10.1128/aem.56.11.3450-3457.1990.

Hartman TL, Wacker W, Roll RM. 1955. Methyl chloride intoxication - report of two cases, one complicating pregnancy. N Engl J Med 253(13):552-554. http://doi.org/10.1056/nejm195509292531304.

Hartmans S, Schmuckle A, Cook AM, et al. 1986. Methyl chloride: Naturally occurring toxicant and C-1 growth substrate. J Gen Microbiol 132(4):1139-1142. http://doi.org/10.1099/00221287-132-4-1139.

Häsänen E, Soininen V, Pyysalo H, et al. 1979. On the occurrence of aliphatic chlorine and bromine compounds in automobile exhaust. Atmos Environ 13(8):1217-1219. http://doi.org/10.1016/0004-6981(79)90049-0.

Hatch GG, Mamay PD, Ayer ML, et al. 1982. Methods for detecting gaseous and volatile carcinogens using cell transformation assays. In: Tice RR, Costa DL, Schaich KM, eds. Genotoxic effects of airborne agents. Vol. 25. Boston, MA: Springer, 75-90.

Hatch GG, Mamay PD, Ayer ML, et al. 1983. Chemical enhancement of viral transformation in Syrian hamster embryo cells by gaseous and volatile chlorinated methanes and ethanes. Cancer Res 43(5):1945-1950.

Heck HD, White EL, Casanova-Schmitz M. 1982. Determination of formaldehyde in biological tissues by gas chromatography/mass spectrometry. Biomed Mass Spectrom 9(8):347-353. http://doi.org/10.1002/bms.1200090808.

Heppolette RL, Robertson RE, Steacie EWR. 1959. The neutral hydrolysis of the methyl halides. Proc R Soc Lond A Math Phys Sci 252(1269):273-285. http://doi.org/10.1098/rspa.1959.0152.

Holmes TM, Buffler PA, Holguin AH, et al. 1986. A mortality study of employees at a synthetic rubber manufacturing plant. Am J Ind Med 9(4):355-362. http://doi.org/10.1002/ajim.4700090407.

Horst A, Bonifacie M, Bardoux G, et al. 2019. Isotopic characterization (2H, 13C, 37Cl, 81Br) of abiotic degradation of methyl bromide and methyl chloride in water and implications for future studies. Environ Sci Technol 53(15):8813-8822. http://doi.org/10.1021/acs.est.9b02165.

Hsu CY, Chiang HC, Shie RH, et al. 2018. Ambient VOCs in residential areas near a large-scale petrochemical complex: Spatiotemporal variation, source apportionment and health risk. Environ Pollut 240:95-104. http://doi.org/10.1016/j.envpol.2018.04.076.

IARC. 1999. Methyl chloride. IARC monographs on the evaluation of carcinogenic risks to humans. Volume 71. Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide. Lyon, France: International Agency for Research on Cancer. https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono71.pdf. September 10, 2022.

IARC. 2019. Agents classified by the IARC monographs, volumes 1-123. International Agency for Research on Cancer.

IPCC. 1995. Climate change 1995: The science of climate change. Cambridge: Intergovernmental Panel on Climate Change. https://www.ipcc.ch/site/assets/uploads/2018/02/ipcc_sar_wg_I_full_report.pdf. September 14, 2022.

Jaeger N, Besaury L, Röhling AN, et al. 2018. Chloromethane formation and degradation in the fern phyllosphere. Sci Total Environ 634:1278-1287. http://doi.org/10.1016/j.scitotenv.2018.03.316.

Jager R, Peter H, Sterzel W, et al. 1988. Biochemical effects of methyl chloride in relation to its tumorigenicity. J Cancer Res Clin Oncol 114(1):64-70. http://doi.org/10.1007/bf00390487.

Jiang XZ, White R, Morgan KT. 1985. An ultrastructural study of lesions induced in the cerebellum of mice by inhalation exposure to methyl chloride. Neurotoxicology 6(1):93-103.

Johanson G, Jonsson F, Bois F. 1999. Development of new technique for risk assessment using physiologically based toxicokinetic models. Am J Ind Med Suppl 1:101-103. http://doi.org/10.1002/(sici)1097-0274(199909)36:1+%3C101::aid-ajim36%3E3.0.co;2-i.

8. REFERENCES

John-Greene JA, Welsch F, Bus JS. 1985. Comments on heart malformations in B6C3F1 mouse fetuses induced by methyl chloride--continuing efforts to understand the etiology and interpretation of an unusual lesion. Teratology 32(3):483-487. http://doi.org/10.1002/tera.1420320317.

Jones MA. 1942. Methyl chloride poisoning. Quart J Med 41:29-43.

Jonsson F, Bois FY, Johanson G. 2001. Assessing the reliability of PBPK models using data from methyl chloride-exposed, non-conjugating human subjects. Arch Toxicol 75(4):189-199. http://doi.org/10.1007/s002040100221.

Jury WA, Winer AM, Spencer WF, et al. 1987. Transport and transformation of organic chemicals in the soil-air-water ecosystem. Rev Environ Contam Toxicol 99:119-164. http://doi.org/10.1007/978-1-4613-8719-0_5.

Kavouras IG, DuBois DW, Nikolich G, et al. 2015. Monitoring, source identification and health risks of air toxics in Albuquerque, New Mexico, U.S.A. Aerosol Air Qual Res 15(2):556-571. http://doi.org/10.4209/aaqr.2014.04.0075.

Kegel AH, McNally WD, Pope AS. 1929. Methyl chloride poisoning from domestic refrigerators. J Am Med Assoc 93(5):353-358. http://doi.org/10.1001/jama.1929.02710050007003.

Kempkes M, Wiebel FA, Golka K, et al. 1996. Comparative genotyping and phenotyping of glutathione S-transferase GSTT1. Arch Toxicol 70(5):306-309. http://doi.org/10.1007/s002040050278.

Keppler F, Harper DB, Rockmann T, et al. 2005. New insight into the atmospheric chloromethane budget gained using stable carbon isotope ratios. Atmos Chem Phys 5(9):2403-2411. http://doi.org/10.5194/acp-5-2403-2005.

Keppler F, Fischer J, Sattler T, et al. 2017. Chloromethane emissions in human breath. Sci Total Environ 605-606:405-410. http://doi.org/10.1016/j.scitotenv.2017.06.202.

Keppler F, Röhling AN, Jaeger N, et al. 2020. Sources and sinks of chloromethane in a salt marsh ecosystem: constraints from concentration and stable isotope measurements of laboratory incubation experiments. Environ Sci Process Impacts 22(3):627-641. http://doi.org/10.1039/c9em00540d.

Kernan GJ, Ji B, Dosemeci M, et al. 1999. Occupational risk factors for pancreatic cancer: A case-control study based on death certificates from 24 U.S. states. Am J Ind Med 36(2):260-270. http://doi.org/10.1002/(sici)1097-0274(199908)36:2%3C260::aid-ajim5%3E3.0.co;2-p.

Khalil MAK, Rasmussen RA. 1999. Atmospheric methyl chloride. Atmos Environ 33(8):1305-1321. http://doi.org/10.1016/S1352-2310(98)00234-9.

Khindaria A, Grover TA, Aust SD. 1995. Reductive dehalogenation of aliphatic halocarbons by lignin peroxidase of Phanerochaete chrysosporium. Environ Sci Technol 29(3):719-725. http://doi.org/10.1021/es00003a020.

Kopfler FC, Melton RG, Mullaney JL, et al. 1977. Human exposure to water pollutants. Adv Environ Sci Technol 8:419-433.

Kornbrust DJ, Bus JS. 1983. The role of glutathione and cytochrome P-450 in the metabolism of methyl chloride. Toxicol Appl Pharmacol 67(2):1983. http://doi.org/10.1016/0041-008x(83)90231-4.

Kornbrust DJ, Bus JS. 1984. Glutathione depletion by methyl chloride and association with lipid peroxidation in mice and rats. Toxicol Appl Pharmacol 72(3):388-399. http://doi.org/10.1016/0041-008x(84)90115-7.

Kornbrust DJ, Bus JS, Doerjer G, et al. 1982. Association of inhaled [14C]methyl chloride with macromolecules from various rat tissues. Toxicol Appl Pharmacol 65(1):122-134. http://doi.org/10.1016/0041-008x(82)90370-2.

Kosson DS, Dienemann EA, Ahlert RC. 1985. Characterization and treatability studies of an industrial landfill leachate (KIN-BUC I). Proc Ind Waste Conf 39:329-341.

Krishnan K, Clewell HJ, Andersen ME. 1994. Physiologically-based pharmacokinetic modeling of chemical mixtures. In: Yang RSA, ed. Toxicology of chemical mixtures. New York, NY: Academic Press, 399-437.

Kröber E, Wende S, Kanukollu S, et al. 2021. 13C-chloromethane incubations provide evidence for novel bacterial chloromethane degraders in a living tree fern. Environ Microbiol 23(8):4450-4465. http://doi.org/10.1111/1462-2920.15638.

8. REFERENCES

Kröber E, Kanukollu S, Wende S, et al. 2022. A putatively new family of alphaproteobacterial chloromethane degraders from a deciduous forest soil revealed by stable isotope probing and metagenomics. Environ Microbiome 17(1):24. http://doi.org/10.1186/s40793-022-00416-2.

Krotoszynski BK, O'Neill HJ. 1982. Involuntary bioaccumulation of environmental pollutants in nonsmoking heterogeneous human population. J Environ Sci Health A Tox Hazard Subst Environ Eng 17(6):855-883. http://doi.org/10.1080/10934528209375082.

Landry TD, Ramsey JC, McKenna MJ. 1983b. Pulmonary physiology and inhalation dosimetry in rats: development of a method and two examples. Toxicol Appl Pharmacol 71(1):72-83. http://doi.org/10.1016/0041-008x(83)90046-7.

Landry TD, Gushow TS, Langvardt PW, et al. 1983a. Pharmacokinetics and metabolism of inhaled methyl chloride in the rat and dog. Toxicol Appl Pharmacol 68(3):473-486. http://doi.org/10.1016/0041-008X(83)90292-2.

Landry TD, Quast JF, Gushow TS, et al. 1985. Neurotoxicity of methyl chloride in continuously versus intermittently exposed female C57BL/6 mice. Fundam Appl Toxicol 5(1):87-98. http://doi.org/10.1016/0272-0590(85)90052-1.

Lanham JM. 1982. Methyl chloride: an unusual incident of intoxication. Can Med Assoc J 126(6):593.

Laughton PM, Robertson RE. 1956. Solvolysis in deuterium and hydrogen oxide. Can J Chem 34(12):1714-1718. http://doi.org/10.1139/v56-223.

Lestari F, Hayes AJ, Green AR, et al. 2011. An alternative method for in vitro fire smoke toxicity assessment of polymers and composites using human lung cells. Fire Mater 35(6):411-429. http://doi.org/10.1002/fam.1062.

Linge KL, Blair P, Busetti F, et al. 2012. Chemicals in reverse osmosis-treated wastewater: occurrence, health risk, and contribution to residual dissolved organic carbon. J Water Supply Res T 61(8):494-505. http://doi.org/10.2166/aqua.2012.047.

Liu R, Chen J, Li G, et al. 2017. Using an integrated decontamination technique to remove VOCs and attenuate health risks from an e-waste dismantling workshop. Chem Eng J 318:57-63. http://doi.org/10.1016/j.cej.2016.05.004.

Lof A, Johanson G, Rannug A, et al. 2000. Glutathione transferase T1 phenotype affects the toxicokinetics of inhaled methyl chloride in human volunteers. Pharmacogenetics 10(7):645-653. http://doi.org/10.1097/00008571-200010000-00007.

Logue JM, Price PN, Sherman MH, et al. 2012. A method to estimate the chronic health impact of air pollutants in U.S. residences. Environ Health Perspect 120(2):216-222. http://doi.org/10.1289/ehp.1104035.

Lurker PA, Clark CS, Elia VJ, et al. 1983. Worker exposure to chlorinated organic compounds from the activated-sludge wastewater treatment process. Am Ind Hyg Assoc J 44(2):109-112. http://doi.org/10.1080/15298668391404464.

Ma JJ, Zhu Hl, Zhao SP, et al. 2008. Impact of artificial waterfall using reclaimed water to VOCs and its health risk assessment. J Harbin Inst Technol 15(3):331-340.

Mabey W, Mill T. 1978. Critical review of hydrolysis of organic compounds in water under environmental conditions. J Phys Chem Ref Data 7(2):383-415. http://doi.org/10.1063/1.555572.

MacDonald JD. 1964. Methyl chloride intoxication. Report of 8 cases. J Occup Med 6:81-84.

Mackie IJ. 1961. Methyl chloride intoxication. Med J Aust 48(1):203-205. http://doi.org/10.5694/j.1326-5377.1961.tb82386.x.

Manca D, Birmingham B, Raha D. 1997. Toxicological screening of chemical emissions from municipal solid waste landfills. Application of a predictive framework to a state-of-the-art facility. Hum Ecol Risk Assess 3(2):257-286. http://doi.org/10.1080/10807039709383684.

McAnulla C, McDonald IR, Murrell JC. 2001. Methyl chloride utilising bacteria are ubiquitous in the natural environment. FEMS Microbiol Lett 201(2):151-155. http://doi.org/10.1111/j.1574-6968.2001.tb10749.x.

8. REFERENCES

McCulloch A, Aucott ML, Benkovitz CM, et al. 1999. Global emissions of hydrogen chloride and chloromethane from coal combustion, incineration and industrial activities: Reactive Chlorine Emissions Inventory. J Geophys Res 104(D7):8391-8403. http://doi.org/10.1029/1999JD900025.

McKenna MJ, Gushow TS, Bell TJ, et al. 1981a. Initial submission: Methyl chloride: A 72-hour continuous (abt 23-1/2 hr/day) inhalation toxicity study in dogs and cats (final report) w/attchmt & ltr dated 10/25/91 (sanitized). Dow Chemical Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8E. OTS0534633. 88900001839. 8EHQ109115379. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0534633.xhtml. September 14, 2022.

McKenna MJ, Burek JD, Henck JW, et al. 1981b. Methyl chloride: A 90-day inhalation toxicity study in rats, mice and beagle dogs. Dow Chemical Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 4. OTS0511317. 408120723. 47002B3B17. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0511317.xhtml. September 14, 2022.

McNally WD. 1946. Eight cases of methyl chloride poisoning with three deaths. J Ind Hyg Toxicol 28:94-97.

Minami M. 1998. Does industrial and environmental toxicology have relevance to forensic toxicology? J Toxicol Toxin Rev 17(1):39-55. http://doi.org/10.3109/15569549809006489.

Minami M, Katsumata M, Miyake K, et al. 1992. Dangerous mixture of household detergents in an old-style toilet: a case report with simulation experiments of the working environment and warning of potential hazard relevant to the general environment. Hum Exp Toxicol 11(1):27-34. http://doi.org/10.1177/096032719201100104.

Minami M, Inagaki H, Katsumata M, et al. 1993. Inhibitory action of chloramine on formate-metabolizing system. Studies suggested by an unusual case record. Biochem Pharmacol 45(5):1059-1064. http://doi.org/10.1016/0006-2952(93)90250-z.

Mitchell RI, Pavkov K, Everett RM, et al. 1979. A 90-day inhalation toxicology study in F-344 rats and B6C3F1 mice exposed to atmospheric methyl chloride gas. Columbus, OH: Battelle Columbus Laboratory.

Mohamed MF, Kang D, Aneja VP. 2002. Volatile organic compounds in some urban locations in United States. Chemosphere 47(8):863-882. http://doi.org/10.1016/s0045-6535(02)00107-8.

Moore RM. 2008. A photochemical source of methyl chloride in saline waters. Environ Sci Technol 42(6):1933-1937. http://doi.org/10.1021/es071920l.

Moore RM, Gut A, Andreae MO. 2005. A pilot study of methyl chloride emissions from tropical woodrot fungi. Chemosphere 58(2):221-225. http://doi.org/10.1016/j.chemosphere.2004.03.011.

Morgan A, Black A, Belcher DR. 1970. The excretion in breath of some aliphatic halogenated hydrocarbons following administration by inhalation. Ann Occup Hyg 13(4):219-233. http://doi.org/10.1093/annhyg/13.4.219.

Morgan KT, Swenberg JA, Hamm TE, et al. 1982. Histopathology of acute toxic response in rats and mice exposed to methyl chloride by inhalation. Fundam Appl Toxicol 2(6):293-299. http://doi.org/10.1016/S0272-0590(82)80008-0.

NAS/NRC. 1989. Biological markers in reproductive toxicology. National Academies of Science. National Research Council.

NIOSH. 1976. Behavioral and neurological effects of methyl chloride. Behavioral and neurological evaluation of workers exposed to industrial solvents: Methyl chloride. Cincinnati, OH: National Institute for Occupational Safety and Health. PB274770. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/PB274770.xhtml. August 8, 2022.

NIOSH. 1991. National occupational exposure survey 1981-1983. National Institute of Occupational Safety and Health.

NIOSH. 1994. Methyl chloride: Method 1001, Issue 2. NIOSH Manual of Analytical Methods (NMAM). National Institute of Occupational Safety and Health. https://www.cdc.gov/niosh/docs/2003-154/pdfs/1001.pdf. August 2, 2019.

8. REFERENCES

NIOSH. 2018. NIOSH Pocket guide to chemical hazards - Methyl chloride. National Institute for Occupational Safety and Health. https://www.cdc.gov/niosh/npg/npgd0403.html. August 2, 2019.

NIOSH. 2019. Methyl chloride. NIOSH pocket guide to chemical hazards. National Institute for Occupational Safety and Health. https://www.cdc.gov/niosh/npg/npgd0403.html. February 26, 2023.

Nolan RJ, Rick DL, Landry TD, et al. 1985. Pharmacokinetics of inhaled methyl chloride (CH3Cl) in male volunteers. Fundam Appl Toxicol 5(2):361-369. http://doi.org/10.1016/0272-0590(85)90084-3.

Novak BJ, Meinardi S, Blake DR. 2008. Methyl chloride and the U.S. cigarette. Nicotine Tob Res 10(11):1621-1625. http://doi.org/10.1080/14622200802410014.

NTP. 2013. Draft OHAT approach for systematic review and evidence integration for literature-based health assessments- February 2013. National Toxicology Program. https://ntp.niehs.nih.gov/ntp/ohat/evaluationprocess/draftohatapproach_february2013.pdf. August 2, 2019.

NTP. 2015. Handbook for conducting a literature-based health assessment using OHAT approach for systematic review and evidence integration. National Toxicology Program. https://ntp.niehs.nih.gov/ntp/ohat/pubs/handbookjan2015_508.pdf. August 2, 2019.

NTP. 2016. Substances listed in the fourteenth report on carcinogens. National Toxicology Program. http://ntp.niehs.nih.gov/go/roc. August 2, 2019.

NTP. 2019. Chemical effects in biological systems (CEBS): CASRN: 74-87-3: Ames conclusions. National Toxicology Program. https://cebs.niehs.nih.gov/cebs/. September 14, 2022.

NTP. 2021. CASRN index. In: Report on carcinogens. 15th ed. National Toxicology Program, https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html#P. January 10, 2022.

