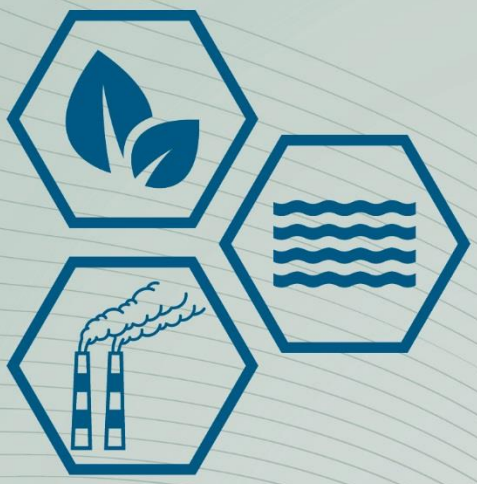

Toxicological Profile for Chloromethane

Draft for Public Comment

January 2022

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

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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 and EPA.

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 and the associated acute, intermediate, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine the levels of exposure that present a significant risk to human health due to acute, intermediate, and chronic duration exposures; 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. ATSDR plans to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Electronic comments may be submitted via: www.regulations.gov. Follow the on-line instructions for submitting comments.

Written comments may also be sent to: Agency for Toxic Substances and Disease Registry
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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.

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 is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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Date	Description
January 2022	Draft for public comment released
June 2009	Addenda released
December 1998	Final toxicological profile released

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These experts collectively have knowledge of toxicology, chemistry, and/or health effects. All reviewers were selected in conformity with Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

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.

CONTENTS

LIST OF FIGURES

LIST OF TABLES

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. The production of vinyl chloride could be a source of chloromethane in the environment because chloromethane is a degradation product of and an impurity in vinyl chloride (PubChem 2021; WHO 1999). Therefore, chloromethane can be released to the environment during the manufacture of vinyl chloride or 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).

The most likely route of exposure to chloromethane is through inhalation, as the chemical is highly volatile. In the U.S., the median concentration of chloromethane in air in 2018 was 0.60 ppb, with the maximum concentration of 1.41 ppb (EPA 2018b). 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). In a study of groundwater samples from 479 active waste disposal sites, chloromethane was detected at 20 of these sites (Plumb Jr. 1991). 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 EPA under the Clean Air Act as a hazardous air pollutant (EPA 2017a) and is identified as a toxic waste under Resource Conversation and Recovery Act (RCRA) (EPA 2018g).

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 toxicological studies which evaluated a variety of endpoints including respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal, neurological, and reproductive health effects. Additionally, some smaller studies evaluated the potential for chloromethane to be a developmental toxicant. Further, chloromethane has been tested for its genotoxic potential.

As illustrated in Figure 1-1, the neurological, hepatic, renal, cardiovascular, developmental, and reproductive systems appear to be sensitive to chloromethane exposure. A systematic review of the human and animal literature was conducted on the respiratory, cardiovascular, and neurological endpoints, and a review on animal literature only for the hepatic, renal, and developmental endpoints. The review resulted in the following hazard identification[1] conclusions:

- Neurological effects are a presumed health effect with inhalation exposure.
- Hepatic effects are a presumed health effect with inhalation exposure.
- Renal effects are a suspected health effect with inhalation exposure.
- Reproductive effects are a suspected health effect with inhalation exposure.
- Developmental effects are not classifiable with inhalation exposure.
- Cardiovascular effects are not classifiable with inhalation exposure.
- Hepatic effects are not classifiable with oral exposure.

Cardiovascular Effects. Although case studies (Hansen et al. 1953; Kegel et al. 1929; McNally 1946; Spevak et al. 1976; Verriere and Vachez 1949; Scharnweber et al. 1974) and epidemiologic evidence (Rafnsson and Gudmundsson 1997; Rafnsson and Kristbjornsdottir 2014) have noted increases in cardiovascular effects in human populations (e.g., Rafnsson and Kristbjornsdottir 2014) observed an increased risk of mortality due to cardiovascular diseases), these studies are limited in that the participants' levels of exposure are often unavailable. Additionally, in the case of the cohort studies, there was little information on lifestyle factors for individuals being assessed (e.g., smoking and drinking

[1] For additional details on the definitions on the hazard identification categories the reader is referred to Appendix C.

water). This lack of information on confounding increases the risk of bias of these studies (Rafnsson and Gudmundsson 1997; Rafnsson and Kristbjornsdottir 2014). Animal studies noted changes in cardiovascular outcomes however these were deemed likely secondary to neurologic effects (von Oettingen et al. 1949, 1950). No increases in histopathologic lesions in the cardiovascular system were noted in animal studies after exposure to chloromethane with intermediate and chronic exposure durations when compared to controls (CIIT 1981; McKenna et al. 1981b; McKenna et al. 1981a; Mitchell et al. 1979).

Hepatic Effects. The only available human data regarding hepatic effects is from case studies which demonstrated chloromethane's potential to affect the liver through associated disease such as cirrhosis (Wood 1951) and jaundice (Spevak 1976) (case studies are not included in the systematic review). However, there was a high level of evidence from experimental animal studies. Mice appear to be more susceptible than rats in these studies. Acute, intermediate, or chronic exposure of mice to approximately 100-2,000 ppm generally resulted in decreased liver weight (considered by the authors to be secondary to decreased body weight), necrosis, and degeneration of the liver (Burek et al. 1981; Chellman et al. 1986b; CIIT 1981; Landry et al. 1985; Mitchell et al. 1979; Morgan KT et al. 1982). Additionally, chloromethane exposure was associated with changes in liver enzyme levels (Chapin et al. 1984; Dodd et al. 1982 ; CIIT 1981). Only one animal study was located where chloromethane was administered orally, and it was administered by gavage. In this study, the hepatotoxic effects of chloroform, carbon tetrachloride, dichloroethane, and chloromethane were compared, and no liver necrosis was found in the rats treated with chloromethane (Reynolds and Yee 1967).

Renal Effects. 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). No evidence from human studies was evaluated in the systematic review. Experimental animals provide moderate evidence of an association between chloromethane exposure and renal health effects. Effects to the kidneys range from changes in serum enzymes (Burek et al. 1981; Dodd et al. 1982; Jager et al. 1988), to histopathological lesions (Burek et al. 1981; CIIT 1981; Landry et al. 1985), to kidney failure (Burek et al. 1981).

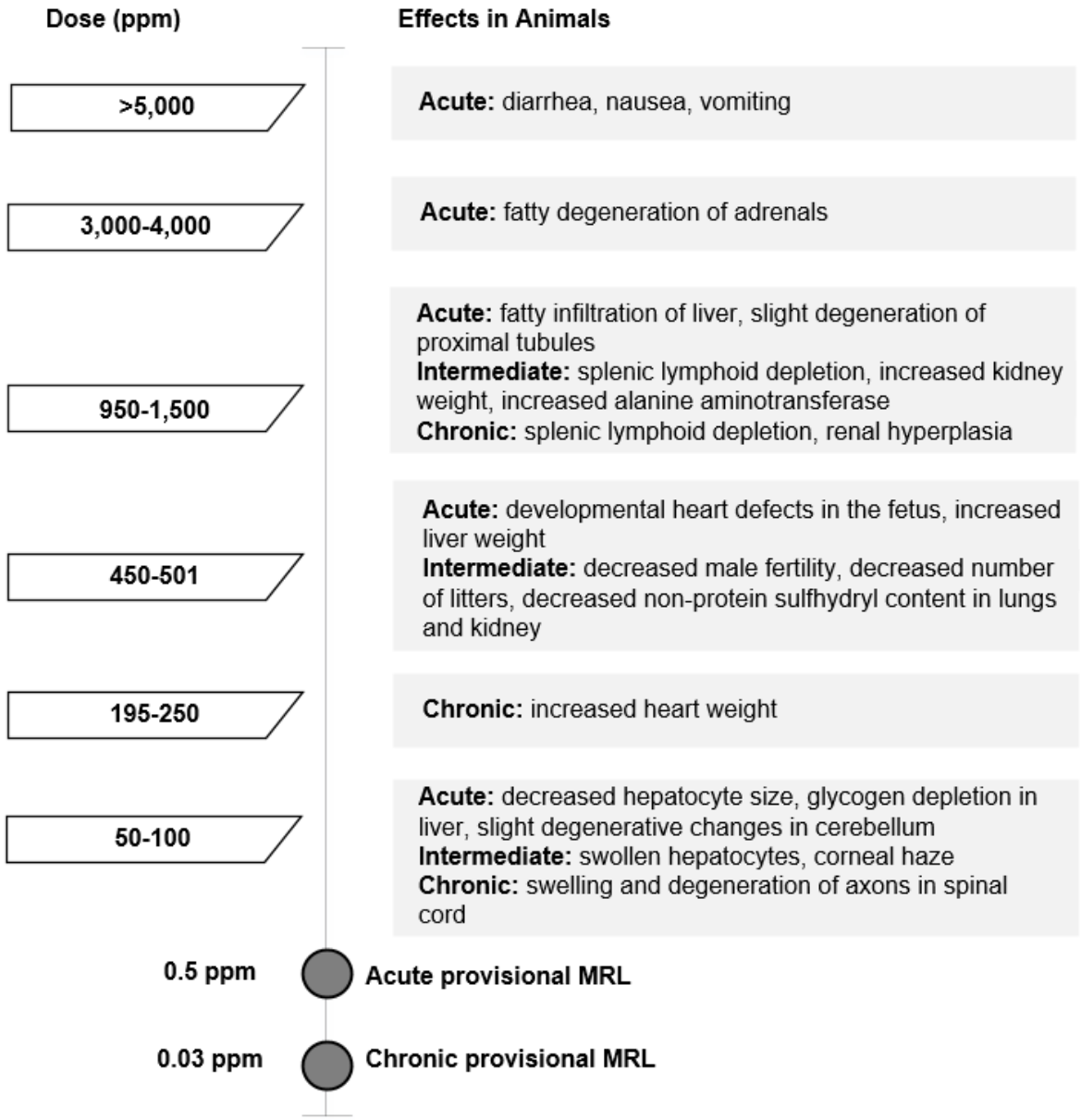
***Neurologic Effects*.** Numerous case studies of individuals who were highly exposed to chloromethane resulting from refrigeration system leaks consistently reported neurological effects, including fatigue, progressive drowsiness, staggering, headache, nausea, slurred speech, blurred and double vision, mental confusion, tremor, vertigo, muscular weakness, muscular cramping and rigidity, sleep disturbances,

ataxia, convulsions, and cyanosis alternating with coma, delirium, and restlessness (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; Raalte and van Velzen 1945; Scharnweber et al. 1974; Spevak et al. 1976; Wood 1951; case studies are not included in the systematic review). Human controlled trials with low levels of chloromethane (i.e., range 100-200ppm) exposure did not show nervous system effects. However, these studies were designed with exposure levels not anticipated to find such an effect. Experimental animal studies show a range of neurological impacts from acute, intermediate, and chronic duration exposures. Impacts in animals range from observable changes in outcomes such as behavior, gait, ataxia, and tremors to histopathological lesions on the brain and axonal swelling (Chellman et al. 1986a; Chellman et al. 1986b; CIIT 1981; McKenna et al. 1981a; Morgan KT et al. 1982; Jiang et al. 1985; Landry et al. 1985; Wolkowski-Tyl et al. 1983b; Wolkowski-Tyl et al. 1983a).

Reproductive Effects. One case study was located which described a potential relationship between high chloromethane exposure and impotence (Mackie 1961). No other human studies were located evaluating the impact of chloromethane toxicity. Therefore, no evidence from human studies was evaluated in the systematic review. Experimental animal studies provide moderate evidence of an association between chloromethane exposure and reproductive health effects. The reproductive endpoints are mainly seen in male rodents and consist of testicular and epididymal lesions (Burek et al. 1981; Hamm et al. 1985; Chellman et al. 1987; Working et al. 1985b), incomplete spermatogenesis, and corresponding decreases in fertility via pre- and post-implantation loss. It is thought these reproductive effects may be due to chloromethane-induced sperm damage (Working and Bus 1986; Working et al. 1985a). The impacts have been seen follow acute, intermediate, and chronic exposure.

Developmental Effects. No evidence from human studies was located or evaluated in this systematic review for developmental endpoints. Experimental animal studies provide low evidence of an association between chloromethane exposure and adverse developmental outcomes. The fetal effects varied between species with rats experiencing reduced fetal body weight and crown-rump length, and reduced ossification in the metatarsals and phalanges (bones of the hands and feet), the centra of the thoracic vertebrae (small bones of the backbone), the pubis of the pelvic girdle (hip bone), and the metatarsals of the hind limbs (bones of the back leg) at doses which were also maternally toxic (Wolkowski-Tyl et al. 1983a). These same impacts were not observed in New Zealand White Rabbits (Theuns-van Vliet 2016) or in mice (Wolkowski-Tyl et al. 1981a, 1981b, 1983a, 1983b). Additionally, heart malformations were also observed in mice exposed to chloromethane during gestation (Wolkowski-Tyl et al. 1983b). These same malformations were not observed in rats (Wolkowski-Tyl 1981a, 1983a) or in rabbits (Theuns-van Vliet 2016).

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



1.3 MINIMAL RISK LEVELS (MRLS)

The oral database was not considered adequate for deriving oral provisional MRLs.

The inhalation database was considered adequate for derivation of acute- and chronic-duration inhalation provisional MRLs for chloromethane. The database was considered inadequate for an intermediate-duration inhalation provisional MRL. As illustrated in Figure 1-2, the hepatic and neurologic systems appear to be the most sensitive targets of chloromethane toxicity. Cardiovascular, renal, reproductive and developmental effects also have relatively low LOAEL values. The provisional MRL values are summarized in Table 1-1 and discussed in greater detail in Appendix A.

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

The neurological and hepatic endpoints are the most sensitive targets of chloromethane inhalation exposure.

Numbers in circles are the lowest LOAELs among health effects in animals.

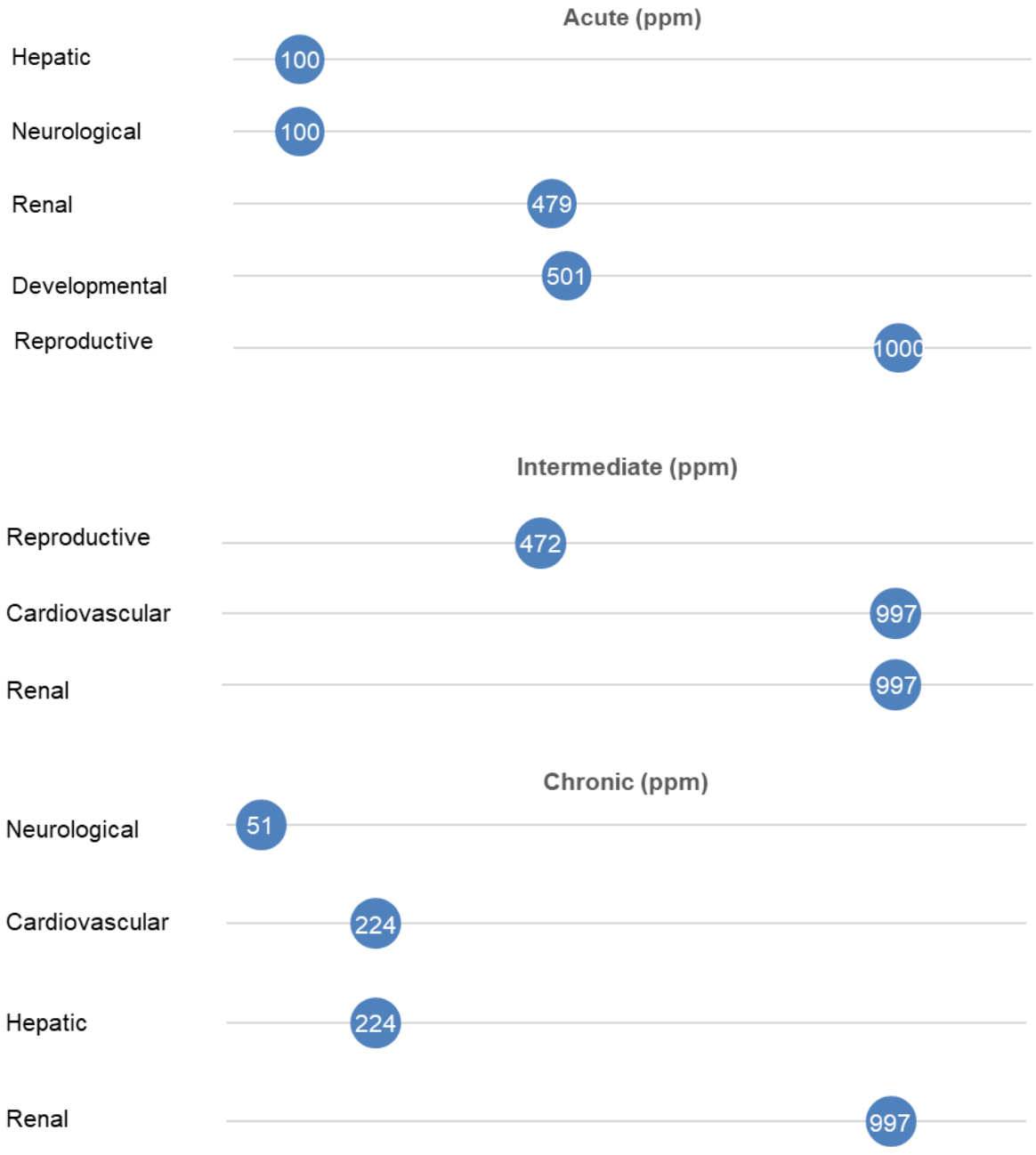


Table 1-1. Provisional Minimal Risk Levels for Chloromethane

Exposure Duration	Provisional MRL	Critical Effect	Point of Departure/Human Equivalent Concentration	Uncertainty & Modifying Factor	Reference
Inhalation Exposure (ppm)					
Acute	0.5	degenerative changes in the cerebellum granule cells with nuclear pyknosis and karyorrhexis	NOAEL: 50 ($NOAEL_{HEC}$: 46)	90	Landry et al. 1985
Intermediate	Insufficient data for MRL derivation				
Chronic	0.03	Axonal swelling and slight degeneration of axons in the spinal cord	LOAEL: 51 ($LOAEL_{HEC}$: 9)	300	CIIT 1981
Oral Exposure					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic	Insufficient data for MRL derivation				

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 2-2and Figure 2-2.

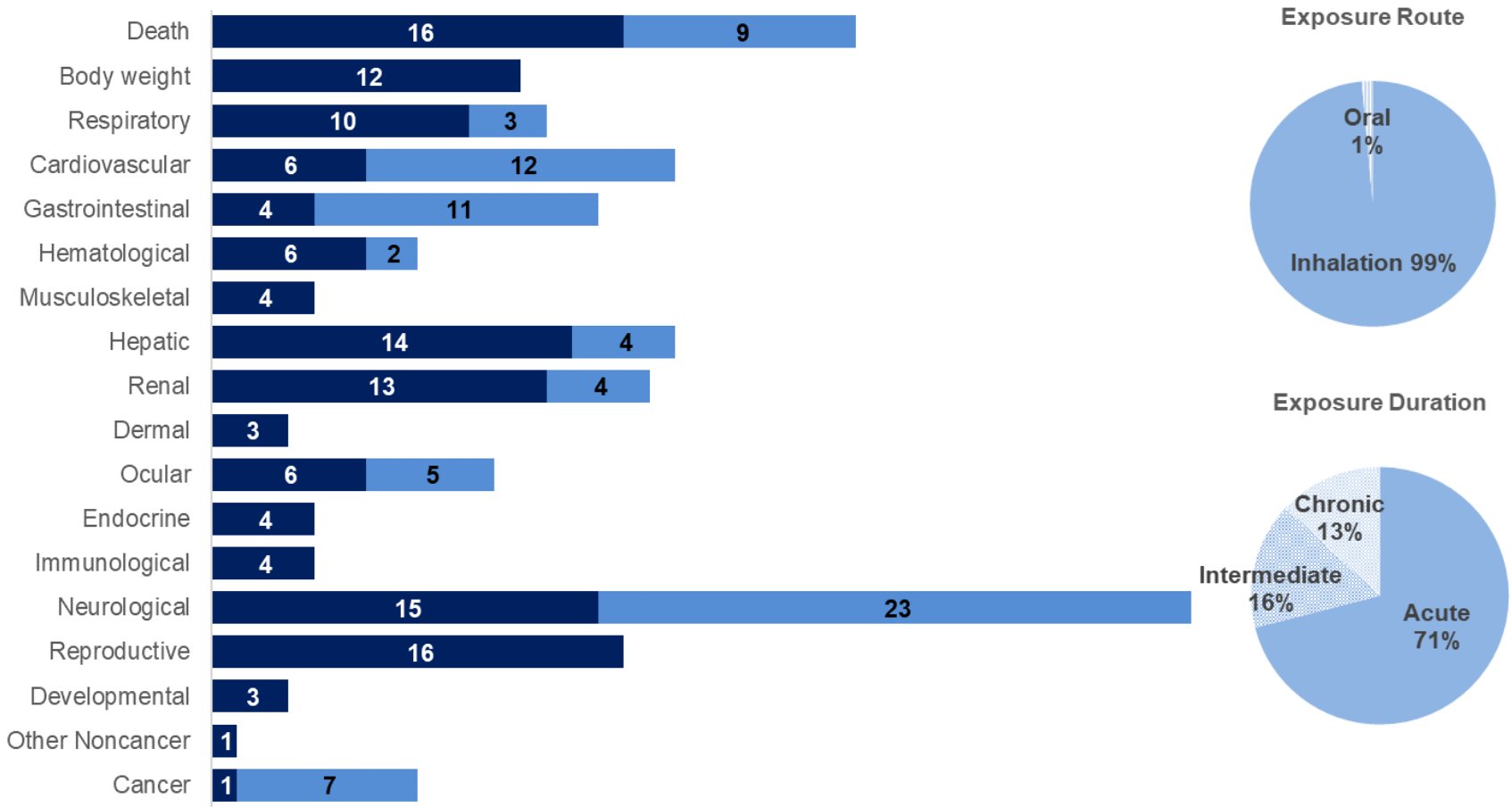
A User's Guide has been provided at the end of this profile see Appendix E. This guide should aid in the interpretation of the tables and figures for LSEs and MRLs.

The health effects of chloromethane have been evaluated in epidemiological, human controlled trial and experimental animal studies. As illustrated in Figure 2-1, most of the health effects data come from inhalation exposure studies in animals. Animal data 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, hepatic, gastrointestinal and cardiovascular 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.

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

Most studies examined the potential reproductive, neurological, renal, hepatic, gastrointestinal and cardiovascular effects of chloromethane

Fewer studies evaluated health effects in **humans** than **animals** (counts represent studies examining endpoint)



As outlined in Chapter 1, the neurological, hepatic, renal, cardiovascular, developmental, and reproductive systems appear to be sensitive to chloromethane exposure; the neurological and hepatic endpoints appear to be the most sensitive (see Figure 1-2). A systematic review was conducted on the available human and animal 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 (e.g., Hansen et al. 1953; Scharnweber et al. 1974) and data from a cohort of accidentally exposed individuals (Rafnsson and Gudmundsson 1997; Rafnsson and Kristbjornsdottir 2014) suggest 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. Similar results have not been seen in experimental animal studies ((CIIT 1981; McKenna et al. 1981a; McKenna et al. 1981b; Mitchell et al. 1979).
- **Hepatic Endpoints**. Hepatic effects are a presumed health effect for humans exposed to chloromethane via inhalation based on evidence in rodents, mainly mice, following acute and intermediate and chronic exposure. The liver effects include changes in liver function serum enzymes (Chapin et al. 1984; Dodd et al. 1982, CIIT 1981), lesions, swelling of hepatocytes and changes in relative and absolute liver weight (Burek et al. 1981; Chellman et al. 1986b; CIIT 1981; Landry et al. 1985; Mitchell et al. 1979; Morgan KT et al. 1982). There is inadequate data on to conclude whether hepatic effects are associated with oral exposure.
- **Renal Endpoints.** Renal effects are a suspected health effect associated with chloromethane exposure based on evidence in experimental animal studies following acute, intermediate, and chronic exposure. Effects to the kidneys range from changes in serum enzymes (Burek et al. 1981; Dodd et al. 1982; Jager et al. 1988), to histopathological lesions (Burek et al. 1981; CIIT 1981; Landry et al. 1985), to kidney failure (Burek et al. 1981).
- **Neurological Endpoints**. Neurological effects are a presumed health effect associated with chloromethane exposure via inhalation based on the systematic review. Case studies and case reports clearly indicate neurological effects associated with chloromethane exposure (e.g., Baird 1954; Baker 1927; Battigelli and Perini 1955; Borovska et al. 1976). Epidemiological studies provide limited evidence in humans, while rodent studies provide strong evidence from acute, intermediate, and chronic assessments. The nervous system impacts range from observable changes in outcomes such as behavior, gait, ataxia, and

tremors to histopathological lesions on the brain, and axonal swelling (Chellman et al. 1986a; Chellman et al. 1986b; CIIT 1981; McKenna et al. 1981a Morgan et al. 1982; Jiang et al. 1985; Landry et al. 1985; Wolkowski-Tyl et al. 1983a; Wolkowski-Tyl et al. 1983b).

- **Reproductive Endpoints**. Reproductive effects are a suspected health effect associated with chloromethane exposure via inhalation based on evidence from rodent studies. The reproductive endpoints are mainly seen in male rodents and consist of testicular and epididymal lesions, incomplete spermatogenesis, and corresponding decreases in fertility via pre- and post-implantation loss (Burek et al. 1981; Hamm et al. 1985; Chellman et al. 1987; Working et al. 1985b; Working and Bus 1986). The impacts have been seen follow acute, intermediate, and chronic exposure.
- **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. In addition, there is no data on developmental toxicity of chloromethane in humans. The fetal effects vary between species. For example, reduced ossification was seen in rats but not in mice (Wolkowski-Tyl 1981a,b; 1983a,b); heart malformations were observed in mice but not in rabbits (Theuns-van Vliet et al. 2016) or rats (Wolkowski-Tyl 1981a, 1983a).

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

Reference and Study Population	Exposure	Outcome
Epidemiological studies		
Barry et al. 2011 Case-control study of 518 Connecticut women with non-Hodgkin's lymphoma (NHL), classified by NHL subtype, and occupational exposure to chlorinated solvents with 597 control participants	**Exposure:** Interview and job-exposure matrix used to estimate subject's probability and intensity of exposure to chloromethane, and blood or buccal cell specimens were collected for genotyping **Logistic regression adjustments:** age (continuous) and race (white/nonwhite)	**Cancer Effect:** When comparing participants ever exposed to chloromethane to those never exposed to chloromethane: *Total NHL* OR >1 (OR = 1.44; 95% CI: 0.94, 2.20); *Diffuse large B-cell lymphoma* OR >1 (OR = 1.46; 95% CI: 0.80, 2.65); *Follicular lymphoma* OR >1 (OR = 1.96; 95% CI: 1.06, 3.63). Genotyping revealed that the odds of total NHL associated with occupational exposure to chlorinated solvents only increased in women with the homozygous TT wild-type genotype for the CYP2E1 rs2070673 polymorphism (functional significance unclear). Women with this genotype who were exposed to chloromethane had increased odds of total NHL (OR = 2.37, 95% CI: 1.24, 4.51), increased odds of follicular lymphoma (OR = 2.73, 95% CI: 1.11, 6.73), and increased odds of DLBCL (OR = 2.14, 95% CI: 0.90, 5.08). TT population that was ever exposed to chloromethane was small (n=29) with potential co-exposure to other chlorinated solvents.

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

Reference and Study Population	Exposure	Outcome
Delfino et al. 2003 Panel study of 22 Hispanic children (10-16 years old) with asthma living in Los Angeles community with high traffic density.	**Exposure:** Daily mean = 0.58 (SD: 0.14) ppb **Logistic regression adjustments:** weekend vs. weekday, maximum temperatures, respiratory infections	**Respiratory Effect:** The OR for asthma symptom scores was greater than one (OR = 1.07 95% CI: 0.92-1.23). OR for asthma symptom score >2 was less than one (OR = 0.92, 95% CI: 0.75-1.12). Authors report no relationship seen between chloromethane and peak expiratory flow; data not reported in paper.
Dosemeci et al. 1999 Case-control study of 438 white Minnesotans (273 men and 165 women). Participants were aged 20-85 yrs, newly diagnosed with renal cell carcinoma (RCC) and potentially occupationally exposed to chlorinated aliphatic hydrocarbons	**Exposure:** Interview and job-exposure matrix used to determine whether or not subject had been exposed to chloromethane. Prevalence of exposure was low (0.08 for male cases and 0.04 for female cases). **Logistic regression adjustments:** age, smoking, hypertension status (including use of diuretics and/or anti-hypertension drugs), BMI	**Cancer Effect:** OR of RCC <1 (0.85) for men (95% CI: 0.5-1.5); OR of RCC <1 (0.88) for women (95% CI: 0.3-2.4); OR of RCC <1 (0.87) for men and women combined (95% CI: 0.5-1.4)
Holmes et al. 1986 Cohort of 852 male employees who had worked at least one month at a synthetic rubber manufacturing plant in Louisiana	**Exposure:** Job title, dates of employment, and responsibilities were used to estimate relative potential for exposure (low, medium, high) to chloromethane **Model Adjustments:** age, race, sex (used to compare to expected number of deaths), first year of employment in butyl rubber operations, duration of exposure, time period of employment (process changes led to changes in exposure)	**Death:** The Standardized Mortality Ratio (SMR) for all causes of death was (18%) lower for white chloromethane-exposed factory workers than expected for white U.S. males (SMR= 82, 95% CI: 68-98). The SMR for all causes of death was 41% lower for non-white chloromethane-exposed factory workers than expected for non-white U.S. males (SMR= 59, 95% CI: 4.5-76). The authors reported that elevated SMRs for white workers evaluated according to exposure duration were not statistically significant, but did not provide confidence

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

Reference and Study Population	Exposure	Outcome
		intervals. A healthy worker effect is assumed to be at play. **Cancer**: SMR for all malignant neoplasms was lower than expected for white workers (SMR= 66, 95% CI: 40-103) and non-white workers (SMR=63, 95% CI: 32-113). SMRs for specific cancers in white workers were 75 (95% CI: 27-163) for digestive, 70 (95% CI: 28-144) for respiratory, 35 (95% CI: 1-194) for lymphatic, and 65 (95% CI: 8-235) for unspecified neoplasms. The only cancer-specific SMRs calculated for non-white workers were 54 (95% CI: 11-158) for digestive and 120 (95% CI: 44-261) for lung.
Jiao et al. 2012 Case-control study of 518 Connecticut women (21-84 years of age) with non-Hodgkin's lymphoma and occupational exposure to chlorinated solvents	**Exposure:** Interview and job-exposure matrix used to determine whether or not subject had been exposed to chlorinated solvents, including chloromethane **Logistic regression adjustments:** exposure considered dichotomous (never/ever), hetero- and homozygous variant genotypes were combined for all genes to increase statistical power, age (<50 years, 50-70 years, >70 years), race (white, black, other), false discovery rate. Other common variables (ex. smoking, alcohol consumption, and family history) were nonsignificant and not included in final model.	**Cancer Effect:** Women occupationally exposed to any chlorinated solvents had increased odds of developing non-Hodgkin's lymphoma if they carried the *MGMT* (rs12917) CT/TT genotypes (OR = 3.05, 95% CI: 1.76–5.29) or *NBS1* (rs1805794) CG/CC genotypes (OR = 2.40, 95% CI: 1.40–2.98) compared to those not exposed.

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

Reference and Study Population	Exposure	Outcome
Kernan et al. 1999 Case-control study based on death certificates identifying 63,097 individuals from 24 U.S. states who died from pancreatic cancer from 1984-1993 and evaluating their occupational exposure to solvents	**Exposure:** Used occupation codes, industry codes, and a job-exposure matrix to estimate probability and intensity of exposure **Logistic regression adjustments:** age, marital status, metropolitan and residential status, race, and gender adjustments used in combined models	**Cancer Effect:** the assessment did not find an increased odds of pancreatic cancer based on estimated chloromethane exposure intensity (low, medium, high) compared to unexposed individuals for any of the populations evaluated (Black and white, males and females). Considering the probability of chloromethane exposure, there was no dose-response relationship seen between intensity of chloromethane exposure and risk of pancreatic cancer, when compared to individuals with no exposure. Additionally, results varied between sex and race -Black women with a low probability of exposure had a slightly increased odds of pancreatic cancer (OR = 1.1, 95% CI: 1.0-1.3) compared to those not exposed. The same was not seen for black women with medium probability of exposure (OR = 0.8, 95% CI: 0.6-1.2). No black women had a high probability of exposure. For black men with a high probability of exposure to chloromethane there was an increased odds of pancreatic cancer (OR = 3.3, 95% CI: 1.3-8.6); however few individuals were in this category (n=8). Black men with medium probability of exposure did not have any association with pancreatic cancer when compared to individuals without exposure (OR = 0.7 95%CI: 0.4-1.3) No effect of intensity of

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

Reference and Study Population	Exposure	Outcome
		chloromethane exposure on white males or females was observed.
Rafnsson and Gudmundsson 1997 24 male crew members from an Icelandic fishing boat that experienced accidental exposure (chloromethane refrigerant leaked from refrigerator on boat).	**Exposure:** No estimates available, acute exposure occurred due to leaking refrigerant on fishing vessel **Case-Controls Matched On:** age and occupation, and social class	**Cancer Effect:** Exposed officers had a slight excess of all cancers when compared to unexposed fishermen (RR = 5.0, 95% CI: 0.4-43.8), and cancer was elevated for the entire crew (Mantel-Haenszel point estimate = 1.5, 95% CI: 0.3-5.6). There was an excess of lung cancer among the deckhands (RR= 2.7, 95% CI: 0.1-52.6) but no officer developed lung cancer. However, the small sample size makes the significance of these effects difficult to determine. **Cardiovascular Effect:** There was an excess of death due to cardiovascular diseases in exposed fishermen when compared with unexposed fishermen (M-H = 2.1, 95% CI: 1.2-3.8). However, the exposed deckhands had the most prominent increase in relative risk (RR = 3.9, 95% CI: 1.0-14.4). **Death:** When compared with unexposed fishermen, exposed fishermen had an excess of death (M-H = 2.0, 95% CI: 1.3-3.1) and an increased risk of death among deckhands (RR = 2.5, 95% CI: 1.0-5.7) and officers (RR = 2.2, 95% CI: 0.6-6.4).

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

Reference and Study Population	Exposure	Outcome
Rafnsson and Kristbjornsdottir 2014 27 male crew members from an Icelandic fishing boat that experienced accidental exposure (chloromethane refrigerant leaked from refrigerator on boat)	**Exposure:** No estimates available, acute exposure occurred due to leaking refrigerant on fishing vessel **Cox Proportional Hazards Model Adjustments:** age and occupation	When comparing the cohort of exposed fisherman to unexposed fisherman the results were as follows: **Cancer Effect:** The hazard ratio (HR) for all cancers was 2.07 (95% CI: 0.85-5.04) and for kidney cancer was 9.35 (95% CI: 1.28-68.24). HR for death from all cancers was 2.34 (95% CI: 0.77-7.07). **Cardiovascular Effect:** The HRs for deaths due to cardiovascular events were all elevated. The HR was 2.06 (95% CI: 1.02-4.15) for all cardiovascular-related deaths, 3.12 (95% CI: 1.11-8.78) for deaths from acute coronary heart disease, and 5.35 (95% CI: 1.18-24.35) for deaths from cerebrovascular disease. **Death:** The HR for all causes of death was 2.10 (95% CI: 1.28-3.46). **Neurological Effect:** The HR for death from suicide was 13.76 (95% CI: 1.18-160.07).

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

Reference and Study Population	Exposure	Outcome
Repko et al. 1976 Case-control: Study of 122 unexposed workers (8 female, 114 male) aged 18-61 compared to 49 unexposed workers (3 female, 46 male) aged 20-59 from 7 different locations of the same company in 6 U.S. states who were or were not occupationally exposed to chloromethane	**Exposure:** Facility air and worker breath concentrations varied and were measured periodically. Chloromethane in facility air averaged 33.57 ppm (range of means by facility = 8.46-58.72 ppm). Worker breath concentrations averaged 13.32 ppm (range of means by facility = 10.81-24.19 ppm). Exposure, urine pH, and task performance were correlated. **Model Adjustments:** Correlation coefficients were used to relate performance with exposure. Exposed and control populations were matched by age, race, sex, and educational level. Differences in education and length of exposure between the cases and controls were evaluated, but do not appear to have been used in modeling.	**Neurological and Behavioral Effect:** Appears to be a slight negative correlation between chloromethane measurements in ambient air and performance on some task-related tests (ex. red and green warning light latency, probability monitoring latency, percent of 1-digit math problems attempted). The number of two-digit math problems attempted was correlated ($p<0.005$) with facility and worker breath concentrations). No notable differences were found in EEG examination results between the groups. Exposure to chloromethane reduced performance on cognitive time-sharing tasks, and increased hand tremor magnitude.
Human controlled trials		
Putz-Anderson et al. 1981a 56 volunteers (17 female, 39 male) aged 18-32 years from U.S. universities	**Exposure:** 0, 100, or 200 ppm chloromethane inhalation for 3 hours with taking either a placebo capsule or a 10-mg diazepam capsule	**Neurological Effect:** treatment with chloromethane did not strongly affect the ability of participants to perform tasks ($F_{10, 35} = 2.09$, Wilk's $\psi = 0.62$, $p < 0.053$). Chloromethane was calculated to cause a net impairment of 4%. There was also no interaction between chloromethane and diazepam ($F_{10, 35} = 0.45$, Wilk's $\psi = 0.88$, no p value presented).

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

Reference and Study Population	Exposure	Outcome
Putz-Anderson et al. 1981b 84 volunteers (32 female, 52 male) aged 18-32 from U.S. universities	**Exposure:** 200 ppm chloromethane with and without co-exposure to ethanol (0.8 mL/kg) or caffeine (3 mg/kg) **Model Adjustments:** threshold performance level adjustments during tasks	**Neurological Effect:** Chloromethane exposure did not have a behavioral effect based on the behavioral tests administered ($F_{12,65}$ = 1.39, Wilk's ψ = 0.79, p = 0.19). Concurrent exposure to chloromethane and either alcohol or caffeine showed no interaction or potentiation (i.e., additivity) ($F_{24,130}$ = 1.29, Wilk's ψ = 0.65, p = 0.18).
Stewart et al. 1980 11 male volunteers (2 left the study before exposure; n = 9) aged 19-34 and 9 female volunteers (1 left the study before exposure; n = 8) aged 19-36 from Milwaukee, WI	**Exposure** Over the course of 6 weeks individuals were assigned to one of 3 time groups (1, 3, or 7.5 exposure hours per day), then exposed for 1 week (3-5 consecutive days based on participation) to one concentration of chloromethane (0, 20, 100, or 150 ppm for males, and 0 or 100 ppm for females). Control periods of 0 ppm occurred during weeks 1, 4, and 6 for males and weeks 1 and 3 for females. Each week, all groups were exposed to the same concentration, and the concentration was changed by week. Additionally, during 1 week, males were exposed sequentially to 50 ppm, then 100 ppm, and then 150 ppm for equal time periods to an average of 100 ppm. **Model Adjustments:** no adjustments appear to have been made, but the authors acknowledged potential for bias resulting from the significantly lower age of the controls, the lack of information on	No significant effects of chloromethane exposure were identified, but some subjects exhibited higher breath and blood levels than their peers. Four participants had 60 to 110% higher mean chloromethane concentrations in their breath at the beginning of exposure and three to six times the mean chloromethane concentrations 1 hour post exposure. The blood concentrations of chloromethane in these four participants were also elevated compared to the other participants. The authors interpreted these results to mean that higher levels of chloromethane in breath result from higher levels of chloromethane in blood.

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

Reference and Study Population	Exposure	Outcome
	participants' diet, and inconsistent participation	

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
ACUTE EXPOSURE									
1	CAT (NS) 3M	3 days 23.5 hours/ day	0, 192, 501	BC BW CS GN HE HP OP OW	Resp	501 M			
					Cardio	501 M			
					Gastro	501 M			
					Hemato	501 M			
					Hepatic	501 M			
					Renal	501 M			
					Dermal	501 M			
					Ocular	501 M			
					Endocr	501 M			
					Neuro	501 M			
					Repro	501 M			
McKenna et al. 1981a									
2	HUMAN 8-12B	3 hours	0, 100, 200	NX	Neuro	200			
Putz-Anderson et al. 1981a									
3	HUMAN 4M, 4F	1 week 2-5 days/ week 1, 3 or 7.5 hours/ day	0, 20, 100, 150, 50+100+150 average 100	BC CS HE OF UR	Resp	150			
					Cardio	150			
					Hemato	150			
					Neuro	150			
Stewart et al. 1980									
4	RAT (Fischer-344) 10-30M	5 days 6 hours/day	0, 1000, 3000	CS OF	Repro		1000 M	3000 M	LOAEL: 7.9% decrease in fertilization rate (not significantly different from control) SLOAEL: at least a 47% decrease in fertilization rate
Working and Bus 1986									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
5	RAT (Fischer-344) 40M	5 days 6 hours/day	0, 1000, 3000	CS OF	Bd wt	1000 M	3000 M		16% decreased body weight
					Repro	1000 M		3000 M	post implantation loss in female rats mating with exposed males, and persistent decreased fertility
Working et al. 1985a									
6	RAT (Fischer-344) 5M, 5F	1 day 8 hours/day	1000	BI	Hepatic	1000			
					Renal	1000 F			
					Renal		1000 M		Significantly decreased glutathione-S-transferase activity
Jager et al. 1988									
7	RAT (Fischer-344) 10M, 10F	9 days 6 hours/day	0, 2000, 3500, 5000	CS HP LE RX	Death			5000 F	Killed in extremis
					Death			3500 M	Killed in extremis
					Gastro	2000	3500		Diarrhea
					Hepatic		2000 F		Minimal hepatocyte degeneration
					Hepatic	2000 M	3500 M		Minimal hepatocyte degeneration
					Renal	2000 F		3500 F	Degeneration and necrosis of proximal convoluted tubules
					Renal			2000 M	Degeneration and necrosis of proximal convoluted tubules
					Endocr	2000	3500		Clear droplets in endothelial cytoplasm assumed to be fatty degeneration of adrenals
					Neuro	3500		5000	Hind limb paralysis, forelimb incoordination, cerebellar lesions
					Repro			2000 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

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
Morgan et al. 1982									
8	RAT (Sprague-Dawley) 20M, 20F	48 hours continuous	0, 196 ,501 , 972, 1968	BC BW CS GN HE HP OW UR	Death				
					Death			972 F	1/10F died on post exposure day 6
					Bd wt	196	501		5-6% decreases in body weight that returned to normal by days 1 and 11
					Bd wt			972 M	20% decrease in body weight that persisted
					Resp	1968			
					Hemato		196 F		Increased WBC count during 48 hour recovery period.
					Hemato	196 M	501 M		Increased RBCs and hemoglobin
					Hepatic		196		Decreased liver weight
					Renal	501		972	Increased BUN, tubular cell necrosis
					Neuro	501	972		Lethargy
					Repro	196 M		501 M	Sperm granulomas, decreased sperm in the tubule lumen, interstitial edema, coagulated proteinaceous obstruction of lumen
Burek et al. 1981									
9	RAT (Fischer-344) 2-8M	12 days 4-5 days/ week 6 hours/day	0, 3500	BI HP OF	Cardio	3500 M			
					Hepatic		3500 M		Decreased liver non-protein sulfhydryl content
					Endocr			3500 M	Reduced circulating testosterone
					Repro			3500 M	Sulfhydryl depletion in testicles, delayed spermiation, seminiferous epithelium vacuolation, and bilateral epididymal granulomas
Chapin et al. 1984									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
10	RAT (Fischer-344) 5-12M	2 days 6 hours/day	0, 7500	BW CS HP LE OW	Repro			7500 M	Bilateral epididymal granulomas
Chellman et al. 1986a									
11	RAT (Fischer-344) 5M	5 days 6 hours/day	0, 5004	BW CS HP LE OW	Death			5004 M	1 out of 5 died
					Bd wt			5004 M	20% loss of body weight
					Hepatic		5004 M		Hepatocellular degeneration - cloudy swelling of hepatocytes, obliteration of sinusoids
					Renal			5004 M	Necrosis of proximal convoluted tubules, 27% increase in relative kidney weight
					Endocr		5004 M		Vacuolation of cell cytoplasm in the adrenal cortex, 75% increase in relative adrenal weight
					Neuro			5004 M	Severe cerebellar degeneration, tremors, ataxia, and limb paralysis, 25% increase in relative brain weight
					Repro		5004 M		13% increase in relative testes weight, 22% increase in relative epididymis weight, severe epididymis granulomas, pachytene spermatocytes and early stage spermatids in the tubular lumen, slight separation of early stage spermatids, formation of multinucleated giant cells
Chellman et al. 1986a									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
12	RAT (Fischer-344) 20-40M	5 days 6 hours/day	0, 3009	HP	Repro			3009 M	Preimplantation loss due to testicular toxicity
Chellman et al. 1986c									
13	RAT 18M	5 days 6 hours/day	0, 3056	HP OW RX	Bd wt	3056 M			
					Repro			3056 M	Decreased testes weight; delayed spermiation; decreased sperm production; increase in abnormal sperm; 13 to 14% decrease in the percent of motile sperm in weeks 1 and 2 of recovery; there was no motility at all at week 3 of recovery, and approximately 50% decrease in intact sperm at week 3 of recovery
Chellman et al. 1987									
14	RAT (Fischer-344) 4M	6 hours (doses at 501 ppm also had observations at 1, 3 and 4 hours)	0, 99, 501, 1505	BI	Resp	99 M	501 M		Decrease in nonprotein sulfhydryl levels to 55% of control value (30% at 1500 ppm)
					Hepatic	99 M	501 M		Decrease in NPSH levels to 41% of control value (17% at 1500 ppm)
					Renal	99 M	501 M		Decrease in NPSH levels to 59% of control value (27% at 1500 ppm)
Dodd et al. 1982									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
15	RAT (Fischer-344) 40M	5 days 6 hours/day	0, 1000, 3000	CS GN HP OW RX	Repro	1000 M		3000 M	Number of live and total implants decreased; percent of pre- and post-implantation loss increased; reversible disruption of spermatogenesis; temporary reduced testes weights (50%, 8 weeks post exposure, approx. 4% 16 weeks post exposure)
Working et al. 1985b									
16	RAT (Fischer-344) 25F	13 days 6 hours/day GD 7-19	0, 102, 479, 1492	BW DX FI LE RX WI	Bd wt	102 F		479 F	20.8% reduction in body weight gain from GD 7 to 15 compared to controls, no significant difference in body weight gain between exposed and control rats from GD 15 to 20
					Repro	1492 F			
					Develop	479 F		1492 F	Retarded skeletal development (reduced ossification and fewer caudal bones); decreased fetal body weight (males= 10.1%; females = 10.4%), and decreased crown-rump length in females (3.9%)
Wolkowski-Tyl et al. 1981a, 1983a									
17	RAT (Sprague-Dawley) 20M/F	72 hours continuous	0, 198, 504, 976, 1950	BC BW CS GN HE HP OW UR	Death			976	6/10M and 8/10F died during post exposure days 1-7
					Bd wt	198 F	504 F		28% body weight decrease that persisted
					Bd wt		198 M		6-8% body weight decreases that returned to normal by days 1 & 11
					Resp		1950		Congestion and edema of the lungs
					Hemato	504 F	1950 F		Increased hematocrit and RBCs
					Hemato		198 M		Increased hematocrit and RBCs

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
					Hepatic		198 F		Increased amount of fat
					Hepatic		198 M		Altered staining properties of hepatocytes
					Renal		504 M		Renal lesions
					Repro		504 M		Sperm granulomas, decreased sperm in the tubule lumen, interstitial edema, coagulated proteinaceous obstruction of lumen, inflammation, sperm granuloma formation, scarring, testicular atrophy secondary to alterations
Burek et al. 1981									
18	RAT (Fischer-344) 5M, 5F	4 days 6 hours/day	1000	BI	Hepatic	1000			
					Renal	1000			
Jager et al. 1988									
19	MOUSE (C57BL/6) Fetus (B6C3F1) 74-77F	12 days 6 hours/day GD 6-17	0, 251, 502, 749	BW DX LE OW RX	Death			749 F	6/75 died, 1/75 moribund
					Bd wt	251 F		749 F	41% decrease in maternal total weight gain
					Hepatic	251 F	502 F		9% increase in absolute and 5% increase in relative maternal liver weight
					Neuro	251 F	502 F	749 F	LOAEL: ataxia SLOAEL: tremors, convulsions, increased then reduced hyperactivity, hypersensitivity to sound, ataxia, and piloerection
					Repro	502 F			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
					Develop	251 F		502 F	Significant increase in heart malformations (11 vs. 7 expected at 502 ppm, 17 vs. 14 expected at 749 ppm)
Wolkowski-Tyl et al. 1981b, 1983b									
20	MOUSE (B6C3F1) 5M, 5F	4 days 6 hours/day	1000		Hepatic	1000			
					Renal	1000			
Jager et al. 1988									
21	MOUSE (C57BL/6) 10F	2 weeks 5 days/week 6 hours/day	0, 1500	CS HP NX LE	Death			1500 F	2/10 died
					Renal		1500 F		Slight degeneration of proximal tubules
					Neuro			1500 F	Motor incoordination, coagulative necrosis and edema in cerebellar granule cells
Jiang et al. 1985									
22	MOUSE (C57BL/6) 12F	11 days 5.5 hours/ day	0, 150, 400, 800, 1600, 2400	BW CS GN HP LE OW	Death			2400 F	Killed in extremis
					Bd wt	1600 F	2400 F		16% decrease in body weight
					Hemato	1600 F	2400 F		Hemoglobinuria, enlarged spleen, low packed cell volume
					Hepatic	800 F		1600 F	23% decrease in relative liver weight
					Renal	1600 F	2400 F		Slight multifocal degeneration and regeneration of tubules, non-significant increase in relative kidney weight
					Neuro	150 F	400 F	800 F	LOAEL: slight cerebellar granule cell degeneration SLOAEL: poor motor coordination
Landry et al. 1985									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
23	MOUSE (C57BL/6) 12F	11 days 22 hours/day	0, 15, 50, 100, 150, 200, 400	BW CS GN HP LE OW	Death			150 F	Moribund after 10.5 days; at 200 ppm, all died at 5 days
					Bd wt	100 F	150 F	200 F	SLOAEL: 32% decrease in body weight LOAEL: 12% decrease body weight
					Hepatic	50 F	100 F	150 F	LOAEL: decreased hepatocyte size; glycogen depletion SLOAEL: necrosis
					Renal	150 F			
					Neuro	50[b] F	100 F		Slight degenerative changes in the cerebellum granule cell layer with nuclear pyknosis and karyorrhexis (100% of mice affected)
Landry et al. 1985									
24	MOUSE (C3H) 5M, 5F	12 days 6 hours/day	0, 500, 1000, 2000	CS HP LE	Death			2000 F	All died by day 5
					Death			1000 M	1/5 died by day 11
					Hepatic	2000 F			
					Hepatic			500 M	2/5 male mice showed minimal hepatocellular degeneration at 500 mg/kg/d (no degeneration observed in the males exposed to 1000 mg/kg/d, 4/5 male mice showed degeneration at 2000 mg/kg/d)
					Renal	500			
					Renal		1000 F		5/5 female mice developed basophilic renal tubules (not observed in female mice at 2000 mg/kg/d); 5/5 female mice developed hematuria on day 8

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
					Renal			1000 M	2/5 male mice developed basophilic renal tubules (not observed in male mice exposed to 2000 mg/kg/d, but 5/5 male mice exposed to 2000 mg/kg/d showed degeneration and necrosis of renal proximal convoluted tubules)
					Neuro	2000			
Morgan et al. 1982									
25	MOUSE (B6C3F1) 5-15M	6 hours	500, 1000, 1500, 2000, 2500	BC BI CS HP LE OF UR	Death			2500 M	14/15 mice died, LC50 estimated as 2200 mg/kg/day (method not provided)
					Neuro			2500 M	Cerebellar damage indicated by tremors, ataxia, and forelimb/hind limb paralysis
Chellman et al. 1986b									
26	MOUSE (B6C3F1) 6M	6 hours	0, 1500	BC BI CS HP LE OF UR	Hepatic			1500 M	50-fold increase in ALT, hepatonecrosis
Chellman et al. 1986b									
27	MOUSE B6C3F1 36-45 M	2 weeks 5 days/week 6 hours/day	0, 1500	BC BI CS HP LE OF UR	Death			1500 M	5/45 died on first day, no subsequent deaths
					Neuro			1500 M	Multiple degenerative and necrotic foci in cerebellar granular cell layer
Chellman et al. 1986b									
28	MOUSE (NS) NSB	2 weeks 5 days/week 6 hours/day	0, 1500	BC BI CS HP LE OF UR	Renal		1500		Cell regeneration as indicated by 3 fold increased thymidine incorporation
Chellman et al. 1986b									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
29	MOUSE (B6C3F1) 5M, 5F	1 day 8 hours/day	1000	BI	Hepatic	1000			
					Renal		1000		Significantly decreased GST activity
Jager et al. 1988									
30	MOUSE (C57BL/ 6N) 33F	12 days 6 hours/day GD 6-17	0, 102, 479, 1492	BW DX FI LE RX WI	Death			1492 F	All animals terminated early; 2 died prior to necropsy
					Neuro	479 F		1492 F	Tremors, difficulty righting, degradation and selective necrosis of cerebellar granular cells
					Repro	479 F			
					Develop	102 F		479 F	Heart defects in fetuses (reduction or absence of valves and muscles)
Wolkowski-Tyl et al. 1981a, 1983a									
31	MOUSE (B6C3F1) 5M, 5F	12 days 6 hours/day	0, 500, 1000, 2000	CS HP LE	Death			2000 F	All died by day 5
					Death			2000 M	5/5 died or became moribund by day 2
					Hepatic	1000		2000	Hepatocellular degeneration in 4/5 female mice and 5/5 male mice (male mice had severe hepatic lesions and necrosis)
					Renal	500			
					Renal		1000 F		5/5 female mice developed basophilic renal tubules (not observed in female mice at 2000 mg/kg/d); 5/5 female mice developed hematuria on day 8

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
					Renal		500 M		1/5 male mice developed basophilic renal tubules at 500 mg/kg/d, 3/5 developed basophilic renal tubules at 1000 mg/kg/d (no basophilic renal tubules observed in the 2000 mg/kg/d-exposed males, but 1/5 2000 mg/kg/d exposed males developed necrosis of renal proximal convoluted tubules)
					Neuro	1000 F		2000 F	2/5 female mice showed moderate cerebellar degeneration (granular layer)
					Neuro	2000 M			
Morgan et al. 1982									
32	MOUSE (C57Bl/6) 5M, 5F	12 days 6 hours/day	0, 500, 1000, 2000	CS HP LE	Death			2000 F	All died by day 5
					Death			2000 M	1/5 died by day 2, remaining 4/5 died or became moribund by day 5
					Hepatic			500	Hepatocellular degeneration in 2/5 female mice and 3/5 male mice
					Renal	500			
					Renal		1000 F		5/5 female mice developed hematuria on day 8
					Renal		1000 M		2/5 male mice developed basophilic renal tubules (not observed at 2000 mg/kg/d exposure, but 3/5 male rats exposed to 2000 mg/kg/d showed degeneration and necrosis of renal proximal convoluted tubules)

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
					Neuro	500		1000	3/5 male mice showed minimal cerebellar degeneration (granular layer), 5/5 female mice showed moderate cerebellar degeneration (granular layer)
Morgan et al. 1982									
33	DOG (Beagle) 3M	3 days 23.5 hours/ day	0, 197, 496	BC CS GN HE HP OP OW	Bd wt	496 M			
					Resp	496 M			
					Cardio	496 M			
					Gastro	496 M			
					Hemato	496 M			
					Hepatic	496 M			
					Renal	496 M			
					Dermal	496 M			
					Ocular	496 M			
					Endocr	496 M			
					Neuro	197 M		496 M	Slight, multifocal lesions in brain and spinal cord; vacuolization, swollen axons, loss of axons
					Repro	496 M			
McKenna et al. 1981a									
INTERMEDIATE EXPOSURE									
34	RAT (Sprague-Dawley) 10M, 10F	93 days 5 days/week 6 hours/day	0, 51, 149, 399	BC BW CS GN HE HP OW UR	Bd wt	399			
					Resp	399			
					Cardio	399			
					Gastro	399			
					Hemato	399			
					Musc/skel	399			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
					Hepatic	399			
					Renal	51 F	149 F		Significant decrease in urinary specific gravity (at 149 but not 399 ppm) without pathological findings
					Renal	149 M	399 M		Significant decrease in urinary specific gravity without pathological findings
					Dermal	399			
					Immuno	399			
					Neuro	399			
					Repro	399 M			
McKenna et al. 1981b									
35	RAT (Fischer-344) 10M, 10F	90 days 5 days/week 6 hours/day	0, 368, 741, 1473	BC BW CS FI HE HP OP OW UR	Bd wt	741 F	1473 F		11% decrease in body weight
					Bd wt	368 M	741 M	1473 M	At 741 ppm there was a 10% decrease in body weight; at 1473 there was a 22% decrease in body weight
					Resp	1473			
					Cardio	1473			
					Hemato	1473			
					Musc/skel	1473			
					Hepatic	741 F	1473 F		20% increased relative liver weight
					Hepatic	1473 M			
					Renal	1473 F			
					Renal	741 M	1473 M		Increased relative kidney weight (data illegible to further describe)
					Dermal	1473			
					Ocular	1473			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
					Neuro	1473			
					Repro	1473			
Mitchell et al. 1979									
36	RAT (Fischer-344) 10M, 10F	6 months 5 days/week 6 hours/day	0, 51, 224, 997	BC BI BW CS GN HE HP OP OW UR	Bd wt	224	997		10-11% decreased body weight
					Resp	224 F	997 F		20% increase in lung weight
					Resp		51 M		7% increase in lung weight
					Cardio	997			
					Gastro	997			
					Hemato	997			
					Musc/skel	997			
					Hepatic	997 F			
					Hepatic	224 M	997 M		9% increase in relative liver weight
					Renal	997			
					Ocular	997			
					Endocr	997			
					Immuno	224 F	997 F		Minimal sub-acute tracheitis characterized by lymphocytic and histiocytic inflammatory cells in submucosa in 5/10 mice
					Immuno	997 M			
					Neuro	997 M			5% decrease in brain weight
					Repro	224 M		997 M	Degeneration & atrophy of seminiferous tubules; sperm granulomas
CIIT 1981									
37	RAT (Fischer-344)	10 weeks 5 days/week 6 hours/day,	0, 151, 472, 1502	CS HP GN RX OW	Bd wt	472 F	1502 F		10% decreased body weight gain by 15 days, 10-19% decrease through 70 days

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
	40M, 80F	then 2 weeks 7 days/week, 6 hours/day (males) or 27 weeks, 7 days/week 6 hours/day (females, no exposure GD 18 through postnatal day 4)			Bd wt	472 M		1502 M	14% decreased body weight gain by 29 days, 22% decreased body weight gain by 80 days with partial recovery (3.8% decreased body weight gain) by 110 days
					Repro	151 M	472 M	1502 M	LOAEL: 39% decrease in the number of fertile males, 28% decrease in the number of litters per copulation plug in F0 rats SLOAEL: sterility, atrophy of the seminiferous tubules, epididymal granulomas
Hamm et al. 1985									
38	RAT (F1 generation Fischer-344) 23-40M, 46-80F	10 weeks 5-7 days/ week 6 hours/day	0, 151, 472	CS GN HP OW RX	Repro	151	472		17% fewer males in the F1 generation proven fertile when compared to controls. 12% decrease in number of F1 females producing litters. Neither was statistically significant.
Hamm et al. 1985									
39	MOUSE (B6C3F1) 9M, 11F	6 months 5 days/week 6 hours/day	0, 51, 224, 997	BI BC BW CS GN HE HP OP OW UR	Bd wt		997		M: 11% decrease in body weight; F: 16% decrease in body weight
					Bd wt	224 M			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
					Resp	997			
					Cardio	997			
					Hemato	51			
					Hemato	997 F			
					Hemato	224 M	997 M		Increased reticulocyte count
					Musc/skel	997			
					Hepatic	224	997		M: 7/10 males had diffuse hepatocellular degeneration that was midzonal; F: 6/10 females had diffuse or multifocal centrilobular hepatocellular degeneration
					Renal	224			
					Renal		997 F		14% increase in relative kidney weight
					Renal		997 M		18% decrease in absolute kidney weight
					Ocular	997			
					Endocr	997			
					Immuno	224	997		LOAEL: lymphoid depletion of spleen; thymic lymphoid necrosis (nuclear pyknosis and karyolysis)
					Neuro		997 M		10% decrease in absolute brain weight
CIIT 1981									
40	MOUSE (CD-1) 10M,10F	94 days 5 days/week 6 hours/day	0, 51, 149, 399	BW CS GN HP OW UR	Resp	399			
					Cardio	399			
					Gastro	399			
					Hemato	399			
					Musc/skel	399			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
					Hepatic	399			
					Renal	399			
					Dermal	399			
					Immuno	399			
					Neuro	399			
					Repro	399 F			
McKenna et al. 1981b									
41	MOUSE (B6C3F1) 10M,10F	90 days 5 days/week 6 hours/day	0, 368, 741, 1473	BC BW CS FI HE HP OP OW UR	Bd wt	1473			
					Resp	1473			
					Cardio	1473			
					Gastro	1473			
					Hemato	1473			
					Musc/skel	1473			
					Hepatic	368	741		Increased relative liver weight (not otherwise described)
					Renal	1473			
					Ocular			368	Mucopurulent conjunctivitis leading to loss of eye (3/10 male mice and 4/10 female mice compared to 0/10 control mice). The authors considered this to only potentially be chemically related
					Neuro	1473			
					Repro	1473			
Mitchell et al. 1979									
42	DOG (Beagle) 4M	93 days 5 days/week	0, 51, 149, 399	BW CS GN HE HP OW UR	Resp	399 M			
					Cardio	399 M			
					Gastro	399 M			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
		6 hours/day			Hemato	399 M			
					Musc/skel	399 M			
					Hepatic	399 M			
					Renal	399 M			
					Dermal	399 M			
					Ocular	399 M			
					Immuno	399 M			
					Neuro	399 M			
					Repro	399 M			
McKenna et al. 1981b									
43	RABBIT (New Zealand) 22 F	6 hours/day	0, 250, 500, 1000 ppm	BW CS DX GN RX	Bd wt	1000			
					Develop	1000			
Theuns-van Vliet 2016									
CHRONIC EXPOSURE									
44	RAT (Fischer-344) 10M, 10F	12 months 5 days/week 6 hours/day	0, 51, 224, 997	BC BI BW CS GN HE HP OP OW UR	Bd wt	224	997		M: 9% decrease body weight; F: 10% decreased body weight
					Resp	997			
					Cardio	997			
					Gastro	997			
					Hemato	997			
					Musc/skel	997			
					Hepatic	997 F			
					Hepatic	224 M	997 M		219% increase in ALT levels
					Renal	997			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
					Ocular		51		Slight hazing elliptically patterned over middle of eye (8/10 males and 6/10 females) with virus in exposed and control animals
					Endocr	997			
					Immuno	997			
					Neuro	997			
					Repro			997 M	Degeneration & atrophy of seminiferous tubules (4/10 rats)
CIIT 1981									
45	RAT (Fischer-344) 20M, 20F	18 months 5 days/week 6 hours/day	0, 51, 224, 997	BC BI BW CS GN HE HP NX OP OW UR	Bd wt	997 F			
					Bd wt	224 M	997 M		LOAEL: 12% decreased body weight gain
					Resp	997			
					Cardio	997			
					Gastro	997			
					Hemato	997			
					Musc/skel	997			
					Hepatic	997			
					Renal	997			
					Ocular	51 F	224 F		12/20 with corneal opacity (with and without conjunctivitis)
					Ocular	997 M			
					Endocr	997			
					Immuno	997			
					Neuro	997			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
					Repro	224 M		997 M	Degeneration and atrophy of seminiferous tubules; sperm granulomas
CIIT 1981									
46	RAT (Fischer-344) 65-68M; 57-61F	21 to 24 months 5 days/week 6 hours/day	0, 51, 224, 997	BC BI BW CS GN HE HP NX OP OW UR	Bd wt	224	997		M: 7% decreased body weight gain; F: 9.5% decreased body weight gain
					Resp	997			
					Cardio	997			
					Gastro	997			
					Hemato	997			
					Musc/skel	997			
					Hepatic	997 F			
					Hepatic	224 M	997 M		9% increase in relative liver weight
					Renal	997			
					Ocular	997			
					Endocr	997			
					Immuno	997			
					Repro	997			
					Repro	224 M		997 M	Degeneration and atrophy of seminiferous tubules; sperm granulomas
CIIT 1981									
47	MOUSE (B6C3F1) 10M, 10F	12 months 5 days/week 6 hours/day	0, 51, 224, 997	BC BI BW CS GN HE HP OP OW UR	Death			997 F	Increased mortality
					Bd wt	224	997		18% decreased body weight
					Resp	997			
					Cardio	224 F	997 F		39% increase in relative heart weight
					Cardio	997 M			
					Hemato	997			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
					Musc/skel	997			
					Hepatic	224 F	997 F		55% increase in relative liver weight
					Hepatic	224 M	997 M		219% increase in ALT, necrosis, cytomegaly, karyomegaly, polykaryocytes
					Renal	997 F			
					Renal	224 M	997 M		Renal tubuloepithelial hyperplasia; decreased absolute weight
					Ocular	997			
					Endocr	997			
					Immuno	997			
					Neuro	224	997		10-12% decrease in brain weight, neuronal cytoplasmic vacuolization in 1/18 females
					Repro	997			
CIIT 1981									
48	MOUSE (B6C3F1) 7M; 8-10 F	18 months 5 days/week 6 hours/day	0, 51, 224, 997	BC BI BW CS GN HE HP NX OP OW UR	Death			997	Increased mortality
					Bd wt		997		M:16% decreased body weight; F: 9% decreased body weight
					Resp	997			
					Cardio	224 F	997 F		39% increase in relative heart weight
					Cardio	997 M			
					Hemato	997			
					Musc/skel	997			
					Hepatic	224 F	997 F		44% increase in relative liver weight
					Hepatic	224 M		997 M	280% increase in ALT, centrilobular degeneration, karyomegaly, cytomegaly
					Renal	997 F			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
					Renal	224 M	997 M		Renal hyperplasia
					Ocular	997			
					Endocr	997			
					Immuno	224		997	Splenic lymphoid depletion
					Neuro		51[c]	997	LOAEL: axonal swelling and degeneration of axons in spinal cord with no neurofunctional abnormality SLOAEL: tremor, paralysis; minimal to mild reduction in number of cerebellar neurons in the granular cell layer, and clutch (females only) gait, extensor thrust, and scratch response impairment
					Repro	224 M		997 M	Testicular seminiferous tubule degeneration and atrophy
CIIT 1981									
49	MOUSE (B6C3F1) 20-32M; 57-68F	21-24 months 5 days/week 6 hours/day	0, 51, 224, 997	BC BI BW CS GN HE HP NX OP OW UR	Death			997	0 mice survived to 24 months in the 1000 ppm group
					Bd wt				Insufficient number of remaining animals to calculate mean weight
					Resp	997			Sacrificed at 21 (males) or 22 months (females)
					Cardio	51 F	224 F		Increase in relative heart weight
					Hemato	997			
					Musc/skel	997			
					Hepatic	224		997	Necrosis, cytomegaly, karyomegaly, polykaryocytes (males sacrificed at 21 months, females at 22 months)

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
					Renal	224	997		Renal hyperplasia and renal cortex adenomas
					Ocular	224			
					Endocr	997			
					Immuno	224			
					Immuno			997 F	Splenic atrophy and lymphoid depletion (sacrificed at 22 months)
					Neuro		51	997	LOAEL: swelling and degeneration of axons in spinal cord SLOAEL: tremor, paralysis, hind limb rigidity, cerebellar granular cell atrophy, with abnormal gait, posture, and thrust/clutch responses
					Repro	224 M		997 M	Testicular degeneration and atrophy
					Cancer			997 M	CEL: renal cortex adenocarcinomas, metastatic fibrosarcoma in the lung

CIIT 1981

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 inhalation provisional 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 provisional MRL of 0.5 ppm.

[c] This value was used to derive the chronic inhalation provisional 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 provisional MRL of 0.03 ppm.

ALT = alanine aminotransferase; BC = serum (blood) chemistry; BI = biochemical changes; BW or Bd wt = body weight; CS clinical signs; DX developmental toxicity; F = female(s); FI = food intake; Gastro = gastrointestinal; GD = gestational day; GN = gross necropsy; GST = glutathione S-transferase; HE = hematological; HP = histopathology; IX = immune function; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; NS = not specified; NX = neurological function; OF = organ function; OP = ophthalmology; OW = organ weight; RX = reproductive function; SLOAEL = serious lowest-observed-adverse-effect level

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

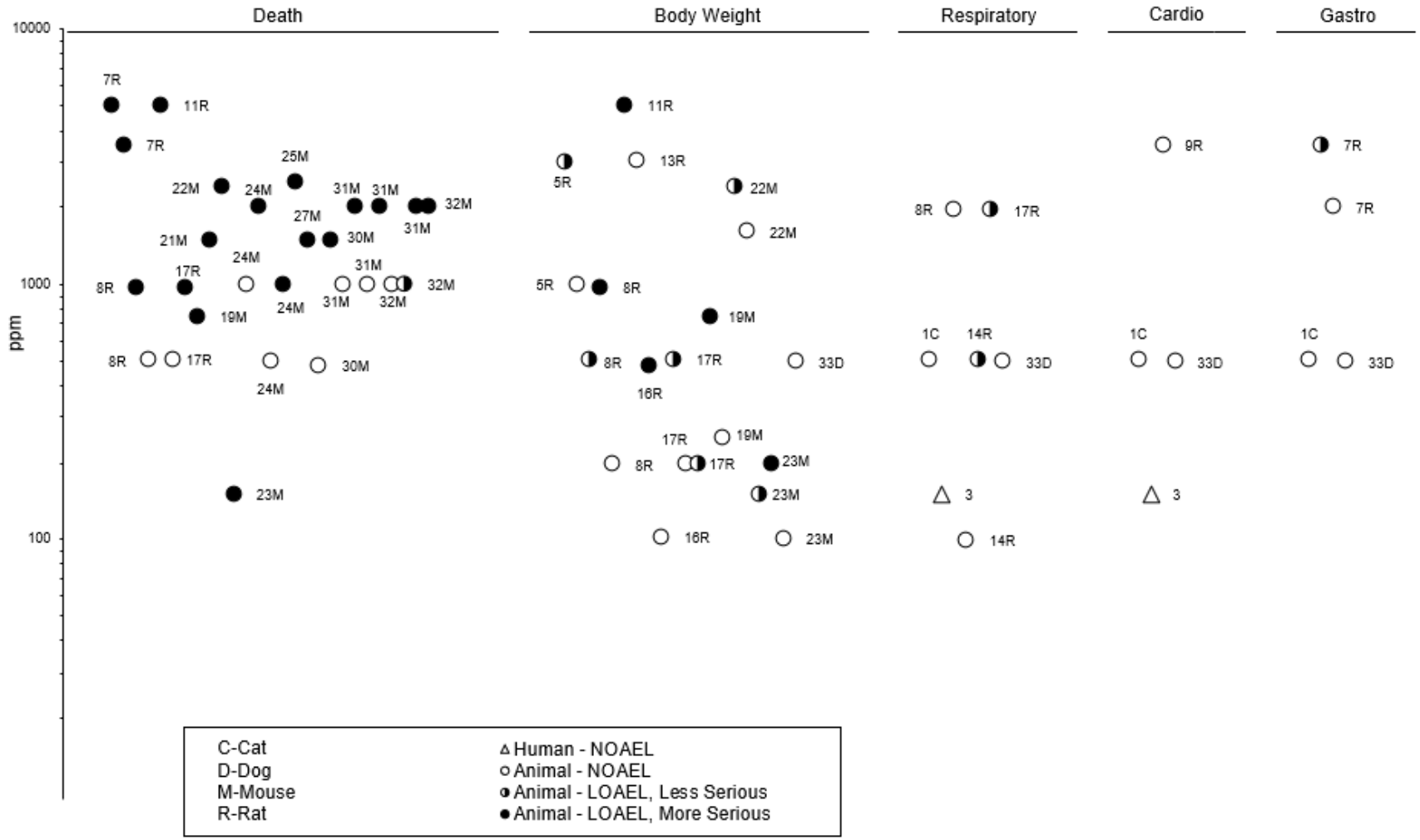


Figure 2-2. Levels of Significant Exposure for Animals and Humans to Chloromethane – Inhalation
Acute (≤14 days)

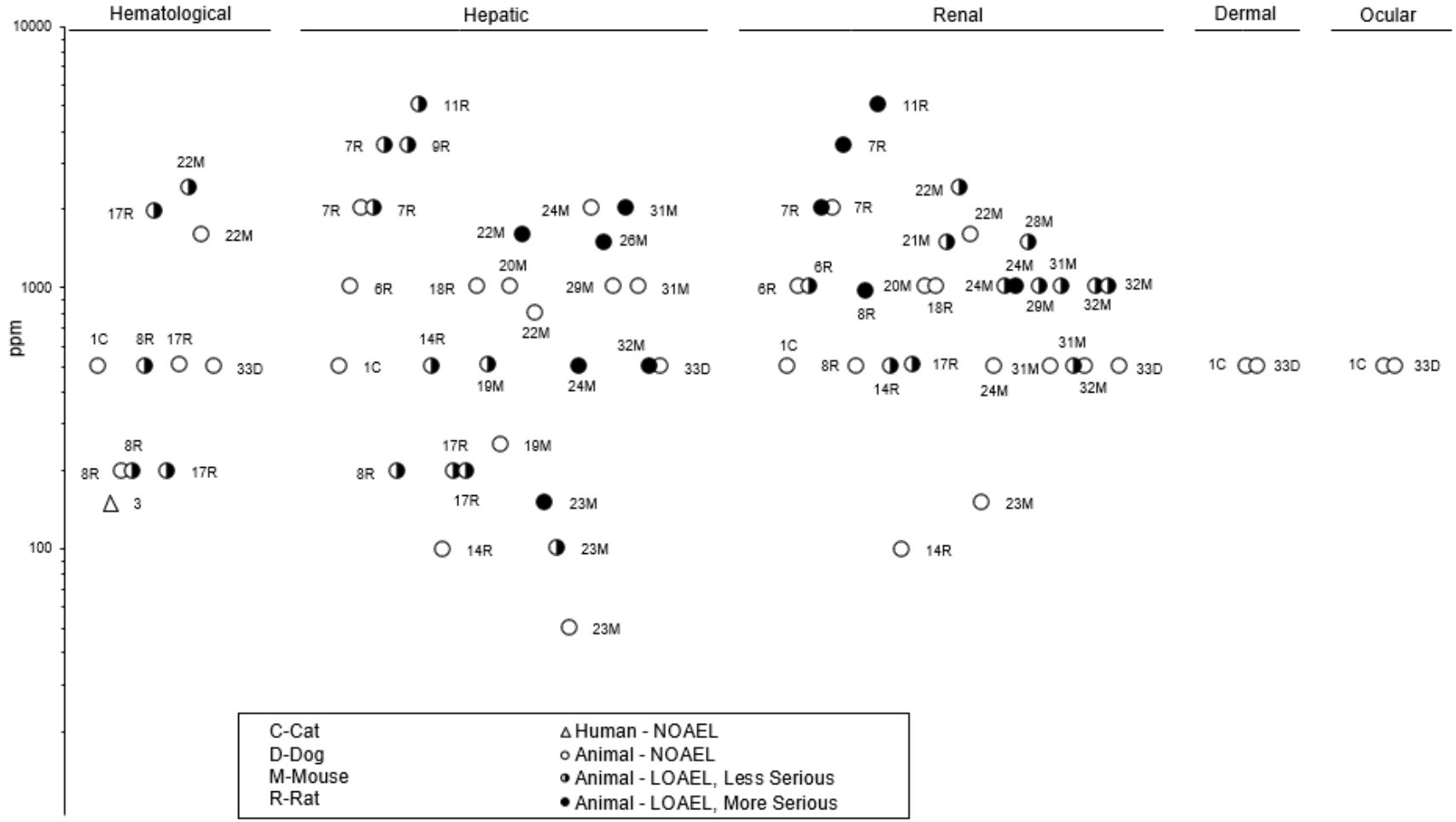


Figure 2-2. Levels of Significant Exposure for Animals and Humans to Chloromethane – Inhalation
Acute (≤14 days)

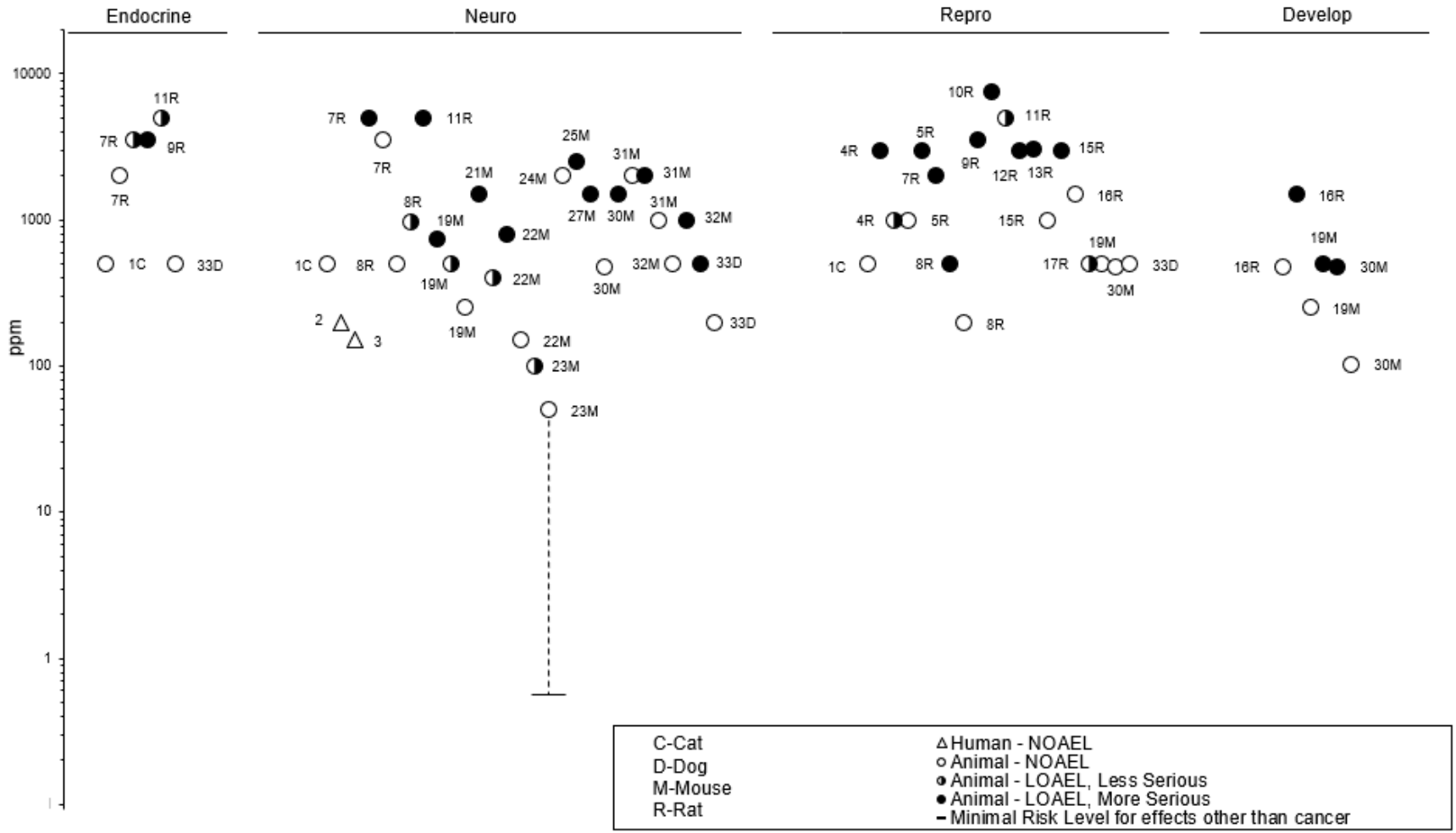


Figure 2-2. Levels of Significant Exposure for Animals and Humans to Chloromethane – Inhalation
Intermediate (15-365 days)

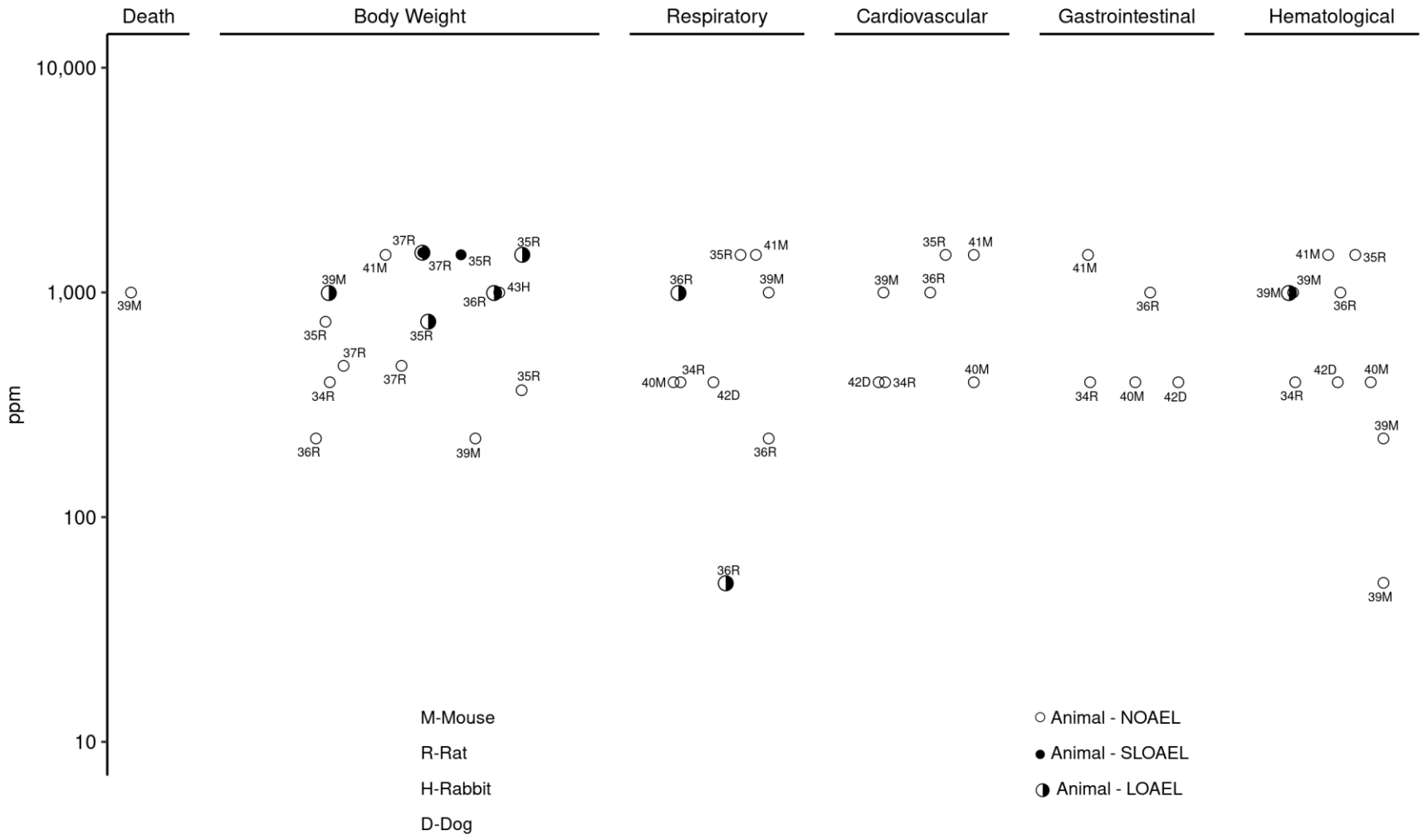


Figure 2-2. Levels of Significant Exposure for Animals and Humans to Chloromethane – Inhalation
Intermediate (15-365 days)