OSHA. 2018. Subpart Z - Toxic and hazardous substances. Air contaminants. Occupational Safety and Health Standards. Code of Federal Regulations. 29 CFR 1915.1000. https://www.govinfo.gov/app/details/CFR-2018-title29-vol7/CFR-2018-title29-vol7-sec1915-1000. August 2, 2019.

OSHA. 2021a. Occupational safety and health standards. Subpart Z - Toxic and hazardous substances. Air contaminants. Table Z-1: Limits for air contaminants. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000. https://www.govinfo.gov/content/pkg/CFR-2021-title29-vol6/pdf/CFR-2021-title29-vol6-sec1910-1000.pdf. August 28, 2022.

OSHA. 2021b. Occupational safety and health standards for shipyard employment. Subpart Z - Toxic and hazardous substances. Air contaminants. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1915.1000. https://www.govinfo.gov/content/pkg/CFR-2021-title29-vol7/pdf/CFR-2021-title29-vol7-sec1915-1000.pdf. August 28, 2022.

Page GW. 1981. Comparison of groundwater and surface water for patterns and levels of contamination by toxic substances. Environ Sci Technol 15(12):1475-1481. http://doi.org/10.1021/es00094a008.

Palmer TY. 1976. Combustion sources of atmospheric chlorine. Nature 263(5572):44-46. http://doi.org/10.1038/263044a0.

Pellizzari ED, Hartwell TD, Harris BS, et al. 1982. Purgeable organic compounds in mother's milk. Bull Environ Contam Toxicol 28(3):322-328. http://doi.org/10.1007/bf01608515.

Perkins AN, Inayat-Hussain SH, Deziel NC, et al. 2019. Evaluation of potential carcinogenicity of organic chemicals in synthetic turf crumb rubber. Environ Res 169:163-172. http://doi.org/10.1016/j.envres.2018.10.018.

Peter H, Deutschmann S, Reichel C, et al. 1989a. Metabolism of methyl chloride by human erythrocytes. Arch Toxicol 63(5):351-355. http://doi.org/10.1007/bf00303122.

Peter H, Deutschmann S, Muelle A, et al. 1989b. Different affinity of erythrocyte glutathione-S-transferase to methyl chloride in humans. Arch Toxicol Suppl 13:128-132. http://doi.org/10.1007/978-3-642-74117-3_17.

8. REFERENCES

Philbrick CA, Aggarwal SK, Puri IK. 1993. The extinction of methan/methyl chloride nonpremixed
    flames. Haz Waste Haz Mater 10(1):71-79. http://doi.org/10.1089/hwm.1993.10.71.

Pincince AB. 1988. Estimating volatile organic emissions from publicly owned treatment works. J
    Water Pollut Cont Fed 59:119-121.

Plumb RH. 1991. The occurrence of appendix IX organic constituents in disposal site ground water.
    Ground Water Monit Remediat 11(2):157-164. http://doi.org/10.1111/j.1745-6592.1991.tb00378.x.

PubChem. 2021. Compound summary. Vinyl chloride. National Library of Medicine.
    https://pubchem.ncbi.nlm.nih.gov/compound/6338. August 2, 2019.

PubChem. 2022. Compound summary: Chloromethane. National Library of Medicine.
    https://pubchem.ncbi.nlm.nih.gov/compound/6327. September 14, 2022.

Putz-Anderson V, Setzer JV, Croxton JS. 1981b. Effects of alcohol, caffeine and methyl chloride on
    man. Psychol Rep 48(3):715-725. http://doi.org/10.2466/pr0.1981.48.3.715.

Putz-Anderson V, Setzer JV, Croxton JS, et al. 1981a. Methyl chloride and diazepam effects on
    performance. Scand J Work Environ Health 7(1):8-13. http://doi.org/10.5271/sjweh.2563.

Rafnsson V, Gudmundsson G. 1997. Long-term follow-up after methyl chloride intoxication. Arch
    Environ Health 52(5):355-359. http://doi.org/10.1080/00039899709602211.

Rafnsson V, Kristbjornsdottir A. 2014. Increased cardiovascular mortality and suicide after methyl
    chloride exposure. Am J Ind Med 57(1):108-113. http://doi.org/10.1002/ajim.22243.

Redford-Ellis M, Gowenlock AH. 1971a. Studies on the reaction of chloromethane with human blood.
    Acta Pharmacol Toxicol (Copenh) 30(1):36-48. http://doi.org/10.1111/j.1600-0773.1971.tb00632.x.

Redford-Ellis M, Gowenlock AH. 1971b. Studies on the reaction of chloromethane with preparations of
    liver, brain and kidney. Acta Pharmacol Toxicol (Copenh) 30(1):49-58.
    http://doi.org/10.1111/j.1600-0773.1971.tb00633.x.

RePORTER. 2022. Chloromethane. Research Portfolio Online Reporting Tools. National Institutes of
    Health. https://reporter.nih.gov/advanced-search. August 2, 2019.

Reynolds ES, Yee AG. 1967. Liver parenchymal cell injury: V. Relationships between patterns of
    chloromethane-C14 incorporation into constituents of liver in vivo and cellular injury. Lab Invest
    16(4):591-603.

Rhew RC, Miller BR, Weiss RF. 2000. Natural methyl bromide and methyl chloride emissions from
    coastal salt marshes. Nature 403(6767):292-295. http://doi.org/10.1038/35002043.

Ristau C, Bolt HM, Vangala RR. 1989. Detection of DNA-protein crosslinks in the kidney of male
    B6C3F1 mice after exposure to methyl chloride. Arch Toxicol 13:243-245.
    http://doi.org/10.1007/978-3-642-74117-3_41.

Ristau C, Bolt HM, Vangala RR. 1990. Formation and repair of DNA lesions in kidneys of male mice
    after acute exposure to methyl chloride. Arch Toxicol 64(3):254-256.
    http://doi.org/10.1007/bf02010734.

Rodriguez C, Cook A, Van Buynder P, et al. 2007. Screening health risk assessment of micropullutants
    for indirect potable reuse schemes: a three-tiered approach. Water Sci Technol 56(11):35-42.
    http://doi.org/10.2166/wst.2007.831.

Rodriguez C, Linge K, Blair P, et al. 2012. Recycled water: potential health risks from volatile organic
    compounds and use of 1,4-dichlorobenzene as treatment performance indicator. Water Res
    46(1):93-106. http://doi.org/10.1016/j.watres.2011.10.032.

Rooney AA, Boyles AL, Wolfe MS, et al. 2014. Systematic review and evidence integration for
    literature-based environmental health science assessments. Environ Health Perspect 122(7):711-718.
    http://doi.org/10.1289/ehp.1307972.

Rudolph J, Khedim A, Koppmann R, et al. 1995. Field study of the emissions of methyl chloride and
    other halocarbons from biomass burning in Western Africa. J Atmos Chem 22(1-2):67-80.
    http://doi.org/10.1007/BF00708182.

Rushbrook CJ. 1984. Evaluation of toxicological test methods used in estimating potential human health
    hazards. Dominant lethal study of chloromethane in rats. U.S. Environmental Protection Agency.
    OTS0511319. 408220726. 47002B3B19.

https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0511319.xhtml. September 14, 2022.

Sabel GV, Clark TP. 1984. Volatile organic compounds as indicators of municipal solid waste leachate contamination. Waste Manag Res 2(2):119-130. http://doi.org/10.1016/0734-242X(84)90135-6.

Saxena D, Aouad S, Attieh J, et al. 1998. Biochemical characterization of chloromethane emission from the wood-rotting fungus Phellinus pomaceus. Appl Environ Microbiol 64(8):2831-2835. http://doi.org/10.1128/aem.64.8.2831-2835.1998.

Scharnweber HC, Spears GN, Cowles SR. 1974. Chronic methyl chloride intoxication in six industrial workers. J Occup Med 16(2):112-113.

Shah JJ, Singh HB. 1988. Distribution of volatile organic chemicals in outdoor and indoor air: a national VOCs data base. Environ Sci Technol 22(12):1381-1388. http://doi.org/10.1021/es00177a001.

Shuckrow AJ, Pajah AP, Touhill CJ. 1982. Chloromethane. In: Hazardous waste leachate management manual, Appendix A. Park Ridge, NJ: Noyes Data Corporation, 126-149.

Sieber WK, Sundin DS, Frazier TM, et al. 1991. Development, use, and availability of a job exposure matrix based on national occupational hazard survey data. Am J Ind Med 20(2):163-174. http://doi.org/10.1002/ajim.4700200204.

Simmon VF, Kauhanen K, Tardiff RG. 1977. Mutagenic activity of chemicals identified in drinking water. Dev Toxicol Environ Sci 2:249-258.

Singh HB, Salas LJ, Stiles RE. 1982. Distribution of selected gaseous organic mutagens and suspect carcinogens in ambient air. Environ Sci Technol 16(12):872-880. http://doi.org/10.1021/es00106a010.

Singh HB, Salas LJ, Stiles RE. 1983. Methyl halides in and over the eastern Pacific (40°N–32°S). J Geophys Res 88(C6):3684-3690. http://doi.org/10.1029/JC088iC06p03684.

Singh HB, Salas L, Shigeishi H, et al. 1977. Urban-nonurban relationships of halocarbons, SF6, N2O, and other atmospheric trace constituents. Atmos Environ (1967) 11(9):819-828. http://doi.org/10.1016/0004-6981(77)90044-0.

Singh HB, Salas LJ, Shigeishi H, et al. 1979. Atmospheric halocarbons, hydrocarbons, and sulfur hexafluoride: global distributions, sources, and sinks. Science 203(4383):899-903. http://doi.org/10.1126/science.203.4383.899.

Singh HB, Salas LJ, Smith AJ, et al. 1981. Measurements of some potentially hazardous organic chemicals in urban environments. Atmos Environ 15(4):601-612. http://doi.org/10.1016/0004-6981(81)90191-8.

Sleiman M, Logue JM, Luo W, et al. 2014. Inhalable constituents of thirdhand tobacco smoke: Chemical characterization and health impact considerations. Environ Sci Technol 48(22):13093-13101. http://doi.org/10.1021/es5036333.

Smith WW. 1947. The acute and chronic toxicity of methyl chloride. III. Hematology and biochemical studies. J Ind Hyg Toxicol 29(3):185-189.

Smith WW, von Oettingen WF. 1947a. The acute and chronic toxicity of methyl chloride: I. Mortality resulting from exposures to methyl chloride in concentrations of 4,000 to 300 parts per million. J Ind Hyg Toxicol 29(1):47-52.

Smith WW, von Oettingen WF. 1947b. The acute and chronic toxicity of methyl chloride: II. Symptomatology of animals poisoned by methyl chloride. J Ind Hyg Toxicol 29(2):123-128.

Smith JH, Mabey WR, Bohonos N, et al. 1977. Environmental pathways of selected chemicals in freshwater systems part 1: Background and experimental procedures. Athens, GA: U.S. Environmental Protection Agency. EPA600777113. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=9101ZFCE.txt. August 2, 2019.

Snider EH, Manning FS. 1982. A survey of pollutant emission levels in wastewaters and residuals from the petroleum refining industry. Environ Int 7(4):237-258. http://doi.org/10.1016/0160-4120(82)90114-3.

Spevak L, Nadj V, Felle D. 1976. Methyl chloride poisoning in four members of a family. Br J Ind Med 33(4):272-274. http://doi.org/10.1136/oem.33.4.272.

8. REFERENCES

Steinemann A. 2015. Volatile emissions from common consumer products. Air Qual Atmos Health 8(3):273-281. http://doi.org/10.1007/s11869-015-0327-6.

Stewart RD, Hake CL, Wu A, et al. 1980. Methyl chloride: Development of a biologic standard for the industrial worker by breath analysis. Milwaukee, WI: National Institute for Occupational Safety & Health. PB8116786. Report No.: NIOSH-MCOW-ENVM-MCM-77-1. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/PB81167686.xhtml. September 14, 2022.

Stirling DI, Dalton H. 1979. The fortuitous oxidation and cometabolism of various carbon compounds by whole-cell suspensions of Methylococcus capsulatus (Bath). FEMS Microbiol Lett 5(4):315-318. http://doi.org/10.1111/j.1574-6968.1979.tb03329.x.

Taylor PH, Dellinger B. 1988. Thermal degradation characteristics of chloromethane mixtures. Environ Sci Technol 22(4):438-447. http://doi.org/10.1021/es00169a012.

Theuns-van Vliet JG. 2016. A prenatal development study in New Zealand white rabbits with methyl chloride by inhalation. Utrecht, Netherlands: Triskelion.

Thier R, Wiebel FA, Hinkel A, et al. 1998. Species differences in the glutathione transferase GSTT1-1 activity towards the model substrates methyl chloride and dichloromethane in liver and kidney. Arch Toxicol 72(10):622-629. http://doi.org/10.1007/s002040050552.

TRI20. 2022. Toxics Release Inventory (TRI) program. U.S. Environmental Protection Agency. https://www.epa.gov/enviro/tri-search. May 26, 2022.

TRI21. 2022. Toxics Release Inventory (TRI) program. U.S. Environmental Protection Agency. https://www.epa.gov/enviro/tri-search. May 26, 2022.

Tsai WT. 2017. Fate of chloromethanes in the atmospheric environment: Implications for human health, ozone formation and depletion, and global warming impacts. Toxics 5(4):23. http://doi.org/10.3390/toxics5040023.

U.S. Census Bureau. 2018. Trade definitions. U.S. Census Bureau. https://www.census.gov/foreign-trade/reference/definitions/index.html#general_imports. May 2, 2019.

UNEP. 1999. Synthesis of the reports of the scientific, environmental effects, and technology and economic assessment panels of the Montreal Protocol, a decade of assessments for decision makers regarding the protection of the ozone layer: 1988 - 1999. United Nations Environment Programme. https://ozone.unep.org/sites/default/files/2019-05/Synthesis-Complete.pdf. May 2, 2019.

University of Wisconsin. 1986. Drosophila sex linked recessive lethal test on chloromethane. University of Wisconsin. Submitted to the U.S. Environmental Protection Agency under TSCA Section 4. OTS0511305. 408320709. 47002B3B2. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0511305.xhtml. September 14, 2022.

USGS. 2014. Water quality in principal aquifers of the United States, 1991–2010. Reston, VA: U.S. Geological Survey. Circular 1360. https://pubs.er.usgs.gov/publication/cir1360. December 1, 2022.

USGS. 2015. The Reston groundwater dating laboratory: Low-level VOCs lab. U.S. Geological Survey. https://water.usgs.gov/lab/voc/lab/. August 5, 2019.

USITC. 2019. Chloromethane import and export data. United States International Trade Commission. https://dataweb.usitc.gov/. August 2, 2019.

Vallero DA. 2014. Dynamics within an organism. In: Fundamentals of air pollution. 5th ed. New York, NY: Elsevier Science, 469.

van Doorn R, Borm PJ, Leijdekkers CM, et al. 1980. Detection and identification of S-methylcysteine in urine of workers exposed to methyl chloride. Int Arch Occup Environ Health 46(2):99-109. http://doi.org/10.1007/BF00378189.

Van Winkle MR, Scheff PA. 2001. Volatile organic compounds, polycyclic aromatic hydrocarbons and elements in the air of ten urban homes. Indoor Air 11(1):49-64. http://doi.org/10.1034/j.1600-0668.2001.011001049.x.

Vannelli T, Studer A, Kertesz M, et al. 1998. Chloromethane metabolism by methylobacterium sp. strain CM4. Appl Environ Microbiol 64(5):1933-1936. http://doi.org/10.1128/AEM.64.5.1933-1936.1998.

Venkataramani ES, Ahlert RC, Corbo P. 1984. Biological treatment of landfill leachates. CRC Crit Rev Environ Control 14:333-376. http://doi.org/10.1080/10643388409381723.

Verriere MP, Vachez M. 1949. [Gravely acute nephrotoxicity after poisoning by methyl chloride]. Lyon Med 1:296-297. (French)

von Oettingen WF, Powell CC, Sharpless NE, et al. 1949. Relation between the toxic action of chlorinated methanes and their chemical and physicochemical properties. Washington, DC: National Institutes of Health. NIH Bulletin No. 191.

von Oettingen WF, Powell CC, Sharpless NE, et al. 1950. Comparative studies of the toxicity and pharmacodynamic action of chlorinated methanes with special reference to their physical and chemical characteristics. Arch Int Pharmacodyn Ther 81(1):17-34.

von Raalte HGS, van Velzen HGECT. 1945. Methyl chloride intoxication. Ind Med 14:707-709.

Wang Z, Minami M. 1996. Effects of chloramine on neuronal cholinergic factors: Further studies of toxicity mechanism suggested by an unusual case record. Biog Amines 12(3):213-223.

Warholm M, Alexandrie AK, Hogberg J, et al. 1994. Polymorphic distribution of glutathione transferase activity with methyl chloride in human blood. Pharmacogenetics 4(6):307-311.

Warholm M, Rane A, Alexandrie A-K, et al. 1995. Genotypic and phenotypic determination of polymorphic glutathione transferase Tl in a Swedish population. Pharmacogenetics 5:252-254.

Weinstein A. 1937. Methyl chloride (refrigerator) gas poisoning: an industrial hazard. J Am Assoc 108(19):1603-1605. http://doi.org/10.1001/jama.1937.02780190019008.

Weisel CP, Alimokhtari S, Sanders PF. 2008. Indoor air VOC concentrations in suburban and rural New Jersey. Environ Sci Technol 42(22):8231-8238. http://doi.org/10.1021/es8005223.

Weitzman SA, Stossel TP. 1981. Mutation caused by human phagocytes. Science 212(4494):546-547. http://doi.org/10.1126/science.6259738.

WHO. 1999. Vinyl chloride. Geneva, Switzerland: World Health Organization. Environmental Health Criteria 215. https://inchem.org/documents/ehc/ehc/ehc215.htm. September 14, 2022.

WHO. 2000. Concise international chemical assessment document 28: Methyl chloride. Geneva, Switzerland: World Health Organization. https://apps.who.int/iris/bitstream/handle/10665/42324/9241530286.pdf?sequence=1&isAllowed=y. August 2, 2019.

WHO. 2022. Guidelines for drinking-water quality. Fourth edition incorporating the first and second addenda. World Health Organization. https://www.who.int/publications/i/item/9789240045064. June 22, 2022.

Wolkowski-Tyl R. 1985. Response to comments on heart malformations in B6C3F1 mouse fetuses induced by methyl chloride - continuing efforts to understand the etiology and interpretation of an unusual lesion. Teratology 32(3):489-492. http://doi.org/10.1002/tera.1420320318.

Wolkowski-Tyl R, Phelps MC, Barrow CS. 1981a. Structural teratogenicity evaluation of methyl chloride in rats and mice after inhalation exposure. Chemical Industry Institute of Toxicology. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8. OTS0205952. 878212062. Docket No. 12512.

Wolkowski-Tyl R, Phelps M, Davis JK. 1983a. Structural teratogenicity evaluation of methyl chloride in rats and mice after inhalation exposure. Teratology 27(2):181-195. http://doi.org/10.1002/tera.1420270206.

Wolkowski-Tyl R, Lawton AD, Marr MC, et al. 1981b. Methyl chloride structural teratogenicity evaluation in B6C3F1 mice. Chemical Industry Institute of Toxicology. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8DS. OTS84003A. 878212063.