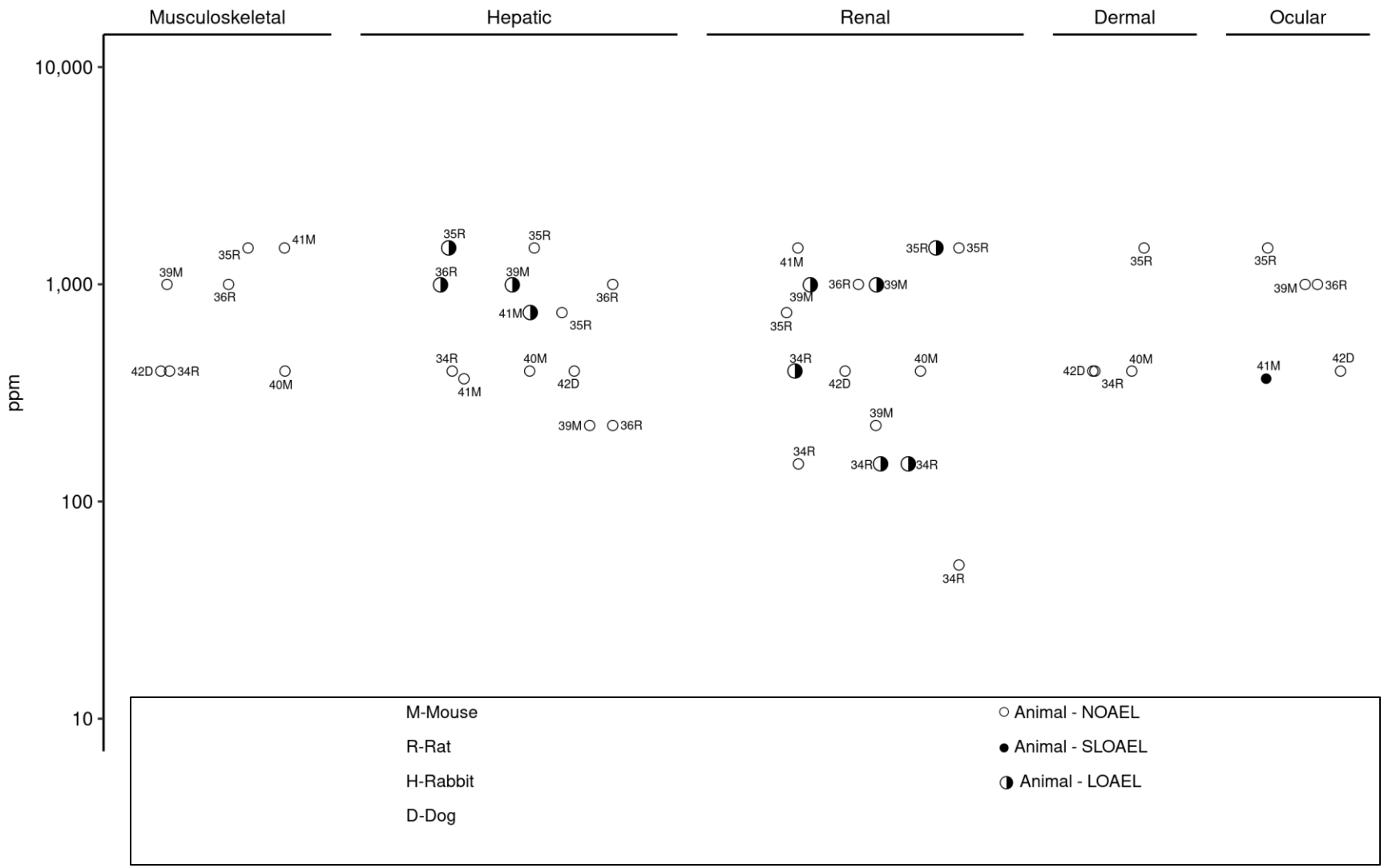


Figure 2-2. Levels of Significant Exposure for Animals and Humans to Chloromethane – Inhalation

Intermediate (15-365 days)

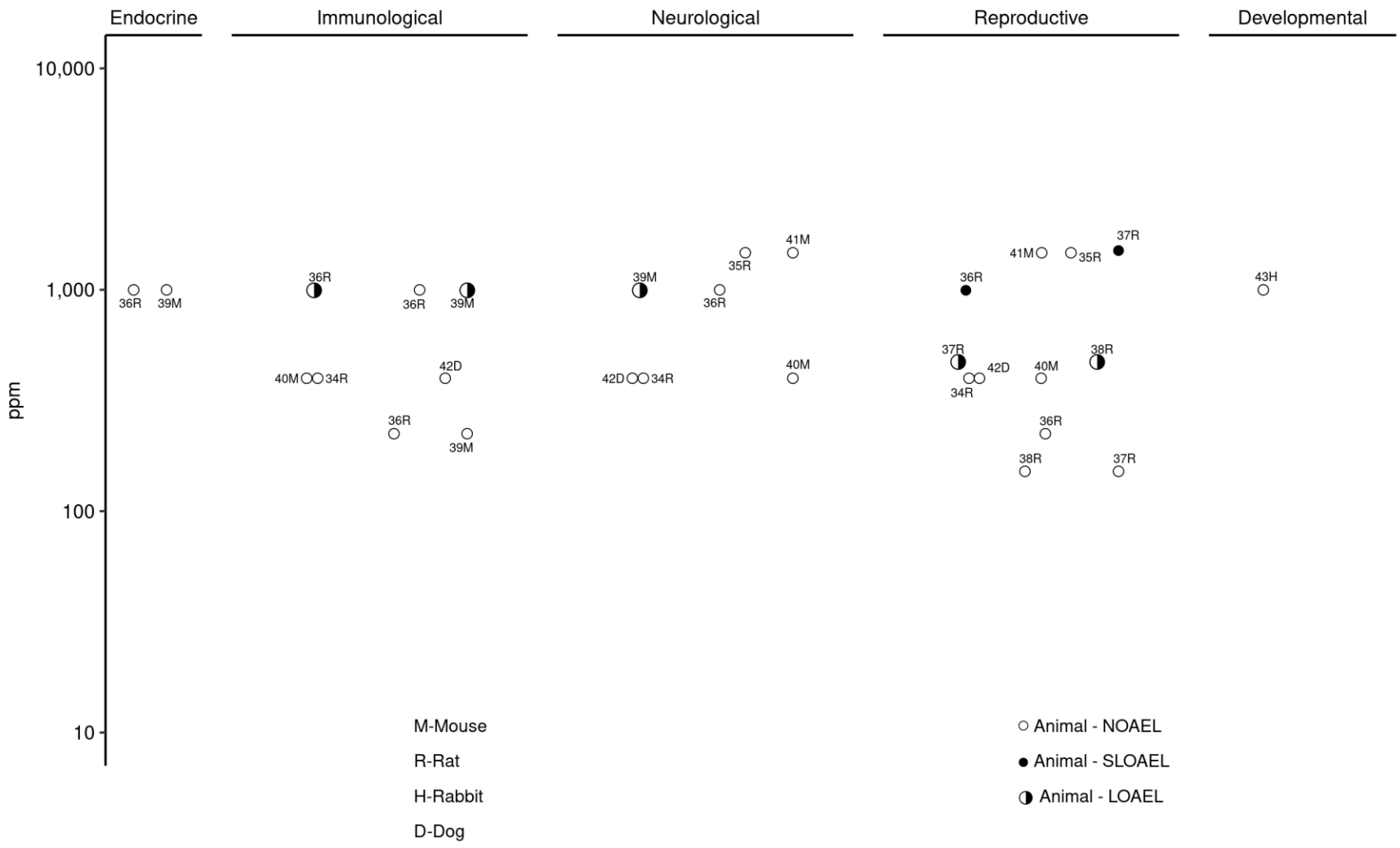


Figure 2-2. Levels of Significant Exposure for Animals and Humans to Chloromethane – Inhalation
Chronic (>365 days)

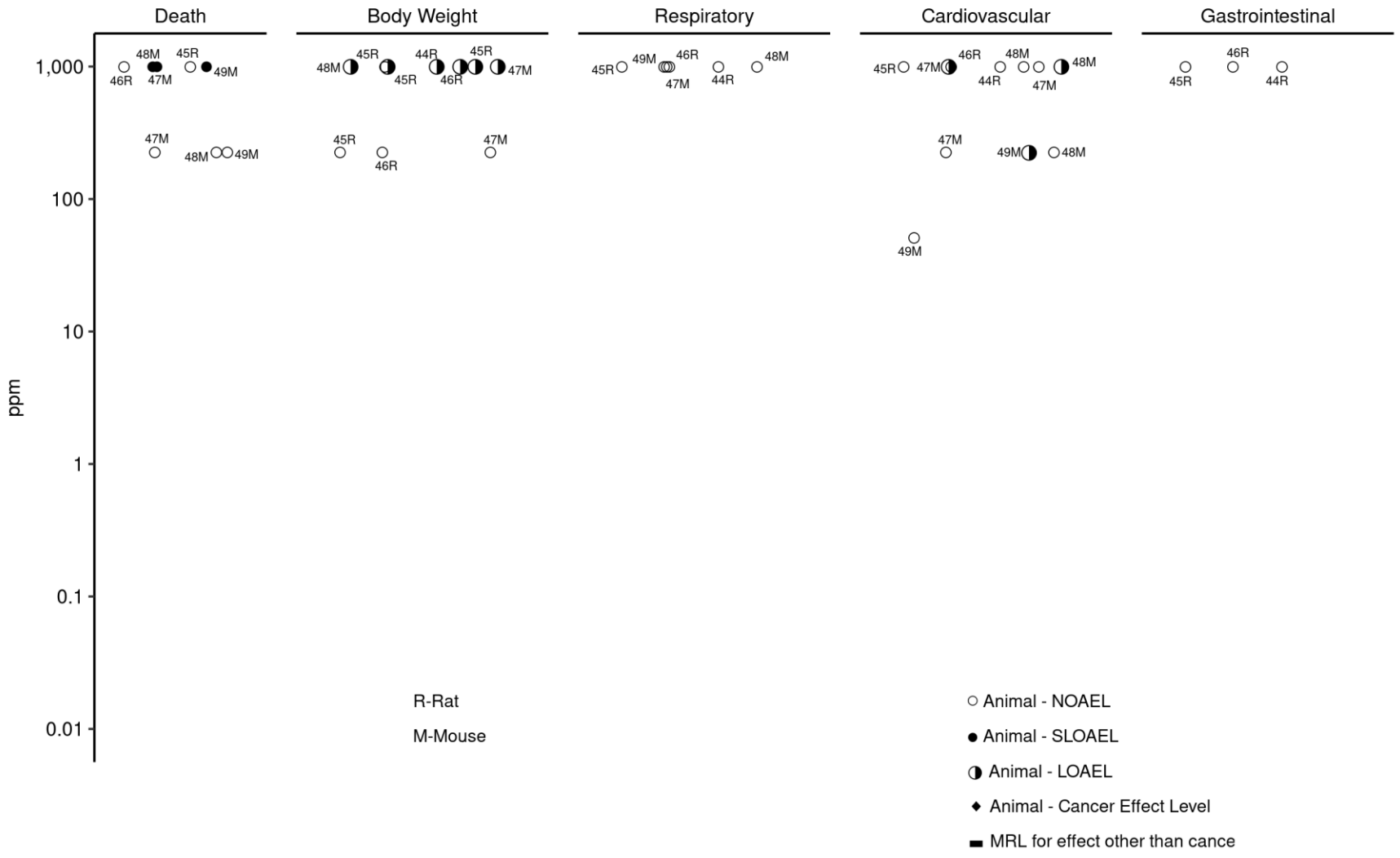


Figure 2-2. Levels of Significant Exposure for Animals and Humans to Chloromethane – Inhalation
Chronic (>365 days)

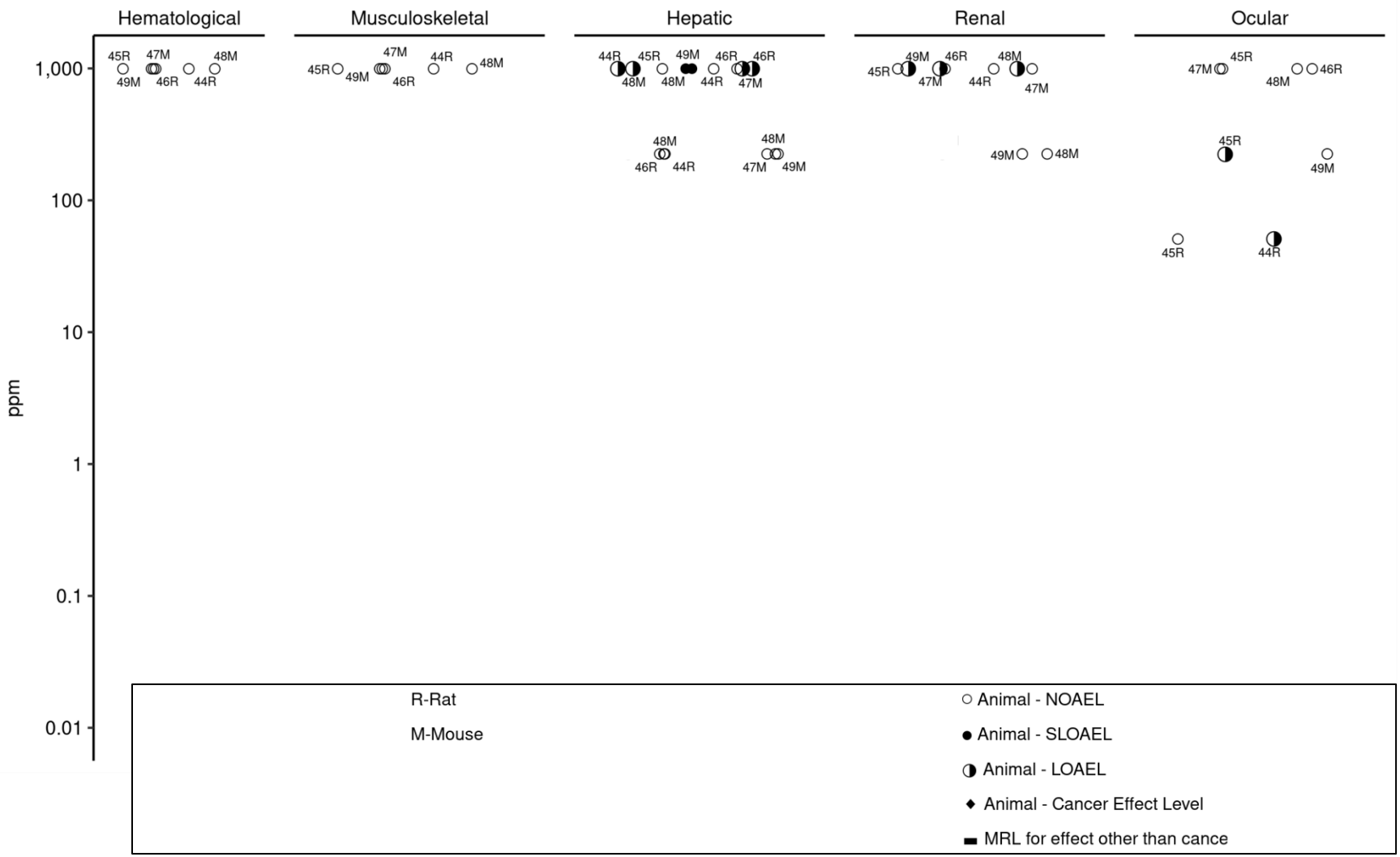


Figure 2-2. Levels of Significant Exposure for Animals and Humans to Chloromethane – Inhalation
Chronic (>365 days)

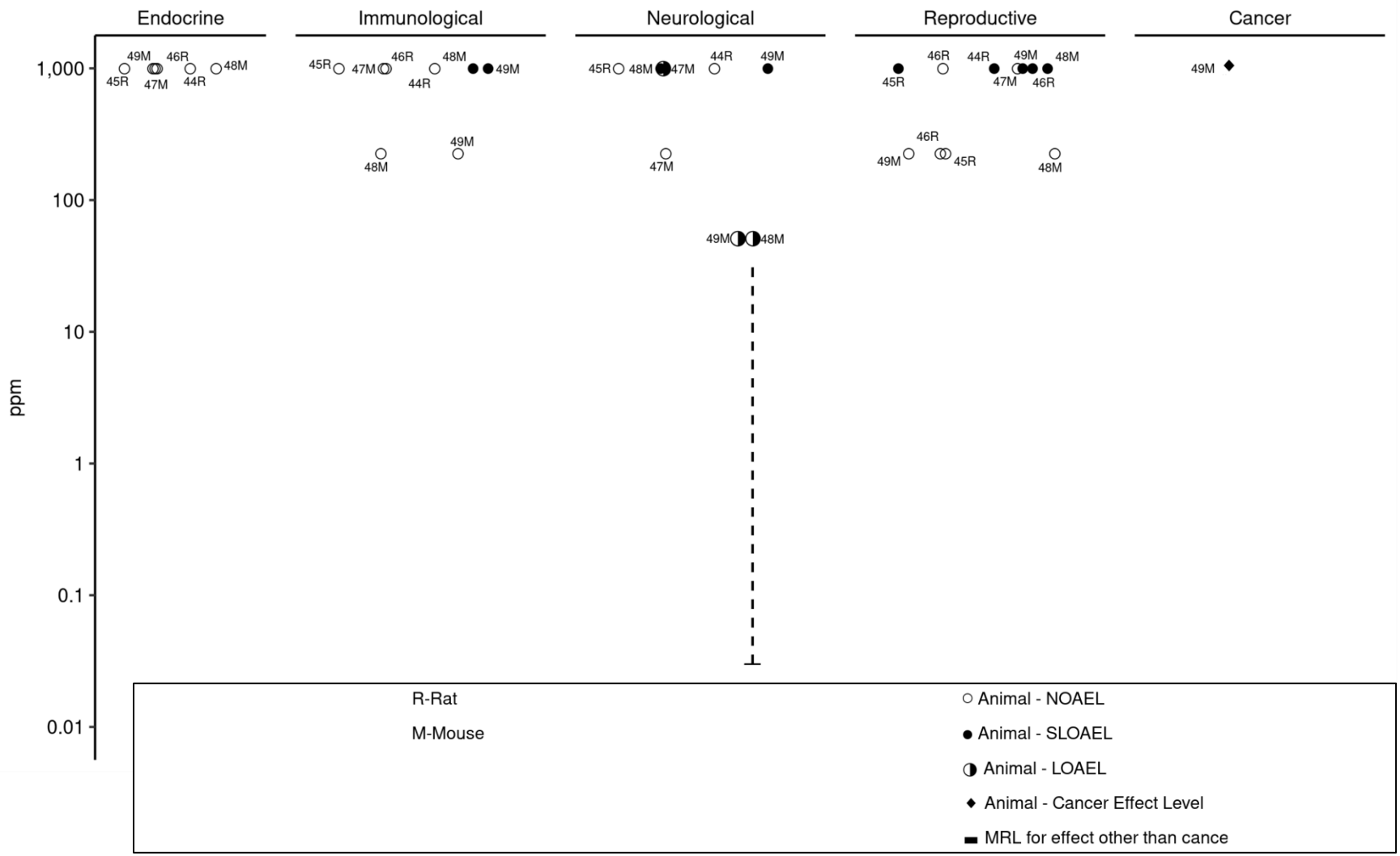


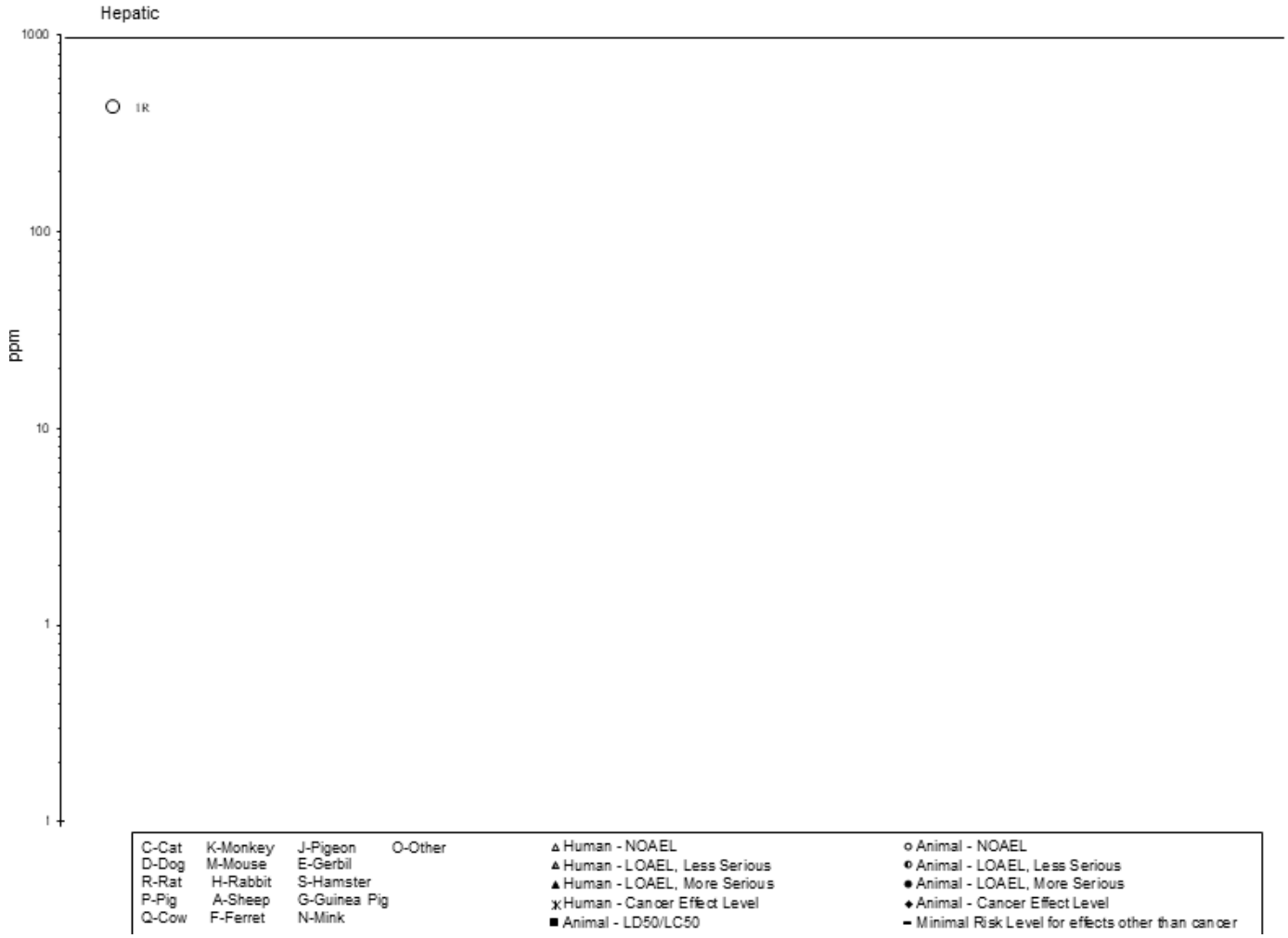
Table 2-3. Levels of Significant Exposure of Animals to Chloromethane – Oral

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)	Effects
ACUTE EXPOSURE									
1	RAT (Charles River) NSM	once (GO)	0, 420	HP	Hepatic	420			
Reynolds and Yee 1967									

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

BW or Bd wt = body weight; F = female(s); Gastro = gastrointestinal; HP = histopathology; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; NS = not specified; OW = organ weight

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



2.2 DEATH

In the late 1920s chloromethane began being used as a refrigerant (UNEP, 1999). Subsequently, several human deaths resulted 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).

Exposure to high concentrations of chloromethane can result in moderate to severe neurological effects (see Section 2.15), but death does not always result if exposure ceases and medical attention is received in time. For example, refrigerator repairmen developed neurological symptoms after exposures to chloromethane from leaks at concentrations as high as 600,000 ppm, but no deaths resulted (Jones 1942). In other cases death did occur, as in when the crew of an Icelandic fishing boat was exposed for up to 4 days in 1963 to chloromethane that leaked from a refrigerator located underneath the sleeping quarters of the deckhands onboard a fishing trawler (no estimates of exposure levels were reported) (Rafnsson and Gudmundsson 1997; Gudmundsson 1977). This leak resulted in the death of one crew member within 24 hours of the exposure (Gudmundsson 1977).

In addition, several follow up assessments have been conducted on the Icelandic fishermen cohort. Thirty-two years after the incident crew members that experienced the exposure had an increased risk of all-cause mortality when compared to unexposed fisherman (Rafnsson and Gudmundsson 1997). The increase in mortality was greater in the deckhands who were estimated to have received the greatest exposure due to the location of their living quarters. Further, Rafnsson and Gudmundsson (1997) reported an excess mortality from cardiovascular diseases in this exposed population compared to a reference group. The excess mortality was significant only for the deckhands who received the higher exposures to chloromethane.

Additional follow up that was conducted 47 years after the exposure also found that the risk of death by suicide was also increased in the cohort of exposed fisherman compared to an unexposed reference group (Rafnsson and Kristbjornsdottir 2014). While the reference and exposure group had similar occupations and thus likely similar socioeconomic status, the authors did not directly control for lifestyle factors, such as smoking habits, intensity of work demands, and diet. The results and conclusions from this cohort are based upon the assumption that the groups had similar lifestyle factors, and as such generalizing these results to the general population must be done with caution. There was also a relatively low number of individuals in the exposure group (n= 27) and the study has the potential to be underpowered.

Conversely, no excess mortality was observed in a mortality study on workers who used chloromethane to manufacture butyl rubber and were exposed to chloromethane for many years with long-term follow-up

(Holmes et al. 1986). However, when evaluating results from occupational cohort studies consideration of the healthy worker effect (i.e., working individuals tend to be healthier on a population group level compared to their non-working counterparts) is necessary. Although the authors acknowledged this study limitation, they did not report any actions they took to combat it. In fact, the authors took evidence of the healthy worker effect to mean the exposures faced by their cohort did not lead to significant adverse outcomes.

Studies which examine the potential association of chloromethane exposure with death from cancer are reviewed in Section 2.19.

Most animals exposed to high levels of chloromethane with short intervals between exposure periods (nearly continuous exposure) died after developing severe signs of neurotoxicity. In an extensive investigation, a variety of species including rats, mice, guinea pigs, rabbits, dogs, cats, chickens, and monkeys were exposed to lethal concentrations of chloromethane. Goats were exposed to much higher concentrations, but for a shorter period of time (Dunn and Smith 1947; Smith and Van Oettingen 1947b; Smith and Von Oettingen 1947a; Von Oettingen et al. 1950). The ED_{50} for mice reported by von Oettingen et al. (1950) was 3,080 ppm for a 7 hour inhalation exposure, with an average survival time of 354 minutes. Severe neurological effects, such as paralysis, convulsions, and opisthotonos (backward arching of the head, neck, and spinal cord due to muscle spasms), developed before death. These earlier studies demonstrated the universal response of animals to the neurotoxic and lethal effects of chloromethane. Increased mortality was associated with dose, duration of exposure, and age. Dogs exposed to 500 ppm survived 3-4 weeks, while those exposed to 3,000 ppm died in 2 days, and adult guinea pigs died in 1 week from exposure to 1,000 ppm, while a young guinea pig survived 12 weeks of the same exposure and was alive, albeit with neurological damage, 14 months later (Smith and Van Oettingen 1947b). Adult guinea pigs survived 9 months of exposure to 500 ppm without pathological changes. Goats exposed to the much higher concentration of 11,000 ppm chloromethane for 2 hours/day for 2 days survived, but demonstrated pathological changes (Dunn and Smith 1947).

Several acute exposure studies in experimental animals observed death or “killed animals in extremis” (at the point of death). In the majority of cases this occurred in both rats and mice exposed to doses of chloromethane at or above 150 ppm, at nearly continuous exposure, and at a 2400 ppm intermittent exposure with varying dosing schedules (e.g., continuous 22.5 hr/day or intermittent 5.5 to 6 hr/day) (Burek et al. 1981; Chellman et al. 1986a; Chellman et al. 1986b; Jiang et al. 1985; Landry et al. 1985; Morgan KT et al. 1982; Wolkowski-Tyl et al. 1983b; Wolkowski-Tyl et al. 1983a). Authors hypothesized that death may have been due to kidney (Burek et al. 1981; Morgan KT et al. 1982) or liver toxicity (Morgan KT et al. 1982). One study, Landry et al. (1985) killed mice in extremis after exposure to 150

ppm chloromethane nearly continuously (i.e., 22 hours/day) for 10.5 days or to 2400 ppm intermittently (i.e., 5.5 hours/day) for 9 days. This study demonstrated that continuous exposures could have a greater toxicological effect than intermittent exposures, even when accounting for the total dose the animals received.

Chellman et al. (1986a; 1986b) also explored the potential mechanism by which chloromethane may cause its lethal toxicity. By comparing rats exposed to chloromethane alone to rats exposed to chloromethane and pre- and post-dosed with a potent anti-inflammatory agent, 3-amino-l-[m-(trifluoromethyl)phenyl]-2-pyrazoline (BW755C) (Chellman et al. 1986a), or the GSH synthesis inhibitor L-buthionine-S,R-sulfoximine (BSO) administered by the intraperitoneal (*i.p.*) route (Chellman et al. 1986b), the authors found a protective effect of each. The authors concluded that protection from chloromethane-induced injury by BW755C 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 glutathione content. The protective effects of BW755C may have been related to promoting the normal metabolism of prostaglandin and leukotriene, or as hypothesized by others, an inhibition of leukotriene and prostaglandin synthesis (Chellman et al. 1986a). The second study found that preexposure to BSO depleted the kidney and liver of GSH, with which chloromethane can conjugate to produce toxic moieties (Chellman et al. 1986b).

In Chellman et al. (1986b) the researchers investigated the role of glutathione in the mediation of chloromethane-induced toxicity in the liver, kidney, and brain of male B6C3F1 mice. Specifically, the authors compared mice exposed to chloromethane alone and mice exposed to chloromethane and pre- and post-treated with L-buthionine-S,R,-sulfoximine (BSO) *i.p.*, a depleter of glutathione (GSH). The resulting mortality data was used to estimate an approximate LC_{50} value. The LC_{50} in the non-pretreated rats was 2,200 ppm, while the LC_{50} for the pretreated rats was 3,200 ppm. The authors concluded that pretreatment with BSO, and hence GSH depletion, protected mice from the lethal effects of chloromethane. The GSH metabolic pathway appeared to be activating a metabolite that increased toxicity rather than detoxifying.

CIIT (1981) is the only study which reported deaths in animal toxicological studies with intermediate or chronic exposure. During the acute exposure time frame (≤14 days), chloromethane exposure had no effect on the survival curves of male or female rats or mice at the exposure levels received. During the intermediate exposure time frame (15-364 days), there was some increased mortality beginning at 10 months in female mice exposed to approximately 1,000 ppm chloromethane (analytical measurement average 997 ppm). Although the authors noted a difference in 50 ppm and 225 ppm exposure groups when compared to the 1000 ppm group, the number of deaths in the 1000 ppm group was not

significantly different from control. No effect was observed on the survival of male or female rats. During the second half of the study (i.e., the chronic exposure of ≥365 days), there was increased mortality in 1,000 ppm exposed male mice beginning at 17 months, with a precipitous drop at 19 months. For 1,000 ppm female mice, increased mortality began at 10 months, continuing to rise and increased dramatically at 20 months. The 1,000 ppm mice groups were terminated at 21 months (2 males) and 22 months (18 females) due to high mortality. Chloromethane had no effect on the survival of male or female rats (CIIT 1981).

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

2.3 BODY WEIGHT

No studies were located regarding body weight effects in humans after inhalation exposure to chloromethane.

A consistent systemic effect of chloromethane exposure in animals is reduced body weight or reduced body weight gain, which was observed in rats and mice exposed to chloromethane for acute, intermediate, and chronic durations (Burek et al. 1981; CIIT 1981; Chellman et al. 1987; Chellman et al. 1986a; Landry et al. 1985; Mitchell et al. 1979; Working et al. 1985a; Wolkowski-Tyl et al. 1983b; Wolkowski-Tyl et al. 1983a). Mitchell et al. (1979) exposed rats to 368, 741, or 1473 ppm for 6 hr/day and 5 d/wk and reported significantly reduced body weights as early as week 5 for all doses, but the reduced body weight gains starting in week 3 disappeared by week 9, indicative of accommodation; however, significant body weight losses in controls and all exposed groups in the final week were not explained. CIIT (1981) exposed male and female mice and rats to approximately 0, 50, 225, and 1,000 ppm methyl chloride for 6, 12, 18, and 24 months and observed a significant body weight decrease in the highest dose group (16-24% for male and female mice at 6-12 months, but not later, and approximately 10% in male and female rats at all time points). Landry et al. (1985) observed that the impact at the lowest dose of 150 ppm with continuous exposure or 2,400 ppm with intermittent exposure was associated with reduced food intake. Male and female rats exposed to 2,000 ppm methyl chloride for 48 hours lost 25% and 18% of their respective body weight compared to controls by that time point; this rapid decrease was accompanied by dehydration and no food consumption (Burek et al. 1981). No effect on body weight was observed in dogs and cats exposed for 72 hours to 500 ppm methyl chloride (McKenna et al. 1981a). Further, no impact on body weight was observed in New Zealand white rabbits exposed to chloromethane to doses up to 1000 ppm 6 hours per day over the course of 22 days (Theuns-van Vliet et al. 2016). These findings may be due to species difference in response to exposure to chloromethane.

No studies were located on body weight effects in humans or animals after oral or dermal exposure to chloromethane.

2.4 RESPIRATORY

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). In a neurological study with human volunteers no effects on pulmonary function were observed following acute 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 increase in self-reported bothersome or more severe asthma symptoms (i.e., symptoms that were anticipated to interfere with daily activities) was seen in a cohort of Hispanic children from East Los Angeles with exposure to low concentrations of chloromethane (24 hour mean: 0.58ppb; Standard deviation: 0.14) (Delfino et al. 2003). However, given the very low levels of exposure and the inability of the authors to separate chloromethane exposure from exposure to other air pollutants near roadways, this study is limited in its evaluation of chloromethane-associated respiratory effects.

Acute exposure of dogs to 15,000 ppm resulted in reduced respiration and increased respiratory volume which was associated with a reduction in blood pressure. However, this effect is likely due to depression of the central nervous system by a metabolite of chloromethane (von Oettingen et al. 1949, 1950). In a series of studies on various species exposed to 500 to 4,000 ppm chloromethane until death, respiratory effects including pulmonary congestion and labored breathing were reported, with occasional slight edema, lung congestion, and/or alveolar hemorrhage (Dunn and Smith 1947; Smith and Van Oettingen 1947b). However, limitations of these reports, including using chloromethane of unknown purity, limit the usefulness of these studies.

Studies using very pure chloromethane (99.5-99.9%) failed to find any exposure-related histopathological lesions in the lungs of dogs and cats exposed acutely to 500 ppm (measured analytical concentration equal to 496 and 501 ppm, respectively) chloromethane (McKenna et al. 1981a), or rats exposed acutely to a target dose of 2,000 ppm (analytically measured concentration equal to 1,958 ppm); concurrent with

death, some rats exhibited congestion and edema of the lungs (Burek et al. 1981). This is in contrast to a reduction in lung congestion reported in female rats exposed to 1,500 ppm chloromethane for 90 days when compared to control female rats (Mitchell et al. 1979). Although an increase in red foci of the lungs was reported for 4/10 male rats exposed to 150 ppm, compared to no foci observed in the control, 4 female mice were observed with red foci in the controls, whereas no others were reported to have foci. Observations were made after 90 days of exposure and when the rats were sacrificed (McKenna et al. 1981b). The significance of such an improvement in the female rat is unclear. Following a 6-hour acute exposure, chloromethane was noted as having a concentration-dependent relationship with decreasing nonprotein sulfhydryl (NPSH) content in male Fischer 344 rat lungs (Dodd et al. 1982), which returned to levels similar to controls within 18 hours post exposure. Chloromethane was also shown to have an exposure time-dependent effect on lung NPSH, in which exposure to 500 ppm chloromethane was found to progressively decrease NPSH as exposure time increased at 1, 2, 4, and 6 hours. Pre-treatment with Aroclor-1254, a metabolic inducer, and SKF-525A, a metabolic inhibitor, in chloromethane exposed rats did not alter the inversely proportional relationship between increasing chloromethane exposure and decreasing NPSH (primarily GSH) content.

Similar to the acute studies, two intermediate duration exposure studies also did not find any association between chloromethane and histopathologic lesions in the lungs when evaluating male dogs exposed to a target dose of 400 ppm and rats and mice exposed to a target dose of up to 1,500 ppm (analytically measured concentration equal to 1,473 ppm) (McKenna et al. 1981b; Mitchell et al. 1979). However, Dunn and Smith (1947) reported lung congestion and signs of bleeding in cats exposed to 2,000 ppm and in dogs exposed to 3,000 ppm. CIIT (1981) found that at 6 months, relative lung weight was significantly increased at 50, 225, and 1,000 ppm in male rats and at 1,000 ppm in female rats (analytical concentrations reported to be 51, 224 and 997 ppm). These effects may have simply been due to a decrease in final body weight. One male and 4 female rats at the target dose of 1,000 ppm, 1 female at 225 ppm, and 2 males and 1 female at 50 ppm had minimal to moderate interstitial pneumonia with lymphocytic peribronchiolitis and perivasculitis. The interstitial lesions consisted of macrophage and lymphocytic infiltration. Also present were alveolar cell hyperplasia and mild alveolar luminal infiltrates consisting of large macrophages, lymphocytes, and in some areas, a few neutrophils. Five females at 1,000 ppm had areas of minimal subacute tracheitis (this lesion also occurred in 1 control male rat). At 12, 18, or 24 months after the initial exposure, no chloromethane-related lung effects were observed. No effects on lungs were observed at any time point in mice. These respiratory effects observed in this study were considered transitory by the authors. Additionally, the authors did not consider the effects to be associated with exposure to chloromethane (CIIT 1981).

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

2.5 CARDIOVASCULAR

Chloromethane has been determined to be not classifiable as it relates to cardiovascular outcomes based on the systematic evaluation of the literature. See Appendix C for more details.

Case reports and epidemiologic studies on humans exposed to chloromethane examined cardiovascular-related death, short- and long-term cardiotoxicity, altered cardiovascular metrics, and loss of cardiovascular function. One epidemiological study evaluated exposure to chloromethane either occupationally or environmentally (Holmes et al. 1986). Neither exposure had an association with death due to cardiovascular diseases (e.g. diseases classified as circulatory system diseases using ICD codes) (Holmes et al. 1986). Similarly in a human controlled exposure experiment, volunteers were exposed for 1, 3 or 7.5 hours per day for 2-5 days per dose 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).

The results of an ongoing retrospective cohort of male crew members of an Icelandic fishing trawler that were accidentally exposed to chloromethane due to a leaking refrigerator over the course of a 4-day trip in 1963 provide suggestive evidence of potential cardiovascular toxicity due to chloromethane exposure. A subset of crew members were exposed to chloromethane while using or servicing the refrigerator or while sleeping, as the refrigerator was located under the sleeping quarters of some of the crew. Thirty two years post exposure Rafnsson and Gudmundsson (1997) studied 24 of the men on board the vessel (6 officers and 18 deckhands), and compared their rates of cardiovascular related mortality with a reference group of seamen from the Icelandic registries. The unexposed controls were matched on age and occupation. The authors did not quantitatively control for lifestyle factors including smoking habits and diet, but assumed similar rates between cases and controls. The authors reported excess mortality from cardiovascular disease (M-H=2.1, 95% CI= 1.2-3.8) in the exposed population (5 cardiovascular deaths out of 18 deckhands and 3 cardiovascular deaths out of 6 officers) compared to the referents (20 cardiovascular deaths out of 120 unexposed referents). 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. Their risk ratio was RR=3.9, 95%; CI=1.0-14.4. Rafnsson and

Kristbjornsdottir (2014) found that with increased follow up time (follow up to 2010) the association between chloromethane and deaths from cardiovascular disease was confirmed (HR=2.06, 95% CI= 1.02-4.15 based on 10 cardiovascular deaths out of 27 crewmembers compared to 41 cardiovascular deaths out of 135 unexposed referents). They subdivided this category into acute coronary heart disease deaths (HR=3.12, 95% CI= 1.11-8.78; 5 crew deaths compared to 15 referent deaths), and cerebrovascular disease deaths (HR=5.35, 95% CI= 1.18-24.35; 3 crew deaths compared to 4 referent deaths), both of which showed increased hazard of death in exposed crew members compared to the referents. The risk of bias in these studies is increased given they did not explicitly control for smoking and diet, the relatively small numbers of individuals with significant exposure, and the lack of exposure concentrations. The exact mechanism by which chloromethane might increase risk of cardiovascular disease related mortality is unclear.