Wolkowski-Tyl R, Lawton AD, Phelps M, et al. 1983b. Evaluation of heart malformations in B6C3F1 mouse fetuses induced by in utero exposure to methyl chloride. Teratology 27(2):197-206. http://doi.org/10.1002/tera.1420270207.

8. REFERENCES

Wood MW. 1951. Cirrhosis of the liver in a refrigeration engineer attributed to methyl chloride. Lancet 1(6653):508-509. http://doi.org/10.1016/s0140-6736(51)91979-4.

Woodruff TJ, Axelrad DA, Caldwell J, et al. 1998. Public health implications of 1990 air toxics concentrations across the United States. Environ Health Perspect 106(5):245-251. http://doi.org/10.1289/2Fehp.98106245.

Working PK, Bus JS. 1986. Failure of fertilization as a cause of preimplantation loss induced by methyl chloride in Fischer 344 rats. Toxicol Appl Pharmacol 86(1):124-130. http://doi.org/10.1016/0041-008x(86)90405-9.

Working PK, Chellman GJ. 1989. The use of multiple endpoints to define the mechanism of action of reproductive toxicants and germ cell mutagens. Prog Clin Biol Res 302:211-224.

Working PK, Bus JS, Hamm TE. 1985a. Reproductive effects of inhaled methyl chloride in the male Fischer 344 rat. I. Mating performance and dominant lethal assay. Toxicol Appl Pharmacol 77(1):133-143. http://doi.org/10.1016/0041-008x(85)90274-1.

Working PK, Bus JS, Hamm TE. 1985b. Reproductive effects of inhaled methyl chloride in the male Fischer 344 rat. II. Spermatogonial toxicity and sperm quality. Toxicol Appl Pharmacol 77(1):144-157. http://doi.org/10.1016/0041-008X(85)90275-3.

Working PK, Doolittle DJ, Smith-Oliver T, et al. 1986. Unscheduled DNA synthesis in rat tracheal epithelial cells, hepatocytes and spermatocytes following exposure to methyl chloride in vitro and in vivo. Mutat Res 162(2):219-224. http://doi.org/10.1016/0027-5107(86)90088-6.

WQP. 2022. Water quality portal: Chloromethane. National Water Quality Monitoring Council. https://www.waterqualitydata.us/. September 16, 2022.

Xing L, Wang L, Zhang R. 2018. Characteristics and health risk assessment of volatile organic compounds emitted from interior materials in vehicles: a case study from Nanjing, China. Environ Sci Pollut Res Int 25(15):14789-14798. http://doi.org/10.1007/s11356-018-1661-7.

Xu DG, Peter H, Hallier E, et al. 1990. Hemoglobin adducts of monohalomethanes. Ind Health 28(3):121-123. http://doi.org/10.2486/indhealth.28.121.

Yokouchi Y, Noijiri Y, Barrie LA, et al. 2000. A strong source of methyl chloride to the atmosphere from tropical coastal land. Nature 403(6767):295-298. http://doi.org/10.1038/35002049.

Yokouchi Y, Ikeda M, Inuzuka Y, et al. 2002. Strong emission of methyl chloride from tropical plants. Nature 416(6877):163-165. http://doi.org/10.1038/416163a.

Yokouchi Y, Saito T, Ishigaki C, et al. 2007. Identification of methyl chloride-emitting plants and atmospheric measurements on a subtropical island. Chemosphere 69(4):549-553. http://doi.org/10.1016/j.chemosphere.2007.03.028.

Zafiriou OC. 1975. Reaction of methyl halides with seawater and marine aerosols. J Mar Res 33:75-81.

Zhang W, Jiao Y, Zhu R, et al. 2020. Methyl chloride and methyl bromide production and consumption in coastal Antarctic tundra soils subject to sea animal activities. Environ Sci Technol 54(20):13354-13363. http://doi.org/10.1021/acs.est.0c04257.

Zitomer DH, Speece RE. 1995. Methanethiol in nonacclimated sewage sludge after addition of chloroform and other toxicants. Environ Sci Technol 29(3):762-768. http://doi.org/10.1021/es00003a025.

APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

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Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Office of Innovation and Analytics, Toxicology Section, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Office of Innovation and Analytics, Toxicology Section, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S106-5, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name:	Chloromethane
CAS Numbers:	74-87-3
Date:	September 2023
Profile Status:	Final
Route:	Inhalation
Duration:	Acute
MRL:	0.5 ppm (1 mg/m^3)
Critical Effect:	Degenerative changes in the cerebellum granule cells
Reference:	Landry et al. (1985)
Point of Departure:	NOAEL of 50 ppm (NOAEL$_{HEC}$ of 46 ppm)
Uncertainty Factor:	30
Modifying Factor:	3
LSE Graph Key:	26
Species:	Mouse

MRL Summary: An acute-duration inhalation MRL of 0.5 ppm was derived for chloromethane based on neurological effects including moderate degenerative changes in the cerebellum granule cells with nuclear pyknosis and karyorrhexis in female C57BL/6 mice following exposure to chloromethane for 22 hours/day for 11 days (Landry et al. 1985). The MRL is based on a NOAEL of 50 ppm, which was adjusted to a human equivalent concentration (NOAEL$_{HEC}$) of 46 ppm and divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability) and a modifying factor of 3 to account for the steepness of the dose-response curve.

Selection of the Critical Effect: Based on systematic review (see Appendix C), it was determined that hepatic, neurological, and male reproductive effects were presumed health effects associated with inhalation exposure. These presumed health effects were subsequently the focus of the acute-duration MRL evaluation.

For presumed health effects, the lowest reported LOAELs and serious LOAELs from acute-duration inhalation studies were reviewed to determine the most sensitive effects (Table A-1). Since studies used a variety of exposure paradigms, ranging from intermittent exposure (5.5 or 6 hours/day) to continuous or near-continuous exposure (22–24 hours/day), LOAELs and serious LOAELs were adjusted for continuous exposure. The lowest reported duration-adjusted LOAELs and serious LOAELs were 92 and 486 ppm, respectively, for neurological effects; 92 and 375 ppm, respectively, for hepatic effects; and 501 and 500 ppm, respectively, for male reproductive effects. Based on duration-adjusted values, the lowest LOAELs are comparable for neurological and hepatic effects, and the severity of effects show a comparable dose-response curve. Therefore, both the nervous and hepatic systems are considered sensitive targets of chloromethane toxicity. However, the human evidence (predominantly from case reports) shows that neurological effects are the main observed adverse outcome after accidental acute-duration exposure to chloromethane (Baird 1954; Baker 1927; Battigelli and Perini 1955; Borovska et al. 1976; Hansen et al. 1953; Hartman et al. 1955; Jones 1942; Kegel et al. 1929; MacDonald 1964; McNally 1946; Minami 1998; Spevak et al. 1976; von Raalte and van Velzen 1945; Wood 1951). Therefore, neurological effects are selected as the critical effect for the acute-duration inhalation MRL.

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Table A-1. Selected NOAEL and LOAEL Values Following Acute-Duration Inhalation Exposure to Chloromethane

Species	Duration	NOAEL (NOAEL$_{ADJ}$) (ppm)	LOAEL (LOAEL$_{ADJ}$) (ppm)	Effect	Reference
Neurological effects					
C57BL/6 mouse	11 days 22 hours/day	50 (46)	100 (92)	Slight cerebellar granule cell degeneration	Landry et al. 1985
C57BL/6 mouse	11 days 5.5 hours/day	150 (34)	400 (92)	Slight cerebellar granule cell degeneration	Landry et al. 1985
Beagle dog	3 days 23.5 hours/day	197 (193)	496 (486) (SLOAEL)	Severe clinical signs of neurotoxicity; lesions in brain and spinal cord; axonal loss	McKenna et al. 1981a
Swiss, Strain A, C3H mouse	2 weeks 6 hours/day 6 days/week	300 (64)	500 (107) (SLOAEL)	Neuromuscular abnormalities, impaired gait, hindlimb drag	Smith and von Oettingen 1947b
Dog (NS)	2 weeks 6 hours/day 6 days/week	300 (64)	500 (107) (SLOAEL)	Tremors, spasticity, impaired gait	Smith and von Oettingen 1947b
C57BL/6 mouse	12 days 6 hours/day GDs 6–17	251 (63)	502 (126) (SLOAEL)	Ataxia in dams	Wolkowski-Tyl et al. 1981b, 1983b
Hepatic effects					
C57BL/6 mouse	11 days 22 hours/day	50 (46)	100 (92)	Decreased hepatocyte size; glycogen depletion	Landry et al. 1985
C57BL/6 mouse	11 days 5.5 hours/day	150 (34)	400 (92)	Decreased hepatocyte size; glycogen depletion	Landry et al. 1985
C57BL/6 or C3H mouse	12 days 6 hours/day	ND	500 (125)	Minimal hepatocellular degeneration	Morgan et al. 1982
Sprague-Dawley rat	48 hours continuous	ND	196 (196)	Decreased liver weight	Burek et al. 1981
Sprague-Dawley rat	72 hours continuous	ND	198 (198)	Decreased absolute and relative liver weight and altered tinctorial[a] appearance in males, lipid accumulation in females	Burek et al. 1981
Guinea pig	6 days 6 hours/day	500	1,000 (250)	Fatty metamorphosis	Dunn and Smith 1947
B6C3F1 mouse	6 hours	ND	1,500 (375) (SLOAEL)	Hepatocellular necrosis and cytoplasmic vacuolization; increased serum ALT	Chellman et al. 1986b
Male reproductive effects					
Sprague-Dawley rat	48 hours continuous	196 (196)	501 (501)	Testicular lesions, decreased sperm in the lumen	Burek et al. 1981
Sprague-Dawley rat	72 hours continuous	198 (198)	504 (504)	Testicular lesions, decreased sperm in the lumen	Burek et al. 1981

APPENDIX A

Table A-1. Selected NOAEL and LOAEL Values Following Acute-Duration Inhalation Exposure to Chloromethane

Species	Duration	NOAEL (NOAEL$_{ADJ}$) (ppm)	LOAEL (LOAEL$_{ADJ}$) (ppm)	Effect	Reference
Fischer-344 rat	9 days 6 hours/day	ND	2,000 (500) (SLOAEL)	Reduced sperm, immature sperm in lumen, testicular lesions	Morgan et al. 1982

[a]Altered staining properties of hepatocyte.

ADJ = adjusted for continuous exposure; ALT = alanine aminotransferase; GD = gestation day; LOAEL = lowest-observed-adverse-effect level; ND = not determined; NOAEL = no-observed-adverse-effect level; SLOAEL = serious LOAEL

Selection of the Principal Study: The 11-day mouse study (Landry et al. 1985) was selected as the principal study because it provides the highest NOAEL below the lowest LOAEL for the critical effect (neurotoxicity).

Summary of the Principal Study:

Landry TD, Quast JF, Gushow TS, et al. 1985. Neurotoxicity of methyl chloride in continuously versus intermittently exposed female c57bl/6 mice. Fundam Appl Toxicol 5(1):87-98.

Landry et al. (1985) evaluated the neurological effects of chloromethane following nearly continuous exposure versus intermittent exposure in female C57BL/6 mice. This species, strain, and sex were chosen due to their high sensitivity to chloromethane-associated neurological effects. Groups of 12 mice each were exposed to chloromethane in whole-body inhalation chambers for 11 days for either 22 hours/day (referred to as "continuous" by the study authors) or 5.5 hours/day (referred to as intermittent by the study authors). Each duration protocol had two distinct experiments, each with their own concurrent control. For the continuous exposure, the first experiment exposed mice to 0, 15, 50, or 150 ppm and the second experiment exposed mice to 0, 100, 200, or 400 ppm. For the intermittent exposure, the first experiment exposed mice to 0, 150, or 2,400 ppm and the second experiment exposed mice to 0, 400, 800, or 1,600 ppm. Mice were evaluated twice daily for clinical signs of toxicity. Motor coordination was evaluated using a rotarod (ability to stay on a rotating 4-cm diameter rod) on exposure days 4, 8, and 11. Mice were weighed prior to exposure, on exposure days 4 and 8, and at necropsy. Animals were sacrificed after exposure, and the following tissues were collected, weighed, and prepared for histological evaluation in six mice/group: brain (cerebellum, cerebrum, and brain stem), sciatic nerve, vertebral bone with spinal cord, liver, kidneys, and thymus.

All mice exposed continuously to ≥150 ppm and intermittently to 2,400 ppm died or were sacrificed moribund prior to scheduled sacrifice. Prior to death/moribund sacrifice, mice displayed inanition (exhaustion caused by lack of nourishment) associated with decreased food consumption. Hematuria was observed in mice exposed to 2,400 ppm. Consistent with this, body weights were decreased by >10% at both continuous and intermittent exposure levels associated with decreased survival. Mice continuously exposed to ≥200 ppm showed ataxia and prostration by day 3; therefore, they were not assessed on the rotarod. In other continuously exposed groups, performance on a rotating rod was significantly decreased following exposure to 150 ppm starting on day 4, with severity of impairment increasing in a duration-related manner; no changes in motor coordination were observed at ≤100 ppm. In mice exposed

intermittently, sedation and hind-limb rigidity were observed in some mice at ≥1,600 ppm. Transient decreases in motor coordination on the rotarod were observed in mice exposed to 800 or 1,600 ppm on day 4; however, decreases were not observed on days 8 or 11. In mice intermittently exposed to 2,400 ppm, motor activity decreased in a duration-related manner starting on day 4.

At sacrifice, gross necropsy showed thymus atrophy at ≥1,600 ppm and an enlarged spleen at 2,400 ppm in mice exposed intermittently. The enlarged spleen was accompanied by hemoglobinuria, which is suggestive of extramedullary hematopoiesis. Absolute and relative thymus weights were reduced in all exposure groups from the first continuous exposure group (15, 50, and 150 ppm); however, no changes in thymus weights were observed in the second experiment at 100 ppm (thymic weights were not weighed at higher exposure levels due to early death). Therefore, the biological significance of decreased thymus weight at low concentrations is unclear due to lack of clear dose-response. In intermittently exposed mice, absolute and relative thymus weights were reduced at ≥1,600 ppm, and absolute and relative liver weights were increased at 1,600 ppm (but not at 2,400 ppm; this may be due to early sacrifice at this concentration). Other observed organ weight changes, including decreased absolute liver weight and increased relative kidney weight after continuous exposure to 150 ppm, were considered secondary to body weight effects.

Histopathological changes were observed in the brain, liver, and kidney. In the brain, degenerative changes in the cerebellum granule cells were observed in 100% of mice continuously exposed to ≥100 ppm, 33% of mice intermittently exposed to 400 ppm, 65–67% of mice intermittently exposed to 800–1,600 ppm, and 100% of mice intermittently exposed to 2,400 ppm. The changes consisted of nuclear pyknosis, karyorrhexis, and hemorrhaged areas, and the severity of the lesions increased in a concentration- and duration-dependent manner. In the liver, decreased hepatocyte size (attributed to glycogen depletion by the study authors) were also observed in mice continuously exposed to ≥100 ppm or intermittently exposed to ≥400 ppm. The study authors noted focal hepatic necrosis at unspecified "higher concentrations." In the kidney, slight multifocal degeneration of the renal tubules was observed after intermittent exposure to 2,400 ppm. Incidence data were not provided for hepatic or renal lesions.

Selection of the Point of Departure for the MRL: In order to select the POD based on neurological effects observed by Landry et al. (1985), data from experiments with the same daily duration were combined for dose-response analysis, and duration adjustments were made to compare across continuous and intermittent exposure scenarios (Table A-2). While the adjusted LOAEL concentrations are comparable across exposure scenarios, the continuous exposure scenario provides the highest NOAEL below the lowest LOAEL; therefore, the continuous exposure scenario was selected for derivation of the acute-duration inhalation MRL. Additionally, due to the steep dose-response curve (cerebellar lesion incidence of 0% at NOAEL and 100% at LOAEL), benchmark dose (BMD) modeling was not conducted to develop the MRL. Subsequently, the NOAEL of 50 ppm ($NOAEL_{ADJ}$ of 46 ppm) was used in derivation of the MRL.

APPENDIX A

Table A-2. Summary of Neurological Effects Observed in Mice Exposed to Chloromethane for 11 Days via Inhalation

Continuous exposure (22 hours/day)		Intermittent exposure (5.5 hours/day)	
Concentration (adjusted[a]) (ppm)	Effect	Concentration (adjusted[a]) (ppm)	Effect
15 (14)	No neurological effects		
50 (46)	No neurological effects	150 (34)	No neurological effects
100 (92)	Slight degenerative changes in the cerebellum granule cells (100% incidence)	400 (92)	Slight degenerative changes in the cerebellum granule cells (33% incidence)
150 (138)	Moderate cerebellar lesions (100% incidence); impaired motor coordination		
200 (183)	Incapacitated after 4 days, severe cerebellar lesions (100% incidence)	800 (183)	Slight degenerative changes in the cerebellum granule cells (67% incidence); transient impairment in motor coordination
400 (367)	Incapacitated after 2 days, severe cerebellar lesions (100% incidence)	1,600 (367)	Slight degenerative changes in the cerebellum granule cells (65% incidence); sedation, hind-limb rigidity, transient impairment in motor coordination
		2,400 (505)	Slight degenerative changes in the cerebellum granule cells (100% incidence); sedation, hindlimb rigidity, impaired motor coordination

[a]Exposure concentration adjusted for continuous exposure.

Source: Landry et al. 1985

Adjustment of Intermittent Exposure: The NOAEL of 50 ppm concentration was adjusted from a 22-hour exposure to a continuous 24-hour exposure scenario:

$$NOAEL_{ADj} = NOAEL \times \frac{22\ hours}{24\ hours} = 50\ ppm \times \frac{22\ hours}{24\ hours} = 46\ ppm$$

The human equivalent concentration (HEC) was calculated by multiplying the duration-adjusted NOAEL by the default ratio of 1 for air:blood partition coefficient for humans and rats (partition coefficient values are not available for chloromethane):

$$NOAEL_{HEC} = NOAEL_{ADJ} \times \frac{(HB/g)_A}{(HB/g)_H} = 46\ ppm \times 1 = 46\ ppm$$

Where:

$\dfrac{(HB/g)_A}{(HB/g)_H} =$ the blood: air partition coefficient ratio for animals (a) to humans (h)

Uncertainty Factors and Modifying Factor: The following uncertainty factors were applied to the NOAEL$_{HEC}$ to derive the MRL:

- uncertainty factor of 3 for extrapolation from animals to humans with dosimetric adjustments
- uncertainty factor of 10 for human variability
- modifying factor of 3 to account for the steep dose-response seen between the NOAEL and the LOAEL (e.g., 100% response rate in the animals evaluated at the LOAEL)

Subsequently, the MRL for acute-duration exposure to chloromethane via inhalation is:

$$MRL = \frac{NOAEL_{HEC}}{(UF \ x \ MF)} = \frac{46 \ ppm}{90} = 0.5 \ ppm$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Systematic review concluded that neurological effects are a presumed health effect following inhalation exposure to chloromethane based on a low level of evidence from human studies and a high level of evidence from animal studies (see Appendix C).

In humans, there are multiple case reports that noted adverse neurological effects as the main observed outcome after exposure to chloromethane (Baird 1954; Baker 1927; Battigelli and Perini 1955; Borovska et al. 1976; Hansen et al. 1953; Hartman et al. 1955; Jones 1942; Kegel et al. 1929; MacDonald 1964; McNally 1946; Minami 1998; Spevak et al. 1976; von Raalte and van Velzen 1945; Wood 1951). Additionally, one occupational cohort study reported neurological effects, some lasting years after exposure, following accidental exposure to high levels of chloromethane from a refrigeration leak (Gudmundsson 1977). At lower concentration levels, neurological effects were not noted in an occupational cohort study (NIOSH 1976) or three human controlled trials (Putz-Anderson et al. 1981a, 1981b; Stewart et al. 1980). In animals, a range of neurological effects have been observed in rats, mice, and dogs, including clinical signs of neurotoxicity, motor impairments, and lesions in the cerebellum and spinal cord. Neurological effects were observed following inhalation exposure for acute durations (Burek et al. 1981; Chellman et al. 1986a, 1986b; Jiang et al. 1985; Landry et al. 1985; McKenna et al. 1981a; Morgan et al. 1982; Smith and von Oettingen 1947b; Wolkowski-Tyl et al. 1983a, 1983b), intermediate durations (McKenna et al. 1981b; Smith and von Oettingen 1947b), or chronic durations (CIIT 1981).

Agency Contact (Chemical Manager): Sam Keith, MS, CPH

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Chloromethane
CAS Numbers: 74-87-3
Date: September 2023
Profile Status: Final
Route: Inhalation
Duration: Intermediate
MRL: 0.3 ppm (0.6 mg/m^3)
Critical Effect: Impaired sensorimotor function
Reference: McKenna et al. 1981b
Point of Departure: NOAEL of 51 ppm
                         (NOAEL$_{HEC}$ of 9 ppm)
Uncertainty Factor: 30
LSE Graph Key: 44
Species: Rat

MRL Summary: An intermediate-duration inhalation MRL of 0.3 ppm was derived for chloromethane based on neurological effects including impaired sensorimotor performance (wire maneuver) in female Sprague-Dawley rats following exposure to chloromethane for 93 days (5 days/week, 6 hours/day) (McKenna et al. 1981b). The MRL is based on a NOAEL of 51 ppm, which was adjusted to continuous duration exposure and converted to a human equivalent concentration (NOAEL$_{HEC}$) of 9 ppm and divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability).

Selection of the Critical Effect: Based on systematic review (see Appendix C), it was determined that hepatic, neurological, and male reproductive effects were presumed health effects associated with inhalation exposure. These presumed health effects were subsequently the focus of the intermediate-duration MRL evaluation.

For presumed health effects, the lowest reported LOAELs from intermediate-duration inhalation studies were 149 ppm for neurological effects, 399 ppm for hepatic effects, and 472 ppm for male reproductive effects (Table A-3). Based on available data, the nervous system appears to be the most sensitive target of chloromethane toxicity and is selected as the critical effect for the intermediate-duration inhalation MRL.

Table A-3. Selected NOAEL and LOAEL Values Following Intermediate-Duration Inhalation Exposure to Chloromethane

Species	Duration	NOAEL (NOAEL$_{ADJ}$) (ppm)	LOAEL (LOAEL$_{ADJ}$) (ppm)	Effect	Reference
Neurological effects					
Sprague-Dawley rat	93 days 5 days/week 6 hours/day	51 (9)	149 (27)	Impaired sensorimotor function (wire maneuver)	McKenna et al. 1981b

Table A-3. Selected NOAEL and LOAEL Values Following Intermediate-Duration Inhalation Exposure to Chloromethane

Species	Duration	NOAEL (NOAEL$_{ADJ}$) (ppm)	LOAEL (LOAEL$_{ADJ}$) (ppm)	Effect	Reference
CD-1 mouse	93 days 5 days/week 6 hours/day	399 (71)	ND	No adverse effects	McKenna et al. 1981b
Monkey (NS)	120 days 6 days/week 6 hours/day	300 (64)	500 (107)[a] (SLOAEL)	Progressive debility, prostration, loss of consciousness	Smith and von Oettingen 1947b
Mouse (NS)	266 days 6 days/week 6 hours/day	300 (64)	500 (107)[a] (SLOAEL)	Persistent neuromuscular abnormalities, impaired gait, hindlimb paralysis	Smith and von Oettingen 1947b
Guinea pig (NS)	266 days 6 days/week 6 hours/day	300 (64)	500 (107)[a] (SLOAEL)	Persistent neuromuscular abnormalities, impaired gait, hindlimb drag	Smith and von Oettingen 1947b
Dog (NS)	211 days 6 days/week 6 hours/day	300 (64)	500 (107) (SLOAEL)	Severe clinical signs of neurotoxicity (e.g., tremors, spasticity, impaired gait)	Smith and von Oettingen 1947b
Hepatic effects					
Sprague-Dawley rat	93 days 5 days/week 6 hours/day	149 (27)	399 (71)	Increased relative liver weight	McKenna et al. 1981b
CD-1 mouse	93 days 5 days/week 6 hours/day	149 (27)	399 (71)	Increased relative liver weight	McKenna et al. 1981b
B6C3F1 mouse	90 days 5 days/week 6 hours/day	368 (66)	741 (132)	Increased relative liver weight	Mitchell et al. 1979
B6C3F1 mouse	6 months 5 days/week 6 hours/day	224 (40)	997 (178)	Hepatocellular degeneration	CIIT 1981
Male reproductive effects					
Fischer 344 rat	12–19 weeks per generation 5–7 days/week 6 hours/day	151 (32)	472 (101)	Decreased number of fertile F0 males, decreased number of litters per copulation plug in F0 rats	Hamm et al. 1985

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Table A-3. Selected NOAEL and LOAEL Values Following Intermediate-Duration Inhalation Exposure to Chloromethane

Species	Duration	NOAEL (NOAEL$_{ADJ}$) (ppm)	LOAEL (LOAEL$_{ADJ}$) (ppm)	Effect	Reference
Fischer 344 rat	6 months 5 days/week 6 hours/day	224 (40)	997 (178)	Degeneration and atrophy of seminiferous tubules; sperm granulomas	CIIT 1981
Sprague-Dawley rat	93 days 5 days/week 6 hours/day	399 (71)	ND	No adverse effects (fertility not assessed)	McKenna et al. 1981b
Fischer 344 rat	90 days 5 days/week 6 hours/day	1,473 (263)	ND	No adverse effects (fertility not assessed)	Mitchell et al. 1979

[a]Decreased survival observed at this concentration

ADJ = adjusted for intermittent exposure; LOAEL = lowest observed adverse effect level; ND = not determined; NOAEL = no-observed-adverse-effect level

Selection of the Principal Study: The 93-day rat study (McKenna et al. 1981b) was selected as the principal study because it provides the highest NOAEL below the lowest LOAEL for the critical effect (neurotoxicity).

Summary of the Principal Study:

McKenna MJ, Burek JD, Henck JW, et al. 1981b. Methyl chloride: A 90-day inhalation toxicity study in rats, mice and beagle dogs. Dow Chemical Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 4. OTS0511317. 408120723. 47002B3B17.

McKenna et al. (1981b) exposed Sprague-Dawley rats (10/sex/group) to chloromethane at nominal concentrations of 0, 50, 150, or 400 ppm for 93 days (5 days/week, 6 hours/day). Analytical concentrations were 0, 51, 149, and 399 ppm, respectively. Animals were observed daily for clinical signs of toxicity. Body weights were measured twice weekly for the first 4 weeks and weekly thereafter. Sensorimotor responses were tested in 5/sex/group weekly for the first 4 weeks of exposure, and every other week thereafter. Sensorimotor tests included evaluation of body position, respiration, piloerection, exophthalmos, tremor, corneal reflex, pinna reflex, tail pinch, toe pinch, righting reflex, grasp irritability, visual placing, wire maneuver, and hindlimb clasping. Blood and urine were collected for hematology and urinalysis prior to the initiation of exposure and at study termination. Serum clinical chemistry endpoints were evaluated at time of necropsy. All animals underwent gross necropsy, and the following organ weights were measured: brain, heart, liver, kidneys, and testes. Histopathological examination of a comprehensive set of tissues was conducted on all rats in the control and 399-ppm group.

Two rats died prior to study termination, 1 female at 51 ppm and 1 female at 399 ppm. These deaths were not attributed to exposure. No clinical signs of toxicity were noted. A dose-related trend toward reduced body weight gain was noted in female rats; however, no statistically or biologically significant findings were observed. No exposure-related changes in clinical chemistry, hematology, or urinalysis were

observed. The only exposure-related change in organ weights was a 10% increase in relative liver weights in male rats at 399 ppm. No exposure-related gross or microscopic lesions were observed.

Sensorimotor testing showed a significant decrease in the ability of female rats to perform the wire maneuver (inability of the animals to raise their hindquarters to the top of the wire while grasping with forelimbs) at 399 ppm beginning at day 16 and 149 ppm beginning at day 40, and persistent throughout the remainder of the study. Hindlimb clasping was significantly impaired in female rats at 399 ppm beginning on day 66 through the end of the study. In males, hindlimb clasping was transiently impaired at ≥149 ppm, observed only on days 16–39.

Selection of the Point of Departure for the MRL: The NOAEL of 51 ppm for neurological effects in the study by McKenna et al. (1981b) was selected as the point of departure (POD). While the study authors reported statistical results for sensorimotor testing, quantitative data were not provided; therefore, BMD modeling was not used to derive this MRL.

Adjustment of Intermittent Exposure: The NOAEL of 51 ppm concentration was adjusted for a continuous exposure scenario:

$$NOAEL_{ADj} = NOAEL \times \frac{6\ hours}{24\ hours} \times \frac{5\ days}{7\ days} = 51\ ppm \times \frac{6\ hours}{24\ hours} \times \frac{5\ days}{7\ days} = 9\ ppm$$

The human equivalent concentration (HEC) was calculated by multiplying the duration-adjusted NOAEL by the default ratio of 1 for air:blood partition coefficient for humans and rats (partition coefficient values are not available for chloromethane):

$$NOAEL_{HEC} = NOAEL_{ADJ} \times \frac{(HB/g)_A}{(HB/g)_H} = 9\ ppm \times 1 = 9\ ppm$$

Where:

$\frac{(HB/g)_A}{(HB/g)_H}$ = the blood: air partition coefficient ratio for animals (a) to humans (h)

Uncertainty Factors used in MRL derivation: The following uncertainty factors were applied to the NOAEL$_{HEC}$ to derive the MRL:

- uncertainty factor of 3 for extrapolation from animals to humans with application of dosimetric adjustment
- uncertainty factor of 10 for human variability.

Subsequently, the inhalation MRL for intermediate-duration exposure to chloromethane is:

$$MRL = \frac{NOAEL_{HEC}}{(UF)} = \frac{9\ ppm}{30} = 0.3\ ppm$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Systematic review concluded that neurological effects are a presumed health effect following inhalation exposure to chloromethane based on a low level of evidence from human studies and a high level of evidence from animal studies (see Appendix C).

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In humans, there are multiple case reports that noted adverse neurological effects as the main observed outcome after exposure to chloromethane (Baird 1954; Baker 1927; Battigelli and Perini 1955; Borovska et al. 1976; Hansen et al. 1953; Hartman et al. 1955; Jones 1942; Kegel et al. 1929; MacDonald 1964; McNally 1946; Minami 1998; Spevak et al. 1976; von Raalte and van Velzen 1945; Wood 1951). Additionally, one occupational cohort study reported neurological effects, some lasting years after exposure, following accidental exposure to high levels of chloromethane from a refrigeration leak (Gudmundsson 1977). At lower concentration levels, neurological effects were not noted in an occupational cohort study (NIOSH 1976) or three human controlled trials (Putz-Anderson et al. 1981a, 1981b; Stewart et al. 1980). In animals, a range of neurological effects have been observed in rats, mice, and dogs, including clinical signs of neurotoxicity, motor impairments, and lesions in the cerebellum and spinal cord. Neurological effects were observed following inhalation exposure for acute durations (Burek et al. 1981; Chellman et al. 1986a, 1986b; Jiang et al. 1985; Landry et al. 1985; McKenna et al. 1981a; Morgan et al. 1982; Smith and von Oettingen 1947b; Wolkowski-Tyl et al. 1983a, 1983b), intermediate durations (McKenna et al. 1981b; Smith and von Oettingen 1947b), or chronic durations (CIIT 1981).

The study author conclusions in the principal study were critically evaluated in deriving the intermediate-duration inhalation MRL. McKenna et al. (1981b) concluded that the wire maneuver findings in female rats may represent a mild muscle weakness but did not attribute findings to chemical exposure because: (1) all groups showed decreased ability as time progressed (attributed to increased body weight), and (2) findings were not associated with any discernable neuromuscular incoordination or apparent neurological deficit in the current study, and (3) no "observable effects of a CNS or neuromuscular character" in rats exposed to concentrations up to 1,500 ppm by Mitchell et al. (1979). However, there are issues with each point of the argument made by McKenna et al. (1981b). First, no statistically significant or biologically relevant body weight effects were noted in exposed female rats, compared to controls. Second, the lack of overt incoordination/deficit argument is considered invalid, as detailed sensorimotor testing is designed to identify subtle deficits not obvious in cage-side observations. Additionally, the study authors neglected to acknowledge or discuss the statistical changes in another sensorimotor test (hindlimb clasping), which found deficits in female rats at the highest exposure concentration. Lastly, Mitchell et al. (1979) only performed cage-side evaluations and did not conduct detailed sensorimotor testing; therefore, findings (or lack thereof) from that study are not directly comparable to the study by McKenna et al. (1981b). Taken together, impairments on the wire maneuver and hindlimb clasping tests provide evidence of sensorimotor dysfunction at ≥149 ppm that is considered toxicologically relevant, especially when considering consistent evidence of progressive dose- and duration-dependent motor impairments (particularly in the hind limbs) observed in other studies and species following inhalation exposure (e.g., Chellman et al. 1986b; Landry et al. 1985; Morgan et al. 1982; Smith and von Oettingen 1947b).

Agency Contact (Chemical Manager): Sam Keith, MS, CPH

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Chloromethane
CAS Numbers: 74-87-3
Date: September 2023
Profile Status: Final
Route: Inhalation
Duration: Chronic
MRL: 0.03 ppm (0.06 mg/m^3)
Critical Effect: Swelling and slight degeneration of axons in the spinal cord
Reference: CIIT (1981)
Point of Departure: LOAEL of 51 ppm
       (LOAEL$_{HEC}$: 9 ppm)
Uncertainty Factor: 300
LSE Graph Key: 60, 61
Species: Mouse

MRL Summary: A chronic-duration inhalation MRL of 0.03 ppm was derived for chloromethane based on neurotoxicity (swelling and degeneration of axons in the spinal cord) in mice exposed to concentrations ≥51 ppm for 18 or 24 months (6 hours/day, 5 days/week); no NOAEL was identified (CIIT 1981). The MRL is based on a LOAEL of 51 ppm, which was adjusted to continuous duration exposure and converted to a human equivalent concentration (LOAEL$_{HEC}$) of 9 ppm and divided by a total uncertainty factor of 300 (10 for use of a LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustments, and 10 for human variability).

Selection of the Critical Effect: Only one chronic-duration inhalation study evaluated potential adverse effects of chloromethane in rats and mice (CIIT 1981). Exposure-related nonneoplastic effects reported in this study included neurological effects in mice at ≥51 ppm; cardiovascular effects in mice at ≥224 ppm and rats at 997 ppm; body weight, hepatic, renal, and male reproductive effects in rats and mice at 997 ppm; and decreased survival and spleen effects in mice at 997 ppm. Of these effects, the most sensitive (neurotoxicity) was selected as the critical effect.

Selection of the Principal Study: The chronic mouse study (CIIT 1981) was selected as the principal study because it provides the lowest POD for the critical effect (neurotoxicity).

Summary of the Principal Study:

CIIT. 1981. Final report on a chronic inhalation toxicology study in rats and mice exposed to methyl chloride. Battelle-Columbus Laboratories. Submitted to the U.S. Environmental Protection Agency under section 4. 40-8120717. OTS0511310.

CIIT (1981) exposed groups of B6C3F1 mice (117–123/sex/group) to chloromethane in whole-body inhalation exposure chambers at target concentrations of 0 (control), 50, 225, or 1,000 ppm, 6 hours/day, 5 days/week for up to 24 months. Analytically measured concentrations were 0, 51, 224, and 997 ppm, respectively. Animals were checked twice daily for mortality, morbidity, and clinical signs of toxicity. Body weights were measured prior to exposure, weekly for the first 6 months, and biweekly thereafter. Neurofunctional assessments were conducted after 18 and 24 months of exposure, including posture and gait analysis, facial tone, and reflexes. Ophthalmological examinations were performed prior to exposure and within a week of scheduled sacrifice. Groups of animals were sacrificed at 6 months (9–11/sex/group), 12 (10/sex/group), 18 (5–10/sex/group), or 24 months (all surviving animals) after the

initial exposure and underwent gross necropsy. At sacrifice, blood was collected for hematology and clinical chemistry analysis and urine was collected for urinalysis. Weights were recorded for the lungs, heart, brain, liver, kidneys, and gonads. A complete set of tissues was examined for histopathological changes from all animals at scheduled sacrifice or were sacrificed/died prematurely.

The number of unscheduled deaths was increased in both males (78%) and females (61%) at 997 ppm, compared to control (63 and 28%, respectively). Body weights were decreased at 997 ppm by 15–18% by 12 months; however, body weight effects were not noted in surviving animals at 18 or 24 months. Clinical signs of neurotoxicity (tremor, paralysis) were seen in both sexes, along with abnormal functional test neurological results (restricted use of rear legs, abnormal gait, poor extensor thrust, leg rigidity) at 997 ppm. No exposure-related changes in ophthalmology or hematology were observed. Clinical chemistry findings were restricted to increased serum ALT in at 12 and 18 months at 997 ppm (not assessed at 24 months due to 100% mortality). Exposure-related changes in organ weight included increased absolute and/or relative heart weight in female mice at 997 ppm after 18 months and at 224 ppm at 24 months, and increased absolute and relative liver weight in females at 997 ppm after 18 months. Histopathological findings identified the CNS as a sensitive target of toxicity. Axonal swelling and degenerative changes of minimal severity were observed in the spinal cord nerves, cauda equina, and dorsal root in the spinal cord at ≥51 ppm after exposure for ≥18 months. In the brain, minimal-to-moderate degeneration of the cerebellar granule cell neurons was observed at 997 ppm after exposure for ≥18 months. Table A-4 provides a summary of neurological effects observed in the chronic exposure study by CIIT (1981). Other exposure-related nonneoplastic findings at 997 ppm following exposure for ≥18 months included hepatic lesions (centrilobular degeneration, karyomegaly, and cytomegaly), renal tubule hyperplasia, testicular seminiferous tubule degeneration and atrophy, splenic atrophy, and lymphoid depletion of the spleen and thymus. Carcinogenic findings included renal cortex adenocarcinomas and metastatic fibrosarcoma in the lungs of male mice at 997 ppm.