Additionally, several case reports of humans exposed occupationally or accidentally due to refrigerator leaks have been described. The effects of these exposures vary by case and include electrocardiogram abnormalities, tachycardia and 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). However, the precise concentrations and durations of exposure 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 per minute, and one child had a pulse rate recorded as 164 beats per minute.

In addition to the studies in humans, several animal toxicological studies also reviewed the potential cardiovascular impacts of chloromethane exposure. For example, von Oettingen et al. (1949, 1950) exposed dogs acutely to 15,000 or 40,000 ppm. The dogs had an initial rise in heart rate and blood pressure (possibly due to the pentothal anesthesia wearing off), followed by markedly reduced respiration with increased respiratory volume, decreased heart rate that slowed gradually by 34%, then increased by 32% remaining high until death, decreased body temperature, and a precipitous fall in blood pressure starting at 3 hours that progressed until death, which occurred within 4-6 hours. These effects are likely to have resulted from vasodilation during a depression of the central nervous system that authors attributed to a metabolite of chloromethane since the respiratory effects occurred after several hours, at which point blood chloromethane levels were low. Chloromethane exposure does not appear to result in histopathological lesions in the heart, as demonstrated by acute studies in male dogs and cats exposed to approximately 500 ppm chloromethane (McKenna et al. 1981a), by intermediate duration studies in male dogs exposed to 400 ppm, and in rats and mice exposed to up to a target dose of 1,500 ppm

chloromethane (analytically measured concentration was equal to 1,473 ppm) (McKenna et al. 1981b; Mitchell et al. 1979).

In CIIT (1981) no significant cardiovascular effects were observed in male or female rats at any time point. No cardiovascular effects were observed in male mice. At 12, 18, and 24 months after the initial exposure, 1,000 ppm female mice and male and female rats had increased relative heart weight, and at 24 months, 225 ppm female mice had increased relative heart weight. These effects were considered to be chloromethane-related, although the authors expressed that this effect was not likely to be biologically significant, that decreases in body weights could have been a major contributing factor, and no associated histopathological lesions were observed (CIIT 1981).

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

2.6 GASTROINTESTINAL

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; Raalte and van Velzen 1945; Spevak et al. 1976; Verriere and Vachez 1949). In all cases, these symptoms were accompanied by central nervous system 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 to 1,282 ppm could be calculated.

Histopathological examination of animals exposed to various concentrations of chloromethane for acute, intermediate, or chronic durations did not show evidence of gastrointestinal damage (CIIT 1981; McKenna et al. 1981b; McKenna et al. 1981a). One study, Morgan et al. (1982) found that within 2 days of treatment, male and female rats in the 5,000 ppm group developed foul-smelling diarrhea. Gastrointestinal effects were not observed in mice in this study. However, decreased ingesta were observed in the gastrointestinal tract of male rats exposed to 1,000 ppm chloromethane for 72 hours (Burek et al. 1981).

No studies were located regarding gastrointestinal effects after oral or dermal exposure to chloromethane.

2.7 HEMATOLOGICAL

No hematological effects were found in volunteers who participated in a controlled human exposure study of neurological and neurobehavioral effects of acute 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.

In a series of case reports, Kegel et al. (1929) reported decreases in blood pressure, 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 fisherman 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).

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). Male mice were not used in this study.

No exposure-related effects on hematological parameters were found in male dogs or cats exposed continuously for 3 days to approximately 500 ppm (measured analytical concentration equal to 496 and 501 ppm respectively; McKenna et al. 1981a). Significant hematological parameter increases in rats exposed continuously for 3 days to a target dose of 2,000 ppm (analytically measured concentration equal to 1,968 and 1,950 ppm) (Burek et al. 1981) were considered to have been due to dehydration resulting in increased blood concentrations in those lethargic or moribund animals. In addition, male dogs exposed to a target dose of 400 ppm (analytically measured concentration equal to 399 ppm), rats and mice exposed to a target dose of up to 1,500 ppm (analytically measured concentration equal to 1,473 ppm) for 90 days (McKenna et al. 1981b; Mitchell et al. 1979), and rats and mice exposed for 6, 12, 18, or 24 months to up to approximately 1,000 ppm (CIIT 1981) did not have hematological effects with the exception of increased reticulocytes observed in male mice exposed to 997 ppm chloromethane for 6 months (CIIT 1981).

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

2.8 MUSCULOSKELETAL

No studies in humans were located regarding the musculoskeletal effects of chloromethane inhalation. Additionally, no effects were seen in male dogs exposed to 400 ppm, and rats and mice exposed to a target dose of 1,500 ppm (1,473 ppm based on analytical measurements) chloromethane for intermediate durations (McKenna et al. 1981b; Mitchell et al. 1979), or rats and mice exposed to up to approximately 1,000 ppm (997 ppm based on analytical measurements) chloromethane for chronic durations (CIIT 1981).

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

2.9 HEPATIC

Based on a systematic evaluation of the literature, hepatic toxicity is a presumed health effect associated with chloromethane exposure. Evidence from human studies is limited to case reports of people exposed to chloromethane (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, each patient had been exposed to chloromethane, and it is unlikely that these liver effects were due to other causes such as infective hepatitis or alcohol consumption.

Hepatic effects have also been observed in animals exposed to chloromethane, and mice appear to be more susceptible than rats. In an acute duration study rats exposed to 2,000 ppm for up to 72 hours showed decreased alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin levels just prior to death that were indicative of liver toxicity; slight liver effects at 198 ppm resolved after 12 days of recovery (Burek et al. 1981). Otherwise, rats exposed to approximately 200 to 3,500 ppm for acute, intermediate, or chronic durations had either no liver effects or relatively mild to moderate changes, such as loss of normal areas of basophilia, cloudy swelling, increased liver weight, fatty infiltration, and increased serum levels of ALT, AST, and bilirubin (Burek et al. 1981; CIIT 1981; Mitchell et al. 1979; Morgan KT et al. 1982). Necrosis was observed in one study on rats exposed to 2,000 to 4,000 ppm chloromethane, where the authors described the observed necrosis as occasional, and provided incidence rates (Dunn and Smith 1947). Acute, intermediate, or chronic exposure of mice to approximately 100-

l,500 ppm generally resulted in increased ALT and cellular changes ranging from vacuolation to necrosis and degeneration (CIIT 1981; Landry et al. 1985 Mitchell et al. 1979; Morgan KT et al. 1982). Mitchell et al. (1979) reported hepatic infarct in 1/10 mice and 1/10 rats exposed to 1,500 ppm which, despite low incidence, the authors considered compound-related due to its unexpected occurrence in both rats and mice and the observed increases in liver weight. Additionally, fat globules were found in the livers of guinea pigs and cats that died after exposure to 1,000 to 3,000 ppm, (Dunn and Smith 1947) though death was likely attributable to pulmonary congestion rather than liver effects. However, no liver effects were observed in male dogs and cats (McKenna et al. 1981b; McKenna et al. 1981a) exposed to 500 ppm (analytically 496 ppm for dogs and 501 for cats) chloromethane for 72 hours.

Chapin et al. (1984), Dodd et al. (1982), and Landry et al. (1983a) evaluated NPSH content in male Fischer 344 rats livers in acute exposure studies. All three found decreases in NPSH in the liver with increasing chloromethane exposure, with exposures as low as 225 ppm for 6 hours (Landry et al. 1983a). Dodd et al. (1982) observed NPSH changes in the liver at approximately 500-1,500 ppm, all of which returned to normal within 8 hours post exposure. Chloromethane was also shown to have an exposure time-dependent effect on liver NPSH, in which exposure to 500 ppm chloromethane was found to progressively decrease NPSH levels as exposure time increased at 1, 2, 4, and 6 hours. Additionally, Dodd et al. (1982) observed that pretreating rats with the metabolic inhibitor SKF-525A did not alter the chloromethane induced liver NPSH content changes. However, pretreatment with metabolic inducer Aroclor-1254 significantly increased liver NPSH, and it increased absolute liver weight 40% and liver EOD activity ~1300%. Chapin et al. (1984) observed significant decreases in NPSH content within one hour of exposure to 3,500 ppm of chloromethane. Jager et al. (1988) investigated the effects of an inhalation chloromethane exposure on tissue levels of glutathione-S-transferase (GST), formaldehyde, and formaldehyde dehydrogenase (FDH) in male and female Fischer 344 rats and B6C3F1 mice. After a single, 8-hour exposure to 1,000 ppm chloromethane in males or female animals, GST activity was significantly reduced 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 male mice. Lipid peroxidation was significantly and markedly increased in the liver of male and female mice. However, formaldehyde was not increased in either species despite a decrease in FDH in male mice.

Chellman et al. (1986a) explored the potential mechanism by which chloromethane may cause its toxicity. By comparing rats exposed to chloromethane alone to rats exposed to chloromethane and pre and post-dosed with a potent anti-inflammatory agent, 3-amino-l-[m-(trifluoromethyl)phenyl]-2-pyrazoline (BW755C), the authors found a protective effect of BW755C. Rats exposed to only chloromethane at a dose of approximately 5,000 ppm exhibited cloudy swelling of hepatocytes in the liver with subsequent

obliteration of the sinusoids. Rats exposed to both chloromethane and BW755C had only very subtle, if any, lesions. The results are surprising because the liver lesions were not inflammatory in nature. The authors concluded that protection from chloromethane-induced injury by BW755C 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 glutathione content. The protection afforded by BW755C may have been related to an inhibition of leukotriene and prostaglandin synthesis.

Chellman et al. (1986b) also investigated the role of glutathione in the mediation of chloromethane-induced toxicity in the liver of male B6C3F1 mice. Specifically, the authors compared mice exposed to chloromethane alone and mice exposed to chloromethane and either fasted or pre- and post-treated *i.p*. with either L-buthionine-S,R,-sulfoximine (BSO), a depleter of glutathione (GSH), or diethyl maleate (DEM). The authors observed a 50-fold increase in ALT activity in mice exposed for 6 hours to 1,500 ppm chloromethane without pretreatment. Fasting or pretreatment with BSO or DEM resulted in a reduction of hepatic GSH to 26, 40, or 50% of control values, while ALT values were similar to those of controls. The authors subsequently concluded that the depletion of GSH protected mice from hepatic toxicity of chloromethane.

Landry et al. (1985) observed liver impacts due to chloromethane exposure in both intermittently and continuously exposed mice, with effects occurring at significantly lower doses in mice continuously exposed. Specifically, with intermittent exposure (i.e., 5.5 hr/day) absolute liver weight remained constant to 800 ppm, then increased 22% at 1,600 ppm, but decreased 8% at 2400 ppm. For continuous exposure (22 hours/day), it remained stable through 50 ppm and then decreased at 100 ppm and by 13% at 150 ppm, and was associated with decreased hepatocyte size. Liver necrosis was also observed with chronic but not at higher intermittent exposures (Landry et al. 1985).

Conversely, McKenna et al. (1981b) observed increased liver weights in 400 ppm females and a trend in 400 ppm males and 150 ppm males and females. The increase was accompanied by equivocal lesions (change in staining properties of liver cells, possibly due to decreased vacuolization). The lesions were subtle and reversible and not considered adverse. Wolkowski-Tyl et al. (1983b) observed a significant increase in maternal absolute liver weight (9%), and relative liver weight (6%) was observed in mice exposed to approximately 500 ppm for 6 hrs/day. A nonsignificant decrease was observed in the 750 ppm mice.

A few studies have also looked at changes to hepatocytes in animals. Burek et al. (1981) reported a slight liver effect characterized as altered staining properties of hepatocytes in rats exposed to 500 ppm for 72

hours and sacrificed immediately. However, this effect was not observed in rats sacrificed after the 12-day recovery period. Rats exposed to 1000 ppm for 72 hours also showed altered staining properties, but the effects were considered to be secondary to anorexia. When McKenna et al. (1981b) exposed Beagle dogs to 99.9% pure chloromethane there were no effects on ALT or AST, but hepatocytes were swollen in 2/4 dogs at 400 ppm, 1/4 dogs at 150 ppm, 2/4 dogs at 50 ppm, and 0/4 controls. No other liver effects were observed, and the toxicological significance of these effects are unclear. Therefore, the authors concluded that the observed hepatocyte changes were unlikely to be treatment-related.

Landry et al. (1985) also observed mild hepatic effects (decreased hepatocyte size apparently related to glycogen depletion) in mice. Some hepatic effects, but without degeneration or necrosis, were observed in mice intermittently exposed to 400 to 2,400 ppm for 11 days. After exposing male C57BL/6 and B6C3F1 mice to 2,000 ppm 6 hours/day for 12 days, Morgan et al. (1982) observed severe hepatic lesions (hepatocellular necrosis with neutrophil infiltration, and hyaline accumulation, and vacuolation), similar to those seen with exposure to carbon tetrachloride or chloroform. At higher levels of exposure with a shorter duration (3,500 and 5,000 ppm for 5 days, 6 hours/day, with a break in exposure for 2 days before continued exposure for an addition 4 days), Morgan et al. (Morgan KT et al. 1982) observed minimal hepatocellular lesions in most mice, consisting of loss of the normal area of cytoplasmic basophilia in 80 to 100 percent of the animals. Mice exposed to lower levels of chloromethane (500 to 1,500 ppm) showed variable degrees of glycogen depletion, cytoplasmic vacuolation, and hydropic degeneration of hepatocytes.

In CIIT (1981) necropsies in male and female rats and mice were completed after either 6, 12, 18, or 24 months of exposure to concentrations ranging from 0 to 1,000 ppm (analytical measurement indicated 997 ppm on average). Increased ALT associated with exposure-related liver lesions was seen in male mice exposed to the target concentration of 1,000 ppm chloromethane at all time points. Following 6 months exposure to 1,000 ppm, lesions in mice were mild to moderate hepatocellular degeneration that were mainly midzonal karyomegaly, cytomegaly with increased cytoplasmic vacuolation and polykaryocytes in males, and centrilobular cytoplasmic vacuolation in females. After12 months of exposure to 1,000 ppm, additional lesions included numerous hepatocytes containing eosinophilic, intranuclear inclusion material. Slight increases in ALT were also seen in males exposed to target doses of 50 and 225 ppm (51 and 224 ppm, based on analytical measurements), but no histopathological changes to the liver were observed at these exposure levels. The Increased ALT in female mice exposed to target doses of 50, 225, and 1,000 ppm (51, 224 and 997 ppm based on analytical measurements) at 6 and 12 months was observed, but no histopathological changes were observed in females at any of the dose levels. The minimal changes in ALT have uncertain toxicological significance. ALT levels returned to normal at 18 and 24 months after

initial exposure in female mice. Females that became moribund or that were exposed to approximately 1,000 ppm for the longer 18- and 24-month exposure periods had liver lesions similar to those found in the males, but with less frequency and severity. Statistically significant increases in relative liver weight were observed in both male and female mice at approximately 1,000 ppm. Male and female rats did not have the histopathological liver lesions seen in mice. Male rats generally had increased relative liver weights at approximately 1,000 ppm. No effect on ALT levels was observed in rats.

No studies were located regarding hepatic effects in humans after oral exposure to chloromethane.

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.

No studies were located regarding hepatic effects in humans or animals after dermal exposure to chloromethane.

2.10 RENAL

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 observed renal impacts from acute and intermediate duration chloromethane exposure at or above 1,000 ppm. Effects to the kidneys range from changes in serum enzymes, to histopathological lesions, to kidney failure. For example, Burek et al. (1981) exposed Sprague-Dawley rats to chloromethane to a target dose of 1,000 ppm (analytically measured mean concentration equal to

976 ppm) for 72 hours and observed slightly increased BUN in the female rats that resolved within 12 days during the post-exposure recovery period. Abnormal urinalysis parameters indicative of renal failure occurred in both sexes of rats exposed to 1,000 or 2,000 ppm for 48 (analytically measured mean concentrations equal to 972 ppm or 1968 ppm) or 72 hours (analytically measured mean concentrations equal to 976 and 1950 ppm). Acute renal failure was considered the cause of the 100% mortality found in the higher-dose longer-exposure group. Histological examination revealed renal tubular cell necrosis, increased homogeneity in renal tubular cells, and increased lipid accumulation in tubule cells at 1,000 ppm for both exposure periods, and evidence of regeneration after the post-exposure recovery period. Guinea pigs exposed to 1,000 ppm for 6 hours per day had slight to moderate fatty metamorphosis of the kidney convoluted tubules, while it was moderate to severe in those that died within 3 days from exposures up to 3000 ppm (Dunn and Smith 1947). At 2,000 ppm Burek et al. (1981) observed statistically significant, greatly increased BUN in 2 male and female rats sacrificed at 48 hours that indicated kidney failure. Male and female mice exposed to 2,000 ppm for 6 hours per day for 6 days per week until death showed signs of kidney injury initially, including pyknotic nuclei in the loops, and later the degeneration of the epithelial lining of the tubules, and necrosis. A moderate number of necrotic tubules were also reported in rats exposed to 3,000 ppm (Dunn and Smith 1947).

Chellman et al. (1986a) exposed male Fischer 344 rats to approximately 5,000 ppm chloromethane for 5 days, and observed necrosis of the proximal convoluted tubules. Similar effects were seen in Morgan et al. (1982) at doses of 2000 ppm in rats and mice or above 1,000 ppm in C3H male mice. Morgan et al. (1982) also observed hematuria in female mice exposed to 1,000 or 2,000 ppm and in male C3H mice exposed to 2000 ppm, though the authors noted it was not clear whether it was due to renal damage or lesions elsewhere in the urogenital tract. Additionally, in a study from Jiang et al. (1985), female C57BL/6 mice exposed to 1,500 ppm chloromethane for 2 weeks showed a slight degeneration of proximal convoluted tubules.

Dodd et al. (1982) exposed male Fischer 344 rats to chloromethane at 0, 100, 500, or 1,500 ppm and observed nonprotein sulfhydryl (NPSH) content of the kidney decrease in a concentration-related manner. Kidney NPSH levels returned to control values within 8 hours of treatment after exposure ceased. Chloromethane was also shown to have an exposure time-dependent effect on kidney NPSH, in which exposure to 500 ppm chloromethane was found to progressively decrease NPSH as exposure time increased at 1, 2, 4, and 6 hours. Additionally, Dodd et al. (1982) observed that pretreating rats with the metabolic inhibitor SKF-525A, dampened the extent to which chloromethane reduced kidney NPSH. Jager et al. (1988) investigated the effects of a chloromethane inhalation exposure on tissue levels of glutathione-S-transferase (GST), formaldehyde, and formaldehyde dehydrogenase (FDH) in male and

female Fischer 344 rats and B6C3F1 mice. Activities of GST were significantly reduced in the kidneys of male and female mice and in male rats, but the effect was lessened with an increased exposure of 6 hours/day for 4 days. Lipid peroxidation was significantly and markedly increased in the liver of male and female mice, and to a lesser extent in the kidney, primarily of females, from the single exposure to chloromethane.

Chellman et al. (1986b) investigated the role of glutathione in the mediation of chloromethane-induced toxicity in the liver, kidney, and brain of male B6C3F1 mice. Mice exposed to 1,500 ppm chloromethane for 6 hr/day, 5 days/week for 2 weeks had no significant changes in kidney weight, glomerular filtration rate, urinary excretion rates of glucose and protein, or urinary concentrating ability, and no apparent effect on normal kidney function. Histologically, the only effect of chloromethane exposure was a slight increase in the number of basophilic cortical tubules. Incorporation of tritiated thymidine into deoxyribonucleic acid (DNA) was 3-fold greater in kidneys of chloromethane-exposed male mice than controls, and in females it was 10-fold greater. When Chellman et al. (1986b) pretreated mice with BSO (administered *i.p.*) and then exposed them to chloromethane, incorporation of tritiated thymidine was not significantly elevated. BSO alone had no effect on DNA synthesis. Therefore, depletion of GSH protected mice from increased DNA synthesis induced by chloromethane. Chellman et al. (1986b) hypothesized that the increased DNA synthesis may result from a compensatory proliferation in response to cell death. They note that although cell death was not observed in kidneys histologically, basophilic foci are consistent with regenerative cellular response following cell death.

Landry et al. (1985) only observed kidney effects in mice intermittently exposed to 2,400 ppm. The effects consisted of a slight multifocal degeneration and regeneration of tubules, and an eosinophilic staining cast within the tubules. The 2,400 ppm intermittently exposed and 150 ppm continuously exposed mice had a 19% and 9% respective increase in relative kidney weight. No other effects on the kidney were seen at other dose levels in either intermittently or continuously exposed mice.

Additionally, no renal effects related to chloromethane exposure were observed in Beagle dogs or cats exposed for 72 hours up to approximately 500 ppm (analytically measured mean concentration equal to 501 ppm) in an acute exposure study (McKenna et al. 1981a). Similarly, intermediate exposure studies in Beagle dogs, Sprague-Dawley rats, and CD-1 mice exposed up to 400 ppm did not result in any impacts to the renal system (McKenna et al. 1981b). Mitchell et al. (1979) also did not observe any histopathological lesions in the kidney in rats and mice exposed up to 1,500 ppm (analytically measured concentration equal to 1,473 ppm) for 13 weeks, but did observe an increase in relative liver weight.

In CIIT (1981) male and female Fischer 344 rats and B6C3F1 mice were exposed to chloromethane in whole body inhalation exposure chambers at target concentrations of approximately 0 (control), 50, 225, or 1,000 ppm, 6 hours/day, 5 days/week (analytical measurements indicated 0, 51, 224 and 997 ppm, respectively) for up to 24 months. Increases in BUN in mice that were significantly increased at 24 months in all groups, including controls, were considered to be treatment related. Necropsies were completed after either 6, 12, 18, or 24 months of exposure. Decreased kidney weights were reported for male mice and female rats exposed to 1,000 ppm. Increased relative kidney weights were noted in female mice at 1,000 ppm, while decreased absolute kidney weights were seen in males at 1,000 ppm; a sex-related difference in body weights (i.e., heavier males) likely contributed to this difference in organ weight changes for males and females. The authors interpreted the decrease in absolute kidney weight in male mice as biologically significant. Males exposed to 1,000 ppm first developed renal tubuloepithelial hyperplasia and karyomegaly at 12 months that became progressively worse, followed by the development of renal cortical adenomas and adenocarcinomas; altogether, 5 types of renal neoplasms were observed in the highest dose animals. Females did not develop these lesions until after 18 months of exposure and to a much lesser extent. Male and female rats had varying levels of increased relative kidney weights throughout the study, but these were not associated with clinical, gross, or histopathological findings; thus, the toxicological significance of these effects is unclear (CIIT 1981).

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

2.11 DERMAL

No studies were located regarding dermal effects in humans after inhalation exposure to chloromethane.

No dermal effects were observed from acute chloromethane exposures up to approximately 500 ppm in Beagle dogs or cats (McKenna et al. 1981a), though one dog with approximately 200 ppm exposure had multiple areas of alopecia. The study authors noted this may have been “secondary to fighting with cage mates.” With intermediate exposures up to 400 ppm in Sprague-Dawley rats or CD-l mice (McKenna et al. 1981b), up to 1,500 ppm in Fischer 344 rats (Mitchell et al. 1979), or up to 400 ppm in Beagle dogs (McKenna et al. 1981b), no effects were seen.

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

2.12 OCULAR

Case reports of humans exposed to chloromethane 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 probably reflect effects on the nervous system rather than effects on the eye itself. One case report identified blindness in a woman following the cleaning of a toilet with sodium hypochlorite and hydrochloric acid. Potential implications of exposure to chlorine gas produced when mixing these two cleaning chemicals was not addressed (Wilken et al. 2017).

Ophthalmological examination of male cats and Beagle dogs exposed to approximately 500 ppm continuously for 3 days (McKenna et al. 1981a), dogs exposed to approximately 400 ppm for 90 days (McKenna et al. 1981b), or of rats and mice exposed to approximately 1,000 ppm for up to 24 months (CIIT 1981) failed to reveal eye lesions other than acute focal scleritis in 3/10 male mice which was always associated with neutrophilic inflammatory infiltrates. Mucopurulent conjunctivitis with total destruction of the eye in some cases was found in mice exposed to approximately ≥375 ppm for 6 hours/day, 5 days/week, for 90 days (Mitchell et al. 1979), these lesions were not attributed to chloromethane because no lesions were found in either controls or the highest dose animals (Mitchell et al. 1979).

In CIIT (1981) male and female F344 rats and B6C3F1 mice were exposed to chloromethane at target concentrations of 0, 50, 225, or 1,000 ppm, 6 hours/day, 5 days/week. Ophthalmic exams were performed at baseline and at sacrifice. At 6 months, corneal cloudiness or opacity without conjunctivitis was noted in control rats (2 /10 male rats and 1/10 females), at 50 ppm (1/10 males), and at 225 ppm (1/10 females). The significance of this lesion is not clear because there was no dose-related incidence pattern at later sacrifices. CIIT (1981) also reported scleritis in control as well as in high dose animals after 6 and 12 months of exposure that was associated with neutrophilic inflammatory infiltrate at the corneoscleral junction, and attributed to orbital bleeding procedures and not to exposure. In mice, no corneal lesions were observed through 18 months of exposure at any dose.

At 12 months of exposure to chloromethane in rats, a corneal lesion described as a haze elliptically patterned over a central portion of the eye was seen in control animals (1/10 males and l/10 females), at 50 ppm (8/10 males and 6/10 females), at 225 ppm (9/10 males and 7/10 females), and at 1,000 ppm (9/10 males and 9/10 females) exposure groups (CIIT 1981). This lesion was only seen at 12 months and was distinctly different from the cornea1 cloudiness or opacity seen at 6 or 18 months of exposure. This cornea1 haze may have been the result of chemical effects upon the eyes in which the lacrimal function was compromised by undercurrent disease (an outbreak of sialodacryo-adenitis [SDA] was

histopathologically diagnosed at 12 months). The authors hypothesized that this disease reduced lacrimal function making the eye more vulnerable to irritation from chloromethane.

At 18 months of exposure in rats, the incidence of cornea1 cloudiness in exposed male rats was similar to that of control males. In females, the incidence of cornea1 cloudiness significantly increased with dose: controls (2/20), at 50 ppm (4/20), at 225 ppm (12/20), and at 1,000 ppm (12/20). Although, 7/10 male and 6/10 female rats exposed to 1,000 ppm had vacuolar degeneration of the anterior lens fibers of minimal severity; this lesion was not observed in excess at 24 months, so its relationship to chloromethane exposure is unclear. At 24 months of exposure in rats, no significant differences in ocular lesions were observed.

In mice, at 6 months of exposure, an acute, focal scleritis was observed in 3/10 males and 1/10 females in the 1,000 ppm group. This lesion was always associated with a neutrophilic inflammatory infiltrate which was present at the corneoscleral junction. At 12 and 18 months of exposure, there were no statistically significant ocular lesions observed in mice. At 24 months of exposure, corneal opacities without a dose relationship were observed in exposed mice, but they were not considered related to chloromethane exposure (CIIT 1981).

No studies were located ocular effects in humans or animals after oral or dermal exposure to chloromethane.

2.13 ENDOCRINE

No studies were located regarding endocrine effects in humans after inhalation exposure to chloromethane.

Researchers have observed some effects have been observed in high-level, acute exposure animal studies. Male Fischer 344 rats exposed to 5,000 ppm chloromethane for 5 days, 6 hours/day developed vacuolar degeneration in the cell cytoplasm of the adrenal cortex in the outer region of the zona fasciculata (Chellman et al. 1986a). Clear, possibly lipid, droplets were seen in the epithelial cells of the zona fasciculata in the adrenal glands of Fischer 344 rats exposed to 3,500 and 5,000 ppm chloromethane for 5 days, 6 hours/day with a break in exposure for 2 days, and then a further 4 days of exposure; the severity of this lesion increased with dose (Morgan KT et al. 1982). Rats exposed to 3,500 ppm chloromethane for 6 hours/day for 5 days followed by a break in exposure for 3 days and then continued exposure for another 4 days showed significantly lower serum testosterone levels after 5 days when compared to controls (Chapin et al. 1984).

Generally adverse effects are not seen at lower levels exposure or longer exposure durations. No chloromethane-related effects on the endocrine organs were observed from acute exposures up to 500 ppm in Beagle dogs or cats (McKenna et al. 1981a), or from intermediate and chronic exposures up to 1,000 ppm in mice or rats (CIIT 1981).

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

2.14 IMMUNOLOGICAL

No studies were located regarding immunological or lymphoreticular effects in humans after inhalation exposure to chloromethane.

In an acute assessment of chloromethane exposure in cats and dogs (McKenna et al. 1981a), dogs presented some signs of altered immune response after approximately 500 ppm chloromethane exposure for 3 days. Specifically, white blood cells were significantly decreased in dogs 4 weeks post exposure compared to controls, but not at any other time in the study. Additionally, there was a statistically significant increase in neutrophils and corresponding decrease in lymphocytes in dogs treated with 500 ppm chloromethane in the first sampling period post-exposure; however, this difference did not persist and the authors did not consider these effects treatment related.

Additionally, Landry et al. (1985) demonstrated the dosing rate may have an impact on resulting immune effects of chloromethane exposure. Specifically, Landry et al. (1985) exposed female C57BL/6 mice to chloromethane for 11 days either continuously for 22 hours/day at 0, 15, 50, 100, 150, 200, or 400 ppm or intermittently for 5.5 hours/day at 0, 150, 400, 800, 1,600, or 2400 ppm. The absolute and relative weight of the thymus was significantly decreased at much higher concentrations (and at a slightly higher total dose) in the intermittently exposed group compared to the continuously exposed group (LOAEL of 1,600 ppm for intermittent exposure group and a LOAEL of 150 ppm for the continuous exposure group).

In an intermediate exposure study, McKenna et al. (McKenna et al. 1981b) did not observe any immune related effects with exposure to chloromethane at levels up to 400 ppm for 6 hours/day, 5 days/week for 90 days in mice, rats, or dogs.

In animals, minimal thymic lymphoid necrotic areas and lymphoid depletion of the spleen and splenic atrophy were observed, more so in male mice compared to female mice, exposed to approximately 1,000 ppm (analytical measurement concentration average 997 ppm) chloromethane for up to 2 years (CIIT 1981). The lymphoid depletion and necrosis were first observed in mice killed after 6 months of exposure, while the splenic atrophy was observed in mice killed after 18 months. The next lower exposure level in

this study (224 ppm) cannot be considered a reliable NOAEL for immunological effects, however, because it was seen in only 1/10 male and in no female mice, and more sensitive tests for immune function were not conducted.

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

2.15 NEUROLOGICAL

A systematic evaluation of the literature concluded that neurological effects are a presumed outcome associated with chloromethane exposure.

Numerous case reports of humans exposed to chloromethane vapors as a result of industrial and refrigeration leaks have described neurological effects. In general, symptoms develop within a few hours after exposure and include 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, 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; Macdonald 1964; McNally 1946; Minami 1998; Raalte and van Velzen 1945; Scharnweber et al. 1974; Spevak et al. 1976; Wood 1951). These symptoms may persist for several months, and depression and personality changes may develop. 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). In some cases, complete recovery eventually occurred. In other cases of more severe poisoning, convulsion, coma, and death ensued; or neurological effects may persist (Kegel et al. 1929; McNally 1946; MacDonald 1964). 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).

Battigelli and Perini (1955) reported two cases of workers in a cooling plant who were exposed to a leak of chloromethane while repairing a refrigeration system with an estimated exposure of >29,000 ppm. Both workers developed symptoms of vertigo, tremors, dulled senses, nausea, vomiting, and abdominal pain. The symptoms appeared 3-4 hours after the inhalation exposure. Disturbances began to recede about 6 hours post exposure and disappeared completely by 1 day post exposure.

A case was reported by Lanham (1982) of a man and wife who developed symptoms of blurred vision, fatigue, vertigo, nausea, vomiting, tremor, and abnormal gait several days after storing insulating boards made of Styrofoam in the basement of their house. Air levels of chloromethane, purportedly released from curing of the Styrofoam, measured by 3 different devices were above 200 ppm. By the time the case report was written, the patients' symptoms had subsided, except for some remaining fatigue. This case prompted the manufacturer to take steps to reduce the likelihood of future significant exposures from this product.

Seven men had acute exposures to chloromethane while repairing refrigeration systems. Four of the cases provided sufficient information to estimate an exposure level of 75, 107, 890, and 1282 ppm. Common symptoms were ataxia, staggering, headache, drowsiness, anorexia, blurred and double vision, convulsions, nausea, and vomiting. Less common were depression, abdominal pain, and ringing in the ears (Jones 1942).

Minami (1998) reported on a case study of a woman co-exposed to chloromethane and chloramine during household cleaning. The patient had cleaned a toilet connected to a sewage storage tank with a mixture of sodium hypochlorite and hydrochloric acid. She experienced insomnia the night after cleaning and developed permanent blindness three days later. Minami (1998) hypothesized that the chloramine exposure inhibited enzymes required for chloromethane metabolism, thereby potentiating the effects of chloromethane exposure. However, the authors did not address potential co-exposure to chlorine gas which is produced when those cleaning chemicals are mixed (Wilken et al. 2017).

Spevak et al. (1976) describe a case of chloromethane poisoning among four family members (one brother [age 64] and three sisters [ages 50, 52, and 60]). All were exposed to fluid and vapors leaking from a refrigerator for approximately 1 hour while cleaning the spill. Approximately 4 hours after their exposure, all four subjects felt weak and had abdominal pains, vomiting, hiccups, and severe headaches; symptoms they thought were due to food poisoning. All subjects lost consciousness until the next day. By 2 days after the exposure, the symptoms had not disappeared, and all four were admitted to the hospital with clinical signs of drunkenness, confusion, somnolence, ataxia, and dysarthria. Nervous system damage progressed with cerebellar symptoms of nystagmus in all four patients, and adiadochokinesis developing in one of the women. All subjects had disturbances of the cranial nerves (optic, oculomotor, and facial), as well as speech disturbances, tremors, and elevated reflexes. Electroencephalograms were normal. The three sisters received symptomatic treatment with isotonic glucose, B complex vitamin, and oxygen. The treatment resulted in a disappearance of all symptoms of intoxication except ataxia. The brother refused treatment. Symptoms of kidney damage disappeared after two weeks, and the outcome of the intoxication was, in the words of the physicians, "good in all cases" (Spevak et al. 1976).

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 (no estimates of exposure levels were reported). The refrigerator was located under the sleeping quarters of the crew. Four of the fifteen crew members with symptoms of severe methyl chloride poisoning died within 10 years of exposure, one within 24 hours of the exposure. Two patients developed severe depression and committed suicide 11 and 18 months later, respectively. 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. Autopsy revealed a recent coronary occlusion which was not necessarily connected with the primary illness (Gudmundsson 1977).

Gudmundsson (1977) described that many of the crew members exposed to chloromethane showed immediate signs of intoxication that continued after exposure ended. In the chronic phase of the illness, 5 out of the 10 patients that were alive 13 years post-exposure and received a neurological examination exhibited abnormal neurological signs. At 13 years post-exposure, 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 (Gudmundsson 1977).

Additional follow-up in this cohort more than 40 years after exposure also found that the risk of death by suicide (2 cases of suicide) was significantly increased in the exposed cohort compared to a reference group of Icelandic fishermen not exposed to chloromethane (HR=13.76, 95% CI=1.18-160.07) (Rafnsson and Kristbjornsdottir 2014). The results and conclusions from this cohort, however, are based upon the assumption that the reference group had similar lifestyle factors including smoking habits and diet, which may not have been the case. There were also few individuals with exposures high enough to be considered chloromethane intoxication (i.e., 15, with 10 patients alive and available for follow up in the initial Gudmundsson (1977) study). Studies which examine the potential association of chloromethane exposure with death from cancer are in Section 2.19.

Some information on longer term exposures to chloromethane used as a catalyst solvent rather than as a refrigerant is available. MacDonald (1964) presented eight case reports of chloromethane poisoning in a synthetic-rubber production plant. Symptoms of blurring vision, mental confusion, severe headache, loss of coordination, and dizziness were common. More severely intoxicated individuals experienced nausea (for a few days) and vomiting (for a few hours). Personality changes, depression and irritability, and unstable emotions, with sleep disturbances were reported by many of the cases, and one included

euphoria (also reported by Spevak et al. 1976). The symptoms persisted for months. Over-exposure induced a heightened sensitivity to the chemical, demonstrated by previously exposed workers feeling weak and dizzy in chloromethane work areas when coworkers had no symptoms, and their symptoms disappearing when reassigned to unrelated work areas.

Scharnweber et al. (1974) presented 6 case studies of workers who were exposed to relatively low levels (200-400 ppm) of chloromethane for at least 2-3 weeks before onset of symptoms. Two cases occurred after "prolonged" (not otherwise specified) exposure to 8-hour time-weighted average (TWA) levels up to 300 ppm. Four cases occurred after work exposure on the order of 265 ppm (8-hour TWA) after 2-3 weeks of 12-16 hour days. A 54-year-old worker initially suffered from confusion, blurry vision, erratic driving, difficulty in eating and swallowing, headache, and disturbance of balance. Three weeks after hospitalization, the patient still complained about headache and had a staggered gait. Memory difficulties persisted for 2 months. The patient improved at three months, but still had tremors and nervousness. A second 58-year-old worker (who replaced the previously described worker) had delirium, confusion, disorientation, and combativeness. Two months after hospitalization, the patient still had poor memory and nervousness. Three months later, the patient was well enough to return to work. A 33-year-old foam plastic worker had blurred vision, increased tiredness, nervousness, and stuttering that resolved after a 6-week recovery period. Other foam workers developed similar symptoms with impairment in memory, gait, speech (tongue swelling, slurring), vision (diplopia, blurred), slight to moderate increase in blood pressure, and an EEG with a predominance of slow waves in the beta range that resolved from 1 to 3 months after removal from exposure. The authors concluded that an 8-hour TWA of 200 ppm or greater is necessary for development of chronic chloromethane intoxication based on these and other industrial experiences (ACIH 1971).

Repko et al. (1976) performed a study on the neurological effects of occupational exposure to chloromethane. The study population was derived from several fabricating plants operated by the same company. Exposed workers (n=122) used chloromethane in the manufacture of foam products, while controls (n=49) had not ever knowingly worked with chloromethane. The amount of time study participants worked at the plants ranged from 1 to 311 months for exposed workers and 11 to 194 months for controls, depending on the plant. Seventy-three behavioral measures of task performance, four indices of exposure, eight indicators of neurological function, and a clinical EEG were obtained. The measured ambient air concentrations of chloromethane at the plants ranged from 1.8 to 70 ppm, with means from each plant ranging from 8.46 to 58.72 ppm. The overall mean was 33.57 ppm. Mean concentration of chloromethane in breath by plant ranged from 10.81 to 24.19 ppm, with an overall mean of 13.32 ppm. Statistically significant positive correlations were found between the duration of exposure and breath

concentration as well as duration of exposure and ambient air concentration, and significant negative correlations were reported for urine pH and hematocrit, and duration and hematocrit. There were no significant differences in neurological tests or EEGs. In the behavioral task performance tests, effects on cognitive time-sharing and finger tremor were found, but the pattern of correlation coefficients indicated that chloromethane in breath is not a sensitive indicator of performance deficit. Workers showed a general tendency toward poorer performance as chloromethane levels in air increased. The authors concluded that occupational exposure to chloromethane below 100 ppm produces subtle, quantifiable behavioral effects, but that data on the threshold at which chloromethane begins to produce these changes in functional capacity are not currently available. A limitation of this study was the inability to achieve perfect matching as to sex, race, age, and level of education.

Three human controlled trials evaluated exposure to chloromethane and potential neurotoxic effects and did not find any association (Putz-Anderson et al. 1981a, Putz-Anderson et al. 1981b; Stewart et al. 1980). In Putz-Anderson et al. (1981a) volunteers inhaled 100 or 200 ppm for 3 hours and were tested for 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) volunteers were exposed to up to 150 ppm for 1, 3, and 7.5 hr/day on 2 or 5 consecutive days and 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. This study, however, had several limitations such as small sample size, subjects lost to attrition, multiple dosing schemes, and a confusing protocol. Additionally, Putz-Anderson assessed whether potential behavioral effects of chloromethane would be modified if exposure occurred in combination with diazepam (a central nervous system depressant) (1981a), alcohol, or caffeine (1981b). Neurobehavioral effects (eye-hand coordination and up to 22 measures of alertness) for single or co-exposure to these substances were characterized as additive and without interaction.

Chloromethane exposure also results in neurological effects in animals. Rats, mice, rabbits, guinea pigs, dogs, cats, chickens, and monkeys exposed to chloromethane until death displayed signs of either severe neurotoxicity, including paralysis and convulsions (Smith and Van Oettingen 1947b; Smith and Von Oettingen 1947a), or less severe neurotoxicity, e.g., disappearance of corneal and pupillary reflex with muscular relaxation, after more than 58 hours of exposure to 15,000 ppm (Von Oettingen et al. 1950). The results demonstrate the universal response of animals to the neurotoxic effects of chloromethane.