Table A-4. Summary of Neurological Effects Observed in Mice Following Chronic-Duration Inhalation Exposure to Chloromethane	
Concentration (ppm)	Effect
51	Swelling and degeneration of axons in the spinal cord 18 months: 4/5 males, 10/10 females
224	Swelling and degeneration of axons in the spinal cord 18 months: 5/5 male, 10/10 females
997	Tremor and paralysis Swelling and degeneration of axons in the spinal cord 18 months: 3/7 males; no data on females 24 months: 13/18 females Minimal-to-mild degeneration of cerebellar granule cell neurons 18–24 months: 45/47 males, 35/37 females (minimal-to-moderate)

Source: CIIT 1981

Selection of the Point of Departure for the MRL: The LOAEL of 51 ppm for neurological effects in the study by CIIT (1981) was selected as the POD. Given that the data do not show a monotonic graded-dose response (Table A-4), BMD modeling was not used to derive this MRL.

Adjustment for Intermittent Exposure: The LOAEL was adjusted from intermittent exposure to account for a continuous exposure scenario:

$$LOAEL_{ADj} = LOAEL \times \frac{6\ hours}{24\ hours} \times \frac{5\ days}{7\ days} = 51\ ppm \times \frac{6\ hours}{24\ hours} \times \frac{5\ days}{7\ days} = 9\ ppm$$

The HEC was calculated by multiplying the duration-adjusted LOAEL by the default ratio of 1 for air:blood partition coefficient for humans and rats (partition coefficient values are not available for chloromethane):

$$LOAEL_{HEC} = LOAEL_{ADJ} \times \frac{(HB/g)_A}{(HB/g)_H} = 9\ ppm \times 1 = 9\ ppm$$

Where:

$\frac{(HB/g)_A}{(HB/g)_H}$ = the blood: air partition coefficient ratio for animals (a) to humans (h)

Uncertainty factors used in MRL derivation: The following uncertainty factors were then applied to the LOAEL$_{HEC}$ to derive the MRL.

- 10 for use of a LOAEL
- 3 for extrapolation from animals to humans with dosimetric adjustments
- 10 for human variability

Subsequently, the MRL becomes:

$$MRL = \frac{LOAEL_{HEC}}{UFs} = \frac{9\ ppm}{300} = 0.03\ ppm$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Systematic review concluded that neurological effects are a presumed health effect following inhalation exposure to chloromethane based on a low level of evidence from human studies and a high level of evidence from animal studies (see Appendix C).

There are shortcomings of the CIIT (1981) study that were considered in deriving the chronic-duration inhalation MRL. Specifically, some of the females were initially mis-sexed and placed in male cages. These animals were kept in their originally assigned cages for the study duration. Still, all animals received their assigned dose, regardless of sex. Therefore, this is unlikely to be of consequence to the study results. In addition, 4 months after the beginning of the study, mice from the 50-ppm group were accidentally exposed to 1,000 ppm, and 1,000 ppm group mice were accidentally exposed to 50 ppm for 3 days at 5.5 hours/day. CIIT (1981) acknowledged that this was a serious mistake but concluded that the mistake did not affect the validity of the results of the study, given the length of the dosing regimen. Additionally, no neurological effects were recorded at either 50 or 1,000 ppm at 6 months, so there appears to be little effect of this error on the results of the study. Therefore, ATSDR has concluded that CIIT (1981) is adequate to inform a chronic-duration inhalation MRL that provides appropriate public health protection. In contrast, EPA (2001) opted to base the chronic reference concentration (RfC) on Landry et al. (1985) due to concerns over procedural errors in CIIT (1981) and cerebellar lesions and mortality at lower administered concentrations in Landry et al. (1985) compared to CIIT (1981), suggesting increased sensitivity C57BL/6 mice, compared to B6C3F1 mice. However, it is not consistent with ATSDR guidance to use an acute-duration study (e.g., Landry et al. 1985) to inform a chronic-duration MRL. Of note, the chronic MRL of 0.03 ppm (0.06 mg/m^3) based on spinal cord lesions reported in the chronic study by CIIT (1981) is comparable to the chronic RfC of 0.09 mg/m^3 based on the acute study by Landry et al. (1985).

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Agency Contact (Chemical Manager): Sam Keith, MS, CPH

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Chloromethane
CAS Numbers: 74-87-3
Date: September 2023
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL.

Rationale for Not Deriving an MRL: The database for deriving an acute-duration oral MRL is inadequate. The only identified study evaluating oral exposure to chloromethane was an acute-duration gavage study in which the hepatotoxic effects of chloroform, carbon tetrachloride, dichloroethane, and chloromethane were compared in rats (Reynolds and Yee 1967). In this study, no exposure-related histopathological changes were observed in rats exposed to a single dose of 420 mg/kg; no additional endpoints were evaluated. Due to the limited scope of this study and the lack of exposure-related effects, this study is not considered appropriate for derivation of an acute-duration oral MRL.

Agency Contact (Chemical Manager): Sam Keith, MS, CPH

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Chloromethane
CAS Numbers: 74-87-3
Date: September 2023
Profile Status: Final
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration oral MRL.

Rationale for Not Deriving an MRL: No intermediate-duration oral studies were located for chloromethane. Subsequently, no MRL is proposed.

Agency Contact (Chemical Manager): Sam Keith, MS, CPH

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Chloromethane
CAS Numbers: 74-87-3
Date: September 2023
Profile Status: Final
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL.

Rationale for Not Deriving an MRL: No chronic-duration oral studies were located for chloromethane. Subsequently, no MRL is proposed.

Agency Contact (Chemical Manager): Sam Keith, MS, CPH

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR CHLOROMETHANE

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to chloromethane.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen were conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for chloromethane. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of chloromethane have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of chloromethane are presented in Table B-1.

Table B-1. Inclusion Criteria for the Literature Search and Screen

Health Effects
   Species
      Human
      Laboratory mammals
   Route of exposure
      Inhalation
      Oral
      Dermal (or ocular)
      Parenteral (these studies will be considered supporting data)
   Health outcome
      Death
      Systemic effects
      Body weight effects
      Respiratory effects
      Cardiovascular effects
      Gastrointestinal effects
      Hematological effects
      Musculoskeletal effects
      Hepatic effects
      Renal effects
      Dermal effects
      Ocular effects
      Endocrine effects
      Immunological effects
      Neurological effects
      Reproductive effects
      Developmental effects

Table B-1. Inclusion Criteria for the Literature Search and Screen

Other noncancer effects
Cancer
Toxicokinetics
   Absorption
   Distribution
   Metabolism
   Excretion
   PBPK models
Biomarkers
   Biomarkers of exposure
   Biomarkers of effect
Interactions with other chemicals
Potential for human exposure
   Releases to the environment
      Air
      Water
      Soil
   Environmental fate
      Transport and partitioning
      Transformation and degradation
   Environmental monitoring
      Air
      Water
      Sediment and soil
      Other media
   Biomonitoring
      General populations
      Occupation populations

B.1.1 Literature Search

The current literature search was intended to update the draft toxicological profile for chloromethane released for public comment in 2022; thus, the literature search was restricted to studies published between January 2018 and June 2022. The following main databases were searched in June 2022:

- PubMed
- National Technical Reports Library (NTRL)
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for chloromethane. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to chloromethane were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
06/2022	(74-87-3[rn] AND (2018:3000[mhda] OR 2018:3000[crdat] OR 2018:3000[edat] OR 2018:3000[dp])) OR ((("Chlormethan"[tw] OR "Chloromethane"[tw] OR "Methane, chloro-"[tw] OR "Methyl chloride"[tw] OR "Methylchloride"[tw] OR "Monochloromethane"[tw]) AND (2018:3000[crdat] OR 2018:3000[edat] OR 2018:3000[dp])) NOT medline[sb])
NTRL	
06/2022	"Chlormethan" OR "Chloromethane" OR "Methane, chloro-" OR "Methyl chloride" OR "Methylchloride" OR "Monochloromethane"
Toxcenter	

06/2022	FILE 'TOXCENTER' ENTERED AT 13:37:02 ON 15 JUN 2022
	CHARGED TO COST=EH038.13.03.LB.04
	L1 4179 SEA FILE=TOXCENTER 74-87-3
	L2 4020 SEA FILE=TOXCENTER L1 NOT TSCATS/FS
	L3 3345 SEA FILE=TOXCENTER L2 NOT PATENT/DT
	L4 348 SEA FILE=TOXCENTER L3 AND PY>=2018
	           ACTIVATE TOXQUERY/Q
	         --------- 	
	L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?)
	L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT,
	            IT)
	L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)
	L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT
	L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
	L10 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
	L11 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR
	            DIETARY OR DRINKING(W)WATER?)
	L12 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	
	L13 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR

APPENDIX B

Table B-2. Database Query Strings

Database search date	Query string
	OVUM?)
L15	QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
L16	QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
L17	QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
L18	QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
L19	QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
L20	QUE (ENDOCRIN? AND DISRUPT?)
L21	QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
L22	QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
L23	QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
L24	QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
L25	QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
L26	QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
L27	QUE (NEPHROTOX? OR HEPATOTOX?)
L28	QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
L29	QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
L30	QUE L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29
L31	QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
L32	QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
L33	QUE L30 OR L31 OR L32
L34	QUE (NONHUMAN MAMMALS)/ORGN
L35	QUE L33 OR L34
L36	QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
L37	QUE L35 OR L36

L38	126 SEA FILE=TOXCENTER L4 AND L37
L39	5 SEA FILE=TOXCENTER L38 AND MEDLINE/FS
L40	8 SEA FILE=TOXCENTER L38 AND BIOSIS/FS
L41	113 SEA FILE=TOXCENTER L38 AND CAPLUS/FS

APPENDIX B

Table B-2. Database Query Strings

Database search date	Query string
	L42 0 SEA FILE=TOXCENTER L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L43 121 DUP REM L39 L40 L41 (5 DUPLICATES REMOVED)
	L*** DEL 5 S L38 AND MEDLINE/FS
	L*** DEL 5 S L38 AND MEDLINE/FS
	L44 5 SEA FILE=TOXCENTER L43
	L*** DEL 8 S L38 AND BIOSIS/FS
	L*** DEL 8 S L38 AND BIOSIS/FS
	L45 6 SEA FILE=TOXCENTER L43
	L*** DEL 113 S L38 AND CAPLUS/FS
	L*** DEL 113 S L38 AND CAPLUS/FS
	L46 110 SEA FILE=TOXCENTER L43
	L47 116 SEA FILE=TOXCENTER (L44 OR L45 OR L46) NOT MEDLINE/FS D SCAN L47

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
06/2022	74-87-3
NTP	
06/2022	"74-87-3" "Methyl chloride" "Chloromethane" "Chlormethan" "Methane, chloro-" "Methylchloride" "Monochloromethane"
Regulations.gov	
06/2022	Limited to dockets, or documents with DocType: Notice, Posted 01/01/2018 to 06/16/2022, Agency: EPA "Methyl chloride" "74-87-3"; "Chlormethan"; "Methane, chloro-"; "Methylchloride"; "Monochloromethane"; "Chloromethane"
NIH RePORTER	
09/2022	Fiscal Year: Active Projects; Text Search: "Chlormethan" OR "Chloromethane" OR "Methane, chloro-" OR "Methyl chloride" OR "Methylchloride" OR "Monochloromethane" (advanced) Limit to: Project Title, Project Terms, Project Abstracts
Other	Identified throughout the assessment process

The 2022 results were:
- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 183
- Number of records identified from other strategies: 26
- Total number of records to undergo literature screening: 209

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on chloromethane:

- Title and abstract screen
- Full text screen

Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

- Number of titles and abstracts screened: 209
- Number of studies considered relevant and moved to the next step: 50

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 50
- Number of studies cited in the pre-public draft of the toxicological profile: 247
- Total number of studies cited in the profile: 274

A summary of the results of the literature search and screening is presented in Figure B-1.

Figure B-1. June 2022 Literature Search Results and Screen for Chloromethane

APPENDIX C. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR CHLOROMETHANE

To increase the transparency of ATSDR's process of identifying, evaluating, synthesizing, and interpreting the scientific evidence on the health effects associated with exposure to chloromethane, ATSDR utilized a slight modification of NTP's Office of Health Assessment and Translation (OHAT) systematic review methodology (NTP 2013, 2015; Rooney et al. 2014). ATSDR's framework is an eight-step process for systematic review with the goal of identifying the potential health hazards of exposure to chloromethane:

- Step 1. Problem Formulation
- Step 2. Literature Search and Screen for Health Effects Studies
- Step 3. Extract Data from Health Effects Studies
- Step 4. Identify Potential Health Effect Outcomes of Concern
- Step 5. Assess the Risk of Bias for Individual Studies
- Step 6. Rate the Confidence in the Body of Evidence for Each Relevant Outcome
- Step 7. Translate Confidence Rating into Level of Evidence of Health Effects
- Step 8. Integrate Evidence to Develop Hazard Identification Conclusions

C.1 PROBLEM FORMULATION

The objective of the toxicological profile and this systematic review was to identify the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to chloromethane. The inclusion criteria used to identify relevant studies examining the health effects of chloromethane are presented in Table C-1.

Data from human and laboratory animal studies were considered relevant for addressing this objective. Human studies were divided into two broad categories: observational epidemiology studies and controlled exposure studies. The observational epidemiology studies were further divided: cohort studies (retrospective and prospective studies), population studies (with individual data or aggregate data), and case-control studies.

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Species
  Human
  Laboratory mammals
Route of exposure
  Inhalation
  Oral
  Dermal (or ocular)
  Parenteral (these studies will be considered supporting data)
Health outcome
  Death
  Systemic effects
  Body weight effects
  Respiratory effects

Table C-1. Inclusion Criteria for Identifying Health Effects Studies
Cardiovascular effects
Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Other noncancer effects
Cancer

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen was conducted to identify studies examining the health effects of chloromethane. The literature search framework for the toxicological profile is discussed in detail in Appendix B.

C.2.1 Literature Search

As noted in Appendix B, the current literature search was intended to update the draft toxicological profile for chloromethane released for public comment in 2022. See Appendix B for the databases searched and the search strategy.

A total of 209 records relevant to all sections of the toxicological profile were identified (after duplicate removal).

C.2.2 Literature Screening

As described in Appendix B, a two-step process was used to screen the literature search to identify relevant studies examining the health effects of chloromethane.

Title and Abstract Screen. In the Title and Abstract Screen step, 209 records were reviewed; 1 document was considered to meet the health effects inclusion criteria in Table C-1 and was moved to the next step in the process.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of 56 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 56 documents (96 studies), 35 documents (65 studies) were included in the qualitative review.

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

Relevant data extracted from the individual studies selected for inclusion in the systematic review were collected in customized data forms. A summary of the type of data extracted from each study is presented in Table C-2. For references that included more than one experiment or species, data extraction records were created for each experiment or species.

Table C-2. Data Extracted From Individual Studies

Citation
Chemical form
Route of exposure (e.g., inhalation, oral, dermal)
   Specific route (e.g., gavage in oil, drinking water)
Species
   Strain
Exposure duration category (e.g., acute, intermediate, chronic)
Exposure duration
   Frequency of exposure (e.g., 6 hours/day, 5 days/week)
   Exposure length
Number of animals or subjects per sex per group
Dose/exposure levels
Parameters monitored
Description of the study design and method
Summary of calculations used to estimate doses (if applicable)
Summary of the study results
Reviewer's comments on the study
Outcome summary (one entry for each examined outcome)
   No-observed-adverse-effect level (NOAEL) value
   Lowest-observed-adverse-effect level (LOAEL) value
   Effect observed at the LOAEL value

A summary of the extracted data for each study is presented in the Supplemental Document for Chloromethane and overviews of the results of the inhalation and oral exposure studies are presented in Sections 2.2–2.19 of the profile and in the Levels Significant Exposures tables in Section 2.1 of the profile (Tables 2-2 and 2-3, respectively).

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for chloromethane identified in human and animal studies are presented in Tables C-3 and C-4, respectively. Available human studies evaluating noncancer effects include a limited number of controlled exposure and epidemiological studies and numerous case reports. When evaluated together, these studies suggest that the cardiovascular and neurological systems may be susceptible to chloromethane toxicity. Animal studies examined a comprehensive set of endpoints following inhalation exposure; oral studies were limited to a single acute-duration study evaluating hepatic endpoints, and no dermal studies were identified. Cardiovascular, hepatic, neurological, male reproductive, and developmental effects were considered sensitive outcomes following inhalation exposure in animals (i.e., effects were observed at low concentrations). Epidemiological and

experimental studies examining these potential outcomes were carried through to Steps 4–8 of the systematic review; case studies were not included in the systematic review. There were 65 studies (published in 35 documents) examining these potential outcomes carried through to Steps 4–8 of the systematic review.

Table C-3. Overview of the Health Outcomes for Chloromethane Evaluated In Human Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Caner
Inhalation studies																	
Cohort			3 / 2										2 / 1				3 / 1
Case control																	3 / 1
Population			1														
Case series	1		7 / 7	11 / 11	2 / 1		6 / 6	5 / 5		3 / 3			15 / 15	1 / 1		1 / 1	
Experimental	1		1		1								3				
Oral studies																	
Cohort																	
Case control																	
Population																	
Case series																	
Dermal studies																	
Cohort																	
Case control																	
Population																	
Case series																	

Number of studies examining endpoint	0	1	2	3	4	5-9	≥10
Number of studies reporting outcome	0	1	2	3	4	5-9	≥10

APPENDIX C

Table C-4. Overview of the Health Outcomes for Chloromethane Evaluated in Experimental Animal Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological[a]	Neurological[a]	Reproductive[a]	Developmental	Other Noncancer	Caner
Inhalation studies																	
Acute-duration	13	9	3	6	4		18	19	2	2	4	5	27	16	3	3	
	9	6	1	1	2		15	13			2	3	26	11	3	3	
Intermediate-duration	7	10	7	6	7	7	8	8	7	5	4	7	13	8	2		
	4	3	1				4	1				1	6	2			
Chronic-duration	6	6	6	6	6	6	6	6	6	6	6	6	6	6			2
	4		4				4	3				2	2	5			1
Oral Studies																	
Acute-duration							1										
Intermediate-duration																	
Chronic-duration																	
Dermal studies																	
Acute-duration																	
Intermediate-duration																	
Chronic-duration																	

		0	1	2	3	4	5-9	≥10
Number of studies examining endpoint		0	1	2	3	4	5-9	≥10
Number of studies reporting outcome		0	1	2	3	4	5-9	≥10

[a]Number of studies examining endpoint includes study evaluating histopathology, but not evaluating function.

APPENDIX C

C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

C.5.1 Risk of Bias Assessment

The risk of bias of individual studies was assessed using OHAT's Risk of Bias Tool (NTP 2015). The risk of bias questions for observational epidemiology studies, human-controlled exposure studies, and animal experimental studies are presented in Tables C-5, C-6, and C-7, respectively. Each risk of bias question was answered on a four-point scale:

- **Definitely low risk of bias (++)**
- **Probably low risk of bias (+)**
- **Probably high risk of bias (-)**
- **Definitely high risk of bias (– –)**

In general, "definitely low risk of bias" or "definitely high risk of bias" were used if the question could be answered with information explicitly stated in the study report. If the response to the question could be inferred, then "probably low risk of bias" or "probably high risk of bias" responses were typically used.

Table C-5. Risk of Bias Questionnaire for Observational Epidemiology Studies

Selection bias

Were the comparison groups appropriate?

Confounding bias

Did the study design or analysis account for important confounding and modifying variables?

Attrition/exclusion bias

Were outcome data complete without attrition or exclusion from analysis?

Detection bias

Is there confidence in the exposure characterization?

Is there confidence in outcome assessment?

Selective reporting bias

Were all measured outcomes reported?

Table C-6. Risk of Bias Questionnaire for Human-Controlled Exposure Studies

Selection bias

Was administered dose or exposure level adequately randomized?

Was the allocation to study groups adequately concealed?

Performance bias

Were the research personnel and human subjects blinded to the study group during the study?

Attrition/exclusion bias

Were outcome data complete without attrition or exclusion from analysis?

Detection bias

Is there confidence in the exposure characterization?

Is there confidence in outcome assessment?

Table C-6. Risk of Bias Questionnaire for Human-Controlled Exposure Studies

Selective reporting bias

Were all measured outcomes reported?

Table C-7. Risk of Bias Questionnaire for Experimental Animal Studies

Selection bias

Was administered dose or exposure level adequately randomized?

Was the allocation to study groups adequately concealed?

Performance bias

Were experimental conditions identical across study groups?

Were the research personnel blinded to the study group during the study?

Attrition/exclusion bias

Were outcome data complete without attrition or exclusion from analysis?

Detection bias

Is there confidence in the exposure characterization?

Is there confidence in outcome assessment?

Selective reporting bias

Were all measured outcomes reported?

After the risk of bias questionnaires were completed for the health effects studies, the studies were assigned to one of three risk of bias tiers based on the responses to the key questions listed below and the responses to the remaining questions.

- Is there confidence in the exposure characterization? (only relevant for observational studies)
- Is there confidence in the outcome assessment?
- Does the study design or analysis account for important confounding and modifying variables? (only relevant for observational studies)

First Tier. Studies placed in the first tier received ratings of "definitely low" or "probably low" risk of bias on the key questions **AND** received a rating of "definitely low" or "probably low" risk of bias on the responses to at least 50% of the other applicable questions.

Second Tier. A study was placed in the second tier if it did not meet the criteria for the first or third tiers.

Third Tier. Studies placed in the third tier received ratings of "definitely high" or "probably high" risk of bias for the key questions **AND** received a rating of "definitely high" or "probably high" risk of bias on the response to at least 50% of the other applicable questions.

The results of the risk of bias assessment for the different types of chloromethane health effects studies (observational epidemiology and animal experimental studies) are presented in Tables C-8, C-9, and C-10, respectively.

Table C-8. Summary of Risk of Bias Assessment for Chloromethane – Epidemiology Studies

Reference	Selection bias — Were the comparison groups appropriate?	Confounding bias — Did the study design or analysis account for important confounding and modifying variables?*	Attrition / exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization?*	Detection bias — Is there confidence in the outcome assessment?*	Selective reporting bias — Were all measured outcomes reported?	Risk of bias tier
Outcome: Cardiovascular effects							
Cohort studies							
Holmes et al. 1986	++	–	+	–	–	++	Second
Rafnsson and Gudmundsson 1997	++	–	+	–	++	++	Second
Rafnsson and Kristbjornsdottir 2014	++	–	+	–	++	++	Second
Outcome: Neurological effects							
Cohort studies							
Gudmundsson 1977	–	– –	–	–	–	+	Third
Population studies							
NIOSH 1976	++	–	++	+	++	++	Second

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; NA = not applicable
*Key question used to assign risk of bias tier

Table C-9. Summary of Risk of Bias Assessment for Chloromethane – Human-Controlled Exposure Studies

Reference	Risk of bias criteria and ratings							Risk of bias tier
	Selection bias		Performance bias	Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Outcome: Cardiovascular effects								
Inhalation acute exposure								
Stewart et al. 1980	–	–	–	–	+	–	++	Third
Outcome: Neurological effects								
Inhalation acute exposure								
Putz-Anderson et al. 1981a	–	–	–	– –	+	+	+	Second
Putz-Anderson et al. 1981b	–	–	–	–	+	+	+	Second
Stewart et al. 1980	–	–	–	–	+	–	++	Third

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; NA = not applicable
*Key question used to assign risk of bias tier

Table C-10. Risk of Bias Assessment for Select Endpoints for Chloromethane – Experimental Animal Studies

| | Risk of bias criteria and ratings | | | | | | | | |
| | Selection bias | | Performance bias | | Attrition/ exclusion bias | Detection bias | | Selective reporting bias | |
Reference	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment?***	Were all measured outcomes reported?	Risk of bias tier
Outcome: Cardiovascular effects									
Inhalation acute exposure									
McKenna et al. 1981a (dog)	+	−	++	−	++	++	++	++	First
McKenna et al. 1981a (cat)	+	−	++	−	++	++	++	++	First
von Oettingen et al. 1949, 1950 (dog)	−	−	−	−	+	++	−	+	Third
Inhalation intermediate exposure									
CIIT 1981 (6 months, rat)	++	++	+	−	++	++	++	++	First
CIIT 1981 (6 month, mouse)	++	++	+	−	++	+	++	++	First
McKenna et al. 1981b (rat)	++	−	++	−	+	++	+	+	First
McKenna et al. 1981b (mouse)	++	−	++	−	+	++	+	+	First
McKenna et al. 1981b (dog)	++	−	++	−	+	++	+	+	First
Mitchell et al. 1979 (rat)	++	−	+	−	++	++	−	+	Second
Mitchell et al. 1979 (mouse)	++	−	+	−	− −	++	−	+	Second
Inhalation chronic exposure									
CIIT 1981 (12 months, rat)	++	++	+	−	++	++	++	++	First
CIIT 1981 (12 months, mouse)	++	++	+	−	++	+	++	++	First
CIIT 1981 (18 months, rat)	++	++	+	−	++	++	++	++	First
CIIT 1981 (18 months, mouse)	++	++	+	−	++	+	++	++	First

Table C-10. Risk of Bias Assessment for Select Endpoints for Chloromethane – Experimental Animal Studies

Reference	Risk of bias criteria and ratings								Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment?***	Were all measured outcomes reported?	
CIIT 1981 (24 months, rat)	++	++	+	–	++	++	++	++	First
CIIT 1981 (24 months, mouse)	++	++	+	–	++	+	++	++	First

Outcome: Hepatic effects

Inhalation acute exposure

Burek et al. 1981 (48 hours, rat)	++	–	++	–	++	++	+	++	First
Burek et al. 1981 (72 hours, rat)	++	–	++	–	++	++	+	++	First
Chellman et al. 1986a (rat)	–	+	++	–	+	++	++	++	First
Chellman et al. 1986b (mouse)	–	+	++	–	–	+	+	+	First
Dunn and Smith 1947 (rat)	–	–	–	–	–	–	–	–	Third
Dunn and Smith 1947 (mouse)	–	–	–	–	–	–	–	–	Third
Dunn and Smith 1947 (guinea pig)	–	–	–	–	–	–	–	–	Third
Landry et al. 1985 (continuous, Experiment 1, mouse)	+	–	++	–	++	++	+	+	First
Landry et al. 1985 (continuous, Experiment 2, mouse)	+	–	++	–	++	++	+	+	First
Landry et al. 1985 (intermittent, Experiment 1, mouse)	+	–	++	–	++	++	+	+	First

Table C-10. Risk of Bias Assessment for Select Endpoints for Chloromethane – Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias		Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment?***	Were all measured outcomes reported?	Risk of bias tier
Landry et al. 1985 (intermittent, Experiment 2, mouse)	+	–	++	–	++	++	+	+	First
McKenna et al. 1981a (dog)	+	–	++	–	++	++	++	++	First
McKenna et al. 1981a (cat)	+	–	++	–	++	++	++	++	First
Morgan et al. 1982 (B6C3F1 mouse)	–	+	++	–	+	++	–	++	Second
Morgan et al. 1982 (C3H mouse)	–	+	++	–	+	++	–	++	Second
Morgan et al. 1982 (C57Bl/6 mouse)	–	+	++	–	+	++	–	++	Second
Morgan et al. 1982 (rat)	–	+	++	–	+	++	–	++	Second
Wolkowski-Tyl et al. 1981b, 1983b (mouse)	+	–	+	–	++	++	–	++	Second
Inhalation intermediate exposure									
CIIT 1981 (6 months, rat)	++	++	+	–	++	++	++	++	First
CIIT 1981 (6 months, mouse)	++	++	+	–	++	+	++	++	First
Dunn and Smith 1947 (rat)	–	–	–	–	–	–	–	–	Third
McKenna et al. 1981b (rat)	++	–	++	–	+	++	+	+	First
McKenna et al. 1981b (mouse)	++	–	++	–	+	++	+	+	First

Table C-10. Risk of Bias Assessment for Select Endpoints for Chloromethane – Experimental Animal Studies

Reference	Risk of bias criteria and ratings								Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
McKenna et al. 1981b (dog)	++	−	++	−	+	++	+	+	First
Mitchell et al. 1979 (rat)	++	−	+	−	++	++	−	+	Second
Mitchell et al. 1979 (mouse)	++	−	+	−	− −	++	−	+	Second
Inhalation chronic exposure									
CIIT 1981 (12 months, rat)	++	++	+	−	++	++	++	++	First
CIIT 1981 (12 months, mouse)	++	++	+	−	++	+	++	++	First
CIIT 1981 (18 months, rat)	++	++	+	−	++	++	++	++	First
CIIT 1981 (18 months, mouse)	++	++	+	−	++	+	++	++	First
CIIT 1981 (24 months, rat)	++	++	+	−	++	++	++	++	First
CIIT 1981 (24 months, mouse)	++	++	+	−	++	+	++	++	First
Outcome: Neurological effects									
Inhalation acute exposure									
Burek et al. 1981 (48 hours, rat)	++	−	++	−	++	++	+	++	First
Burek et al. 1981 (72 hours, rat)	++	−	++	−	++	++	+	++	First
Chellman et al. 1986a (rat)	−	+	++	−	+	++	++	++	First
Chellman et al. 1986b (mouse, 6 hours)	−	+	++	−	−	+	+	+	First
Chellman et al. 1986b (mouse, 2 weeks)	−	+	++	−	−	+	+	+	First

Table C-10. Risk of Bias Assessment for Select Endpoints for Chloromethane – Experimental Animal Studies

Reference	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Risk of bias tier
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Jiang et al. 1985 (mouse)	–	–	++	–	++	+	+	+	First
Landry et al. 1985 (continuous, Experiment 1, mouse)	+	–	++	–	++	++	+	+	First
Landry et al. 1985 (continuous, Experiment 2, mouse)	+	–	++	–	++	++	+	+	First
Landry et al. 1985 (intermittent, Experiment 1, mouse)	+	–	++	–	++	++	+	+	First
Landry et al. 1985 (intermittent, Experiment 2, mouse)	+	–	++	–	++	++	+	+	First
McKenna et al. 1981a (dog)	+	–	++	–	++	++	++	++	First
McKenna et al. 1981a (cat)	+	–	++	–	++	++	++	++	First
Morgan et al. 1982 (B6C3F1 mouse)	–	+	++	–	+	++	–	++	Second
Morgan et al. 1982 (C3H mouse)	–	+	++	–	+	++	–	++	Second
Morgan et al. 1982 (C57Bl/6 mouse)	–	+	++	–	+	++	–	++	Second
Morgan et al. 1982 (rat)	–	+	++	–	+	++	–	++	Second
Smith and von Oettingen 1947a, 1947b (monkey)	–	–	–	–	–	++	–	–	Third

Table C-10. Risk of Bias Assessment for Select Endpoints for Chloromethane – Experimental Animal Studies

| | Risk of bias criteria and ratings | | | | | | | | |
| | Selection bias | | Performance bias | | Attrition/ exclusion bias | Detection bias | | Selective reporting bias | |
Reference	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Risk of bias tier
Smith and von Oettingen 1947a, 1947b (rat)	–	–	–	–	–	++	–	–	Third
Smith and von Oettingen 1947a, 1947b (mouse)	–	–	–	–	–	++	–	–	Third
Smith and von Oettingen 1947a, 1947b (guinea pig)	–	–	–	–	–	++	–	–	Third
Smith and von Oettingen 1947a, 1947b (dog)	–	–	–	–	–	++	–	–	Third
Smith and von Oettingen 1947a, 1947b (cat)	–	–	–	–	–	++	–	–	Third
Smith and von Oettingen 1947a, 1947b (rabbit)	–	–	–	–	–	++	–	–	Third
von Oettingen 1949, 1950 (mouse)	–	–	–	–	–	++	–	–	Third
von Oettingen 1949, 1950 (dog)	–	–	–	–	+	++	–	–	Third
Wolkowski-Tyl et al. 1983a (mouse)	–	–	++	–	+	++	–	++	Second
Wolkowski-Tyl et al. 1983b (mouse)	+	–	+	–	++	++	–	++	Second

Table C-10. Risk of Bias Assessment for Select Endpoints for Chloromethane – Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Risk of bias tier
Inhalation intermediate exposure									
CIIT 1981 (6 months, rat)	++	++	+	−	++	++	+	++	First
CIIT 1981 (6 months, mouse)	++	++	+	−	++	+	+	++	First
McKenna et al. 1981b (rat)	++	−	++	−	+	++	+	+	First
McKenna et al. 1981b (mouse)	++	−	++	−	+	++	+	+	First
McKenna et al. 1981b (dog)	++	−	++	−	+	++	+	+	First
Mitchell et al. 1979 (rat)	++	−	+	−	++	++	−	+	Second
Mitchell et al. 1979 (mouse)	++	−	+	−	− −	++	−	+	Second
Smith and von Oettingen 1947a, 1947b (monkey)	−	−	−	−	−	++	−	−	Third
Smith and von Oettingen 1947a, 1947b (rat)	−	−	−	−	−	++	−	−	Third
Smith and von Oettingen 1947a, 1947b (mouse)	−	−	−	−	−	++	−	−	Third
Smith and von Oettingen 1947a, 1947b (guinea pig)	−	−	−	−	−	++	−	−	Third
Smith and von Oettingen 1947a, 1947b (dog)	−	−	−	−	−	++	−	−	Third
Smith and von Oettingen 1947a, 1947b (cat)	−	−	−	−	−	++	−	−	Third

Table C-10. Risk of Bias Assessment for Select Endpoints for Chloromethane – Experimental Animal Studies

| | Risk of bias criteria and ratings | | | | | | | | |
| | Selection bias | | Performance bias | | Attrition/ exclusion bias | Detection bias | | Selective reporting bias | |
Reference	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment?***	Were all measured outcomes reported?	Risk of bias tier
Inhalation chronic exposure									
CIIT 1981 (12 months, rat)	++	++	+	–	+	++	+	++	First
CIIT 1981 (12 months, mouse)	++	++	+	–	+	+	+	++	First
CIIT 1981 (18 months, rat)	++	++	+	–	++	++	++	++	First
CIIT 1981 (18 months, mouse)	++	++	+	–	++	+	++	++	First
CIIT 1981 (24 months, rat)	++	++	+	–	++	++	++	++	First
CIIT 1981 (24 months, mouse)	++	++	+	–	++	+	++	++	First
Outcome: Male reproductive effects									
Inhalation acute exposure									
Burek et al. 1981 (48 hours, rat)	++	–	++	–	++	++	+	++	First
Burek et al. 1981 (72 hours, rat)	++	–	++	–	++	++	+	++	First
Chapin et al. 1984 (rat)	–	–	++	–	++	++	+	++	First
Chellman et al. 1986a (rat)	–	+	++	–	+	+	++	++	First
Chellman et al. 1986c (rat)	–	+	++	–	–	+	+	+	First
Chellman et al. 1987 (rat)	+	+	++	–	+	++	+	+	First
Morgan et al. 1982 (rat)	–	+	++	–	+	++	–	++	Second
McKenna et al. 1981a (dog)	+	–	++	–	++	++	++	++	First
McKenna et al. 1981a (cat)	+	–	++	–	++	++	++	++	First

Table C-10. Risk of Bias Assessment for Select Endpoints for Chloromethane – Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Risk of bias tier
Working et al. 1985a (rat)	+	–	++	–	–	++	+	++	First
Working et al. 1985b (rat)	++	–	++	–	+	++	–	++	Second
Working and Bus 1986 (rat)	+	–	+	–	+	+	+	++	First
Inhalation intermediate exposure									
CIIT 1981 (6 months, rat)	++	++	+	–	++	++	++	++	First
CIIT 1981 (6 months, mouse)	++	++	+	–	+	+	++	++	First
Hamm et al. 1985 (rat)	+	–	–	–	–	+	+	++	Second
McKenna et al. 1981b (rat)	++	–	++	–	+	++	+	+	First
McKenna et al. 1981b (mouse)	++	–	++	–	+	++	+	+	First
McKenna et al. 1981b (beagle)	++	–	++	–	+	++	+	+	First
Mitchell et al. 1979 (rat)	++	–	+	–	++	++	–	+	Second
Mitchell et al. 1979 (mouse)	++	–	+	–	++	++	–	+	Second
Inhalation chronic exposure									
CIIT 1981 (12 months, rat)	++	++	+	–	++	++	++	++	First
CIIT 1981 (12 months, mouse)	++	++	+	–	+	+	++	++	First
CIIT 1981 (18 months, rat)	++	++	+	–	++	++	++	++	First
CIIT 1981 (18 months, mouse)	++	++	+	–	+	+	++	++	First
CIIT 1981 (24 months, rat)	++	++	+	–	++	++	++	++	First

Table C-10. Risk of Bias Assessment for Select Endpoints for Chloromethane – Experimental Animal Studies

Reference	Risk of bias criteria and ratings								Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment?***	Were all measured outcomes reported?	
CIIT 1981 (24 months, mouse)	++	++	+	–	+	+	++	++	First

Outcome: Developmental effects

Inhalation acute exposure

Wolkowski-Tyl et al. 1983a (mouse)	–	–	++	–	+	++	+	++	First
Wolkowski-Tyl et al. 1983a (rat)	–	–	++	+	++	++	+	++	First
Wolkowski-Tyl et al. 1983b (mouse)	+	–	+	–	++	++	+	++	First

Inhalation intermediate exposure

Hamm et al. 1985 (rat)	+	–	–	–	–	+	+	++	Second
Theuns-van Vliet 2016 (rabbit)	–	–	++	–	++	++	–	+	Second

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias
*Key question used to assign risk of bias tier

C.6 RATE THE CONFIDENCE IN THE BODY OF EVIDENCE FOR EACH RELEVANT OUTCOME

Confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome. ATSDR did not evaluate the confidence in the body of evidence for carcinogenicity; rather, the Agency defaulted to the cancer weight-of-evidence assessment of other agencies including HHS, EPA, and IARC. The confidence in the body of evidence for an association or no association between exposure to chloromethane and a particular outcome was based on the strengths and weaknesses of individual studies. Four descriptors were used to describe the confidence in the body of evidence for effects or when no effect was found:

- **High confidence:** the true effect is highly likely to be reflected in the apparent relationship
- **Moderate confidence:** the true effect may be reflected in the apparent relationship
- **Low confidence:** the true effect may be different from the apparent relationship
- **Very low confidence:** the true effect is highly likely to be different from the apparent relationship

Confidence in the body of evidence for a particular outcome was rated for each type of study: case-control, case series, cohort, population, human-controlled exposure, and experimental animal. In the absence of data to the contrary, data for a particular outcome were collapsed across animal species, routes of exposure, and exposure durations. If species (or strain), route, or exposure duration differences were noted, then the data were treated as separate outcomes.