Other animal studies support the neurotoxic potential of chloromethane, with sufficiently high levels of inhalation exposure leading to ataxia (Chellman et al. 1986b; Morgan et al. 1982; Wolkowski-Tyl et al.

1981b), tremors (Battigelli and Perini 1955), piloerection (Wolkowski-Tyl et al. 1983b), limb paralysis and incoordination (Morgan et al. 1982), and cerebellar lesions consisting of degeneration of the granular layer (Chellman et al. 1986b; CIIT 1981; Wolkowski-Tyl 1983a). Mice appear to be more sensitive than rats, with similar but more severe responses at lower exposure concentrations.

After 48 continuous hours of chloromethane exposure at 1,000 ppm, Sprague-Dawley rats were lethargic compared to the controls, and their condition worsened to sick or moribund by the end of a 72-hour exposure. The 2,000 ppm exposure resulted in death during or immediately following exposure. There were no effects on brain weight, and no exposure-related gross or histopathological lesions in the brain. No effects were seen at 500 ppm for up to 72 hours of exposure; 1000 ppm for up to 72 hours produced decreased absolute but increased relative mean brain weight in males (Burek et al. 1981). The increase in relative mean brain weight may be due to the decreased absolute body weight.

Male Fischer 344 rats exposed to 5,000 ppm chloromethane alone for 5 days, 6 hours/day had more pronounced signs of central nervous system toxicity (tremors, ataxia, forelimb/hind limb paralysis) than those receiving chloromethane plus pre-and post-treatment with the potent anti-inflammatory agent, BW755C (10 mg/kg, intraperitoneally 1 hour pre- and post-exposure). Chloromethane alone caused a degeneration of cerebellar granule cells, while rats exposed to chloromethane and BW755C did not exhibit this effect. The result was surprising because this degeneration of cerebellar granule cells is not usually associated with inflammation. The authors concluded that protection from chloromethane-induced injury by BW755C was not simply the result of altered metabolism because BW755C had no effect on tissue distribution of ^{14}C-chloromethane, the exhalation of $^{14}CO_2$ metabolite, or urinary excretion of ^{14}C, and administration of BW755C did not decrease hepatic glutathione content. The protection of BW755C may have been related to an inhibition of leukotriene and prostaglandin synthesis (Chellman et al. 1986a).

Fischer 344 rats were exposed to 0, 2,000, 3,500, or 5,000 ppm chloromethane for 6 hours/day, 5 days/week, for up to 9 days, with mortality or moribundity occurring at 1000 ppm (1 C3H male), at 2000 ppm in all C57BL/6 males by day 5, and at 2000 ppm in all male B6C3F1 males by day 2. On day 5, hind limb paralysis was observed in two males and one female in the 5,000 ppm group. After the fifth day, 13 animals were killed in extremis (5,000 ppm: 6 males, 5 females; 3,500 ppm: 2 females). By the second week of exposures, the rats' tolerance of chloromethane exposure appeared to have increased. However, during the final exposure, one 5,000 ppm female had convulsive seizures. Histological examination of the brain and thoracic spinal cord revealed minimal to moderate degeneration of cerebellar internal granular layer in two females and three males exposed to 5,000 ppm. The lesions were identical to those seen in mice. There were no lesions in the spinal cord. No neurological or histopathological lesions were observed in the 3,500 ppm group. C3H, C57BL/6, or B6C3F1 mice were exposed to chloromethane for 12

days, 6 hours/day. Mice were exposed to 0, 500, 1,000, or 2,000 ppm. Some of the mice that died had moderate to severe ataxia. Histologically, there were no brain lesions at 500 ppm in any strain. Cerebellar degeneration was seen as follows: C3H mice (none); C57BL/6 mice, 3/5 males and 5/5 females exposed to 1,000 ppm and 0/5 males and 4/4 females exposed to 2,000 ppm; B6C3F1 mice, 2/5 females exposed to 2,000 ppm. The lesions increased in severity only for C57BL/6 females. The cerebellar lesions consisted of focal degeneration of the granular layer, which affects posture and coordination. The authors concluded that this study confirmed the existence of species, sex, and strain differences in susceptibility to chloromethane-induced neurotoxicity (Morgan KT et al. 1982).

Chellman et al. (1986b) investigated the role of glutathione in the mediation of chloromethane-induced toxicity in the brain of male B6C3F1 mice. Mice exposed to 1,500 ppm chloromethane for 6 hours/day, 5 days/week, for 2 weeks developed multiple degenerative, necrotic foci in the internal granule cell layer of the cerebellum; in some areas the foci involved the whole thickness of the granular cell layer. Cerebellar degeneration consisted of granule cells with pyknotic nuclei and clear, swollen perikarya. Cerebellar damage was not observed in chloromethane-exposed mice pretreated with a glutathione depleter. The authors concluded that the depletion of GSH protected mice from cerebellar damage due to exposure to chloromethane.

Jiang et al. (1985) characterized the cerebellar lesions resulting from an acute inhalation exposure of 1,500 ppm chloromethane to female C57BL/6 mice for 2 weeks, 5 days/week, 6 hours/day. Two mice died, several had motor incoordination, and the rest had severe cerebellar degeneration without clinical neurological signs. All exposed mice had varying degrees of cerebellar degeneration located mainly in the ventral paraflocculus. Granule cells were mainly affected, with two distinct types of lesions: (1) nuclear and cytoplasmic condensation of scattered granule cells with slight hydropic swelling of astrocytes (also seen to a lesser extent in controls); and (2) focal malacia with varying degrees of watery swelling of groups or extensive areas of granule cells, nuclear condensation, karyorrhexis, and necrosis. The second type of lesion was more prevalent. Electron microscopy showed that the damage in the areas of malacia (the type 2 lesion above) ranged in severity from edema of granule cell perikarya to severe edema and almost complete destruction of all tissue components. Involvement of cell types other than granule cells occurred only in the most severely affected areas (i.e., Purkinje cells were well preserved while astrocytes adjacent to Purkinje cells [the Bergmann’s glia] showed moderate to severe cytoplasmic distention by translucent edema fluid).

The biochemical mechanism for the induced defects in granule cell fluid/electrolyte balance is unknown. Only one exposure concentration was used, but the study was designed to examine the neurological and kidney effects specifically, and therefore, used an exposure regimen known to produce these effects

(Jiang et al. 1985). Based on the severity of the kidney effects, the authors concluded that the observed brain lesions were probably not a direct consequence of renal lesions; rather, the mechanism may be associated with metabolic changes in granule cells.

Landry et al. (1985) observed transient decreases in performance of mice on the rotating rod starting on day 4 of exposure to 800 ppm or 2,400 ppm intermittently (5.5 hours/day). By day 8 only 150 ppm of continuous (660 ppm intermittent equivalent) and 2,400 ppm of intermittent exposure in mice showed performance decrements. Histological lesions consisted of slight cerebellar granule cell degeneration in some of the mice continuously exposed (22 hours/day) to 100 ppm (440 ppm intermittent equivalent), or intermittently exposed (5 hr/day) to 400, 800, or 1,600 ppm. In the 2,400 ppm intermittent group (at much higher total dose than any continuous exposure), all of the mice were affected to a slight degree. 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.

C57BL/6 mice pregnant with B6C3F1 fetuses lethally exposed to 1,500 ppm chloromethane in whole-body exposure chambers, 6 hours/day developed on gestation days 6-17, tremors, hunched appearance, difficulty righting, disheveled fur, bloody urine, and granular cell degradation in the cerebellum with selective necrosis of neurons in the internal granular layer. All females in this group were sacrificed on gestation days 11-14 prior to the completion of exposure to gestation day 17; two females died prior to necropsy (as early as gestation day 9, after only 4 days of exposure). These effects were not seen in the 479 ppm or lower exposure levels (Wolkowski-Tyl et al. 1983a).

C57BL/6 females were mated to C3H males to produce B6C3F1 offspring. After mating, 74 to 77 females were exposed to chloromethane at concentrations of 0, 250, 500, or 750 ppm on gestation days 6-17. Exposure to 500 ppm chloromethane resulted in ataxia in 6/74 females by gestation day 18; exposure to 750 ppm resulted in hyperactivity, ataxia, piloerection, tremors, and convulsions. The authors concluded that inhalation exposure to chloromethane during gestation days 6-17 resulted in maternal toxicity at 750 ppm; teratogenic effects were seen at 500 and 750 ppm. Exposure of pregnant mice to 250 ppm chloromethane produced neither maternal nor fetal toxicity, nor teratogenicity (Wolkowski-Tyl et al. 1983b).

Beagle dogs (n=3) exposed to 500 ppm chloromethane for 23.5 hours/days for 3 days had moderate to severe limb stiffness, tremors, salivation, and incoordination. These effects became less severe but persisted during a 4-week recovery. All 500 ppm dogs had neurological deficiencies based on clinical testing at 4 days after exposure, but nearly complete recovery on day 26 after exposure. Histological examination revealed brain and spinal cord lesions in all 3 dogs consisting of 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. No lesions were observed in the cerebrum or cerebellum, nor in the dorsal funiculi or grey matter of the spinal cord, or in the peripheral nerves (McKenna et al. 1981a).

Cats (n=3) exposed to 500 ppm chloromethane for 23.5 hours/days for 3 days were less active than controls after 24 hours of exposure, but were alert and had no clinical signs after exposure. Cats did not undergo neurological tests. Histological lesions in cats were seen in l/3 control, l/3 at 200 ppm, and 3/3 at 500 ppm; and consisted of lesions in the brain occurring in a multifocal or random pattern in the white matter of the cerebrum, cerebellum, and midbrain. In the spinal cord they primarily occurred in the lateral and ventral funiculi. The authors did not believe that these were treatment related, but were instead consistent with infection or post-vaccinal reaction (cats were vaccinated for panleukopenia by a supplier whose animals had high incidence of panleukopenia). The authors stated that exposure up to 500 ppm may have resulted in an exacerbation of a viral-induced, spontaneously occurring disease process in the central nervous system of the cats (McKenna et al. 1981a).

Exposures for longer durations also resulted in less severe neurotoxicity. B6C3F1 mice or Fischer 344 rats exposed to target doses of 0, 375, 750, and 1,500 ppm chloromethane for 6 hours/day, 5 days/week, for 13 weeks showed no exposure-related histopathological lesions of brain and spinal cord, and no effect on brain weight (Mitchell et al. 1979). Beagle dogs, CD-l mice, or Sprague-Dawley rats exposed to as high as 400 ppm chloromethane for 6 hours/day, 5 days/week for 90 days showed no apparent neurological effects (McKenna et al. 1981b).

Longer-term higher-level exposures have, however, resulted in neurotoxicity in mice. Male and female Fischer 344 rats and B6C3F1 mice were exposed 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. Necropsies were completed after either 6, 12, 18, or 24 months of exposure. As early as 6 months, the absolute brain weight was reduced in male and female rats and mice exposed to 1,000 ppm chloromethane; however, relative brain weights were not affected by chloromethane exposure, possibly due to body weight reductions. By 18 months, clinical signs of neurotoxicity (clutch response) were observed in both sexes of mice exposed to 1,000 ppm but not at lower doses. 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), and cerebellar lesions (minimal to mild reduction in the number of neurons in the granular cell layer and decreased cell layer width, most prominently in the sulci). Axonal swelling and degenerative changes of minimal to moderate severity were observed in the spinal nerves and cauda equina in the lumbar spinal cord of 6/7 male and 0/8 female mice (1,000 ppm), 5/5 male and 10/10 female mice (225 ppm), 4/5 male and 10/10 female mice (50 ppm), and 1/5 male and 2/10 female mice (control; no changes in granule cell layer). The neurotoxic lesions progressed in frequency and severity in mice to the end of the exposure period. In contrast to its effects in mice, chloromethane did not produce neurotoxicity in rats (i.e., negative clinical, pathological, and functional tests) at levels up to 1,000 ppm for 6/24 months in duration (CIIT 1981). The mechanisms underlying this dramatic difference in species susceptibility are not understood.

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

2.16 REPRODUCTIVE

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).

Based on a systematic review of the literature reproductive effects are a suspected health effect related to chloromethane exposure. Much of the evidence for chloromethane's reproductive toxicity has come from a variety of rodent studies. Rodent studies at doses greater than 400 ppm observed an association. Reproductive effects appear to be particularly pronounced in male rodents, with several studies reporting enzymatic mediation of lesions (Chapin et al. 1984), dose-dependent development of lesions (Burek et al. 1981; Hamm et al. 1985; Morgan et al. 1982; Working et al. 1985b), disrupted or incomplete spermatogenesis (Burek et al. 1981; Chapin et al. 1984; Chellman et al. 1987; Morgan et al. 1982; Working et al. 1985b), and obstruction of the epididymides (Burek et al. 1981), among other effects. Pre- and post-implantation loss in females was attributed to failure of fertilization rather than early embryonic death (Working and Bus 1986), and to decreased sperm quality in chloromethane-exposed males (Working et al. 1985a). Most studies found more pronounced effects at higher levels of chloromethane exposure. On the contrary, two studies evaluated the effects of inhaled chloromethane exposure on

beagles and cats (McKenna et al. 1981b; McKenna et al. 1981a) with doses up to 500 ppm, and did not observe an effect.

Chloromethane exposure in male rats varied by study from 200 ppm (Burek et al. 1981) to 7,500 ppm (Chellman et al. 1986a), with some studies incorporating a range of exposure levels. Most studies that evaluated chloromethane as a testicular and epididymal toxicant established an association between inhaled chloromethane exposure and testicular and epididymal damage, and ineffective spermatogenesis.

Male rodent exposure studies found lesions related to chloromethane inhalation. Burek et al. (1981) exposed Sprague-Dawley rats to 200, 500, 1000, and 2000 ppm chloromethane for 48 and 72 hours at each exposure level. Male Sprague-Dawley rats exposed to 500 ppm chloromethane for 48 hours had increased proteinaceous and cellular aggregates in the epididymis, with interstitial edema (2/5 rats) and focal suppurative inflammation (1/5) immediately after exposure. By 12 days post-exposure, the lesions had increased in severity with the formation of sperm granulomas and inflammation leading to partial lumen occlusion that may have contributed to testicular atrophy, with the most severe lesions found in rats exposed at higher concentrations and/or longer durations. Other than inflammatory and degenerative changes, none of these effects were observed at the highest dose, for which all animals died during or shortly after exposure. Additionally, decreased testicular size (3/10) and white foci on the epididymides (2/10) occurred after exposure to 500 ppm for 72 hours (Burek et al. 1981).

Similarly, studies using higher levels and longer duration of exposure also found chloromethane-associated lesions. Hamm et al. (1985) exposed Fischer 344 rats to 150, 475, or 1,500 ppm chloromethane 6 hours/day, 5 days/week for 10 weeks and 6 hours/day, 7 days/week for an additional 2 weeks and found that only male rats exposed to 1,500 ppm chloromethane exhibited testicular degeneration (10/10) and epididymal granulomas (3/10). Working et al. (1985b) found uni- or bilateral sperm granulomas in over 50% of male Fischer 344 rats exposed to twice the highest level, 3000 ppm chloromethane 6 hours/day for 5 days, and Chellman et al. (1987) also reported sperm granulomas and inflammation at that exposure level. Working et al. (1985a) found sperm granulomas in 30% of exposed male Fischer rats 17 weeks after exposure to 3,000 ppm chloromethane, 6 hours/day, for 5 days. Unlike the results of a continuous exposure study (Burek et al. 1981), no sperm granulomas were noted in the 1,000 ppm exposure group in Working et al. (1985a).

At a slightly higher exposure level of 3500 ppm chloromethane (Chapin et al. 1984), with an interim delay to improve the condition of animals surviving the first 5 days of exposure, testicular and epididymal lesions were visible after 9 days of exposure for 6 hours per day. An observation at that time was delayed spermatogenesis (retention of fully mature step 19 spermatids not undergoing spermiation) on day 9,

followed later by germinal epithelial vacuolation, bilateral epididymal granulomas, a sharp reduction in circulating testosterone, and nonprotein sulfhydryl depletion in the testes and epididymides. Taken together, these effects indicated that Leydig cell and gonadotrope function were not affected, that sulfhydryl depletion was enzymatically mediated, and that the initial testicular effects focused on late stage spermatids or Sertoli cells (Chapin et al. 1984).

Morgan et al. (1982) also observed a reduction in late stage spermatids with 2000 ppm chloromethane exposure in male F344 rats with 9 days of exposure. Further, Male Fischer rats exposed to 5,000 ppm chloromethane, 6 hours/day for 5 days developed sperm granulomas in the epididymides. These abnormalities were observed eighteen hours after their last exposure during necropsy (Morgan et al. 1982). Rats exposed to 7,500 ppm chloromethane, 6 hours/day for 2 days developed epididymal granulomas 3 weeks after exposure during necropsy (Chellman et al. 1986a). These studies show that differences in chloromethane exposure protocols (i.e., continuous vs. intermittent, number of exposure days, dose, and latent length of post exposure follow-up period) lead to differences in the time frame in which reproductive lesions develop.

Across the male rodent studies, lesions were often associated with testicular degeneration and ineffective spermatogenesis. Multiple studies found decreases in testicular weight at exposure levels at or above 1000 ppm chloromethane for 72 hours or more (Burek et al. 1981; Chellman et al. 1987; CIIT 1981;Working et al. 1985b), and later a shrinking width of seminiferous tubules (Chapin et al. 1984), with few tubules showing signs of spermatogenesis months post exposure (Chapin et al. 1984; Working et al. 1985b). In CIIT (1981) male rats exposed to 1,000 ppm exhibited decreased absolute and relative testicular weights starting at 18 months of exposure, which could have been due to decreases in the sizes of age-related interstitial cell tumors. Additional effects seen at later months in both rats and mice included testicular germinal cell degeneration, giant cell formation, and tubular atrophy (CIIT, 1981). Male Fischer 344 rats exposed to chloromethane at 2000, 3500, or 5000 ppm for 9 days, 6 hours/day with a 2-day break in exposure after day 6, all had testicular degeneration with a clear dose-related increase in severity (Morgan KT et al. 1982).

Two studies found no exposure-related gross or histopathological lesions in reproductive organs, and no changes in testes weight. Male and female Sprague-Dawley rats and CD-1 mice and male Beagle dogs exposed to 50, 150 or 400 ppm chloromethane 6 hours/day, 5 days/week for approximately 13 weeks showed no reported physical changes in their reproductive organs (McKenna et al. 1981b). Male and female Fischer 344 rats exposed to 375, 750, and 1,500 ppm chloromethane 6 hours/day, 5 days/week for 13 weeks did not show statistically significant differences in absolute testis or ovary weights when exposed. Rats and mice exposed at approximately 1,500 ppm (analytically measured concentration was

equal to 1,473 ppm) did not show significantly more lesions than controls (Mitchell et al. 1979). Based on the outcomes of studies using higher concentrations of chloromethane, it is likely that the majority of these exposure levels were too low to cause noticeable reproductive effects in rodents.

Additionally, some studies demonstrated prevention of chloromethane-induced lesions through concurrent exposure to the anti-inflammatory agent, amino-l-[m-(trifluoromethyl)-phenyl]-2-pyrazoline (BW755C). No granulomas were found in rats treated concurrently with chloromethane and BW755C. There was also no evidence of epididymal or testicular lesions in rats treated with both 5,000 ppm chloromethane and BW755C. BW755C, therefore, protected rats against chloromethane toxicity. The authors concluded that protection from chloromethane-induced injury by BW755C was not simply the result of altered metabolism because BW755C had no effect on tissue distribution of ^{14}C-chloromethane or excretion of ^{14}C in urine or $^{14}CO_2$ in the breath, and administration of BW755C did not decrease hepatic glutathione content. The protection of BW755C may have been related to an inhibition of leukotriene and prostaglandin synthesis (Chellman et al. 1986a). Accordingly, multiple studies showed that BW755C did not protect against decreased testicular weight, sperm damage, or pre-implantation loss in females mated with exposed males, because these outcomes are related to the cytotoxicity of chloromethane, not chloromethane-induced inflammation (Chellman et al. 1986c, Chellman et al. 1987).

Incomplete spermatogenesis and lowered sperm counts were associated with inhaled chloromethane at differing exposure levels. Burek et al. (1981) found sperm granulomas and decreased sperm in the tubule lumen 12 days post exposure to 500 ppm chloromethane for 48 hours, and testicular atrophy at 1000 ppm for 48 hours. Male rats exposed to 3000 ppm chloromethane showed disruption of spermatogenesis, decreased sperm counts and motility, and increased number of abnormal sperm (Chellman et al. 1987; Working et al. 1985b). Exposure at 3500 ppm for 9 days with a 3-day break after day 5 (due to adverse health issues) was associated with a delay in spermiation due to chloromethane's effects on late stage spermatids or the Sertoli cells. By day 9 all exposed rats had disruption of spermatogenesis, and by day 13, all had disruption and disorganization of seminiferous epithelium and epithelial vacuolation (Chapin et al. 1984).

Sperm damage and incomplete spermatogenesis can cause decreased fertility and pre- and post-implantation loss. Three studies in male and female rats evaluated the reproductive implications of chloromethane-induced germ cell dysfunction. Two additional rodent studies on females found decreased maternal weight gain and maternal toxicity due to chloromethane exposure.

Male Fischer 344 rats exposed to inhaled chloromethane and mated with unexposed females were more likely to show reduced fertility than mated male controls. Unexposed female rats mated with male rats

exposed to 1,000 ppm chloromethane 6 hours/day for 5 days, showed a slight increase in pre-implantation loss only during weeks 2 (10%) and 3 (14%). At 3,000 ppm they showed a slight increase (9.5%) in post-implantation loss only at week 1 post exposure, but increased pre-implantation losses at week 1 (31.4%), peaking at week 2 (93.6%), and a partial recovery by week 8 (14.1%). Fertility in males exposed to 3,000 ppm chloromethane based on implantation rate was significantly decreased (from 11% to 2%) by post exposure week 2, and slowly recovered by week 7. The authors concluded that a cytotoxic rather than genotoxic mechanism may play a role in the observed preimplantation losses, and that chloromethane may not reach the testes in sufficient concentration to produce detectable DNA damage. They further speculated that inflammation-derived reactive metabolites (e.g., superoxide anion) could damage DNA or sperm in epididymides (Working et al. 1985a).

Working and Bus (1986) assessed the effects of inhalation exposure to chloromethane on preimplantation loss to distinguish between cytotoxicity (i.e. fertilization rate) and genotoxicity in rats. Similarly to Working et al. (1985a), Working and Bus (1986) found decreased male fertility. The fertilization rates of unexposed female rats by males exposed to 1000 or 3000 ppm chloromethane for 6 hours/day for 5 days were functions of both exposure and recovery. The combined fertilization rate for all females bred with control males was 88%. However, the fertilization rate decreased when females were bred with males exposed to chloromethane. In females bred with males exposed to 1,000 ppm chloromethane for 5 days, 6 hours/day, 80% of ova were fertilized. In females bred with males exposed to 3,000 chloromethane, fertilization of ova was 39% at week 1 of mating post-exposure, and 3.4% at week 2. By week 3 post-exposure, fertilization of ova had risen to 22.1%, and continued to rise to 41% at week 4, and 72% at week 8. The minimum in week 2, followed by gradual recovery was significant. There were no significant differences in the cleavage rates of ova from females bred to controls (96.5%), or to males exposed to 1,000 or 3,000 ppm chloromethane (92.4-93.8%). The authors concluded that all preimplantation losses observed in previous studies (Working et al. 1985a) could be explained by a cytotoxic effect resulting in failure of fertilization, and not a genotoxic effect resulting in early embryonic death (Working and Bus 1986). Furthermore, testicular toxicity and the cytotoxic effects of chloromethane on the sperm, as seen in Chellman et al. (1987), were likely also contributing factors to failed fertilization and preimplantation losses.

Hamm et al. (1985) exposed both male and female Fischer 344 rats to 150, 475, and 1,500 ppm chloromethane 6 hours/day, 5 days/week for 10 weeks, and then 7 days/week during a 2-week mating period. There was no significant difference in fertility between exposed and unexposed females (as measured by copulation plugs), as males exposed to 475 ppm chloromethane produced significantly fewer litters when mated with both exposed and unexposed females. However, no conclusion can be drawn on

the potential impact of female exposure on their actual post-copulation fertility since unexposed males were not mated to exposed females. Males exposed to 1,500 ppm produced no litters on first breeding, regardless of the exposure status of the female, but after a 10-week recovery period, both their fertility and the ability of unexposed impregnated females to produce litters improved to about one third of the control value. Chloromethane had no statistically significant effect on fertility in the second generation (F1) male and female rats exposed to 151 and 472 ppm chloromethane. However, there was a dose related trend towards fewer litters and fewer males proven fertile in the 475 ppm group; litters in the 475 ppm group had a decreased percentage of males, and reduced male and female F2 pup growth rates only during postnatal days 14 to 21. The significance of these effects is unknown (Hamm et al. 1985).

As with chloromethane-induced reproductive effects for males, maternal toxicity appears to be associated with higher doses of chloromethane. Maternal toxicity was not observed in C57BL/6 female mice exposed to 500 ppm chloromethane; only mice exposed to 750 ppm exhibited signs of maternal toxicity (body weight reduction) (Wolkowski-Tyl et al. 1983b). However, no effects on implantations, resorptions, fetuses per litter, or sex ratio were observed in pregnant female B6C3F1 mice exposed to up to 750 ppm for 6 hours/day (Wolkowski-Tyl et al. 1981). B6C3F1 mice exposed to approximately 1,500 ppm chloromethane (analytically measured concentration was equal to 1,492 ppm) for 6 hours/day on gestation days 6 through 14 (exposure ended early), developed severe maternal toxicity related to the neurological effects described in Section 2.15 (Wolkowski-Tyl et al. 1983a).

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

2.17 DEVELOPMENTAL

No studies were located regarding developmental effects in humans after inhalation exposure to chloromethane. Chloromethane’s association with developmental impacts is not classifiable after a systematic review, as the evidence of an effect is low in animals and non-existent in humans.

Wolkowski-Tyl et al. (1981a, 1983a) explored the developmental toxicity of gestational exposure to chloromethane in both F344 rats and B6C3F1 mice. In their study, they exposed pregnant dams of both species to target concentrations of 0, 100, 500 or 1500 ppm (analytically measured mean concentrations measured to be 0, 102, 479, 1492 ppm) for 6 hours/day from gestational day 6-18. The researchers observed distinct species differences. Specifically, rats demonstrated delayed ossification in several bones and reduced fetal body weight at 1500 ppm, which was also maternally toxic. No other developmental effects were observed in the rats. The 1500 ppm mouse dose group was sacrificed before the end of the study because it was causing death and moribundity in a high proportion of the animals. In addition, the

offspring mice in the 500 ppm dose group demonstrated an increase in the incidence of cardiac malformations. Specifically, Wolkowski-Tyl et al. (1981a, 1983a) observed the absence of atrioventricular valves, chordae tendinea, and papillary muscles in 6/17 litters. The same skeletal malformations observed in rats was not seen in the mice.

To further explore the malformations seen in the mice Wolkowski-Tyl et al. (1981b; 1983b) exposed pregnant female B6C3F1 mice 6 hours/day to 0, 250, 500, and 750 ppm chloromethane on gestational days (GD) 6-18 and then evaluated the fetuses. They observed a dose-response increase in the incidence of malformations in the hearts of the mice exposed in utero. Specifically, the control rate was 3 malformations in 3 control litters or 1 malformation per litter, 500 ppm produced 11 malformations in 7 litters compared to 7 expected, and 750 ppm yielded 17 malformations in 14 litters compared with 14 expected. Specifically, Wolkowski-Tyl et al. (1981b, 1983b) reported a higher incidence of fetal heart defects occurring primarily in females (23 female, 14 male). The observed malformations included absent or abnormal tricuspid valve, reduced number of papillary muscles, small right ventricle, globular heart, and white spots (assumed to be calcium deposits, in the left ventricular wall), and a number of malformed fetuses in both the 500 and 750 ppm groups.

In addition, the authors observed a decrease in maternal body weight, along with increased ataxia and hypersensitivity in the 750 ppm group, but no pregnancy-related effects were observed regarding implantations, resorptions, fetal mortality, fetuses per litter, live fetuses, or sex ratio. The fetal malformation incidence rate was slightly increased as a function of dose.

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 1983b-reported papillary muscle effects were rare and should not have occurred without other expected cardiovascular malformations. In pilot exposures of 250-300 ppm on gestation 11.5 to 12.5 John-Green 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. (1983b; 1983a). However, in a response to the John-Green et al. 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 the difference in timing of exposure during gestation, arguing that the most critical day is gestational day 14.

Theuns-van Vliet 2016, an unpublished study on pregnant New Zealand White rabbits and their fetuses exposed pregnant rabbits (n=22 with 163-178 fetuses per treatment group) to approximately 0, 265, 511 or 1,012 ppm chloromethane 6 hours per day on gestation days 6-28. On gestation day 29, the rabbits were sacrificed, and developmental parameters were measured. Although some developmental effects such as some fetal deaths and flexure of the forepaw were observed in some exposed fetuses, these observations were not considered treatment-related by the authors. With regard to potential heart effects, the author found no significant differences in papillary muscle, chordae tendineae (heart strings), or other heart malformations in the fetuses other than indentation of the apex of the heart in 4 exposed fetuses, which the author considered to be inter-animal variation (Theuns-van Vliet 2016). Therefore, it appears there are species differences as it relates to the developmental toxicity of chloromethane.

No studies were located regarding developmental effects in humans or animals after oral or dermal exposure.

2.18 OTHER NONCANCER

No studies were located regarding other systemic effects in humans after inhalation exposure to chloromethane. However, it should be noted that, following the deaths in 1928 and 1929, acrolein was added to chloromethane as an irritating tracer gas that was intended to warn individuals that they were being exposed to chloromethane. McNally (1946) reported that the tank of refrigerant to which two of the case subjects were exposed was analyzed and found to contain acrolein, and suggested that those individuals may have had a defective sense of smell or were poisoned by chloromethane too rapidly to respond. The majority of the animal studies reported on in this profile confirmed the purity of chloromethane used in the research, and therefore it is unlikely acrolein was the cause of the adverse effects observed and attributed to chloromethane. No studies were located on the impact that adding tracer amounts of acrolein might have on health effects associated with chloromethane exposure.

The only other systemic effect reported in animal studies was a decrease in food consumption in the Landry et al. (1985) study. This study evaluated the neurologic effects of continuous versus intermittent chloromethane exposure in female C57BL/6 mice exposed to chloromethane in whole body inhalation chambers for 11 days, either continuously (C) for 22 hours/day at 0, 15, 50, 100, 150, 200, or 400 ppm, or intermittently (I) for 5.5 hours/day at 0, 150, 400, 800, 1,600, or 2,400 ppm. There was a significant degree of fatigue (likely due to decreased food consumption) in the 200-C and 400-C ppm mice prior to necropsy, with decreased carcass size, amount of abdominal fat, amount of ingesta in the gastrointestinal tract, and small, pale livers. Fatigue was not reported for any intermittent exposure despite the 1,600-I and

2,400-I groups respectively receiving approximately 2 and 3 times more inhaled chloromethane than the 200-C group.

2.19 CANCER

The evidence evaluating chloromethane and its implications on cancer outcomes is limited. This is exemplified by the fact that the U.S. EPA and IARC both classified chloromethane as "not classifiable" as it relates to human carcinogenicity. EPA classified the chemical as a Group D chemical (IRIS 2001) and IARC has classified it as a Group 3 chemical (IARC 2019). The National Toxicology Program (NTP) has not evaluated chloromethane's carcinogenicity potential. However, NIOSH does classify chloromethane as a potential occupational carcinogen (NIOSH 1984).

Several cohorts of workers occupationally exposed to chloromethane have been used to assess the chemical's potential carcinogenicity. Specifically, cohorts include workers from a butyl rubber manufacturing plant that used chloromethane as a diluent, Icelandic fisherman accidentally exposed due to a refrigerant leak, and various occupational populations exposed to chlorinated solvents in the workplace (Barry et al. 2011; Dosemeci et al. 1999; Holmes et al. 1986; Jiao et al. 2012; Kernan et al. 1999; Rafnsson and Gudmundsson 1997; Rafnsson and Kristbjornsdottir 2014).

When evaluating potential associations between deaths from all cancer and chloromethane exposure in both the cohort from the rubber manufacturing plant and the Icelandic fisherman, no association was found (Holmes et al. 1986; Rafnsson and Gudmundsson 1997; Rafnsson and Kristbjornsdottir 2014). The cohort of Icelandic fisherman was also used to assess potential association between chloromethane and death from lung cancer (Rafnsson and Gudmundsson 1997), and death from renal cancer (HR = 9.35; 95% CI: 1.28-68.24) (Rafnsson and Kristbjornsdottir 2014). No association was found with lung cancer (Rafnsson and Gudmundsson 1997), but there was an increased risk of death from renal cancer. However, the Icelandic fisherman cohort is less than 30 men who did not have exposure estimated and had other lifestyle factors such as smoking and diet that were not adjusted for. Therefore, the generalizability of these results is minimal.

Several other case-control studies used data on occupational exposures to solvents, including to chloromethane, to assess potential carcinogenicity. Dosemeci et al. (1999) did not find any association between chloromethane and renal cell carcinoma, and Kernan et al. (1999) found unclear associations with pancreatic cancer that were not dose-, gender-, or race-specific. Barry et al. (2011) evaluated the impact of genetic variation on the relationship between chloromethane or chlorinated solvents combined (Jiao et al. 2012) and non-Hodgkin's Lymphoma. Barry et al. (2011) found an association between chloromethane exposure (never versus ever exposed) and the risk of non-Hodgkin's lymphoma only

among women with the TT (but not TA or AA) genotype of the CYP2E1 rs2070673 gene. This was based on an analysis of 648 women, of which 29 were TT +, had exposure to chloromethane, and had non-Hodgkin's lymphoma. Jiao et al. (2012) evaluated the same group of women as Barry et al. (2011) but assessed only combined exposure to all chlorinated solvents, and looked at a separate set of SNPs in 16 DNA repair genes, and did not find any increased associations with NHL in any of the SNPs evaluated. Additional information on these studies can be found in Table 2-1.

A high incidence of renal tumors was found in male mice that were exposed primarily to approximately 1,000 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. Although the two adenomas observed at 225 ppm after 24 months were not statistically significant compared to controls, they were sufficiently similar to those in the 1,000 ppm group that the authors considered them to be treatment related. No evidence of carcinogenicity was found in female mice or in male or female rats exposed to concentration of 1,000 ppm or less in this study.

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

2.20 GENOTOXICITY

No studies were located regarding genotoxic effects in humans after inhalation exposure to chloromethane. In animals, chloromethane exposure has resulted in dominant lethal mutations in the sperm of male rats (Chellman et al. 1986c; Rushbrook 1984; Working et al. 1985a). This only occurred in sperm that was already in the vas deferens and epididymis when exposure occurred and so was available for fertilization during the first 2 weeks post exposure (Working et al. 1985a). Experiments on the mechanism of the post implantation loss observed in the females mated to the exposed males indicated both a dominant lethal effect and epididymal inflammation potentially play a role in post implantation loss (Chellman et al. 1986c). Chloromethane did not result in unscheduled DNA synthesis in hepatocytes, spermatocytes, or tracheal epithelial cells when male rats were exposed to 3,500 ppm, 6 hours per day for 5 days, but did produce a marginal increase in unscheduled DNA synthesis only in hepatocytes when rats were exposed to 15,000 ppm for 3 hours, a level that did not cause significant mortality (Working et al. 1986).

Jager et al. (1988) exposed male and female mice and rats to 1,000 ppm chloromethane for either 8 hours or for 6 hours per day for 4 days. They evaluated the FDH activities in liver and kidneys, and found a decrease in FDH activity only in male mouse kidneys with 8 hours of exposure, but the significance

disappeared with longer-term exposure (6 hours/day for 4 days). Although Jager et al. (1988) observed increased formaldehyde concentrations in microsomes in vitro, no increase in formaldehyde concentration was observed in vivo in the kidney or liver, refuting the hypothesis that chloromethane exposure might increase tissue formaldehyde concentration and the risk of renal cancer. Glutathione depletion also removes the cofactor for formaldehyde dehydrogenase (FDH), the enzyme that inactivates formaldehyde. Jager et al. (1988), however, did not observe increased formaldehyde levels in mouse liver or kidney after a single 8-hour exposure to 1,000 ppm chloromethane, or an increase in DNA protein cross links (DPC), a typical formaldehyde-induced lesion, after exposure to 1,000 ppm for 6 hours per day for 4 days. Ristau et al. (1990) showed a rapid removal of DPC in male mice whereas single strand breaks appeared to accumulate. Both types of lesions were ascribed to the action of formaldehyde. However, as stated previously, Jager et al. (1988) disputes this assertion. The findings by Jager are in contrast to the findings from Heck et al. (1982) who observed a doubling of formaldehyde concentration in the liver and testes and a sevenfold increase in formaldehyde in the brain of F344 male rats compared to controls after 3000 ppm exposure of chloromethane for 4 days (6 hours per day).

Chloromethane has been tested for genotoxicity in a number of in vitro and in vivo systems (Table 2-4 and Table 2-5). 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; Hatch et al. 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).

Chloromethane induced unscheduled DNA synthesis in rat hepatocytes and spermatocytes, but not tracheal epithelial cells, when incubated in near-toxic concentrations in vitro, and it induced a marginally positive response in hepatocytes, but not the other tissues following in vivo exposure at a near-lethal concentration. Hepatocytes were the most sensitive of these tissues both in vivo and in vitro (Working et al. 1986). Chloromethane exposure consistently produced dominant lethal mutations in the sperm of rats, as measured by post implantation loss in females mated to the exposed males (Chellman et al. 1986c; Rushbrook 1984; Working et al. 1985a). Since concurrent exposure of male rats to chloromethane and BW755C, an anti-inflammatory agent, did not result in post implantation loss, it was suggested that the dominant lethal mutation may be due to chloromethane-induced epididymal inflammation. However, there was a positive response to an assessment of a dominant lethal effect and therefore, this cannot be ruled out as a mechanism of toxicity (Chellman et al. 1986c). Since studies using ^{14}C-chloromethane indicated that the carbon atom from chloromethane becomes incorporated into normal macromolecules via the one-carbon pool, rather than binding to macromolecules as an alkylating agent (Kornbrust and Bus

1983; Peter et al. 1985), it is possible that in vivo genotoxicity and carcinogenicity (see Section 2.19) may be secondary to other toxic effects of chloromethane. Nevertheless, the in vitro studies demonstrate the direct genotoxicity of chloromethane, albeit at high concentrations of exposure.

Positive results have generally been found in the reverse mutation assay in Salmonella typhimurium with and without metabolic activation (Andrews et al. 1976; DuPont 1977; Simmon et al. 1977). In addition, a positive result was obtained in S. typhimurium for 8-azaguanine resistance (Fostel et al. 1985). Further, chloromethane was found to be a potent mutagen in Drosophila melanogaster (University of Wiconsin 1986).

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

Species (test system)	End point	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)			
hepatocytes	Unscheduled DNA synthesis	(+)	Working et al. 1986
spermatocytes	Unscheduled DNA synthesis	—	Working et al. 1986
tracheal epithelial cells	Unscheduled DNA synthesis	—	Working et al. 1986
Drosophila (inhalation)	Recessive lethal	+	University of Wiconsin 1986

— = negative results; + = positive results; (+) = marginally positive result; (+/—) = equivocal results.

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

Species (test system)	End point	Results Activation With	Results Activation Without	Reference
Prokaryotic organisms:				
Salmonella typhimurium (desiccator test for exposure to gases)	Gene mutation	+	+	Simmon et al. 1977
S. typhimurium TA1535 (gas exposure)	Gene mutation	+	+	Andrews et al. 1976
S. typhimurium (gas exposure)	Gene mutation			DuPont 1977
TA1535		+	+	
TA100		+	+	
TA1537		—	—	
TA18		—	—	
S. typhimurium TA677 (gas exposure)	Gene mutation	ND	+	Fostel et al. 1985
Mammalian cells:				
Human lymphoblasts	Gene mutation	ND	+	Fostel et al. 1985
Human lymphoblasts	Sister-chromatid exchange	ND	+	Fostel et al. 1985
Human lymphoblasts	DNA strand breaks	ND	—	Fostel et al. 1985
Rat hepatocytes	Unscheduled DNA synthesis	NA	+	Working et al. 1986
Rat spermatocytes	Unscheduled DNA synthesis	ND	+	Working et al. 1986
Rat tracheal epithelial cells	Unscheduled DNA synthesis	ND	—	Working et al. 1986
Primary hamster embryo cells	Unscheduled DNA synthesis	ND	+	Hatch et al. 1982; Hatch et al. 1983
Chinese hamster lung cells	Chromosomal aberrations	+	+	Asakura et al. 2008

+ = positive result; — = negative result; NA = not applicable; ND = no data

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. 1981b; Putz-Anderson et al. 1981a).
- 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 (Kornburst et al. 1982, Chellman et al. 1986a, 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 glutathione transferase is the main form of metabolism in humans and animals. Cytochrome P-450 may dehalogenate chloromethane to formaldehyde, but oxidation of GSH–chloromethane conjugation intermediates by cytochrome P-450 may also be involved in the formation of formaldehyde (Heck et al. 1982; Kornburst 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. 1981b; Putz-Anderson et al. 1981a). 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; Landry et al. 1983b). Absorbed doses (and absorption rates) for 6-hour exposures were calculated as 67 mg/kg (0.167 mg/min/kg) for rats exposed to 1,000 ppm, and 3.8 mg/kg (0.01 mg/min/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 ppm 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 one hour of exposure at 20,000 ppm. As a result of this analysis a skin notation was assigned by ACGIH (2018).

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. One study was located regarding distribution in humans after inhalation 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 ppm and 63±23.6 ppm for the respective doses. The respective blood concentrations were 7.7±6.3 ppm 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 5000 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.

In a group of 6 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 glutathione

(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 glutathione-S-transferase that catalyzes the conjugation of chloromethane with glutathione. Other possible reasons for the differences in chloromethane elimination among subjects include differences in tissue glutathione 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 five-fold difference in the first order rate constant for elimination with slow metabolizers demonstrating a K_m of 0.039 to 0.069/ min and fast metabolizers demonstrated a K_m of 0.284 to 0.342/min. 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 Antheunius (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 Antheunius (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.

Peter et al. (Peter et al. 1989b; Peter et al. 1989a) 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 glutathione S-transferase 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 glutathione, but that in contrast to

chloromethane, methyl iodide and methyl bromide also showed significant non-enzymatic conjugation with glutathione.

Warholm et al. (1994) studied the polymorphic distribution of the erythrocyte glutathione 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 glutathione 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).

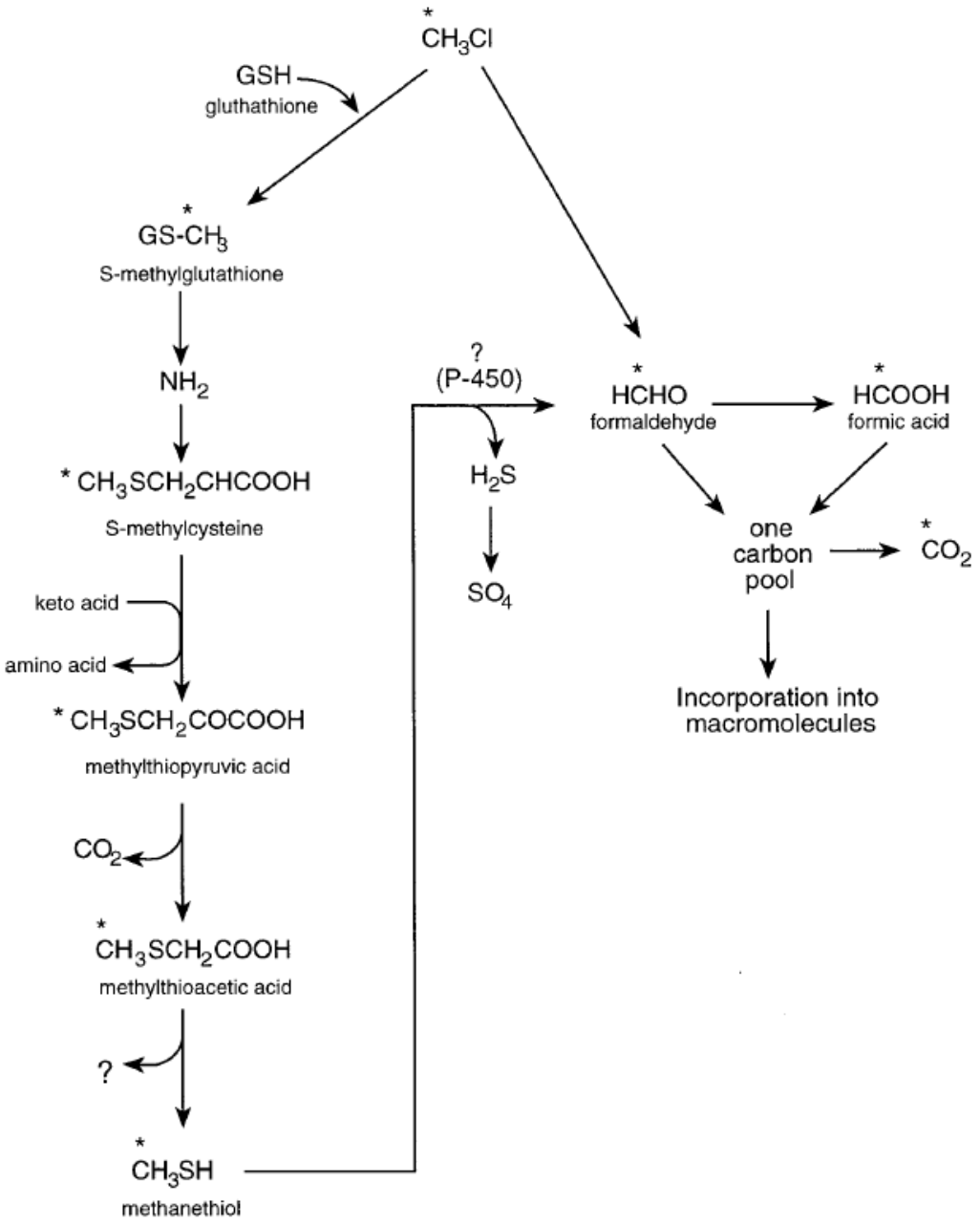
Lof et al. (2000) exposed 24 volunteers, (eight with high, eight with medium, and eight with no GSTT) activity) to 10 ppm chloromethane for 2 hours. The concentration of chloromethane was measured in inhaled air, exhaled air, and blood. The experimental data were used in a 2-compartment model with pathways 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/min 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 glutathione to yield S-methylglutathione, S-methylcysteine, and other sulfur-containing compounds
(Kornbrust and Bus 1984; Landry et al. 1983a; Landry et al. 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 P-450 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 glutathione 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 P-450 (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 3000 ppm of chloromethane compared to the control rats. In this same study there was a sevenfold 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.

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 activity in the liver and kidney tissue from the high GSTT1 humans were twice as high as in the low metabolizing group, and two to seven 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: Kornburst 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 %/min (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 one 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 hr) 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 2-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 glutathione 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.

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 3rd 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 over predicted. 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 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 (1949a) provided acute mortality data indicating that species susceptibility follows the general order of mice >guinea pig >dog >goat >monkey >rat >rabbit, with a fourfold difference between mice and rabbits. The greater susceptibility of mice may be due to different metabolic rates involving glutathione or different oxidative rates for the production of formaldehyde. Chloromethane conjugates with glutathione to a much greater extent in mouse liver, kidney, and brain compared with rats (Kornburst and Bus 1984). Pretreatment (*i.p.*) of mice with L-buthionine-S,R-sulfoximine (BSO), a glutathione depleter, protected mice from the chloromethane-induced lethal effects (Chellman et al. 1986b). Thus, the reaction of chloromethane with glutathione to produce S-methylglutathione appears to be a toxifying rather than a detoxifying reaction (Chellman et al. 1986b).

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

Different P-450 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 in children would be similar to those in adults for either accidental short-term exposures or longer-term lower level exposures. There is a lack of human data on whether chloromethane affects the developing fetus or the development of young children.

There are limited data on the toxicity of chloromethane in children and it is assumed that the toxicity of chloromethane in children is similar to 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.

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, glutathione-S-

transferase, 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 glutathione or from the depletion of GSH (Chellman et al. 1986b; Kornbrust and Bus 1983, 1984; Landry et al. 1985). If a polymorphism is present in children, then some children with the same polymorphism as adults (i.e., those with higher levels of glutathione-S-transferase) would be more susceptible to the toxic effects of chloromethane. However, if the mechanism is a result of decreasing GSH (which may protect again peroxidation), these individuals may actually be protected against the impact of chloromethane.

Certain characteristics of the developing human may increase exposure or susceptibility while others may decrease susceptibility to the same chemical.

It is not known whether chloromethane or one of its metabolites (e.g., methanethiol or an altered macromolecule) can cross the placenta and enter into the developing young, or if either compound can enter into breast milk. However, 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 gestation day 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. Chloromethane is broken down and eliminated from the body very quickly in adult humans (Nolan et al. 1985) and animals (Landry et al. 1983a; von Oettingen et al. 1949, 1950).

Although the breakdown and elimination of chloromethane is expected to be the same in children as in adults, two distinct groups of humans with different metabolic rates have been identified, so more studies are needed to answer this and other questions concerning the movement of chloromethane into the fetus or breast milk, and what levels might result in harmful effects. There is only one PBPK model for chloromethane exposure based on data for GSTT1 deficient individuals. There are otherwise no PBPK models for children, adults, or test animals. There are no good 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. Attempts to use urinary levels of S-methylcysteine as an indicator of chloromethane exposure have not been successful, so the approach is considered to be invalid (Nolan et al. 1985).

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 per day during gestational days (GD) 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, the centra of the thoracic vertebrae, the pubis of the pelvic girdle, and the metatarsals of the hind limbs.

In a mouse study, dams were exposed by inhalation to chloromethane during gestation days 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 gestation days 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 gestation days 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. (Wolkowski-Tyl et al. 1983b; 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 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 gestational day 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, Chellman et al. 1986b, Chellman et al. 1987; CIIT 1981; Hamm et al. 1985; Morgan KT et al. 1982; Working and Bus 1986; Working et al. 1985a, Working et al. 1985b). Testicular effects of chloromethane have been 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, Chellman et al. 1987; Working and Bus 1986; Working et al. 1985a, Working et al. 1985b). However, these findings do not negate the possibility of a dominant lethal mutation leading to post-implantation loss. Both mechanism 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. 1981; Goldstein et al. 1979; Working et al. 1985a).

Chloromethane has been tested for genotoxicity in a number of *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; Hatch et al. 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 *Drosophila melanogaster* (University of Wiconsin 1986).

3.3 BIOMARKERS OF EXPOSURE, EFFECT, AND SUSCEPTIBILITY

Biomarkers are broadly defined as indicators of 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.

A biomarker of effect is 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 6 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). On the basis of variable excretion of S-methyl-cysteine in 6 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-methyl-cysteine; 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 samples were collected starting immediately after to 3 hr after exposure, and early samples for 20 or 100 ppm correlated well with exposure; however, they decreased 5-fold or more in 15 min, 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 et al. 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 (Repko et al. 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, smoking, etc.

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 non-significant average decrease of 4%, and diazepam and chloromethane together produced a combined 13.5% decrease. The authors suggest that there is no interaction between diazepam and chloromethane exposure, but instead that effects are additive. Group average blood and breathing air concentrations were highly correlated, but there were large interindividual differences.

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 ascribe this increase to an inhibitory effect of chloramine on formyl tetrahydrofolate dehydrogenase and formaldehyde dehydrogenase. More recently, Wang and Minami (1996) extended their proposed mechanism to include a potentiation of formaldehyde on chloramine inhibition of acetylcholinesterase activity. In their study they state 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 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 glutathione, were

administered i.p. to rats or mice exposed to chloromethane by inhalation to study the mechanism of chloromethane-induced toxicity (Chellman et al. 1986a, Chellman et al. 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.

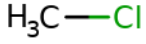
CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Industrial chloromethane is a colorless liquid or compressed gas while environmental chloromethane is a trace component of the atmosphere. Chloromethane is composed of a single carbon atom bound to three hydrogen atoms and one chlorine atom. The chemical was previously used widely as a refrigerant, but this use has been replaced by other chemicals such as hydrofluorocarbons. 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 used mainly in the production of adhesives, sealants, and in the production of silicones, but it is also an impurity in vinyl chloride, such that is it present in polyvinyl chloride (PVC) products. Chloromethane is produced from methanol and hydrogen chloride using an aluminum oxide catalyst.

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

Table 4-1. Chemical Identity of Chloromethane

Characteristic	Information	Reference
Chemical name	Chloromethane	PubChem 2019
Synonym(s) and Registered trade name(s)	R 40; Artic; methyl chloride; methane, chloro-; Freon 40; MeCl; monochloromethane	PubChem 2019
	Chloride, Methyl; chloromethane; methyl chloride	PubChem 2019
Chemical formula	CH_3Cl	PubChem 2019
Chemical structure		PubChem 2019
CAS registry number	74-87-3	PubChem 2019
UNII:	A6R43525YO	PubChem 2019
EPA hazardous waste number	U045	PubChem 2019

CAS = Chemical Abstracts Service; EPA = Environmental Protection Agency; UNII = Unique Ingredient Identifier

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Chloromethane exists as a gas at room temperate and atmospheric pressure. It is moderately soluble in water and several other organic solvents. It is miscible in chloroform and ether. Chloromethane has a relatively high vapor pressure, which contributes to its flammability. In addition to being highly water soluble, chloromethane has a relatively low K_{ow} 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 2019
Physical state	Gas (can leak as a liquid or vapor)	PubChem 2019
Melting point(s)	-97.6 °C	PubChem 2019
Boiling point(s)	-23.7 °C	PubChem 2019
Critical temperature and pressure	416.25 K and 6.679 MPa	PubChem 2019
Density	0.911 g/cm^3 at 25 °C 0.997 g/cm^3 at -24 °C	PubChem 2019; Tsai 2017
Viscosity	0.106 mPas (gas at 20 °C)	Tsai 2017
Taste	Sweet taste	PubChem 2019
Odor	Faint sweet ethereal odor Mild odor[a]	PubChem 2019
Odor threshold:		PubChem 2019
Water	No data	
Air	21 mg/m^3 [a]	
Solubility:		PubChem 2019
Water	5040 mg/L at 25 °C	
Organic solvent(s) at 20 °C	benzene 4723 mg/L, carbon tetrachloride 3756 mg/L, glacial acetic acid 3679 mg/L, ethanol 3740 mg/L; miscible with ethyl ether, acetone, benzene, chloroform	
Partition coefficients:		
Log K_{oa}	1.565	Vallero 2014
Log K_{ow}	0.91	PubChem 2019
Log K_{oc}	13	PubChem 2019
Relative Vapor Density	1.8 (air=1)	PubChem 2019; Tsai 2017
Vapor pressure at 25 °C	4300 mmHg	PubChem 2019
Henry's law constant at 24 °C	8.82x10^{-3} atm-m^3/mol	PubChem 2019
Degradation half-life in air via reaction with OH radicals	3.6x10^{-14} cu cm/molecule-sec at 25 °C	PubChem 2019
Dissociation constants:	No data	PubChem 2019
Heat of combustion	-5290 Btu/lb	PubChem 2019
Heat of vaporization	18.92 kJ/mol at 25 °C 21.40 kJ/mol at boiling point	PubChem 2019

Table 4-2. Physical and Chemical Properties of Chloromethane

Property	Information	Reference
Autoignition temperature	1170 °F	PubChem 2019
Flashpoint	-50 °F (closed cup)	PubChem 2019
Flammability limits in air	8.1 - 17.4%	PubChem 2019; Tsai 2017
Conversion factors:	1 mg/L = 484 ppm; 1 ppm = 2.06 mg/m^3 at 25 °C and 760 torr	PubChem 2019
Explosive limits	Moderate explosion hazard when exposed to flames and sparks	PubChem 2019
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 2019

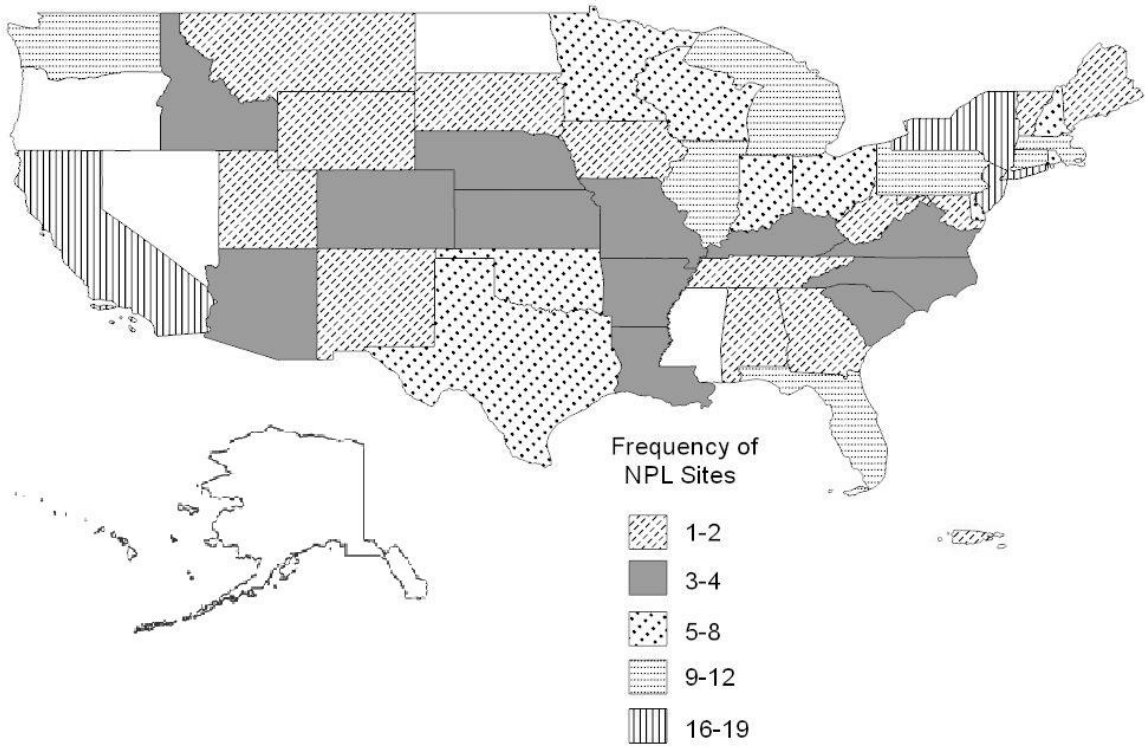
[a] Chloromethane is not noticeable at dangerous concentrations.

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Chloromethane has been identified in at least 236 of the 1,867 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 20179). However, the number of sites evaluated for chloromethane is not known. The number of sites in each state is shown in Figure 5-1.

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



Source: ATSDR 2019

- The most likely route of exposure for the general public to chloromethane is through inhalation; the general public 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 by 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 (PubChem 2021; 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 various estimates in the range of 0.6-3 years (see Section 5.4). Chloromethane is the dominant organochlorine species in the atmosphere. In the upper atmosphere, chloromethane, through its sheer abundance, plays a role in chemical reactions that remove ozone from the upper troposphere and stratosphere (Crutzen and Gidel 1983; Gidel et al. 1983; Singh H.B. 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 Clean Air Act (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. In soil, chloromethane is expected to volatilize from the surface, but when present in a landfill, it will probably 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 parts per billion 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 ≈0.7-0.9 ppb. The database for occupational exposure is outdated (late 1980s or earlier). The OSHA 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 so as to allow reliable predictions of average or probable occupational exposure levels. The population with the highest potential exposures probably would include those 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 hydrogen chloride (HCl) or by chlorination of methane (Edwards et al. 1982a; Key et al. 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 (Key et al. 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 (Key et al. 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 (Key et al. 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 by-product 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 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; (4) Praxair Distribution, Inc. in Toledo, Ohio; (5) Formosa Plastics Corp. in Point Comfort, Texas; (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 (CDR 2016). The production volume at each of these sites 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 (CDR 2016). National aggregate production volumes of chloromethane from 2012 to 2014 were also between 1,000,000,000 and 5,000,000,000 pounds (CDR 2016). National aggregate production volumes in 2011 were 1,396,155,238 pounds (CDR 2012).

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

State[a]	Number and Name of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	2	1,100	10,998	1, 5, 13
	AMVAC CHEMICAL CO	1,000	9,999	1, 5
	EVONIK CORP	100	999	1, 13
AR	2	10,000	100,098	1, 5
	EVERGREEN PACKAGING	0	99	1, 5
	FUTUREFUEL CHEMICAL CO	10,000	99,999	1, 5
CA	1	No data	No data	No data
	AMVAC CHEMICAL CORP	No data	No data	No data
FL	2	1,000	10,098	1, 5, 6
	SIVANCE LLC	1,000	9,999	6
	WESTROCK CP LLC (FORMERLY ROCK-TENN & SMURFIT-STONE)	0	99	1, 5
GA	1	1,000,000	9,999,999	6
	CHEMTALL INC	1,000,000	9,999,999	6
IL	4	1,200,000	11,999,997	6
	RHO CHEMICAL CO INC	No data	No data	No data
	AKZO NOBEL SURFACE CHEMISTRY LLC	100,000	999,999	6
	EVONIK CORP	1,000,000	9,999,999	6
	LONZA INC	100,000	999,999	6
KS	1	1,000,000	9,999,999	1, 4, 6
	OCCIDENTAL CHEMICAL CORP	1,000,000	9,999,999	1, 4, 6
KY	2	1,100,000	10,999,998	1, 3, 6
	DOW SILICONES CORP	1,000,000	9,999,999	1, 3, 6

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

State[a]	Number and Name of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
	PMC ORGANOMETALLIX INC	100,000	999,999	6
LA	12	51,441,100	114,410,988	1, 3, 4, 5, 6, 9, 10, 12, 13, 14
	AXIALL LLC	10,000	99,999	1, 5, 12
	BASF CORP	100,000	999,999	6
	BLUE CUBE OPERATIONS LLC - PLAQUEMINE SITE	100,000	999,999	9, 12, 14
	ECO-SERVICES OPERATIONS	10,000	99,999	12
	EXXONMOBIL BATON ROUGE CHEMICAL PLANT (PART)	10,000	99,999	10
	GALATA CHEMICALS LLC - GALATA TAFT FACILITY	1,000,000	9,999,999	6
	HONEYWELL INTERNATIONAL INC-BATON ROUGE PLANT	10,000	99,999	1, 13
	MONSANTO LULING	1,000	9,999	1, 13
	OCCIDENTAL CHEMICAL HOLDING CORP - GEISMAR PLANT	50,000,000	99,999,999	1, 3, 4, 6
	SHINTECH PLAQUEMINE PLANT	100	999	1, 4, 5
	SOLVAY USA INC	100,000	999,999	6
	THE DOW CHEMICAL CO - LOUISIANA OPERATIONS	100,000	999,999	1, 5, 6, 12, 13
MD	1	100	999	1, 5
	VERSO LUKE LLC	100	999	1, 5
MI	2	110,000	1,099,998	1, 3, 5, 6, 10, 12, 13
	EES COKE BATTERY LLC	10,000	99,999	1, 5
	THE DOW CHEMICAL CO	100,000	999,999	1, 3, 5, 6, 10, 12, 13
MO	1	10,000	99,999	6
	BCP INGREDIENTS INC	10,000	99,999	6
MS	2	0	198	1, 5

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

State[a]	Number and Name of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
	GEORGIA-PACIFIC MONTICELLO LL C	0	99	1, 5
	INTERNATIONAL PAPER-VICKSBURG MILL	0	99	1, 5
NC	2	0	198	1, 5
	BLUE RIDGE PAPER PRODUCTS LLC	0	99	1, 5
	INTERNATIONAL PAPER RIEGELWOOD MILL	0	99	1, 5
NJ	2	1,100	10,998	1, 12, 13, 14
	DUPONT CHAMBERS WORKS	1,000	9,999	1, 12, 13, 14
	VEOLIA - MORSES MILL	100	999	14
NY	1	1,000,000	9,999,999	1, 3, 6
	MPM SILICONES LLC	1,000,000	9,999,999	1, 3, 6
OH	4	121,000	1,209,996	6, 9, 12, 14
	CHEMTRADE REFINERY SOLUTIONS LP	10,000	99,999	14
	HERITAGE THERMAL SERVICES	1,000	9,999	12
	PRAXAIR DISTRIBUTION INC	100,000	999,999	9
	SOLVAY SPECIALTY POLYMERS USA LLC	10,000	99,999	6
PA	1	10,000	99,999	6
	CRODA INC	10,000	99,999	6
SC	4	20,000	200,097	1, 5, 6
	SANTOLUBES MANUFACTURING LLC DBA BLACKMAN UHLER SPECIALTIES	No data	No data	No data
	HALOCARBON PRODUCTS CORP	10,000	99,999	6
	INTERNATIONAL PAPER GEORGETOWN MILL	0	99	1, 5

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

State[a]	Number and Name of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
	SUN CHEMICAL BUSHY PARK FACILITY	10,000	99,999	6
TN	1	1,000	9,999	6
	ALBEMARLE US INC	1,000	9,999	6
TX	11	3,511,000	35,110,089	1, 3, 4, 5, 6, 7, 10, 12, 13, 14
	AKZO NOBEL FUNCTIONAL CHEMICALS LLC	10,000	99,999	6
	ALBEMARLE CORP PASADENA PLANT	100,000	999,999	6
	BAKER PETROLITE BAYPORT FACILITY	100,000	999,999	6, 7
	BASF CORP - BEAUMONT	1,000,000	9,999,999	6
	EASTMAN CHEMICAL CO TEXAS OPERATIONS	0	99	1, 13
	EXXONMOBIL BAYTOWN CHEMICAL PLANT (PART)	100,000	999,999	1, 5, 10, 12, 14
	FORMOSA PLASTICS CORP TEXAS	100,000	999,999	1, 5, 13, 14
	NALCO CHAMPION - AN ECOLAB CO	1,000,000	9,999,999	6
	OLIN BLUE CUBE FREEPORT TX	1,000,000	9,999,999	1, 3, 4, 6
	SACHEM INC	100,000	999,999	6
	VEOLIA ES TECHNICAL SOLUTIONS LLC PORT ARTHUR FACILITY	1,000	9,999	12
UT	1	10,000	99,999	12
	CLEAN HARBORS ARAGONITE LLC	10,000	99,999	12
WA	1	1,000,000	9,999,999	1, 5
	LONGVIEW FIBRE PAPER & PACKAGING INC	1,000,000	9,999,999	1, 5
WI	4	210,100	2,100,996	1, 5, 6
	CHEMDESIGN PRODUCTS INC	10,000	99,999	6

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

State[a]	Number and Name of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
	EVONIK INDUSTRIES	100,000	999,999	6
	EVONIK MATERIALS CORP	100,000	999,999	6
	WISCONSIN RAPIDS PULP MILL	100	999	1, 5
WV	1	10,000	99,999	1, 5, 6
	MPM SILICONES LLC	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. Product
2. Import
3. Used Processing
4. Sale/ Distribution
5. Byproduct
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacture Aid
12. Ancillary
13. Manufacture Impurity
14. Process Impurity

Source: TRI17 2018; Data are from 2017

5.2.2 Import/Export

Exports of chloromethane from the U.S. are considerably larger than imports. In the period from 2014 to 2018, general imports[2] and imports for consumption[3] of chloromethane were equal. 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

[2] General imports are total physical arrivals of chloromethane to the United States from other countries that either enter consumption channels immediately or enter into 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 (U.S. Census Bureau 2018). 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).

[3] Imports for consumption are the total amount of merchandise that has physically cleared through customs by either entering consumption channels immediately or leaving bonded warehouses or FTZs (U.S. Census Bureau 2018).

exports[4] of chloromethane fluctuated from 2014 to 2018, ranging from 22,042,539 kg in 2015 to 10,430,816 kg in 2017 (USITC 2019). U.S. total exports[5] of chloromethane also fluctuated from 2014 to 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 2019; 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 2019). 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 2019). 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 individual who were being exposed (McNally 1946). At the present time, virtually all of the 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 (CDR 2016). Industry function categories include laboratory chemicals, intermediates, adhesives and sealant chemicals, paint additives, and coating additives not described by other categories (CDR 2016).

According to CDR data for 12 sites, 4 report chloromethane use for commercial and 3 report for both commercial and consumer use (CDR 2016). Product categories for consumer and commercial use include adhesives and sealants; fabric, textile, and leather products not covered elsewhere; paints and coatings;

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[4] 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).

[5] 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).

personal care products; and plastic and rubber products not covered elsewhere (CDR 2016). Of these twelve sites, six reported that chloromethane is not used in children's products (CDR 2016).

5.2.4 Disposal

Of 22 sites that reported industrial processing and use of chloromethane in 2016, four reported that the chemical was recycled and four reported that it was not (CDR 2016). In 2012, one of 22 sites reported that chloromethane was recycled while five of 22 reported that it was not (CDR 2012).

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

Limited information was located 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 2018). 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's North American Industry Classification System (NAICS) codes is covered under EPCRA Section 313 or is a federal facility; and if their facility manufactures (defined to include importing) or processes any TRI chemical in excess of 25,000 pounds, or otherwise uses any TRI chemical in excess of 10,000 pounds, in a calendar year (EPA 2018).

According to the Toxics Release Inventory (TRI), in 2017, a total of 1,094,537 pounds (496,474 kilograms) of chloromethane was released to the environment from 66 processing facilities (TRI17 2018). This total consists of chloromethane released to air (955,937 pounds), water (6661 pounds), soil (31 pounds), and via underground injection (131,890 pounds). Table 5-2 lists the amounts released to the environment in each state. In addition, there were no releases from manufacturing and processing facilities to POTWs and an estimated 5,811 pounds (2,636 kg) were transferred off-site (TRI17 2018).

Chloromethane has been identified in a variety of environmental media (air, surface water, groundwater, soil, and sediment) collected at 236 of the 1,867 current and former NPL hazardous waste sites (ATSDR 2019).

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
TX	11	349,041	21	14,800	5,806	0	363,878	5,790	369,668
LA	12	46,208	3	74,660	0	0	120,871	0	120,871
MS	2	76,976	434	0	0	0	77,410	ND	77,410
SC	4	68,714	0	0	0	0	68,714	ND	68,714
WI	4	57,298	0	0	0	0	57,298	ND	57,298
AR	2	56,112	0	0	10	0	56,122	ND	56,122
IL	4	51,260	0	0	4	0	51,260	4	51,264
KS	1	5,602	0	42,430	0	2	48,032	2	48,034
NC	2	47,920	1	0	1	0	47,922	ND	47,922
FL	2	46,413	0	0	0	16	46,413	16	46,429
NY	2	35,372	15	0	0	0	35,387	ND	35,387
KY	2	30,340	49	0	0	0	30,389	ND	30,389
WA	1	26,790	0	0	0	0	26,790	ND	26,790
MI	2	25,100	130	0	0	0	25,230	ND	25,230
OH	4	19,250	0	0	0	0	19,250	ND	19,250
GA	1	6,500	7	0	0	0	6,507	ND	6,507

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
WV	1	5,311	211	0	0	0	5,522	ND	5,522
NJ	2	703	0	0	0	0	703	ND	703
TN	1	609	0	0	0	0	609	ND	609
UT	1	238	0	0	0	0	238	0	238
PA	1	167	0	0	0	0	167	ND	167
AL	2	13	0	0	0	0	13	ND	13
MO	1	0	0	0	0	0	0	ND	0
CA	1	ND	ND	ND	ND	ND	ND	ND	ND
Total	66	955,937	871	131,890	5,821	18	1,088,725	5,812	1,094,537

[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 by a given facility.
[f] The sum of on-site surface water discharges, and off-site transfers to wastewater treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g] The sum of on-site and off-site disposal to underground injection wells (Class I wells and Class II-V).
[h] The sum of on-site and off-site disposal to: Resource Conservation and Recovery Act (RCRA) subtitle C landfills, other landfills, RCRA subtitle C surface impoundments, other surface impoundments, land treatment, other land disposal.
[i] Includes the sum of off-site transfers to: storage only, solidification/stabilization (metals only) disposal, other off-site management, waste broker for disposal, unknown.
[j] Total on-site disposal or other releases of the chemical including emissions to air, surface water discharges, land and underground injection wells.
[k] Total amount of chemical transferred off-site for disposal or other releases, including to POTWs.

ND = No data; RF = Reporting Facilities; UI = Underground Injection

Source: TRI17 2018; Data are from 2017

5.3.1 Air

Estimated releases of 955,937 pounds (~434 metric tons) of chloromethane to the atmosphere from 64 domestic manufacturing and processing facilities in 2017, accounted for about 87% of the estimated total environmental releases from facilities required to report to the TRI (TRI17 2018). These releases are summarized in Table 5-3.

Table 5-3. Releases to the Atmosphere from Facilities that Produce, Process, or Use Chloromethane[a]

		Reported amounts released in pounds per year[b]	
Facility	State	Fugitive Air Emissions	Point Source Air Emissions
EASTMAN CHEMICAL CO TEXAS OPERATIONS	TX	63	233,920

Table 5-3. Releases to the Atmosphere from Facilities that Produce, Process, or Use Chloromethane[a]

		Reported amounts released in pounds per year[b]	
Facility	State	Fugitive Air Emissions	Point Source Air Emissions
EXXONMOBIL BAYTOWN CHEMICAL PLANT (PART)	TX	86,000	1,200
MONSANTO LULING	LA	1,888	7,000
INTERNATIONAL PAPER GEORGETOWN MILL	SC	0	68,714
EVERGREEN PACKAGING	AR	8	56,084
GEORGIA-PACIFIC MONTICELLO LLC	MS	5	48,696
OCCIDENTAL CHEMICAL CORP	KS	3,831	1,771
WESTROCK CP LLC	FL	2	46,371
INTERNATIONAL PAPER RIEGELWOOD MILL	NC	17	38,929
WISCONSIN RAPIDS PULP MILL	WI	0	35,797
AKZO NOBEL SURFACE CHEMISTRY LLC	IL	12,823	19,219
VERSO LUKE LLC	NY	0	30,022
INTERNATIONAL PAPER-VICKSBURG MILL	MS	0	28,275
DOW SILICONES CORP	KY	7,100	20,100
LONGVIEW FIBRE PAPER & PACKAGING INC	WA	0	26,790
SOLVAY SPECIALTY POLYMERS USA LLC	OH	12,793	6,237
FORMOSA PLASTICS CORP TEXAS	TX	0	17,991
NALCO CHAMPION - AN ECOLAB CO	TX	1,566	250
EXXONMOBIL BATON ROUGE CHEMICAL PLANT (PART)	LA	14,000	2,500
GALATA CHEMICALS LLC - GALATA TAFT FACILITY	LA	1,167	4,523
THE DOW CHEMICAL CO	MI	1,100	12,000
EVONIK CORP	IL	1,614	11,080
EES COKE BATTERY LLC	MI	0	12,000
EVONIK MATERIALS CORP	WI	229	9,830
BASF CORP - BEAUMONT	TX	3,501	234
BLUE RIDGE PAPER PRODUCTS LLC	NC	4	8,970
LONZA INC	IL	157	6,367
CHEMTALL INC	GA	2,900	3,600
THE DOW CHEMICAL CO - LOUISIANA OPERATIONS	LA	756	5,337
OCCIDENTAL CHEMICAL HOLDING CORP - GEISMAR PLANT	LA	3,669	2,419
EVONIK INDUSTRIES	WI	905	5,108
MPM SILICONES LLC	WV	4,907	404
CHEMDESIGN PRODUCTS INC	WI	86	5,343

Table 5-3. Releases to the Atmosphere from Facilities that Produce, Process, or Use Chloromethane[a]

		Reported amounts released in pounds per year[b]	
Facility	State	Fugitive Air Emissions	Point Source Air Emissions
MPM SILICONES LLC	NY	250	5,100
PMC ORGANOMETALLIX INC	KY	494	2,646
OLIN BLUE CUBE FREEPORT TX	TX	1,851	83
BLUE CUBE OPERATIONS LLC - PLAQUEMINE SITE	LA	1,392	374
ALBEMARLE CORP PASADENA PLANT	TX	1,622	21
DUPONT CHAMBERS WORKS	NJ	0	702
ALBEMARLE US INC	TN	609	0
SACHEM INC	TX	589	6
HONEYWELL INTERNATIONAL INC-BATON ROUGE PLANT	LA	262	235
SOLVAY USA INC	LA	424	0
CLEAN HARBORS ARAGONITE LLC	UT	238	0
PRAXAIR DISTRIBUTION INC	OH	41	169
CRODA INC	PA	10	156
BASF CORP	LA	57	98
AKZO NOBEL FUNCTIONAL CHEMICALS LLC	TX	37	86
AXIALL LLC	LA	42	11
SHINTECH PLAQUEMINE PLANT	LA	0	41
SIVANCE LLC	FL	0	40
FUTUREFUEL CHEMICAL CO	AR	13	7
BAKER PETROLITE BAYPOR FACILI TY	TX	0	15
ECO-SERVICES OPERATIONS	LA	12	0
CHEMTRADE REFINERY SOLUTIONS LP	OH	5	5
AMVAC CHEMICAL CO	AL	5	5
VEOLIA ES TECHNICAL SOLUTIONS LLC PORT ARTHUR FACILITY	TX	6	0
EVONIK CORP	AL	1	2
VEOLIA - MORSES MILL	NJ	1	0
HERITAGE THERMAL SERVICES	OH	0	0
SUN CHEMICAL BUSHY PARK FACILITY	SC	0	0
HALOCARBON PRODUCTS CORP	SC	0	0
BCP INGREDIENTS INC	MO	0	0
SANTOLUBES MANUFACTURING LLC DBA BLACKMAN UHLER SPECIALTIES	SC	No data	No data
RHO CHEMICAL CO INC	IL	No data	No data

Table 5-3. Releases to the Atmosphere from Facilities that Produce, Process, or Use Chloromethane[a]

		Reported amounts released in pounds per year[b]	
Facility	State	Fugitive Air Emissions	Point Source Air Emissions
AMVAC CHEMICAL CORP	CA	No data	No data

[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.

Source: TRI17 2018; Data are from 2017

Chloromethane has been identified in air samples collected at 23 of the 236 NPL hazardous waste sites at which it was detected in one or more environmental media (ATSDR 2017ATSDR 2019). The geometric mean of maximum concentrations in air at these sites was 0.0029 ppm (0.006 mg/m^3).

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 waste waters 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 (parts per trillion) 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 (Rhew et al. 2000; Cox et al. 2004), wetlands (Keppler et al. 2005), dead or senescent plant material (Derendorp et al. 2012) and tropical vegetation (Yokouchi et al. 2002; Yokouchi et al. 2000; Yokouchi et al. 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 to 33 ppbv or less than .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 4000 to 5000 Gg (8,818,490,487 to 11,023,113,109 pounds) (Keppler et al. 2005). Total releases to environmental media estimated from the 2018 TRI are around 955,937 pounds (~433,606 kg) (TRI17 2018). Thus, more 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 less than 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) estimate 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 grams 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 µg/m^3) (Woodruff et al. 1998) to 0.87 ppm (1.8 µg/m^3) (Logue et al. 2012). Chloromethane concentrations are often in excess of rural background concentrations in the ambient air of cities in the United States (Singh H.B. et al. 1982; Singh H.B. et al. 1983) (see Section 5.5.1). The authors suggested that this elevation may be the result of manufacturing or other anthropogenic emission sources in the urban areas, over and beyond releases from combustion or other background sources that would determine the levels in more rural areas. However, concentrations of chloromethane in air monitored by EPA in 2018 show that mean concentrations were highest in Florida, Michigan, Arizona, Delaware, and Washington D.C. (EPA 2018l), while only Florida and Michigan are accounted for in TRI (TRI17 2018). This suggests that emissions from sources aside from manufacturing contribute to chloromethane in the air in many states. 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.

5.3.2 Water

Estimated releases of 871 pounds (~.40 metric tons) of chloromethane to surface water from 14 domestic manufacturing and processing facilities in 2017, accounted for about 0.08% of the estimated total environmental releases from facilities required to report to the TRI (TRI17 2018).

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 2017ATSDR 2019). The geometric mean of maximum concentrations at these sites was 0.013 mg/L.

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 a number of 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 hydrochloric acid [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 probably 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 waste water effluents, possibly as a result of its formation (EPA 1975) or incomplete removal during industrial waste water 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 31 pounds (~.014 metric tons) of chloromethane to soils from 8 domestic manufacturing and processing facilities in 2017, accounted for about 0.003% of the estimated total environmental releases from facilities required to report to the TRI (TRI17 2018). An additional 131,890 million pounds (~60 metric tons), constituting about 12% of the total environmental emissions, were released via underground injection (TRI17 2018). These releases are summarized in Table 5-4.