C.6.1 Initial Confidence Rating

In ATSDR's modification to the OHAT approach, the body of evidence for an association (or no association) between exposure to chloromethane and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions, which were customized for epidemiology, human controlled exposure, or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies, human controlled exposure, and experimental animal studies are presented in Tables C-11, C-12, and C-13, respectively. The initial confidence in the study was determined based on the number of key features present in the study design:

- **High Initial Confidence:** Studies in which the responses to the four questions were "yes".

- **Moderate Initial Confidence:** Studies in which the responses to only three of the questions were "yes".

- **Low Initial Confidence:** Studies in which the responses to only two of the questions were "yes".

- **Very Low Initial Confidence:** Studies in which the response to one or none of the questions was "yes".

Table C-11. Key Features of Study Design for Observational Epidemiology Studies

Exposure was experimentally controlled

Exposure occurred prior to the outcome

Outcome was assessed on individual level rather than at the population level

A comparison group was used

Table C-12. Key Features of Study Design for Human-Controlled Exposure Studies

A comparison group was used or the subjects served as their own control

A sufficient number of subjects were tested

Appropriate methods were used to measure outcomes (i.e., clinically-confirmed outcome versus self-reported)

Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

Table C-13. Key Features of Study Design for Experimental Animal Studies

A concurrent control group was used

A sufficient number of animals per group were tested

Appropriate parameters were used to assess a potential adverse effect

Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

The presence or absence of the key features and the initial confidence levels for studies examining cardiovascular, hepatic, renal, neurologic, reproductive and developmental effects.

A summary of the initial confidence ratings for each outcome is presented in Tables C-14, C-15, C-16, and C-17. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence; any exceptions were noted in Tables C-14, C-15, C-16, and C-17.

Table C-14. Presence of Key Features of Study Design for Chloromethane—Observational Epidemiology Studies

Reference	Key features				
	Controlled Exposure	Exposure prior to outcome	Outcome assess on individual level	Comparison group	Initial study confidence
Outcome: Cardiovascular effects					
Cohort studies					
Holmes et al. 1986	No	Yes	Yes	Yes	Moderate
Rafnsson and Gudmundsson 1997	No	Yes	Yes	Yes	Moderate
Rafnsson and Kristbjornsdottir 2014	No	Yes	Yes	Yes	Moderate
Outcome: Neurological effects					
Cohort studies					
Gudmundsson 1977	No	Yes	Yes	No	Low
Population studies					
NIOSH 1976	No	Yes	Yes	Yes	Moderate

Table C-15. Presence of Key Features of Study Design for Chloromethane—Experimental Controlled Human Exposure

Reference	Key Features				
	Comparison group or served as own controls	Sufficient number of subjects tested	Appropriate outcome assessment	Appropriate statistical analysis	Initial study confidence
Outcome: Cardiovascular effects					
Inhalation acute exposure					
Stewart et al. 1980	Yes	No	No	Yes	Low
Outcome: Neurological effects					
Inhalation acute exposure					
Putz-Anderson et al. 1981a	Yes	Yes	Yes	Yes	High
Putz-Anderson et al. 1981b	Yes	Yes	Yes	Yes	High
Stewart et al. 1980	Yes	No	Yes	Yes	Moderate

Table C-16. Presence of Key Features of Study Design for Chloromethane— Experimental Animal Studies

Reference	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Outcome: Cardiovascular effects					
Inhalation acute exposure					
McKenna et al. et al. 1981a (dog)	Yes	No	Yes	Yes	Moderate
McKenna et al. et al. 1981a (cat)	Yes	No	Yes	Yes	Moderate
von Oettingen et al. 1949, 1950	No	Yes	Yes	No	Low
Inhalation intermediate exposure					
CIIT 1981 (6 months, rat)	Yes	Yes	Yes	Yes	High
CIIT 1981 (6 months, mouse)	Yes	Yes	Yes	Yes	High
McKenna et al. 1981b (rat)	Yes	Yes	Yes	Yes	High
McKenna et al. 1981b (mouse)	Yes	Yes	Yes	Yes	High
McKenna et al. 1981b (dog)	Yes	No	Yes	Yes	Moderate
Mitchell et al. 1979 (rat)	Yes	Yes	Yes	Yes	High
Mitchell et al. 1979 (mouse)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
CIIT 1981 (12 months, rat)	Yes	Yes	Yes	Yes	High
CIIT 1981 (12 months, mouse)	Yes	Yes	Yes	Yes	High
CIIT 1981 (18 months, rat)	Yes	Yes	Yes	Yes	High
CIIT 1981 (18 months, mouse)	Yes	Yes	Yes	Yes	High
CIIT 1981 (24 months rat)	Yes	Yes	Yes	Yes	High
CIIT 1981 (24 months, mouse)	Yes	Yes	Yes	Yes	High
Outcome: Hepatic effects					
Inhalation acute exposure					
Burek et al. 1981 (rat)	Yes	Yes	Yes	Yes	High
Chellman et al. 1986a (rat)	Yes	Yes	Yes	Yes	High
Chellman et al. 1986b (mouse)	Yes	Yes	Yes	Yes	High
Landry et al. 1985 (mouse)	Yes	Yes	Yes	No	Moderate
Dunn and Smith 1947 (rat)	No	Yes	Yes	No	Low
Dunn and Smith 1947 (mouse)	No	Yes	Yes	No	Low
Dunn and Smith 1947 (guinea pig)	No	Yes	Yes	No	Low
McKenna et al. 1981a (dog)	Yes	No	Yes	Yes	Moderate

Table C-16. Presence of Key Features of Study Design for Chloromethane—Experimental Animal Studies

Reference	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
McKenna et al. 1981a (cat)	Yes	No	Yes	Yes	Moderate
Morgan et al. 1982 (mouse)	Yes	Yes	Yes	Yes	High
Morgan et al. 1982 (rat)	Yes	Yes	Yes	Yes	High
Inhalation intermediate exposure					
CIIT 1981 (6 months, rat)	Yes	Yes	Yes	Yes	High
CIIT 1981 (6 months, mouse)	Yes	Yes	Yes	Yes	High
Dunn and Smith 1947 (rat)	No	Yes	Yes	No	Low
McKenna et al. 1981b (rat)	Yes	Yes	Yes	Yes	High
McKenna et al. 1981b (mouse)	Yes	Yes	Yes	Yes	High
McKenna et al. 1981b (dog)	Yes	No	Yes	Yes	Moderate
Mitchell et al. 1979 (rat)	Yes	Yes	Yes	Yes	High
Mitchell et al. 1979 (mouse)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
CIIT 1981 (12 months, rat)	Yes	Yes	Yes	Yes	High
CIIT 1981 (12 months, mouse)	Yes	Yes	Yes	Yes	High
CIIT 1981 (18 months, rat)	Yes	Yes	Yes	Yes	High
CIIT 1981 (18 months, mouse)	Yes	Yes	Yes	Yes	High
CIIT 1981 (24 months, rat)	Yes	Yes	Yes	Yes	High
CIIT 1981 (24 months, mouse)	Yes	Yes	Yes	Yes	High
Outcome: Neurological effects					
Inhalation acute exposure					
Burek et al. 1981 (rat)	Yes	Yes	No	Yes	Moderate
Chellman et al. 1986a (rat)	Yes	Yes	Yes	Yes	High
Chellman et al. 1986b (mouse, 6 hours)	Yes	Yes	Yes	Yes	High
Chellman et al. 1986b (mouse, 2 weeks)	Yes	Yes	Yes	Yes	High
Jiang et al. 1985 (mouse)	Yes	Yes	Yes	No	Moderate
Landry et al. 1985 (mouse)	Yes	Yes	Yes	Yes	High
McKenna et al. 1981a (dog)	Yes	No	Yes	Yes	Moderate
McKenna et al. 1981a (cat)	Yes	No	Yes	Yes	Moderate
Morgan et al. 1982 (mouse)	Yes	Yes	Yes	Yes	High
Morgan et al. 1982 (rat)	Yes	Yes	Yes	Yes	High

Reference	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Smith and von Oettingen 1947a, 1947b (monkey)	No	No	Yes	No	Low
Smith and von Oettingen 1947a, 1947b (rat)	Yes	Yes	Yes	No	Moderate
Smith and von Oettingen 1947a, 1947b (mouse)	Yes	Yes	Yes	No	Moderate
Smith and von Oettingen 1947a, 1947b (guinea pig)	Yes	Yes	Yes	No	Moderate
Smith and von Oettingen 1947a, 1947b (dog)	Yes	Yes	Yes	No	Moderate
Smith and von Oettingen 1947a, 1947b (cat)	No	No	Yes	No	Very low
Smith and von Oettingen 1947a, 1947b (rabbit)	Yes	No	Yes	No	Low
von Oettingen 1949, 1950 (mouse)	No	Yes	Yes	No	Low
von Oettingen 1949, 1950 (dog)	No	Yes	No	No	Very low
Wolkowski-Tyl et al. 1983a (mouse)	Yes	Yes	Yes	Yes	High
Wolkowski-Tyl et al. 1983b (mouse)	Yes	Yes	No	Yes	Moderate
Inhalation intermediate exposure					
CIIT 1981 (6 months, Rat)	Yes	Yes	No	Yes	Moderate
CIIT 1981 (6 months, mouse)	Yes	Yes	No	Yes	Moderate
McKenna et al. 1981b (rat)	Yes	Yes	Yes	Yes	High
McKenna et al. 1981b (mouse)	Yes	Yes	Yes	Yes	High
McKenna et al. 1981b (dog)	Yes	Yes	No	Yes	Moderate
Mitchell et al. 1979 (rat)	Yes	Yes	Yes	Yes	High
Mitchell et al. 1979 (mouse)	Yes	Yes	Yes	Yes	High
Smith and von Oettingen 1947a, 1947b (monkey)	No	No	Yes	No	Low
Smith and von Oettingen 1947a, 1947b (rat)	Yes	Yes	Yes	No	Moderate
Smith and von Oettingen 1947a, 1947b (mouse)	Yes	Yes	Yes	No	Moderate
Smith and von Oettingen 1947a, 1947b (guinea pig)	Yes	Yes	Yes	No	Moderate
Smith and von Oettingen 1947a, 1947b (dog)	Yes	Yes	Yes	No	Moderate

Table C-16. Presence of Key Features of Study Design for Chloromethane— Experimental Animal Studies

Table C-16. Presence of Key Features of Study Design for Chloromethane— Experimental Animal Studies

Reference	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Smith and von Oettingen 1947a, 1947b (cat)	No	No	Yes	No	Very low
Inhalation chronic exposure					
CIIT 1981 (12 months, rat)	Yes	Yes	No	Yes	Moderate
CIIT 1981 (12 months mouse)	Yes	Yes	No	Yes	Moderate
CIIT 1981 (18 months, rats	Yes	Yes	Yes	Yes	High
CIIT 1981 (18 months, mouse)	Yes	Yes	Yes	Yes	High
CIIT 1981 (24 months, rat)	Yes	Yes	Yes	Yes	High
CIIT 1981 (24 months, mouse)	Yes	Yes	Yes	Yes	High
Outcome: Male reproductive effects					
Inhalation acute exposure					
Burek et al. 1981 (rat)	Yes	Yes	Yes	Yes	High
Chapin et al. 1984 (rat)	Yes	Yes	Yes	Yes	High
Chellman et al. 1986a (rat)	Yes	Yes	Yes	Yes	High
Chellman et al. 1986c (rat)	Yes	Yes	Yes	Yes	High
Chellman et al. 1987 (rat)	Yes	Yes	Yes	Yes	High
Morgan et al. 1982 (rat)	Yes	Yes	Yes	Yes	High
McKenna et al. 1981a (dog)	Yes	No	Yes	Yes	Moderate
McKenna et al. 1981a (cat)	Yes	No	Yes	Yes	Moderate
Working et al. 1985a (rat)	Yes	Yes	Yes	Yes	High
Working et al. 1985b (rat)	Yes	Yes	Yes	Yes	High
Working and Bus 1986 (rat)	Yes	Yes	Yes	Yes	High
Inhalation intermediate exposure					
CIIT 1981 (6 months, rat)	Yes	Yes	Yes	Yes	High
CIIT 1981 (6 months, mouse)	Yes	Yes	Yes	Yes	High
Hamm et al. 1985 (rat)	Yes	Yes	Yes	Yes	High
McKenna et al. 1981b (rat)	Yes	Yes	Yes	Yes	High
McKenna et al. 1981b (mouse)	Yes	Yes	Yes	Yes	High
McKenna et al. 1981b (dog)	Yes	No	Yes	Yes	Moderate
Mitchell et al. 1979 (rat)	Yes	Yes	Yes	Yes	High
Mitchell et al. 1979 (mouse)	Yes	Yes	Yes	Yes	High

Table C-16. Presence of Key Features of Study Design for Chloromethane—Experimental Animal Studies

Reference	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Inhalation chronic exposure					
CIIT 1981 (12 months, rat)	Yes	Yes	Yes	Yes	High
CIIT 1981 (12 months, mouse)	Yes	Yes	Yes	Yes	High
CIIT 1981 (18 months, rat)	Yes	Yes	Yes	Yes	High
CIIT 1981 (18 months, mouse)	Yes	Yes	Yes	Yes	High
CIIT 1981 (24 months, rat)	Yes	Yes	Yes	Yes	High
CIIT 1981 (24 months, mouse)	Yes	Yes	Yes	Yes	High
Outcome: Developmental effects					
Inhalation acute exposure					
Wolkowski-Tyl et al. 1983a (mouse)	Yes	Yes	Yes	Yes	High
Wolkowski-Tyl et al. 1983a (rat)	Yes	Yes	Yes	Yes	High
Wolkowski-Tyl et al. 1983b (mouse)	Yes	Yes	Yes	Yes	High
Inhalation intermediate exposure					
Hamm et al. 1985 (rat)	Yes	Yes	Yes	Yes	High
Theuns-van Vliet 2016 (rabbit)	Yes	Yes	Yes	Yes	High

Table C-17. Initial Confidence Rating for Chloromethane Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Cardiovascular effects		
Inhalation acute exposure		
Human studies		
Stewart et al. 1980	Low	
Rafnsson and Gudmundsson 1997	Moderate	Moderate
Rafnsson and Kristbjornsdottir 2014	Moderate	
Animal studies		
McKenna et al. et al. 1981a (Beagle)	Moderate	
McKenna et al. et al. 1981a (cat)	Moderate	Moderate
von Oettingen et al. 1949, 1950	Low	

Table C-17. Initial Confidence Rating for Chloromethane Health Effects Studies

	Initial study confidence	Initial confidence rating
Inhalation intermediate exposure		
Animal studies		
CIIT 1981 (6 months, rat)	High	
CIIT 1981 (6 months, mouse)	High	
McKenna et al. 1981b (rat)	High	
McKenna et al. 1981b (mouse)	High	High
McKenna et al. 1981b (dog)	Moderate	
Mitchell et al. 1979 (rat)	High	
Mitchell et al. 1979 (mouse)	High	
Inhalation chronic exposure		
Human studies		
Holmes et al. 1986	Moderate	Moderate
Animal studies		
CIIT 1981 (12 months, rat)	High	
CIIT 1981 (12 months, mouse)	High	
CIIT 1981 (18 months, rat)	High	
CIIT 1981 (18 months, mouse)	High	High
CIIT 1981 (24 months, rat)	High	
CIIT 1981 (24 months, mouse)	High	
Outcome: Hepatic effects		
Inhalation acute exposure		
Animal studies		
Burek et al. 1981 (rat)	High	
Chellman et al. 1986a (rat)	High	
Chellman et al. 1986b (mouse)	High	
Dunn and Smith 1947 (rat)	Low	
Dunn and Smith 1947 (mouse)	Low	
Dunn and Smith 1947 (guinea pig)	Low	High
Morgan et al. 1982 (mouse)	High	
Morgan et al. 1982 (rat)	High	
Landry et al. 1985 (mouse)	Moderate	
McKenna et al. 1981a (dog)	Moderate	
McKenna et al. 1981a (cat)	Moderate	
Inhalation intermediate exposure		
CIIT 1981 (6 months, rat)	High	
CIIT 1981 (6 months, mouse)	High	
McKenna et al. 1981b (rat)	High	
McKenna et al. 1981b (mouse)	High	High
McKenna et al. 1981b (dog)	Moderate	
Mitchell et al. 1979 (rat)	High	

Table C-17. Initial Confidence Rating for Chloromethane Health Effects Studies

	Initial study confidence	Initial confidence rating
Mitchell et al. 1979 (mouse)	High	
Inhalation chronic exposure		
Animal studies		
CIIT 1981 (12 months, rat)	High	
CIIT 1981 (12 months, mouse)	High	
CIIT 1981 (18 months, rat)	High	High
CIIT 1981 (18 months, mouse)	High	
CIIT 1981 (24 months, rat)	High	
CIIT 1981 (24 months, mouse)	High	
Outcome: Neurological effects		
Inhalation acute exposure		
Animal studies		
Burek et al. 1981 (rat)	Moderate	
Chellman et al. 1986a (rat)	High	
Chellman et al. 1986b (mouse, 6 hours)	High	
Chellman et al. 1986b (mouse, 2 weeks)	High	
Jiang et al. 1985 (mouse)	Moderate	
Morgan et al. 1982 (mouse)	High	
Morgan et al. 1982 (rat)	High	
Landry et al. 1985 (mouse)	High	
McKenna et al. 1981a (dog)	Moderate	
McKenna et al. 1981a (cat)	Moderate	
Smith and von Oettingen 1947a, 1947b (monkey)	Low	High
Smith and von Oettingen 1947a, 1947b (rat)	Moderate	
Smith and von Oettingen 1947a, 1947b (mouse)	Moderate	
Smith and von Oettingen 1947a, 1947b (guinea pig)	Moderate	
Smith and von Oettingen 1947a, 1947b (dog)	Moderate	
Smith and von Oettingen 1947a, 1947b (cat)	Very low	
Smith and von Oettingen 1947a, 1947b (rabbit)	Low	
von Oettingen 1949, 1950 (mouse)	Low	
von Oettingen 1949, 1950 (dog)	Very low	
Wolkowski-Tyl et al. 1983a (mouse)	High	
Wolkowski-Tyl et al. 1983b (mouse)	Moderate	

Table C-17. Initial Confidence Rating for Chloromethane Health Effects Studies

	Initial study confidence	Initial confidence rating
Human studies		
Gudmundsson 1977	Low	High
NIOSH 1976	Moderate	
Putz-Anderson et al. 1981a	High	
Putz-Anderson et al. 1981b	High	
Stewart et al. 1980	Moderate	
Inhalation intermediate exposure		
Animal studies		
CIIT 1981 (6 months, rat)	Moderate	
CIIT 1981 (6 months, mouse)	Moderate	
McKenna et al. 1981b (rat)	High	
McKenna et al. 1981b (mouse)	High	
McKenna et al. 1981b (dog)	Moderate	
Mitchell et al. 1979 (rat)	High	
Mitchell et al. 1979 (mouse)	Moderate	
Smith and von Oettingen 1947a, 1947b (monkey)	Low	High
Smith and von Oettingen 1947a, 1947b (rat)	Moderate	
Smith and von Oettingen 1947a, 1947b (mouse)	Moderate	
Smith and von Oettingen 1947a, 1947b (guinea pig)	Moderate	
Smith and von Oettingen 1947a, 1947b (dog)	Moderate	
Smith and von Oettingen 1947a, 1947b (cat)	Very low	
Inhalation chronic exposure		
Animal studies		
CIIT 1981 (12 months, rat)	Moderate	
CIIT 1981 (12 months, mouse)	Moderate	
CIIT 1981 (18 months, rat)	High	High
CIIT 1981 (18 months, mouse)	High	
CIIT 1981 (24 months, rat)	High	
CIIT 1981 (24 months, mouse)	High	
Outcome: Male reproductive effects		
Inhalation acute exposure		
Animal studies		
Burek et al. 1981 (rat)	High	High
Chapin et al. 1984 (rat)	High	
Chellman et al. 1986a (rat)	High	
Chellman et al. 1986c (rat)	High	

Table C-17. Initial Confidence Rating for Chloromethane Health Effects Studies

	Initial study confidence	Initial confidence rating
Chellman et al. 1987 (rat)	High	
Morgan et al. 1982 (rat)	High	
McKenna et al. 1981a (dog)	Moderate	
McKenna et al. 1981a (cat)	Moderate	
Working et al. 1985a	High	
Working et al. 1985b	High	
Working and Bus 1986	High	
Inhalation intermediate exposure		
Animal studies		
CIIT 1981 (6 months, rat)	High	
CIIT 1981 (6 months, mouse)	High	
Hamm et al. 1985 (rat)	High	
McKenna et al. 1981b (rat)	High	High
McKenna et al. 1981b (mouse)	High	
McKenna et al. 1981b (dog)	Moderate	
Mitchell et al. 1979 (rat)	High	
Mitchell et al. 1979 (mouse)	High	
Inhalation chronic exposure		
Animal studies		
CIIT 1981 (12 months, rat)	High	
CIIT 1981 (12 months, mouse)	High	
CIIT 1981 (18 months, rat)	High	
CIIT 1981 (18 months, mouse)	High	High
CIIT 1981 (24 months, rat)	High	
CIIT 1981 (24 months, mouse)	High	
Outcome: Developmental effects		
Inhalation acute exposure		
Animal studies		
Wolkowski-Tyl et al. 1983a (mouse)	High	
Wolkowski-Tyl et al. 1983a (rat)	High	High
Wolkowski-Tyl et al. 1983b (mouse)	High	
Inhalation intermediate exposure		
Animal studies		
Hamm et al. 1985 (rat)	High	High
Theuns-van Vliet 2016 (rabbit)	High	High

C.6.2 Adjustment of the Confidence Rating

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the

confidence in the body of evidence for cardiovascular, renal, hepatic, neurologic, reproductive, and developmental effects are presented in Table C-18. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with chloromethane exposure is presented in Table C-19.