Table 5-4. Releases to Soil from Facilities that Produce, Process, or Use Chloromethane[a]

		Reported amounts released in pounds per year[b]	
Facility	State	Underground Injection Class I Wells	Underground Injection Class II-V Wells
EASTMAN CHEMICAL CO TEXAS OPERATIONS	TX	0	0
EXXONMOBIL BAYTOWN CHEMICAL PLANT (PART)	TX	0	0
MONSANTO LULING	LA	67,000	0
INTERNATIONAL PAPER GEORGETOWN MILL	SC	0	0
EVERGREEN PACKAGING	AR	0	0
GEORGIA-PACIFIC MONTICELLO LLC	MS	0	0
OCCIDENTAL CHEMICAL CORP	KS	42,430	0
WESTROCK CP LLC	FL	0	0
INTERNATIONAL PAPER RIEGELWOOD MILL	NC	0	0
WISCONSIN RAPIDS PULP MILL	WI	0	0
AKZO NOBEL SURFACE CHEMISTRY LLC	IL	0	0
VERSO LUKE LLC	NY	0	0
INTERNATIONAL PAPER-VICKSBURG MILL	MS	0	0
DOW SILICONES CORP	KY	0	0
LONGVIEW FIBRE PAPER & PACKAGING INC	WA	0	0
SOLVAY SPECIALTY POLYMERS USA LLC	OH	0	0
FORMOSA PLASTICS CORP TEXAS	TX	0	0
NALCO CHAMPION - AN ECOLAB CO	TX	14,800	0
EXXONMOBIL BATON ROUGE CHEMICAL PLANT (PART)	LA	0	0
GALATA CHEMICALS LLC - GALATA TAFT FACILITY	LA	7,660	0
THE DOW CHEMICAL CO	MI	0	0
EVONIK CORP	IL	0	0
EES COKE BATTERY LLC	MI	0	0
EVONIK MATERIALS CORP	WI	0	0
BASF CORP - BEAUMONT	TX	0	0

Table 5-4. Releases to Soil from Facilities that Produce, Process, or Use Chloromethane[a]

		Reported amounts released in pounds per year[b]	
Facility	State	Underground Injection Class I Wells	Underground Injection Class II-V Wells
BLUE RIDGE PAPER PRODUCTS LLC	NC	0	0
LONZA INC	IL	0	0
CHEMTALL INC	GA	0	0
THE DOW CHEMICAL CO - LOUISIANA OPERATIONS	LA	0	0
OCCIDENTAL CHEMICAL HOLDING CORP - GEISMAR PLANT	LA	0	0
EVONIK INDUSTRIES	WI	0	0
MPM SILICONES LLC	WV	0	0
CHEMDESIGN PRODUCTS INC	WI	0	0
MPM SILICONES LLC	NY	0	0
PMC ORGANOMETALLIX INC	KY	0	0
OLIN BLUE CUBE FREEPORT TX	TX	0	0
BLUE CUBE OPERATIONS LLC - PLAQUEMINE SITE	LA	0	0
ALBEMARLE CORP PASADENA PLANT	TX	0	0
DUPONT CHAMBERS WORKS	NJ	0	0
ALBEMARLE US INC	TN	0	0
SACHEM INC	TX	0	0
HONEYWELL INTERNATIONAL INC-BATON ROUGE PLANT	LA	0	0
SOLVAY USA INC	LA	0	0
CLEAN HARBORS ARAGONITE LLC	UT	0	0
PRAXAIR DISTRIBUTION INC	OH	0	0
CRODA INC	PA	0	0
BASF CORP	LA	0	0
AKZO NOBEL FUNCTIONAL CHEMICALS LLC	TX	0	0
AXIALL LLC	LA	0	0
SHINTECH PLAQUEMINE PLANT	LA	0	0
SIVANCE LLC	FL	0	0
FUTUREFUEL CHEMICAL CO	AR	0	0
BAKER PETROLITE BAYPOR FACILI TY	TX	0	0
ECO-SERVICES OPERATIONS	LA	0	0
CHEMTRADE REFINERY SOLUTIONS LP	OH	0	0
AMVAC CHEMICAL CO	AL	0	0
VEOLIA ES TECHNICAL SOLUTIONS LLC PORT ARTHUR FACILITY	TX	0	0
EVONIK CORP	AL	0	0
VEOLIA - MORSES MILL	NJ	0	0
HERITAGE THERMAL SERVICES	OH	0	0
SUN CHEMICAL BUSHY PARK FACILITY	SC	0	0
HALOCARBON PRODUCTS CORP	SC	0	0
BCP INGREDIENTS INC	MO	0	0

Table 5-4. Releases to Soil from Facilities that Produce, Process, or Use Chloromethane[a]

		Reported amounts released in pounds per year[b]	
Facility	State	Underground Injection Class I Wells	Underground Injection Class II-V Wells
SANTOLUBES MANUFACTURING LLC DBA BLACKMAN UHLER SPECIALTIES	SC	No data	No data
RHO CHEMICAL CO INC	IL	No data	No data
AMVAC CHEMICAL CORP	CA	No data	No data

[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.

Source: TRI17 2018; Data are from 2017

Chloromethane is probably 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 has been identified in the soil of 11 of the 236 NPL hazardous waste sites at which it was detected in one or more environmental media (ATSDR 2019). The geometric mean of maximum concentrations at these sites was 0.058 mg/kg.

A significant source of release of chloromethane to soil in tropical locations comes from wood-rotting fungi (Moore et al. 2005).

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 H.B. et al. 1979; Singh H.B. et al. 1982; Singh H.B. et al. 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 located in the literature.

Water. The dominant transport process from water will be volatilization. The results of two EXAMS model runs 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 waste water and in the air above the waste water at the Memphis North Wastewater Treatment Plant in Memphis, Tennessee. Based on the estimated log octanol/water partition coefficient and the sorption coefficient and BCF calculated from it (see Table 4-2.), chloromethane is not expected to concentrate in sediments or in biota.

Sediment and Soil. In soil, the dominant transport mechanism for chloromethane present near the surface probably will be volatilization (based on its Henry's law constant, water solubility, and vapor pressure), but no experimental information was located in the literature to confirm this. The actual volatilization rate for a chemical in soil is influenced by a number of factors, including surface roughness, soil type, rainfall, leaching, depth of incorporation, temperature, and ground cover (Jury et al. 1987). Since chloromethane is not expected to sorb to soils, any 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 H.B. et al. 1979). These studies estimate

the half-life to be in the neighborhood of 1 year, with values ranging 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. Additionally, Tsai et al. (2017) estimates that chloromethane has an atmospheric lifetime of 1 year. Such values suggest that transport is likely.

Water. In water, chloromethane can degrade by hydrolysis or by biodegradation. Although few data are available on the biodegradation of chloromethane in water, neither hydrolysis nor biodegradation in surface waters appears to be rapid when compared with volatilization. Chloromethane hydrolysis proceeds via an SN2 mechanism (bi-molecular) in which no intermediate ions are formed, and methanol and HCl are the only products. The kinetics of chloromethane hydrolysis have been measured by Heppolette and Robertson (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 $7.6x10^{-7}$ sec^{-1}, with a half-life of 10.6 days. When extrapolated to 20 °C and neutral conditions using the thermodynamic constants calculated by Heppolette and Robertson (1959), a rate constant was calculated of $1.04x10^{-8}$ sec^{-1} with a half-life of ≈ 2.1 years. More recent 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: $k(in\ s^{-1})=9.5x10^{10}e^{-12,800/T}$. 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). The hydrolysis half-lives are too long to be of environmental significance in surface waters, considering the rapid volatilization of chloromethane from surface water (Mabey and Mill 1978). In groundwater, however, hydrolysis may be the only degradation mechanism available and, hence, may be a more significant factor. Biodegradation may also occur in groundwater, but rates are thought to be highly variable.

Very little information is available concerning the biodegradation of chloromethane in water. In studies involving such bacteria as *Methylococcus capsulatus,* formaldehyde was a product of chloromethane biodegradation (Stirling and Dalton 1979). In pure culture conditions, some microbial strains can degrade chloromethane. Hartmans et al. (1986) reported that pure cultures of a *Hyphomicrobium sp.* were obtained with a chloromethane-minima1 medium. Abiotic hydrolytic dehalogenation was not significant, so that the observed cell growth and chloride formation confirmed biodegradation as the predominant transformation process (Hartmans et al. 1986). Since these laboratory conditions do not commonly occur in the environment, these same species may not degrade chloromethane in the environment to any significant degree. Biodegradation of chloromethane, however, cannot be ruled out based on the available

information. As with reactions of other chloroalkanes, chloromethane may degrade anaerobically via reductive dechlorination to form methane (Vogel et al. 1987).

Sediment and Soil. Very limited information concerning soil transformation and degradation of chloromethane was located 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 suggests that members of the so-called white rot fungus family may degrade (mineralize) chloromethane (Harper et al. 1990). These same fungi (especially *Phanerochaete 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.

Doronina et al. (1996) isolated eight strains of non-methane-utilizing bacteria that are able to grow on 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. 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.

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. The biochemistry of chloroaliphatics degradation in the newer aerobic isolates is largely unexplored, but progress has been made in understanding some of the anaerobic dehalogenation reactions (Leisinger 1996).

Other Media. Six new *Hyphomicrobium* strains, strain CMC related to *Aminobacter* spp, two previously isolated bacteria CC495 and IMB-1, and a Gram-positive isolate related to *Nocardiodides* spp. from a variety of pristine terrestrial, freshwater, estuarine, and marine environments were determined as chloromethane utilizing bacteria (McAnulla et al. 2001).

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 5-5 shows the limit of detections typically achieved by analytical analysis in environmental media. Presented in Table 5-6 is a summary of the range of concentrations detected in environmental media (Table 5-5 and Table 5-6).

Table 5-5. 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 1986c
Secondary treated effluent	.066 µg/L	Rodriguez et al. 2012
Exhaled Air	243 pptv/200mL	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	1mg/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 5-6. 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
Air (ppbv)	1.04	3.29	24.0	32	23

[a] Concentrations found in ATSDR site documents from 1981 to 2019 for 1,867 NPL sites (ATSDR 2019). 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 has been the subject of numerous studies conducted to determine the atmospheric chloride balance. A volatile organic carbon (VOC) database reported by Shah and Singh (Shah and Singh 1988) contained 706 data points (300 cities from 42 states). The average value is higher than the upper quartile (75% value) and may be skewed because of a few high values or because the underlying distribution is approximately lognormal as are many distributions of environmental concentration values. Thus, the median may be a better summary representation of chloromethane concentration. The data were also grouped by types of air mass so that the influence of urban centers could be estimated. From these data, it appears that source contributions from industrial processes do not have a significant impact on the ambient concentration of chloromethane, although some elevation may occur. There are fewer data points, however, for rural/remote data than for urban/suburban data, so a direct comparison is difficult. Average urban levels reported by Singh et al. (Singh H.B. et al. 1982; Singh H.B. et al. 1983) were 660-960 ppt, while background levels were 600-700 ppt. For these results, the ambient air levels of chloromethane in cities in the United States may be slightly elevated from background levels, due to the higher numbers of combustion sources.

In accordance with provisions of the Clean Air Act Amendments (CAAAs) of 1990, chloromethane (or methyl chloride) was among 189 compounds designated as hazardous air pollutants (HAPS). Aside from the public health impacts from direct exposures to these chemicals, most of the HAPS are VOCs that, in combination with other air pollutants, can lead to the formation of ozone and photochemical smog. The EPA has collected available ambient measurements to compile an HAP database (Kelly et al. 1994). This database adds monitoring information to earlier databases that focused on VOCs. The national median ambient air concentration from the HAP database for chloromethane is 1.3 µg/m^3 (629 ppt [v/v]).

Data from the EPA Air Quality System (AQS) database were used to calculate the annual mean percentile distributions of chloromethane from multiple monitoring locations across the nation for the years 2014–2018 (EPA 2018b). The results of these data are summarized in Table 5-7. The AQS database is EPA's source of criteria air pollutant and hazardous air pollutant (HAP) monitoring data. Monitoring data for other years may be obtained directly from the EPA AQS website.

Table 5-7. Percentile Distribution of Annual Mean Chloromethane Concentrations (ppbv) Measured in Ambient Air at Locations Across the United States

Year	Number of US locations	25th	50th	75th	95th	Maximum
2014	230	0.53	0.60	0.63	0.73	1.86
2015	180	0.54	0.59	0.63	0.71	2.24
2016	163	0.52	0.57	0.61	0.81	2.33
2017	156	0.52	0.56	0.62	0.71	1.35
2018	127	0.51	0.60	0.63	1.12	1.41

Source: EPA 2018b

Several studies have been conducted to measure chloromethane concentrations in outdoor air at specific locations. The results of these studies are summarized in Table 5-8.

Table 5-8. Outdoor Air Monitoring Data for Chloromethane

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Reference
Del Norte, Albuquerque, NM	Not specified	Not specified	0.1-15.3 ppbv	1.1 ppbv	Kavouras et al. 2015
North Valley, Albuquerque, NM	Not specified	Not specified	0.4-5.1 ppbv	1.1 ppbv	Kavouras et al. 2015
South Valley, Albuquerque, NM	Not specified	Not specified	0.1-2.7 ppbv	0.7 ppbv	Kavouras et al. 2015
Baton Rouge, LA	Urban	9/96-8/97	Not specified	0.537 ppbv	Mohamed et al. 2002
Brownsville, TX	Urban	9/96-8/97	Not specified	1.222 ppbv	Mohamed et al. 2002
Brattleboro, VT	Urban	9/96-8/97	Not specified	0.511 ppbv	Mohamed et al. 2002
Burlington, VT	Urban	9/96-8/97	Not specified	0.495 ppbv	Mohamed et al. 2002
Camden, NJ	Urban	9/96-8/97	Not specified	0.542 ppbv	Mohamed et al. 2002
El Paso, TX	Urban	9/96-8/97	Not specified	0.676 ppbv	Mohamed et al. 2002
Garyville, LA	Urban	9/96-8/97	Not specified	0.641 ppbv	Mohamed et al. 2002
Galveston, TX	Urban	9/96-8/97	Not specified	0.952 ppbv	Mohamed et al. 2002
Hahnville, LA	Urban	9/96-8/97	Not specified	0.576 ppbv	Mohamed et al. 2002
Port Neches, TX	Urban	9/96-8/97	Not specified	1.093 ppbv	Mohamed et al. 2002
Rutland, VT	Urban	9/96-8/97	Not specified	0.483 ppbv	Mohamed et al. 2002
Underhill, VT	Urban	9/96-8/97	Not specified	0.481 ppbv	Mohamed et al. 2002
Winooski, VT	Urban	9/96-8/97	Not specified	0.526 ppbv	Mohamed et al. 2002
Flag Plaza, Pittsburgh, PA	Not specified	2/4/06-1/19/08	1.14-1.57 µg/m3	0.00065 ppm (1.34 µg/m^3)	Logue et al. 2012
South Fayette, Pittsburgh, PA	Not specified	2/4/06-1/19/08	1.03-1.47 µg/m3	0.0006 ppm (1.23 µg/m^3)	Logue et al. 2012

Table 5-8. Outdoor Air Monitoring Data for Chloromethane

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Reference
Avalon, Pittsburgh, PA	Not specified	2/4/06-1/19/08	1.03-1.40 µg/m3	0.00059 ppm(1.22 µg/m$^{3)}$	Logue et al. 2012
Stowe, Pittsburgh, PA	Not specified	2/4/06-1/19/08	1.04-1.44 µg/m3	0.00061 ppm (1.25 µg/m^3)	Logue et al. 2012
Houston, TX	Urban/suburban	5/15-24/80	531-1,015 ppt	955 ppt	Singh H.B. et al. 1982
St. Louis, MO	Urban/suburban	5/30/80-6/8/80	519-1,157 ppt	732 ppt	Singh H.B. et al. 1982
Denver, CO	Urban/suburban	6/16-26/80	437-1,593 ppt	763 ppt	Singh H.B. et al. 1982
Riverside, CA	Urban/suburban	7/2-12/80	437-1,593 ppt	703 ppt	Singh H.B. et al. 1982
Staten Island, NY	Urban/suburban	3/27/80-4/5/80	466-1,280 ppt	701 ppt	Singh H.B. et al. 1982
Pittsburgh, PA	Urban/suburban	4/8-16/80	450-852 ppt	665 ppt	Singh H.B. et al. 1982
Chicago, IL	Urban/suburban	4/21-30/80	575-1,311 ppt	856 ppt	Singh H.B. et al. 1982
Los Angeles, CA	Urban/suburban	4/29/76-5/4/76	708-944 ppt	834 ppt	Singh H.B. 1977
Stanford Hills, CA	Urban/suburban	11/24-30/75	700-1,700 ppt	1,022 ppt	Singh H.B. 1977
Pullman, WA	Rural/remote	12/74-2/75	503-566 ppt	530 ppt	Grimsrud and Rasmussen 1975
Alaska	Rural/remote	5/24-30/75	505-970 ppt	Not specified	Robinson et al. 1977
Point Barrow, AK	Rural/remote	5/7 & 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, CA	Rural/remote	12/2-12/75	680-1,700a ppt	1,260 ppt	Singh et al. 1977
Yosemite Park, CA	Rural/remote	5/12-17/75	654-999 ppt	713 ppt	Singh et al. 1977
Palm Springs, CA	Rural/remote	5/24-27/76	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 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 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 apparently is 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 less than 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).

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. Seven positive detections of chloromethane in industrial effluents out of more than 4,000 samples from 46 industrial categories and subcategories were reported in the EPA database (Bursey and Pellizzari 1983). Concentrations ranged from 6 to 4,194 mg/L in these effluents. Thirty-four 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.

In a study of groundwater samples from 479 active waste disposal sites, chloromethane was detected at 20 (Plumb Jr. 1991). 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. 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. Chloromethane appears to be a constituent of both municipal and industrial waste landfills. In these landfills, volatilization may be hindered and leaching to groundwater could become an important transport pathway. Chloromethane may also be a product from the anaerobic metabolism of higher chlorinated methane present in the soil (Vogel et al. 1987).

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). Table 5-9 shows surface water monitoring data for chloromethane, Table 5-10 represents groundwater monitoring data for chloromethane. Table 5-12 contains most recent data from landfill

leachate monitoring data for chloromethane and Table 5-13 contains effluent monitoring data for chloromethane.

Table 5-9. Surface Water Monitoring Data for Chloromethane

Location(s)	Type	Date(s)	Range (ng/L)	Mean concentration (ng/L)	Notes	Reference
38 streams in 24 states and Puerto Rico	34 urban/ agricultural impacted sites 4 undeveloped sites	November 2012 – June 2014	Not detected	Not detected		Bradley et al. 2017
Delaware River and Raritan Canal	Not specified	Not specified	Not detected	Not specified		Grantsrom et al. 1984
Lake Ontario	Not specified	Not specified	Detected	Not specified		Great Lakes Water Quality Board 1981
Surface Waters in New Jersey	Not specified	Not specified	<0.1-222	Not specified	605 samples were analyzed	Page 1981

Table 5-10. Groundwater Monitoring Data for Chloromethane

Location(s)	Type	Date(s)	Range (ng/L)	Mean concentration (ng/L)	Notes	Reference
New Jersey	Not specified	Not specified	<0.1-6	Not specified	1,058 samples from 408 wells were analyzed	Page 1981; Greenberg et al. 1982
Minnesota	Not specified	Not specified	Detected	Not specified	13 samples of groundwater were taken from under municipal solid waste landfills	Sabel and Clark 1984
Minnesota	Not specified	Not specified	Detected	Not specified	7 samples were analyzed	Sabel and Clark 1984
Massachusetts	Not specified	Not specified	Detected	44		Burmaster 1982

Table 5-11. Drinking Water Monitoring Data for Chloromethane

Location(s)	Type	Date(s)	Range (µg/L)	Mean concentration (µg/L)	Notes	Reference
Tap Water Sites in CA, CO, FL, IA, KS, MI, NJ, OK, OR, SC, and VA	Tap Water	May-September 2016	ND – 0.269	0.194	Limit of Quantification = 0.1 µg/L Chloromethane was detected in 6 of 26 sites	Bradley et al. 2018
Cincinnati, OH	Not specified	Not specified	Detected	Not specified		Kopfler et al. 1977

ND = not detected

Table 5-12. Landfill Leachate Monitoring Data for Chloromethane

Location(s)	Type	Date(s)	Range (ng/L)	Mean concentration (ng/L)	Notes	Reference
Minnesota	Not specified	Not specified	Detected	Not specified	Samples of municipal solid waste leachate were analyzed	Sabel and Clark 1984
Wisconsin	Not specified	Not specified	170	170	Samples of municipal solid waste leachate were analyzed	Sabel and Clark 1984
Love Canal, NY	Not specified	Not specified	180	180	Samples were from industrial landfill	Shuckrow et al. 1982
Kin-Buc Landfill, NJ	Not specified	Not specified	3.1	3.1	Samples were from industrial landfill	Shuckrow et al. 1982

Table 5-13. Effluent Monitoring Data for Chloromethane

Location(s)	Type	Date(s)	Range (ng/L)	Mean concentration (ng/L)	Notes	Reference
Petroleum refinery effluents	Not specified	Not specified	<100 - >100	Not specified	17 samples of biotreatment effluents were analyzed	Snider and Manning 1982
Petroleum refinery effluents	Not specified	Not specified	<10	Not specified	17 samples of final effluent were analyzed	Snider and Manning 1982

5.5.3 Sediment and Soil

Information from ATSDR (2019) documents the presence of chloromethane in soils at 28 waste sites and in sediments at 16 waste sites. 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 a number of fungi (Harper 1988), and to its presence in both landfill leachate and groundwater.

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; Sleiman et al. 2014; Filipiak et al. 2012; Novak et al. 2008; Keppler et al. 2005; Liu et al. 2017; Xing et al. 2018; Steinemann 2015). 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). 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).

Chloromethane was present in the expired air of all 3 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 non-smokers and smokers, and suggest that concentrations are influenced by environmental pollutants, food and beverages, and smoking-related compounds (Filipiak et al. 2012). Keppler (2017) estimates that based on testing of 31 human subjects ages 3 to 87, all subjects exhaled between 2.5 to 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 intakes of ≈ 140.4, 108.6, and 59.7 µg/day, respectively (Singh H.B. et al.

1981a), 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 probably found at very low concentrations 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 all times, 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 volatile organic chemicals (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 to 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. Of the 236 current or past NPL sites (ATSDR 20179) showing site contamination with chloromethane, 174 (about 74%) also showed site contamination related to vinyl chloride.

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 gestation day17 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 gestation day19 to 1500 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 present in 2 of 8 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 source of the chloromethane in the milk.

Parents can inadvertently carry certain hazardous materials home from work on their clothes, shoes, skin, hair, tools, and in their vehicles. However, since chloromethane is so 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 are probably 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 236 NPL hazardous waste sites where chloromethane has been detected in environmental media (ATSDR 2017ATSDR 2019). The geometric mean of maximum concentrations in air at the 23 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 (Woodruff et al. 1998; Logue et al. 2012). 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 National Institute for Occupational Safety and Health's (NIOSH's) 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 Jr. 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). The majority 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. A number of 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 and 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 duration. The evidence on chloromethane's carcinogenicity is mixed in epidemiological studies (Barry et al. 2011; Dosemeci et al. 1999; Holmes et al. 1986; Jiao et al. 2012; 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 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).

Jiao et al. (2012) found that the job matrix used in their study had insufficient statistical power to evaluate effects of chloromethane, so they combined all chlorinated solvents and found an association with NHL for women with two specific genotypes. 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.

There have been no studies to determine if children are more or less susceptible than adults to adverse health effects from a given amount or duration of exposure to chloromethane. In a study on experimental animals, Wolkowski-Tyl et al. (Wolkowski-Tyl et al. 1983b; Wolkowski-Tyl et al. 1983a) demonstrated there may be adverse impacts on the developing heart, though the technique used in the study to section the heart raises questions about the validity of the result. There is no direct information on the potential movement of chloromethane or its metabolites across the placenta in humans and into the developing young; information is limited on the potential transplacental transfer in animals. However, Wolkowski-Tyl et al. (Wolkowski-Tyl et al. 1983b; 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 gestation day17 had significant NPSH concentration reductions in both dams and fetuses, indicative of transplacental passage of chloromethane or its metabolites. Chloromethane has been measured in 2 of 8 samples of human breast milk, however the source of the chloromethane is not known (Pellizzari et al. 1982), Additionally, it is not known whether chloromethane or its metabolites can migrate into breast milk.

A number of studies have evaluated the health effects of chloromethane exposure in animals for the inhalation route, although only a single comprehensive chronic study in rats and mice has been performed (CIIT 1981). Health effects of acute, intermediate, and chronic inhalation exposure 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

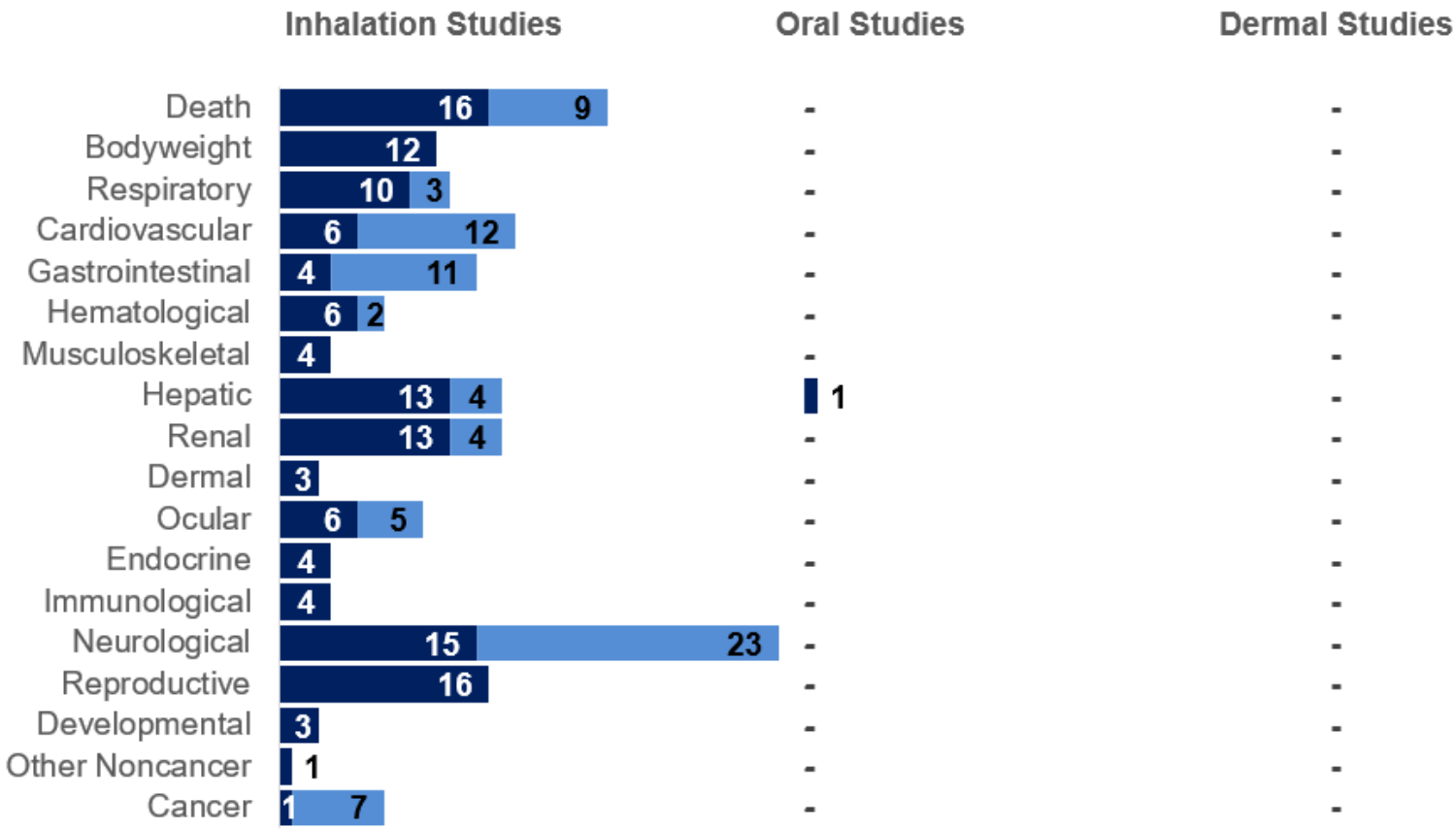
Missing information in Figure 6-1 should not be interpreted as a “data need.” A data need, as defined in ATSDR’s *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public

health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Chloromethane is highly volatile, and chloromethane in surface water or soil will likely evaporate to the air (CHAPTER 5.). Given the volatility of chloromethane, inhalation exposures and toxicity are of primary concern and have been the most studied. The oral and dermal routes of exposure are less of a potential exposure concern given that chloromethane is a gas at normal temperature and pressure, making inhalation the main route of exposure. Other than the Reynolds and Yee (1967) study, no information was located regarding the health effects of chloromethane in humans or animals after oral or dermal exposure. It is not possible to predict whether effects following oral or dermal exposure to chloromethane would be similar to those following inhalation exposure, partially because the pharmacokinetic disposition of chloromethane has not been compared for the three routes of exposure. Differences in absorption, distribution, and metabolic pathways could lead to differences in toxic response and different target organs following the three routes of exposure. Since the most likely route of exposure is inhalation, these studies would be the most relevant, and oral and dermal exposure to a lesser extent.

Figure 6-1. Summary of Existing Health Effect 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**)



*Includes studies discussed in Chapter 2; the number of studies includes those finding no effect. Some studies may have looked at more than endpoint.

Acute-Duration MRLs. The data for acute effects in animals were sufficient to derive an acute inhalation provisional MRL for chloromethane based on a NOAEL for neurological effects in mice. Some information on the mechanism of hepatic, renal, neurological, and reproductive effects in mice is available, but more is needed. Only one acute oral study was reported, and this was not sufficient to derive a provisional MRL. In this study, rats were dosed orally with chloromethane, livers were examined for pathology, and measures of potential to induce liver toxicity were assessed. The administered dose did not cause hepatic effects, and higher doses were neither administered nor warranted because they traumatized the animals and produced deep anesthesia and death within minutes. Orally administered chloromethane did not suppress glucose 6-phosphatase activity, it did not increase cell sap RNA, and little of the radioactive ^{14}C from labeled chloromethane was incorporated into the lipid constituents of microsomes (Reynolds and Yee 1967). Several case studies and environmental epidemiologic studies support the association between chloromethane exposure and adverse neurologic outcomes. No studies were located regarding effects in animals after dermal exposure to chloromethane. Pharmacokinetic data are insufficient to identify whether target organs of chloromethane are the same for inhalation, oral, and dermal exposure and more studies are needed. As discussed above, the potential for humans to be exposed to chloromethane is likely greater through the inhalation route than for the oral and dermal routes therefore inhalation studies would be the most relevant to ongoing exposure scenarios in humans.

Intermediate-Duration MRLs. Information regarding effects in humans after intermediate-duration exposure to chloromethane is limited to findings of neurological symptoms in humans occupationally exposed. Inhalation studies conducted in rats, mice, and dogs have identified the liver as a target organ in rats and mice (CIIT 1981; Mitchell et al. 1979; Smith and Von Oettingen 1947a); the testes as a target organ in rats (CIIT 1981; Hamm et al. 1985); and the kidney and spleen as targets in mice (CIIT 1981). The data were insufficient to derive an intermediate-duration inhalation provisional MRL. Although CIIT (1981) evaluated neurological effects in their chronic duration study these effects were not assessed in their 6-month study. No studies were located regarding effects in humans or animals after intermediate-duration oral or dermal exposure, and pharmacokinetic data are insufficient to identify or predict target organs of chloromethane for these routes of exposure. As discussed above, the potential for humans to be exposed to chloromethane is likely greater through the inhalation route than for the oral and dermal routes therefore inhalation studies would be the most relevant to ongoing exposure scenarios in humans.

Chronic-Duration MRLs. Only one study was located regarding effects of chloromethane in humans after chronic inhalation exposure. No chronic-duration studies were located for other routes. A 2-year inhalation study in animals has been conducted in which both sexes of rats and mice were exposed to several concentrations of chloromethane (CIIT 1981). The liver, kidneys, spleen, and brain were

identified as target organs in mice, and the testes were identified as target organs in rats and mice. Data were sufficient to derive a chronic inhalation provisional MRL. No studies were located regarding effects in animals after chronic oral or dermal exposure to chloromethane, subsequently no provisional MRLs were developed for these exposure routes. Pharmacokinetic data are insufficient to identify or predict target organs of chloromethane for these routes of exposure. As discussed above, the potential for humans to be exposed to chloromethane is likely greater through the inhalation route than for the oral and dermal routes therefore inhalation studies would be the most 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.

Cardiovascular. Case reports and epidemiological studies have indicated a potential for chloromethane to result in adverse cardiovascular outcomes (Hansen et al. 1953; Kegel et al. 1929; McNally 1946; Rafnsson and Gudmundsson 1997; Rafnsson and Kristbjornsdottir 2014; Scharnweber et al. 1974; Spevak et al. 1976; Stewart et al. 1980; Verriere and Vachez 1949). However, these studies are lacking quantitative exposure level information, and the epidemiological studies are lacking data on key confounders such as smoking, alcohol consumption, and lifestyle factors. Additionally, Holmes et al. (1986) found no apparent cardiovascular outcomes. Most animal studies evaluating cardiovascular effects due to chloromethane exposure did not find an association. When cardiovascular effects were found they included increased relative heart weight (not accompanied by lesions) (CIIT 1981), increased pulse, and decreased blood pressure (Kegel et al. 1929), likely related to effects of a metabolite since some effects were delayed to times when blood levels were low (von Oettingen et al. 1949, 1950). Additional data elucidating whether cardiovascular impacts are associated with chloromethane exposure are needed.

Dermal. No studies evaluated the effects of dermal exposure to chloromethane on humans. Only one study examined dermal effects in animals following acute inhalation exposure to chloromethane. However, the authors questioned if the effects observed were secondary to fighting with cage mates (McKenna et al. 1981b). Intermediate exposures ranging from 400 ppm to 1,500 ppm did not produce similar dermal effects; however, chloromethane was reported to penetrate human skin in vitro (Gaskin et al. 2018). Therefore, additional data is needed to understand if the alopecia noted in the acute exposure study was a result of chloromethane exposure or another cause (i.e., fighting).

Ocular. The relationship between chloromethane exposure and ocular effects is not clear as some short-term studies noted mucopurulent conjunctivitis with total destruction of the eye; however, other longer-term studies did not find the same impact. Additionally, in CIIT (1981) ocular impacts were seen at various time points for different species or sexes, but there was no consistency in the results (e.g., experimental animals exposed for 24 months did not show any ocular effects, whereas some animals with shorter term exposure did). A case report identified blindness in a woman who had been cleaning a toilet with a mixture that resulted in exposure to a chlorine gas; however, this was suspected to be due to a neurological effect rather than an ocular effect (Wilken et al. 2017). Therefore, additional data are needed to understand if chloromethane is associated with ocular effects.

Immunological. No information was located regarding immunotoxic effects in humans after exposure to chloromethane by any route. The immunotoxic effects reported in the literature in animals from exposure to chloromethane were lymphoid depletion of the spleen and splenic atrophy observed in mice exposed by inhalation to 1,000 ppm chloromethane for 2 years (CIIT 1981). Cats exposed continuously to chloromethane for 3 days had higher incidences of brain lesions than controls (McKenna et al. 1981a), but the lesions were consistent with infection or post-vaccinal reaction (the cats were vaccinated for panleukopenia by the supplier). Exacerbation of viral-induced central nervous system disease could not be ruled out. Additional studies are needed to further evaluate the potential immunotoxicity of chloromethane to humans.

Neurological. The neurotoxic effects in humans from inhalation exposure to chloromethane are described in numerous case studies (Baird 1954; Battigelli and Perini 1955; Gudmundsson 1977; Hansen et al. 1953; Hartman et al. 1955; Jones 1942; Kegel et al. 1929; Lanham 1982; Macdonald 1964; McNally 1946; Raalte and van Velzen 1945; Spevak et al. 1976; Wood 1951), but the mechanism is unclear. S-methylcysteine appears to be a metabolite in humans (Kornbrust and Bus 1983), and mechanisms involving conjugation with glutathione are likely to be relevant to human toxicity. Methanethiol produces similar central nervous system effects as seen in humans and animals exposed to chloromethane (Jager et al. 1988; Kornbrust and Bus 1983). The neurotoxic effects of inhalation exposure to chloromethane are also well defined in animals (Burek et al. 1981;Chellman et al. 1986a, Chellman et al. 1986b; CIIT 1981; Landry et al. 1985; McKenna et al. 1981a; Morgan KT et al. 1982; Smith and Van Oettingen 1947b). The mechanism for the induction of cerebellar lesions in mice exposed by inhalation may involve conjugation of chloromethane with glutathione, with further metabolism leading to production of methanethiol (Chellman et al. 1986b). The relative importance of conjugation with glutathione in other species has not been determined. More studies in animals are needed to understand the mechanisms of neurotoxicity from inhalation exposure to chloromethane.

Reproductive. One case study described potential reproductive effects (i.e., impotence) in an occupationally exposed individual. No data on exposure levels were provided in this study (Mackie 1961). Several inhalation studies, however, have demonstrated that chloromethane is a reproductive toxicant in male rats (Burek et al. 1981; Chapin et al. 1984; Chellman et al. 1986a, Chellman et al. 1986b, Chellman et al. 1987; CIIT 1981; Hamm et al. 1985; Morgan KT et al. 1982; Working and Bus 1986; Working et al. 1985a, Working et al. 1985b). The mechanism of this reproductive toxicity has been studied extensively only in rats because testicular lesions in mice occurred at lower incidences and later time periods than in rats in the 2-year inhalation study by CIIT (1981). Testicular effects were not observed in male dogs and cats exposed to chloromethane by inhalation (McKenna et al. 1981a), but the exposure concentrations may not have been high enough. Species differences in sensitivity exist for other end points as well. No studies were located regarding the reproductive effects of chloromethane in animals after oral or dermal exposure, and pharmacokinetic data are insufficient to support the potential for reproductive effects across routes of exposure. Therefore, additional studies for reproductive effects in other species at higher exposure levels are needed to further evaluate the potential adverse reproductive effects in humans from exposure to chloromethane.

Developmental. No information was located regarding developmental effects in humans after exposure to chloromethane by any route.

The teratogenicity of inhalation exposure to chloromethane has been studied in rats, mice, and rabbits (Wolkowski-Tyl et al. 1983a, Wolkowski-Tyl et al. 1983ab, Theuns-van Vliet 2016). In rats, delayed fetal development was found at a concentration that also resulted in maternal toxicity. The same was not seen in mice (Wolkowski-Tyl et al. 1981a, 1983a). Mice demonstrated cardiac heart malformations after gestational exposure to chloromethane (Wolkowski-Tyl et al. 1983a, Wolkowski-Tyl et al. 1983ab). However, neither rats nor rabbits have experienced these effects after chloromethane exposure (Wolkowski-Tyl et al. 1981a, 1983a, Theuns-van Vliet 2016). Therefore, additional studies are needed to further evaluate the relevance of the delayed fetal development and cardiac effects seen in rats and mice, respectively, to humans given no other species has demonstrated the same effects.

Cancer. Epidemiological studies have evaluated the relationship between occupational exposures to chloromethane and subsequent cancer outcomes. In the cohort of Icelandic fisherman there was an increased risk of death from renal cancer in the exposed cohort compared to unexposed fisherman (Rafnsson and Kristbjornsdottir 2014). However, as previously noted, there are limitations with these studies which limit their generalizability. An association between occupational exposure to chloromethane and non-Hodgkin’s lymphoma has been observed in a small number of individuals with the TT genotype of the genetic phenotype CYP2E1 rs2070673 for which the functional significance is

unclear (Barry et al. 2011). Additional research is needed to validate whether chloromethane exposure is associated with non-Hodgkin's lymphoma.

In animal studies, carcinogenic effects of chloromethane were observed in male, but not female mice, nor in rats of either sex (CIIT 1981). Male mice had increased incidences of kidney tumors at the highest exposure level. The rats and mice were exposed to the same concentrations, but differences in ventilation rate, the ability to conjugate chloromethane with glutathione, the further metabolism of the glutathione conjugate, and body weight effects make it probable that mice received a higher internal dose than rats. It is possible, therefore, that the exposure concentration was not sufficient in rats to produce detectable increases in kidney tumors. Additional chronic inhalation studies are needed to provide more information on differences in species susceptibility and to further evaluate the potential for and the mechanisms of chronic and carcinogenic effects of chloromethane exposure in humans.

Genotoxicity. Chloromethane has been shown to be genotoxic (Chellman et al. 1986c; Ristau et al. 1990; Rushbrook 1984; Working et al. 1985a). DNA strand breaks have been evaluated in human lymphoblasts (Fostel et al. 1985). Genotoxic effects have also been evaluated for mutations in *S. typhimurium* (Andrews et al. 1976; DuPont 1977; Simmon et al. 1977), sister-chromatid exchange (Fostel et al. 1985) unscheduled DNA synthesis in rat hepatocytes (Working et al. 1986), effects on spermatocytes and tracheal epithelial cells (Working et al. 1986), and DNA viral transformation in primary hamster embryo cells (Hatch et al. 1982; Hatch et al. 1983). According to the study authors, dominant lethal mutations in rat sperm resulting from inhalation exposure of male rats to chloromethane suggest that the dominant lethal effects may be secondary to inflammation of the epididymides (Chellman et al. 1986c). However, this is not definitively known and dominant lethal effects are still a concern. Research has explored why male mice were susceptible to renal tumors, whereas animals of different sex and species were not. Genotoxicity a result of the metabolites of chloromethane were explored as a potential mechanism given there may be sex and species differences in metabolizing enzymes. However, it is unclear if this is the reason for the difference. Therefore, additional data is needed to elucidate if the renal cancers seen in CIIT (1981) were due to genotoxicity.

Mechanisms of Action. Additional studies are needed to further define the mechanism of chloromethane's toxicity. Especially important are studies to determine whether depletion or protection of glutathione pools is needed to protect against toxicity for any given exposure route or target organ. The mechanisms and the beneficial or detrimental contribution of glutathione may be different for different species or genders.

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; Jiao et al. 2012; 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. No biomarker that can be associated quantitatively with exposure to chloromethane has been identified (see Section 3.3.1). Methods are available for the analysis of chloromethane in blood, expired air, and breast milk. In addition, a method exists for the analysis of 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. 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. Thus, methods for biomarkers of exposure and effect are needed.

Exposure. A number of 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). The blood and alveolar air levels of chloromethane and the urinary levels of S-methylcysteine are highly variable. Symptoms resembling drunkenness and food poisoning, along with a sweet odor on the breath, may alert a physician that a

person has been exposed to chloromethane, but such symptoms could easily be mistaken for the conditions they resemble.

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. Attempts to correlate blood levels and expired air concentrations of chloromethane with health effects of occupational and experimental inhalation exposures of humans were successful on a group average basis (Putz-Anderson et al. 1981a; Repko et al. 1976). Since blood and alveolar levels show individual variability they may be of limited use as indicators of neurological function or behavior. Further studies are needed to identify a metabolite or biomarker that can be correlated with the known toxic end point and that would lead to early detection and potential treatment.