Five properties of the body of evidence were considered to determine whether the confidence rating should be downgraded:

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Tables C-8 and C-9). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
  - No downgrade if most studies are in the risk of bias first tier
  - Downgrade one confidence level if most studies are in the risk of bias second tier
  - Downgrade two confidence levels if most studies are in the risk of bias third tier

- **Unexplained inconsistency.** Evaluation of whether there is inconsistency or large variability in the magnitude or direction of estimates of effect across studies that cannot be explained. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for unexplained inconsistency:
  - No downgrade if there is little inconsistency across studies or if only one study evaluated the outcome
  - Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect
  - Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direct of the effect

- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
  - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans
  - Directness of the endpoints to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects
  - Nature of the exposure in human studies and route of administration in animal studies— inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
  - Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

  Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for indirectness:
  - No downgrade if none of the factors are considered indirect
  - Downgrade one confidence level if one of the factors is considered indirect
  - Downgrade two confidence levels if two or more of the factors are considered indirect

- **Imprecision.** Evaluation of the narrowness of the effect size estimates and whether the studies have adequate statistical power. Data are considered imprecise when the ratio of the upper to lower 95% Cis for most studies is ≥10 for tests of ratio measures (e.g., odds ratios) and ≥100 for absolute measures (e.g., percent control response). Adequate statistical power is determined if the study can detect a potentially biologically meaningful difference between groups (20% change from control response for categorical data or risk ratio of 1.5 for continuous data). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for imprecision:
    - No downgrade if there are no serious imprecisions
    - Downgrade one confidence level for serious imprecisions
    - Downgrade two confidence levels for very serious imprecisions

- **Publication bias.** Evaluation of the concern that studies with statistically significant results are more likely to be published than studies without statistically significant results.
    - Downgrade one level of confidence for cases where there is serious concern with publication bias

Table C-18. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Cardiovascular effects			
Human studies	Moderate	-1 risk of bias -1 imprecision	Very low
Animal studies	Moderate	-1 unexplained inconsistency -1 imprecision	Very low
Outcome: Hepatic Effects			
Animal studies	High	None	High
Outcome: Neurological Effects			
Human studies	High	-1 risk of bias -1 imprecision	Low
Animal studies	High	+Consistency +Large magnitude of effect	High
Outcome: Male reproductive Effects			
Animal studies	High	None	High
Outcome: Developmental Effects			
Animal studies	High	-1 indirectness -1 unexplained inconsistency	Low

Table C-19. Confidence in the Body of Evidence for Chloromethane		
	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Cardiovascular	Very low	Very low
Hepatic	No data	High
Neurological	Low	High
Reproductive	No data	High
Developmental	No data	Low

Four properties of the body of evidence were considered to determine whether the confidence rating should be upgraded:

- **Large magnitude of effect.** Evaluation of whether the magnitude of effect is sufficiently large so that it is unlikely to have occurred as a result of bias from potential confounding factors.
  - o Upgrade one confidence level if there is evidence of a large magnitude of effect in a few studies, provided that the studies have an overall low risk of bias and there is no serious unexplained inconsistency among the studies of similar dose or exposure levels; confidence can also be upgraded if there is one study examining the outcome, provided that the study has an overall low risk of bias

- **Dose response.** Evaluation of the dose-response relationships measured within a study and across studies. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - o Upgrade one confidence level for evidence of a monotonic dose-response gradient
  - o Upgrade one confidence level for evidence of a non-monotonic dose-response gradient where there is prior knowledge that supports a non-monotonic dose-response and a non-monotonic dose-response gradient is observed across studies

- **Plausible confounding or other residual biases.** This factor primarily applies to human studies and is an evaluation of unmeasured determinants of an outcome such as residual bias towards the null (e.g., "healthy worker" effect) or residual bias suggesting a spurious effect (e.g., recall bias). Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - o Upgrade one confidence level for evidence that residual confounding or bias would underestimate an apparent association or treatment effect (i.e., bias toward the null) or suggest a spurious effect when results suggest no effect

- **Consistency in the body of evidence.** Evaluation of consistency across animal models and species, consistency across independent studies of different human populations and exposure scenarios, and consistency across human study types. Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - o Upgrade one confidence level if there is a high degree of consistency in the database

C.7 TRANSLATE CONFIDENCE RATING INTO LEVEL OF EVIDENCE OF HEALTH EFFECTS

In the seventh step of the systematic review of the health effects data for chloromethane, the confidence in the body of evidence for specific outcomes was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted. The level of evidence for health effects was rated on a five-point scale:

- **High level of evidence:** High confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Moderate level of evidence:** Moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Low level of evidence:** Low confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Evidence of no health effect:** High confidence in the body of evidence that exposure to the substance is not associated with the health outcome
- **Inadequate evidence:** Low or moderate confidence in the body of evidence that exposure to the substance is not associated with the health outcome OR very low confidence in the body of evidence for an association between exposure to the substance and the health outcome

A summary of the level of evidence of health effects for chloromethane is presented in Table C-20.

Table C-20. Level of Evidence of Health Effects for Chloromethane

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Cardiovascular	Very low	Health effect	Inadequate
Hepatic	No data	No data	Inadequate
Neurological	Low	Health effect	Low
Male Reproductive	No data	No data	Inadequate
Developmental	No data	No data	Inadequate
Animal studies			
Cardiovascular	Very low	Health effect	Inadequate
Hepatic	High	Health effect	High
Neurological	High	Health effect	High
Male Reproductive	High	Health effect	High
Developmental	Low	Health effect	Low

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

The initial hazard identification was based on the highest level of evidence in the human studies and the level of evidence in the animal studies; if there were no data for one evidence stream (human or animal), then the hazard identification was based on the one data stream (equivalent to treating the missing evidence stream as having low level of evidence). The hazard identification scheme is presented in Figure C-1 and described below:

- **Known:** A health effect in this category would have:
  - High level of evidence for health effects in human studies **AND** a high, moderate, or low level of evidence in animal studies.
- **Presumed:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** high or moderate level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** high level of evidence in animal studies
- **Suspected:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** low level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** moderate level of evidence in animal studies
- **Not classifiable:** A health effect in this category would have:
  - Low level of evidence in human studies **AND** low level of evidence in animal studies
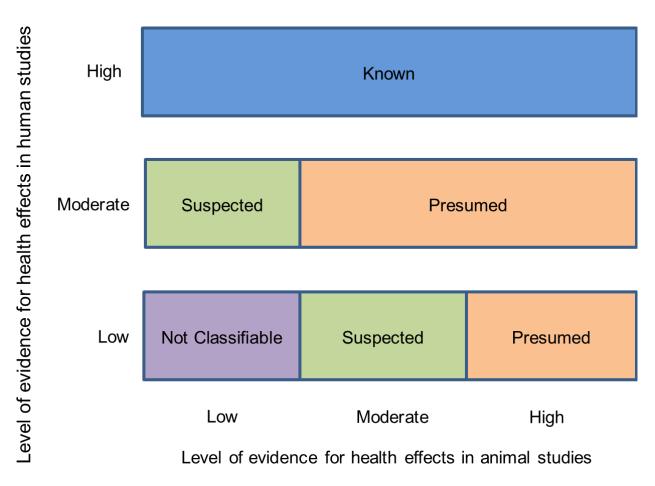
Figure C-1. Hazard Identification Scheme

Other relevant data such as mechanistic or mode-of-action data were considered to raise or lower the level of the hazard identification conclusion by providing information that supported or opposed biological plausibility.

Two hazard identification conclusion categories were used when the data indicated that there may be no health effect in humans:

- **Not identified** to be a hazard in humans
- **Inadequate** to determine hazard to humans

If the human level of evidence conclusion of no health effect was supported by the animal evidence of no health effect, then the hazard identification conclusion category of "not identified" was used. If the human or animal level of evidence was considered inadequate, then a hazard identification conclusion category of "inadequate" was used. As with the hazard identification for health effects, the impact of other relevant data was also considered for no health effect data.

The hazard identification conclusions for chloromethane are listed below and summarized in Table C-21.

Presumed Health Effects
- Hepatic effects following inhalation exposure
  - No evidence from human studies was evaluated in the systematic review.
  - High level of evidence of hepatic lesions in rats and mice following inhalation exposure for acute durations (Burek et al. 1981; Chellman et al. 1986a, 1986b; Landry et al. 1985; Morgan et al. 1982), intermediate durations (CIIT 1981), or chronic durations (CIIT 1981).
- Neurologic effects following inhalation exposure
  - Low level of evidence from human studies, with one occupational cohort study reporting neurological effects, some lasting years after exposure, following exposure to high levels of chloromethane (Gudmundsson 1977), but one occupational cohort study (NIOSH 1976) and three human controlled trials that did not show significant nervous system effects with low levels of exposure to chloromethane (Putz-Anderson et al. 1981a, 1981b; Stewart et al. 1980).
  - High level of evidence for a range of neurological effects in rats, mice, and dogs, including clinical signs of neurotoxicity, motor impairments, and lesions in the cerebellum and spinal cord. Neurological effects were observed following inhalation exposure for acute durations (Burek et al. 1981; Chellman et al. 1986a, 1986b; Jiang et al. 1985; Landry et al. 1985; McKenna et al. 1981a; Morgan et al. 1982; Smith and von Oettingen 1947b; von Oettingen et al. 1949, 1950; Wolkowski-Tyl et al. 1983a, 1983b), intermediate durations (McKenna et al. 1981b; Smith and von Oettingen et al. 1947b), or chronic durations (CIIT 1981).
- Male reproductive effects following inhalation exposure
  - No evidence from human studies was evaluated in the systematic review.
  - High level of evidence of adverse effects on the male reproductive system of rats, including sperm effects, testicular lesions, and infertility, following inhalation exposure for acute durations (Burek et al. 1981; Chapin et al. 1984; Chellman et al. 1986a, 1986c, 1987; Morgan et al. 1982; Working and Bus 1986; Working et al. 1985a, 1985b), intermediate durations (CIIT 1981; Hamm et al. 1985), or chronic durations (CIIT 1981). In mice, testicular lesions were observed after chronic-duration inhalation exposure (CIIT 1981); reproductive function has not been assessed in mice.

Not Classifiable Health Effects
- Cardiovascular effects following inhalation exposure
  - Although occupational cohort studies suggest adverse cardiovascular outcomes (Rafnsson and Gudmundsson 1997; Rafnsson and Kristbjornsdottir 2014), the human data were considered inadequate for evaluating the potential hazard due to the moderate initial confidence in these studies, their imprecision, and the high risk of bias.
  - Animal data are inadequate to evaluate the potential hazard. One study in dogs reported increased blood pressure and heart rate followed by a precipitous drop in blood pressure prior to death at very high concentrations; these effects are likely secondary to CNS depression (von Oettingen 1949, 1950). No other studies evaluating cardiovascular function were identified. Some studies reported elevated heart weight in rats and mice following intermediate- or chronic-duration exposure (CIIT 1981; McKenna et al. 1981b); however, no histopathologic lesions were noted in any inhalation study (CIIT 1981; McKenna et al. 1981a, 1981b; Mitchell et al. 1979).
- Developmental effects following inhalation exposure
  - No evidence from human studies was evaluated in this systematic review for developmental endpoints.
  - Low evidence of an association between chloromethane exposure and adverse developmental outcomes. In rats, developmental effects were limited to decreased fetal growth and delayed skeletal development at concentrations associated with severe maternal toxicity (Wolkowski-Tyl et al. 1983a). In mice, heart malformations were observed following gestational exposure

(Wolkowski-Tyl et al. 1983a, 1983b). In rabbits, no developmental effects were noted following gestational exposure (Theuns-van Vliet 2016). The lack of cardiac findings in rats and rabbits brings into question whether the effects seen in the mice were specific to that species; and whether there is human health relevance for the cardiac malformation findings.

Table C-21. Hazard Identification Conclusions for Chloromethane

Outcome	Hazard identification
Cardiovascular	Not classifiable
Hepatic	Presumed
Neurologic	Presumed
Male reproductive	Presumed
Developmental	Not classifiable

APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a

substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND
See Sample LSE Table (page D-5)

(1)   Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2)   Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3)   Figure key. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4)   Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(5)   Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to "Chemical X" via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6)   Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), food intake (FI), gross necropsy (GN), hematology (HE), histopathology (HP), immune function (IX), lethality (LE), neurological function (NX), organ function (OF), ophthalmology (OP), organ weight (OW), reproductive function (RX), urinalysis (UR), and water intake (WI).

(7)   Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8)   NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9)   LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10)   Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11)   Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND
See Sample LSE Figure (page D-6)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(12)   Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

(13)   Endpoint. These are the categories of health effects for which reliable quantitative data exist.
         The same health effect endpoints appear in the LSE table.

(14)   Levels of exposure. Concentrations or doses for each health effect in the LSE tables are
         graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log
         scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in
         mg/kg/day.

(15)   LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL
         critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number
         51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the
         extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to
         the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(16)   CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol
         refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE
         table.

(17)   Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

APPENDIX D

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral ← 1

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
CHRONIC EXPOSURE									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

Annotation callouts: 1, 2 (→CHRONIC EXPOSURE), 3, 4 (Species (strain) No./group), 5 (Exposure parameters / Doses), 6 (Parameters monitored), 7 (Endpoint), 8 (NOAEL), 9 (Less serious LOAEL / Serious LOAEL), 10, 11

[a]The number corresponds to entries in Figure 2-x.
[b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).
[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).
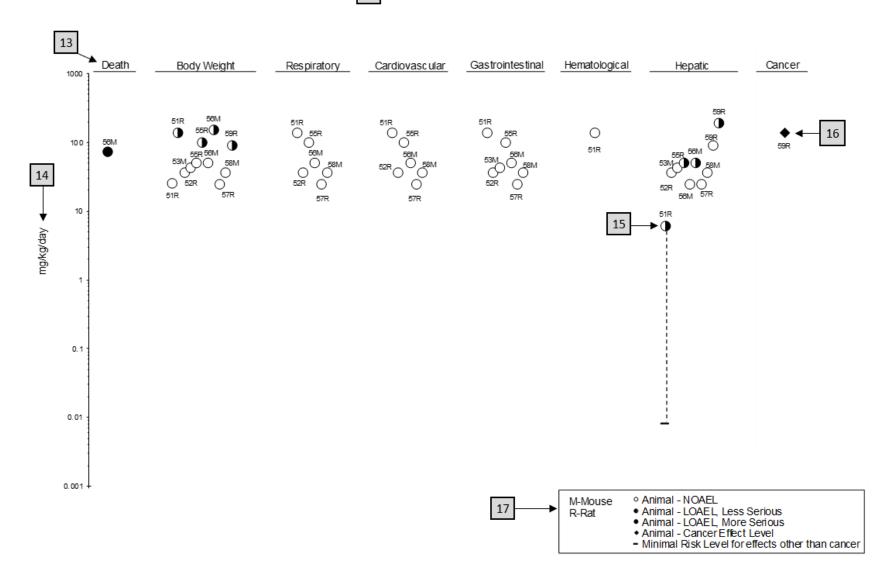
Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral

APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:
    Section 3.2   Children and Other Populations that are Unusually Susceptible
    Section 3.3   Biomarkers of Exposure and Effect

ATSDR Information Center

    Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
    Internet: http://www.atsdr.cdc.gov

ATSDR develops educational and informational materials for health care providers categorized by hazardous substance, clinical condition, and/or by susceptible population. The following additional materials are available online:

Physician Briefs discuss health effects and approaches to patient management in a brief/factsheet style. *Physician Overviews* are narrated PowerPoint presentations with Continuing Education credit available (see https://www.atsdr.cdc.gov/emes/health_professionals/index.html).

Managing Hazardous Materials Incidents is a set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.html).

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

APPENDIX E

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX F. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

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Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

In Vitro—Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo—Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC$_{LO}$)—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC$_{50}$)—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD$_{Lo}$)—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD$_{50}$)—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT$_{50}$)—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

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Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

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Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register

FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactate dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences

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NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SLOAEL	serious lowest-observed-adverse-effect level
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey

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USNRC   U.S. Nuclear Regulatory Commission
VOC   volatile organic compound
WBC   white blood cell
WHO   World Health Organization

>   greater than
≥   greater than or equal to
=   equal to
<   less than
≤   less than or equal to
%   percent
α   alpha
β   beta
γ   gamma
δ   delta
μm   micrometer
μg   microgram
q_1^* cancer slope factor
−   negative
+   positive
(+)   weakly positive result
(−)   weakly negative result