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; Landry et al. 1983b; Putz-Anderson et al. 1981b; Putz-Anderson et al. 1981a; 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 is 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; Kornbrust and Bus 1984; Kornbrust et al. 1982; Landry et al. 1983a; Landry et al. 1983b; Putz-Anderson et al. 1981b; Putz-Anderson et al. 1981a; Redford-Ellis and Gowenlock 1971a; Redford-Ellis and Gowenlock 1971b; Repko et al. 1976; 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 2-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 glutathione conjugation and P-450 oxidation to the toxicity of chloromethane. These studies should be performed in different tissues, species, and sexes to resolve potential differences. Additional studies are needed to evaluate the importance of varying levels of human endogenous erythrocyte glutathione transferase (as has been recently shown to exist) to the toxicity of chloromethane, 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 more or less 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 hind limbs. 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 gestation day 6-17. In a letter to an editor, John-Green 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 gestation day 11.5-12.5 (John-Greene et al. 1985). Theuns-van Vliet exposed rabbits to up to 1000 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 no information on the movement of chloromethane or its metabolites across the placenta or into the developing young nor information on the movement of chloromethane or its metabolites into a

nursing women's milk. Information is limited on the potential transplacental transfer in animals. Wolkowski-Tyl et al. (Wolkowski-Tyl et al. 1983b; 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 gestation day 17 had significant NPSH concentration reductions in both dams and fetuses, indicative of transplacental passage of chloromethane or its metabolites. 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). Thus, it is unlikely that chloromethane would be stored in maternal tissues or be mobilized (i.e., released from stores) during pregnancy or lactation. However, one study measured chloromethane in 2 of 8 sample of human breast milk but the source of the substance is not known (Pellizzari et al. 1982). Further studies are needed that examine the presence of chloromethane in breastmilk sample of exposed populations.

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, glutathione-S-transferase (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 glutathione or from the depletion of glutathione (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 glutathione-S-transferase) would potentially be more susceptible to the toxic effects of chloromethane. Moreover, cytochrome P-450 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 CO2 (Heck et al. 1982; Kornbrust and Bus 1983). However, Jager et al. (1988) disputes this conclusion. Guengerich and Shimada (1991) suggest that the human cytochrome P-450 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 P-450 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 estimating the partitioning of a chemical in the environment. Most of the necessary data on physical and chemical properties are available for chloromethane, and many of these have experimental descriptions accompanying them so that accuracy 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. 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.

Use. 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 considered to be confidential business information (CBI) for those industries that manufacture chloromethane.

Release. Release information, which can be used to estimate environmental burdens and potentially exposed populations, is obtained from the Toxic Release Inventory. Data from industries that are not required to report to the TRI is difficult to obtain and is a data need.

Disposal. Limited data is 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.

Regulatory Information. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 2017, became available in October of 2018. This database is updated yearly and should provide a list of industrial production facilities and emissions required to report to TRI.

As a HAP, chloromethane is regulated by the Clean Air Act. 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, 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 are made regarding chloromethane's tendency to accumulate in sediment or biota. Measured values are needed to better understand chloromethane's tendency to bioaccumulate.

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 $_{Kow}$ for chloromethane is in the range of 0.91 to 1.086 (see CHAPTER 4. , 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. The database for chloromethane exposure levels in humans is limited to determinations of chloromethane in breast milk. A more 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). 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 information. The available NOES database of potential occupational exposures was assembled in the late 1980s and is outdated. An update to this statistically based database of potential occupational exposures is needed. Additionally, information on background levels in the general population would be useful.

Exposures of Children. Chloromethane was present in 2 of 8 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 source of the chloromethane in the milk. Studies to determine current chloromethane residues and sources in breast milk of women in the general population and in the workforce are needed. Well water surveys should be conducted 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.

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.

Chloromethane is on the list of chemicals subject to the requirements of "The Emergency Planning and Community Right-to-Know Act of 1986 (EPCRA) (EPA 2018g). Section 313 of Title III of EPCRA, requires owners and operators of certain facilities that manufacture, import, process, or otherwise use the chemicals on this list to report annually their release of those chemicals to any environmental media (EPA 2015aa).

OSHA requires employers of workers who are occupationally exposed to chloromethane to institute engineering controls and work practices to reduce and maintain employee exposure at or below permissible exposure limits (PELs). The employer must use controls and practices, if feasible, to reduce exposure to or below an 8-hour time-weighted average (TWA) of 100 ppm (OSHA 2018). The acceptable ceiling concentration for chloromethane is 200 ppm. The acceptable maximum peak above this ceiling concentration is 300 ppm. Therefore, during an 8-hour work shift a person may be exposed to a concentration of chloromethane measuring 200 ppm or greater, but never more than 300 ppm and only for a maximum period of 5 minutes within any 3-hour period. An exposure such as this must be compensated by exposures to concentrations less than 100 ppm so that the cumulative exposure for the 8-hour shift does not exceed the 100 ppm exposure limit (OSHA 2018).

The EPA regulates chloromethane under the Clean Air Act (CAA) and has designated chloromethane as a hazardous air pollutant (HAP) (EPA 2017aa). The major source category for which chloromethane emissions are controlled is the synthetic organic chemicals manufacturing industry (SOCMI) and includes equipment leaks (EPA 2018l), distillation operations (EPA 2018c), and reactor processes (EPA 2018d).

Chloromethane is regulated by the Clean Water Effluent Guidelines in Subchapter N of Title 40 of the Code of Federal Regulations. Electroplating is the point source category for which chloromethane is controlled as a total toxic organic (EPA 2018k). The point source categories for which chloromethane has

specific regulatory performance standards include organic chemicals, plastics, and synthetic fibers (EPA 2018h), steam electric power generator use (EPA 2018i), and metal finishing processes (EPA 2018j).

The Resource Conservation and Recovery Act (RCRA) identifies chloromethane as a toxic waste with toxicity and ignitability hazardous properties, and has assigned it the hazardous waste number U045 (EPA 2018e).

Under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), owners of vessels or facilities are required to immediately report release of chloromethane equal to or greater than the reportable quantity of 100 pounds (45.4 kg) (EPA 2018f).

Table 7-1. Regulations and Guidelines Applicable to Chloromethane

Agency	Description	Information	Reference
	Air		
EPA	RfC	0.09 mg/m^3	IRIS 2001
	Subchronic provisional RfC	3 mg/m^3	EPA 2012
WHO	Air quality guidelines	0.018 mg/m^3	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	
	DWEL	No data	
	MCL (total trihalomethanes)	No data	
	National primary drinking water regulations	No data	EPA 2009
	RfD	No data	IRIS 2001
WHO	Disinfection by-products-drinking-water	No data	WHO 2017
FDA	Substances Added to Food	No data[a]	FDA 2019
	Cancer		
HHS	Carcinogenicity classification	No data	NTP 2016
EPA	Carcinogenicity classification	Group D[b]	IRIS 2001
IARC	Carcinogenicity classification	Group 3[c]	IARC 2019
NIOSH	Carcinogenicity classification	Potential occupational carcinogen	NIOSH 1984
	Occupational		
OSHA	PEL (8-hour TWA)	100 ppm	OSHA 2018 29 CFR 1915.1000 Table Z
NIOSH	REL (up to 10-hour TWA)	Lowest feasible concentration	NIOSH 2018
ACGIH	TLV		ACGIH 2012
	TLV-TWA	50 ppm	
	TLV-STEL	100 ppm	
	Emergency Criteria		
EPA	AEGLs-air		AEGLs 2018
	AEGL 1		
	10 min	NR[d]	
	30 min	NR	
	60 min	NR	

Table 7-1. Regulations and Guidelines Applicable to Chloromethane

Agency	Description	Information	Reference
	4 hr	NR	
	8 hr	NR	
	AEGL 2		
	10 min	1100 ppm	
	30 min	1100 ppm	
	60 min	910 ppm	
	4 hr	570 ppm	
	8 hr	380 ppm	
	AEGL 3		
	10 min	3800 ppm	
	30 min	3800 ppm	
	60 min	3000 ppm	
	4 hr	1900 ppm	
	8 hr	1300 ppm	
AIHA	ERPGs		AIHA 2016
	ERPG-1	150 ppm	
	ERPG-2	1000 ppm	
	ERPG-3	3000 ppm	
DOE	PACs		DOE 2016
	PAC-1	310 mg/m^3	
	PAC-2	1900 mg/m^3	
	PAC-3	6200 mg/m^3	

[a]The Substances Added to Food (formerly EAFUS) contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as generally recognized as safe (GRAS).
[b] Group D: Not classifiable as to its human carcinogenicity
[c]Group 3: Not classifiable as to its carcinogenicity to humans
[d]NR: Not recommended due to insufficient data

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; CFR = Code of Federal Regulations; HHS = Department of Health and Human Services; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; GRAS = Generally Recognized As Safe; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; 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; STEL = short-term exposure limit; TLV = threshold limit values; TWA = time-weighted average; WHO = World Health Organization

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APPENDIX A. ATSDR MINIMAL RISK LEVELS AND 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.

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. MRLs are considered to be provisional until the profile is finalized. For additional information regarding MRLs, please contact the Agency for Toxic Substances and Disease Registry Office of Innovation and Analytics, Toxicology Section 1600 Clifton Road, N.E. Mail Stop S102-1 Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name(s):	Chloromethane
CAS number(s):	74-87-3
Date:	January 2022
Profile status:	Draft 4, Public Comment
Route:	Inhalation
Duration:	Acute
Provisional MRL:	0.5 ppm (1 mg/m^3)
Critical Effect:	degenerative changes in the cerebellum granule cells with nuclear pyknosis and karyorrhexis
Reference:	Landry et al. (1985)
Point of Departure:	NOAEL of 50 ppm ($NOAEL_{HEC}$ of 46 ppm)
Uncertainty Factor:	90
LSE Key Graph:	23
Species:	Mouse

MRL Summary: A acute-duration inhalation provisional MRL of 0.5 ppm was derived for chloromethane based on neurological effects including degenerative changes in the cerebellum granule cells with nuclear pyknosis and karyorrhexis in C57BL/6 mice following exposure to chloromethane for 11 days (Landry et al. 1985). The provisional MRL is based on a NOAEL of 50 ppm ($NOAEL_{HEC}$ of 46 ppm) and a total uncertainty factor of 90 (3 for animal to human after dosimetric adjustment, 3 for a modifying factor to account for the steepness for the dose-response curve and 10 for intrahuman variability). The steep dose-response in the data do not allow for benchmark dose modeling (BMD), that is 100 percent of mice at exposure levels 100 ppm and above had damage to cerebellar cells. Therefore, BMD modeling was not used.

Selection of the Critical Effect: Based on our systematic review it was determined that hepatic and neurological effects were presumed health effects associated with inhalation exposure. Additionally, these effects were seen at the lowest levels of exposure and subsequently were the focus of our MRL evaluation.

Neurological effects are a primary health effect reported for acute human exposure to chloromethane and are the most sensitive endpoint for this duration. 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; Raalte and van Velzen 1945; Spevak et al. 1976; Wood 1951). Additionally, in a follow-up of a cohort of fisherman accidentally exposed to chloromethane as a result of a refrigeration leak, the risk of latent death by suicide and death from cerebrovascular disease was significantly increased in the exposed cohort compared to a reference group of Icelandic fishermen not exposed to chloromethane (Rafnsson and Kristbjornsdottir 2014). Human controlled trials did not show nervous system effects of chloromethane exposure since the low doses used in these studies were selected to prevent neurological harm.

Multiple experimental animal studies found neurological effects due to chloromethane exposure. The nervous system effects ranged from observable changes in outcomes such as behavior, gait, ataxia, and tremors to histopathological lesions on the brain and axonal swelling (Chellman et al. 1986a, 1986b; Morgan et al. 1982; Jiang et al. 1985; Landry et al. 1985; Wolkowski-Tyl et al. 1983a, 1983b; McKenna 1981a; CIIT 1981).

Similar to the neurologic data, evidence of hepatic toxicity of chloromethane in humans is limited to case studies. In these case studies, markers of liver toxicity, such as jaundice, cirrhosis, and lipoid granules in Kupffer cells were observed (Kegel et al. 1929; Weinstein 1937; Wood 1951). In acute experimental animal studies, effects observed included changes in liver weight (Burek et al. 1981), changes in NPSH (Chapin et al. 1984; Dodd et al. 1982), alterations in hepatocyte size or appearance (Burek et al. 1981; Landry et al. 1985), and degeneration of hepatocytes at higher doses (Morgan et al. 1982).

The NOAELs and LOAELs for neurologic and hepatic effects considered for derivation of the MRL are summarized in Table A-1. NOAELs and LOAELS for serious effects are not considered for MRL derivation and are therefore not included in this table.

Other effects observed after acute duration chloromethane exposure include heart defects in the offspring of dams exposed to doses around 500 ppm, though this association has been debated in the literature by authors of the same research organization who argue the observed heart defects are potentially an artifact of the sectioning technique used in the assessment (John-Greene et al. 1985). Additionally, Landry et al. (1984) observed decreases in thymus weight at 15 ppm exposure (22 hours per day exposure). However, the authors stated that the decreases seen at this low exposure level were considered “spurious based on lack of corroborating histopathology.” Also, thymus weight was only affected at intermittent exposures of at least 1,600 ppm (equivalent to 364 ppm continuous exposure based on equal quantities of chloromethane inhaled).

Table A-1. Summary of Relevant NOAEL and LOAEL Values Considered for Derivation of an Acute Duration Inhalation Provisional MRL for Chloromethane

Species	Duration	NOAEL ($NOAEL_{ADJ}$) (ppm)	LOAEL ($LOAEL_{ADJ}$) (ppm)	Effect	Reference
Neurological					
RAT (Sprague-Dawley) 20M, 20F	48 hours continuous	501 (501)	972 (972)	Lethargy	Burek et al. 1981
MOUSE (C57BL/6) Fetus (B6C3F1) 74-77F	12 days 6 hours/day GD 6-17	251 (63)	502 (126)	Ataxia	Wolkowski-Tyl et al. 1981b, 1983b
MOUSE (C57BL/6) 12F	11 days 5.5 hours/day	150 (34)	400 (92)	slight cerebellar granule cell degeneration	Landry et al. 1985
MOUSE (C57BL/6) 12F	11 days 22 hours/day	50 (46)	100 (92)	Slight degenerative changes in the cerebellum granule cell layer with nuclear pyknosis and karyorrhexis (100% of mice affected)	Landry et al. 1985
Hepatic					
RAT (Fischer-344) 10M, 10F	9 days 6 hours/day	2000M (500)	3500M (875)	minimal hepatocyte degeneration	Morgan et al. 1982
RAT (Sprague-Dawley) 20M, 20F	48 hours continuous		196 (196)	Decreased liver weight	Burek et al. 1981
RAT (Fischer-344) 2-8M	12 days 4-5 days/week 6 hours/day		3500M (875)	decreased liver non-protein sulfhydryl content	Chapin et al. 1984
RAT (Fischer-344) 5M	5 days 6 hours/day		5004 (1251)	hepatocellular degeneration - cloudy swelling of hepatocytes, obliteration of sinusoids	Chellman et al. 1986a

APPENDIX A

Table A-1. Summary of Relevant NOAEL and LOAEL Values Considered for Derivation of an Acute Duration Inhalation Provisional MRL for Chloromethane

Species	Duration	NOAEL ($NOAEL_{ADJ}$) (ppm)	LOAEL ($LOAEL_{ADJ}$) (ppm)	Effect	Reference
RAT (Fischer-344) 4M	6 hours (doses at 501 ppm also had observations at 1, 3 and 4 hours)	99M (25)	501M (125)	decrease in NPSH levels to 55% of control value (30% at 1500 ppm)	Dodd et al. 1982
RAT (Sprague-Dawley) 20M/F	72 hours continuous		198M (198)	altered tinctorial[1] appearance	Burek et al. 1981
MOUSE (C57BL/6) Fetus (B6C3F1) 74-77F	12 days 6 hours/day GD 6-17	251 (63)	502 (126)	9% increase in absolute and 5% increase in relative maternal liver weight	Wolkowski-Tyl et al. 1981b, 1983b
MOUSE (C57BL/6) 12F	11 days 22 hours/day	50 (46)	100 (92)	decreased hepatocyte size; glycogen depletion	Landry et al. 1985
RAT (Fischer-344) 10M, 10F	9 days 6 hours/day		2000F (500)	minimal hepatocyte degeneration	Morgan et al. 1982

[1]altered staining properties of hepatocyte

Adj = adjusted; F = females; GD = gestation day; LOAEL = lowest observed adverse effect level; M = males; NOAEL = no observed adverse effect level; NPSH = non-protein sulfhydryl

Table A-1 shows that the study with the lowest LOAELs is Landry et al. (1985). We recognize that when considering the exposure duration-adjusted values with Dodd et al. (1982), there is the potential to select a lower NOAEL adjusted. However, this study has a higher associated LOAEL when compared to Landry et al. (1985). Additionally, as outlined in the subsequent paragraphs, the study design in Landry et al. (1985) makes it the strongest study from which to derive a provisional MRL.

Selection 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 neurologic effects of nearly continuous exposure versus intermittent chloromethane 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 study authors) at 0, 15, 50, 100, 150, 200, or 400 ppm, or 5.5 hours/day (referred to as intermittent by the study authors) at 0, 150, 400, 800, 1,600, or 2,400 ppm. The mice were subjected to neurofunctional testing (rotarod or rotating rod: ability to stay on a rotating 4 cm diameter rod) on days 4, 8, and 11. Mice were weighed prior to exposure, on exposure days 4 and 8, and at necropsy. Animals were sacrificed at various times during the experimental period, and the following tissues were collected, weighed, and prepared for histological evaluation: brain (cerebellum, cerebrum, and brain stem), sciatic nerve, vertebral bone with spinal cord, liver, kidneys, and thymus.

No effects were seen at exposure to ≤50 ppm continuous exposure or ≤150 ppm intermittent exposure. Histologically, degenerative changes in the cerebellum granule cells were seen at 100 ppm of continuous exposure or 400 ppm intermittent exposure. The changes consisted of nuclear pyknosis, karyorrhexis, and hemorrhaged areas. On day 4 of 150 ppm continuous exposure, there was a moderate intracellular and extracellular cerebellar vacuolation in the Purkinje and/or molecular cell layer and in the white matter. This vacuolation was transient and not seen after day 6, and these effects were more pronounced in the 400 ppm mice.

Performance on a rotating rod was significantly decreased at intermittent exposure to 150 ppm, and further decreased in the continuously exposed group. At 150 to 400 ppm continuous exposure, the mice developed motor incoordination. The authors also noted that there was an increase in rotating rod performance in the 50 ppm group when compared to controls. However, this increase was described by the authors as "probably the result of day to day variation in control and exposed group". Landry et al. (1985) also observed transient decreases in performance of mice on the rotating rod starting on day 4 of exposure to 800 ppm or 2,400 ppm intermittently (5.5 hours/day). However, by day 8 only 150 ppm of continuous and 2,400 ppm of intermittent exposure in mice showed performance decrements.

Mice exposed to 150 ppm continuous exposure were sacrificed in moribund condition by day 10.5. At 200 ppm continuous exposure, the mice were ataxic and fell on their sides after 3 days. By day 5, mice at this exposure level were deceased. The 400 ppm continuously exposed mice died or were sacrificed by day 4. Similar effects were seen in mice exposed to higher concentrations of intermittent exposure.

The apparent greater sensitivity to continuous exposure may be related to the conversion of chloromethane to an active metabolite and/or diurnal susceptibility. Diurnal susceptibility (in this case lower sensitivity during the daytime intermittent exposure) could result from the lower activity of mice during the daytime and the corresponding lower respiratory minute volume.

For the continuously exposed mice, a NOAEL of 50 ppm was determined based on no observations of neurological effects or histopathologic changes. See additional data on the doses and responses in Table A-2

Table A-2. Summary of Neurological Effects Observed in Mice with Continuous Exposure (22 hrs/day) to Chloromethane

Dose Group	Effect
15 and 50 ppm	No neurological effects or histopathological changes observed
100 ppm	Slight degenerative changes in the cerebellum granule cells (100% of mice affected)
150 ppm	Moderate cerebellar lesions (100% of mice affected) and severe neurological performance decrement on rotarod tests
200 ppm	Incapacitated after 4 days, severe cerebellar lesions (100% of mice affected)
400 ppm	Incapacitated after 2 days, severe cerebellar lesions (100% of mice affected)

Selection of the Point of Departure for the MRL:

The doses used and LOAEL observed in the Landry et al. (1985) study for continuous exposure were the lowest of the acute duration studies. Additionally, due to the steep dose response curve as evidenced by 100 percent of mice at 100 ppm developing cerebellar lesions, benchmark dose modeling was not conducted to develop the MRL. Subsequently the NOAEL of 50 ppm was used in derivation of the MRL.

Adjustment of Intermittent Exposure:

Given the levels of chloromethane in the serum increase rapidly, but also decrease with a half-life of 60-90 minutes (Nolan et al. 1985), the 50 ppm concentration was adjusted to a 24-hour exposure from the 22 hours of continuous exposure. This results in the following duration adjusted value:

$$NOAEL_{ADj} = NOAEL \times \frac{22\ hrs}{24\ hrs} = 50\ ppm \times \frac{22\ hrs}{24\ hrs} = 46\ ppm$$

The human equivalent concentration (HEC) was calculated using Formula 4-48 from Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA 1994b). Interspecies extrapolation requires consideration of the chloromethane air:blood partition coefficient for humans and rats. However, this data is not available and therefore, as recommended by EPA (1994b), in the absence of this data, unity is assumed. Therefore, the HEC is determined by the following equation:

$$NOAEL_{HEC} = NOAEL_{ADJ} \times \frac{(HB/g)_A}{(HB/g)_H} = 46\ ppm \times 1 = 46\ ppm$$

Where:

$\frac{(HB/g)_A}{(HB/g)_H}$ = the blood: air partition coefficient for animals (a) to humans (h)

Uncertainty Factors:

The following uncertainty factors will be applied to the $NOAEL_{HEC}$ to derive the MRL:

- 3 for animal to human extrapolation after applying dosimetric adjustment
- 3 for a modifying factor 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)
- 10 for intra human variability.

Subsequently the provisional MRL for acute-duration exposure to chloromethane via inhalation is:

$$MRL = \frac{NOAEL_{HEC}}{UFs} = \frac{46\ ppm}{90} = 0.5\ ppm\ (1\ mg/m^3)$$

Agency Contacts (Chemical Manager): Sam Keith, MS, CPH

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name(s): Chloromethane
CAS number(s): 74-87-3
Date: January 2022
Profile status: Draft 4, Public Comment
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL.

Selection of the Critical Effect: Effects seen with intermediate duration exposure included several endpoints which have uncertain toxicological significance such as changes in urinary specific gravity or changes in organ weights, both without associated pathological findings. These effects were not considered for MRL derivation. Increases in liver enzymes and liver lesions were observed in B6C3F1 mice with 6 months of exposure to 997 ppm chloromethane. At similar doses of observed serious effects, splenic lymphoid depletion was also observed. Additionally, Mitchell et al. (1979) observed ocular effects on B6C3F1 mice. In addition, in CIIT (1981), reproductive effects were observed in male rodents Specifically, CIIT (1981) observed degeneration and atrophy of seminiferous tubules at approximately 1000 ppm in male rats exposed for 6 months. Hamm et al. (1982) also observed a decreased fertility in rats after 10 and 20 weeks of exposure to 472 ppm chloromethane. These are serious effects which were not considered for MRL derivation.

The most sensitive effect, as suggested by the LOAELs, was the ocular effect observed in Mitchell et al. (1979). However, the association of these effects with chloromethane is uncertain; the authors state the lesions in the rats were such that they were assumed to not be compound related. The justification provided in Mitchell et al. (1979) does not further expand on this point. Given the uncertainty associated with this outcome, it was not selected as a critical effect. CIIT (1981) shows an effect on the hepatic system starting at 997 ppm exposure, with an associated NOAEL of 224 ppm. Hepatic effects were determined to be a presumed health effect associated with chloromethane exposure based on the systematic review of literature and evaluation of studies. However, using a NOAEL of 224 ppm as the basis for a point of departure would result in an intermediate MRL which is higher than the acute duration MRL.

Agency Contacts (Chemical Manager): Sam Keith, MS, CPH

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name(s):	Chloromethane
CAS number(s):	74-87-3
Date:	January 2022
Profile status:	Draft 4, Public Comment
Route:	Inhalation
Duration:	Chronic
Provisional MRL:	0.03 ppm (0.06 mg/m^3)
Critical Effect:	Axonal swelling and slight degeneration of axons in the spinal
Reference:	cord CIIT (1981)
Point of Departure:	LOAEL of 51 ppm
	($LOAEL_{HEC}$ 9 ppm)
Uncertainty Factor:	300
LSE Key Graph:	48
Species:	Mouse

MRL Summary: A chronic-duration inhalation provisional MRL of 0.03 ppm was derived based on the critical effect of axonal swelling. This was based on CIIT 1981 which presented a LOAEL of 51 ppm for this effect. The duration adjusted $LOAEL_{HEC}$ was determined to be 9 ppm. A total UF of 300 was applied to account for animal to human extrapolation (3, after dosimetric adjustment), human to human variability (10) and use of a LOAEL (10).

Selection of the Critical Effect: Based on our systematic review it was determined that hepatic and neurological effects were presumed health effects associated with inhalation exposure.

Multiple animal studies found neurological effects due to chloromethane exposure. The nervous system impacts ranged from observable changes in outcomes such as behavior, gait, ataxia, and tremors to histopathological lesions on the brain and axonal swelling (Chellman et al. 1986a, 1986b; Morgan et al. 1982, Jiang et al. 1985, Landry et al. 1985, Wolkowski-Tyl et al. 1983a, 1983b; McKenna 1981a, 1981b; CIIT 1981). The critical study selected for MRL development was CIIT (1981), which is the only publication with data on chronic inhalation exposure to chloromethane.

Other systems for which CIIT observed effects with chronic exposure included hepatic, renal, ocular, and reproductive. Cancer was also observed with chronic exposure (997 ppm). The reproductive effects observed in CIIT also occurred at 997 ppm and were serious effects and were therefore not considered for MRL derivation. The NOAELs and LOAELs considered for MRL derivation are summarized in Table A-3

Table A-3. Summary of Relevant NOAEL and LOAEL Values Considered for Derivation of a Chronic Duration Inhalation Provisional MRL for Chloromethane

Species	Duration	NOAEL ($NOAEL_{ADJ}$) (ppm)	LOAEL ($LOAEL_{ADJ}$) (ppm)	Effect	Reference
Neurological					
MOUSE (B6C3F1) 10M, 10F	12 months 5 days/week 6 hours/day	224 (40)	997 (178)	10-12% decrease in brain weight	CIIT 1981
MOUSE (B6C3F1) 7M; 8-10 F	18 months 5 days/week 6 hours/day		51 (9)	axonal swelling and degeneration of axons in spinal cord with no neurofunctional abnormality	CIIT 1981
MOUSE (B6C3F1) 20-32M; 57-68F	21-24 months 5 days/week 6 hours/day		51 (9)	swelling and degeneration of axons in spinal cord	CIIT 1981
Hepatic					
RAT (Fischer-344) 65-68M; 57-61F	21-24 months 5 days/week 6 hours/day	224M (40)	997M (178)	9% increase in relative liver weight	CIIT 1981
MOUSE (B6C3F1) 10M, 10F	12 months 5 days/week 6 hours/day	224 (40)	997 (178)	F: 55% incr. relative liver weight M: 219% incr. ALT, necrosis, cytomegaly, karyomegaly, polykaryocytes	CIIT 1981
Renal					
MOUSE (B6C3F1) 10M, 10F	12 months 5 days/week 6 hours/day	224M (40)	997M (178)	renal tubuloepithelial hyperplasia; decreased absolute weight	CIIT 1981
MOUSE (B6C3F1) 20-32M; 57-68F	21-24 months 5 days/week 6 hours/day	224 (40)	997 (178)	Renal hyperplasia	

Table A-3. Summary of Relevant NOAEL and LOAEL Values Considered for Derivation of a Chronic Duration Inhalation Provisional MRL for Chloromethane

Species	Duration	NOAEL ($NOAEL_{ADJ}$) (ppm)	LOAEL ($LOAEL_{ADJ}$) (ppm)	Effect	Reference
Ocular					
RAT (Fischer-344) 10M, 10F	12 months 5 days/week 6 hours/day		51 (9)	Slight hazing elliptically patterned over middle of eye (8/10 males and 6/10 females) with virus in exposed and control animals	CIIT 1981
RAT (Fischer-344) 20M, 20F	18 months 5 days/week 6 hours/day	51 (9)	224 F (40)	12/20 with corneal opacity (with and without conjunctivitis)	CIIT 1981

Adj = adjusted; ALT = alanine aminotransferase; F = females; GD = gestation day; incr. = increased LOAEL = lowest observed adverse effect level; M = males; NOAEL = no observed adverse effect level

From reviewing the data in Table A-3 it can be seen that neurological and ocular effects were the most sensitive. However, there are difficulties interpreting the results of the ocular effects observed. For example, there was a high incidence of scleritis in the rats in the study, to which the authors attributed some ocular effects. Additionally, although effects were observed at 12 and 18 months, no differences in ocular observations were recorded when comparing the dosed groups to the controls after 24 months of exposure. Therefore, the neurological effects, which are a presumed health effect of chloromethane exposure, were selected as the critical effect for the chronic provisional MRL with CIIT 1981 as the critical study.

Selection of the Principal Study:

CIIT. 1981. Final report on a chronic inhalation toxicology study in rats and mice exposed to methyl chloride. Columbus, OH: Battelle-Columbus Laboratories.

The objective of the chronic study (CIIT 1981) was to evaluate the toxicologic and oncogenic effects of inhaled chloromethane in male and female Fischer 344 rats and B6C3F1 mice. The animals were exposed to chloromethane in whole body inhalation exposure chambers at target concentrations of approximately 0 (control), 50, 225, or 1,000 ppm (analytically measured concentrations were 0, 51, 224, and 997 ppm, respectively), 6 hours/day, 5 days/week for up to 24 months. Necropsies were completed 6, 12, 18, or 24 months after the initial exposure. As early as 6 months, the absolute brain weight was reduced in male and female mice exposed to 1,000 ppm chloromethane; however, relative brain weights were not affected by chloromethane exposure. Through 18 months, decreased absolute brain weights were noted in female mice, and by 18 months, this was observed in both male and female rats exposed to 1,000 ppm chloromethane. 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) and cerebellar lesions (minimal to mild reduction in the number of neurons in the granular cell layer, most prominently in the sulci). Axonal swelling and degenerative changes of minimal severity were observed in the spinal cord nerves, cauda equina, and dorsal root in the lumbar spinal cord of 3 of 7 male mice (1,000 ppm), 5 of 5 male and 10 of 10 female mice (225 ppm), 4 of 5 male and 10 of 10 female mice (50 ppm), and 1 of 5 male and 2 of 10 female mice (control). The neurotoxic lesions progressed in frequency and severity in mice to the end of the exposure period. In contrast to its effects in mice, chloromethane did not produce neurotoxicity in rats (i.e., no clinical, pathological, or functional test findings) at levels up to 1,000 ppm for 6 to 24 months in duration (CIIT 1981).

There are shortcomings of the CIIT study which were considered in deriving the chronic 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, four months after the beginning of the study, mice from the 50 ppm group were accidentally administered 1,000 ppm doses, and 1,000 ppm group mice were accidentally administered 50 ppm doses for three days at 5.5 hours per day. CIIT acknowledged 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 ppm or 1,000 ppm at 6 months, so there appears to be little effects of this error on the results of the study. While Landry et al. (1985) demonstrated that essentially continuous exposure (22 hours/day) has a greater impact on neurological effects than intermittent exposure (6 hr/day), continuous exposures were not conducted in CIIT (1981), and ATSDR guidance does not allow for use of an acute duration study (e.g., Landry et al. 1985) to inform a chronic duration MRL. Nevertheless, comparing ATSDR's analysis of the MRL informed by CIIT (1981) to the chronic-duration RfC informed by Landry (EPA 2001), the reference values are very similar (a provisional chronic MRL of 0.06 mg/m^3 compared to the final RfC of 0.09 mg/m^3). The issues with the study do not substantially impact the MRL derivation and the derived MRL is similar to other reference levels derived for chronic-duration exposure by other federal agencies. Therefore, despite the shortcomings of the CIIT

(1981) study, ATSDR has concluded it is adequate to inform a chronic MRL that provides appropriate public health protection. Table A-4 provides a summary of neurological effects observed in an 18-month chronic exposure study (CIIT 1981).

Table A-4. Summary of Neurological Effects Observed in CIIT 1981 with Chronic (18 month) Chloromethane Exposure

Dose group (6hr/day)	Effect
51 ppm	Swelling and degeneration of axons in the spinal cord (100% of female mice; 80% of male mice)
224 ppm	Swelling and degeneration of axons in the spinal cord (100% both male and female mice)
997 ppm	Tremor, paralysis, mild reduction in number of cerebellar neurons in the granular cell layer (42% of male mice; no data for female mice)

Selection of the Point of Departure for the MRL: The point of departure from this data was selected as the LOAEL of 51 ppm. Given the data do not show a monotonic graded-dose response, benchmark dose modeling was not used to derive this provisional MRL.

Adjustment for Intermittent Exposure:

Given the levels of chloromethane in the serum increase rapidly, but also decrease with a half-life of 60-90 minutes (Nolan et al. 1985), the 51 ppm concentration was adjusted to a 24 hour exposure from the 5.5 hours of continuous exposure. Additionally, it was further adjusted from 5 days per week to 7 days per week. This results in the following duration adjusted value:

$$LOAEL_{ADj} = LOAEL \times \frac{6\ hrs}{24\ hrs} \times \frac{5\ days}{7\ days} = 51\ ppm \times \frac{6\ hrs}{24\ hrs} \times \frac{5\ days}{7\ days} = 9\ ppm$$

The human equivalent concentration (HEC) was calculated using Formula 4-48 from Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA 1994b). Interspecies extrapolation requires consideration of the chloromethane air:blood partition coefficient for humans and rats. However, this data is not available and therefore, as recommended by EPA (1994b) in the absence of this data, unity is assumed. Therefore, the HEC is determined by the following equation:

$$LOAEL_{HEC} = LOAEL_{ADJ} \times \frac{(HB/g)_A}{(HB/g)_H} = 9\ ppm \times 1 = 9\ ppm$$

Where:

$\frac{(HB/g)_A}{(HB/g)_H}$ = the blood: air partition coefficient 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 provisional MRL.

- 3 for animal to human extrapolation after dosimetric adjustment
- 10 for human variability
- 10 for use of a LOAEL

Subsequently the provisional MRL becomes:

$$MRL = \frac{LOAEL_{HEC}}{UFs} = \frac{9\ ppm}{300} = 0.03\ ppm\ (0.06\ mg/m^3)$$

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APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name(s): Chloromethane
CAS number(s): 74-87-3
Date: January 2022
Profile status: Draft 4, Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL.

Rationale for Not Deriving an MRL: 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. The database for deriving an acute-duration oral MRL is inadequate.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name(s): Chloromethane
CAS number(s): 74-87-3
Date: January 2022
Profile status: Draft 4, Public Comment
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.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name(s): Chloromethane
CAS number(s): 74-87-3
Date: January 2022
Profile status: Draft 4, Public Comment
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.

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 the health effects of chloromethane. Studies for other sections of the toxicological profile were also identified in the literature search and screen step. Although these studies were not included in the systematic review process, the results of some studies (e.g., parenteral administration, mechanistic studies, toxicokinetic studies) were considered in the final steps of the systematic review. 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.

APPENDIX B

Table B-1. Inclusion Criteria for the Literature Search and Screen

Health Effects
Species
Human
Laboratory mammals Drosophila (for genotoxicity studies) *In vitro* assay (for genotoxicity and for supporting data for other endpoints)
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Respiratory effects
Cardiovascular effects
Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Endocrine effects
Dermal effects
Ocular effects
Body weight effects
Metabolic effects
Other systemic effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects Genotoxicity
Cancer

B.1.1 Literature Search

The current literature search was intended to update the existing toxicological profile for chloromethane (ATSDR 1998); thus, the literature search was restricted to studies published between January 1996 and February 2019. The following databases were searched in February 2019:

- MEDLINE
- ProQuest
- PubMed
- Science Direct
- SciFinder
- National Library of Medicine's TOXLINE
- BIOSIS
- IPA
- National Pesticide Information Retrieval System (NPIRS)

The search strategy used the chemical name, CAS number (i.e., 74-87-3), synonyms, and Medical Subject Headings (MeSH) terms for chloromethane. The query strings used for the literature search are presented in Table B-2.

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
MEDLINE 1/29/2019	((MH "Methyl Chloride")) OR "chloromethane" OR "chloride, methyl" OR "R 40" OR "artic" OR "chloormethaan" OR "chlormethan" OR "Chlorure de methyle" OR "clorometano" OR "methane, chloro-" OR "methylchlorid" OR " RN 74-87-3"
2/7/2019	"clorometano" OR "chlormethan" OR "chlorometany" OR "chloormethaan" OR "klormetan" OR "chlorométhane"
ProQuest 1/29/2019	noft("methyl chloride" OR "chloromethane" OR "chloride methyl" OR "chloromethane" OR "methyl chloride" OR "r 40" OR artic OR "chloormethaan" OR "chlormethan" OR "chlorure de methyle" OR "clorometano" OR "cloruro di metile" OR "methane chloro" OR "methylchlorid" OR "metylu chlorek" OR "monochloromethane" OR "freon 40" OR "74-87-3")
PubMed 1/29/2019	(((((("methyl chloride"[Supplementary Concept] OR "chloromethane"[Supplementary Concept])) AND ("1996"[Date - Publication] : "3000"[Date - Publication]))) OR ((((chloride, methyl[MeSH Terms]) OR chloromethane[MeSH Terms]) OR methyl chloride[MeSH Terms]) AND ("1996"[Date - Publication] : "3000"[Date - Publication]))) OR ((((((((((("R 40"[Tw]) OR Artic[Tw]) OR Chloormethaan[Tw]) OR Chlormethan[Tw]) OR "Chlorure de methyle"[Tw]) OR Clorometano[Tw]) OR "Cloruro di metile"[Tw]) OR "Methane, chloro"[Tw]) OR Methylchlorid[Tw]) OR "Metylu chlorek"[Tw]) OR Monochloromethane[Tw]) OR "Freon 40"[Tw]) AND ("1996"[Date - Publication] : "3000"[Date - Publication]))) OR ((74-87-3[EC/RN Number]) AND ("1996"[Date - Publication] : "3000"[Date - Publication]))

Table B-2. Database Query Strings

Database Search date	Query string
2/7/2019	(clorometano"[Tw] OR "chlormethan"[Tw] OR "chlorometany"[Tw] OR "chloormethaan "[Tw] OR "klormetan"[Tw] OR "chlorométhane"[Tw])) AND ("1996/01/01"[PDAT] : "2019/12/31"[PDAT]))
Science Direct 1/29/2019	"methyl chloride" OR “chloromethane” OR "chloride methyl" OR "R 40" OR "artic" OR "freon 40" OR "74-87-3"
2/7/2019	“clorometano" OR "chlormethan" OR "chlorometany" OR " chloormethaan" OR klormetan" OR "chloromethane”
SciFinder 1/29/2019	In SUBSTANCE IDENTIFIER, list one phrase per line, no quotes, as shown here: 74-87-3 methyl chloride chloromethane chloride methyl chloromethane methyl chloride r 40 artic chloormethaan chlormethan chlorure de methyle clorometano cloruro di metile methane chloro methylchlorid metylu chlorek monochloromethane freon 40
TOXLINE 1/29/2019	"methyl chloride" OR “chloromethane” OR "chloride methyl" OR “chloromethane” OR "methyl chloride" OR “r 40" OR “artic” OR “chloormethaan” OR “chlormethan” OR "chlorure de methyle" OR “clorometano” OR "cloruro di metile" OR "methane chloro" OR “methylchlorid” OR "metylu chlorek" OR “monochloromethane” OR "freon 40" OR 74-87-3 [rn]
2/7/2019	clorometano” OR “chlormethan” OR “chlorometany” OR “chloormethaan” OR “klormetan” OR "chloromethane
BIOSIS 2/8/2019	CH=("methyl chloride" OR "chloromethane" OR "chloride methyl" OR "chloromethane" OR "methyl chloride" OR "r 40" OR "artic" OR "chloormethaan" OR "chlormethan" OR "chlorure de methyle" OR "clorometano" OR "cloruro di metile" OR "methane chloro" OR "methylchlorid" OR "metylu chlorek" OR "monochloromethane" OR "freon 40" OR "74-87-3") Indexes=BIOSIS Previews Timespan=1996-2019
IPA 2/8/2019	74-87-3.rn. or ("methyl chloride" or chloromethane or "chloride methyl" or chloromethane or "methyl chloride" or "r 40" or artic or chloormethaan or chlormethan or "chlorure de methyle" or clorometano or "cloruro di metile" or "methane chloro" or methylchlorid or "metylu chlorek" or monochloromethane or "freon 40").rw. or ("methyl chloride" or chloromethane).sh.

The 2019 results were:

- Number of records identified from sources (after duplicate removal): 3,535.

B.1.2 Literature Screening

A two-step process was used to screen the literature search results to identify relevant studies examining the health effects of chloromethane:

- Title and Abstract Screen
- Full Text Screen

Title and Abstract Screen. Within the reference libraries, 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. In the Title and Abstract Screen step, 3,535 records were reviewed; 193 studies were considered potentially relevant to CHAPTER 2. in the toxicological profile and were moved to the next step in the process.

- Number of titles and abstracts screened: 3,535
- Number of studies considered potentially relevant and moved to the next step: 193

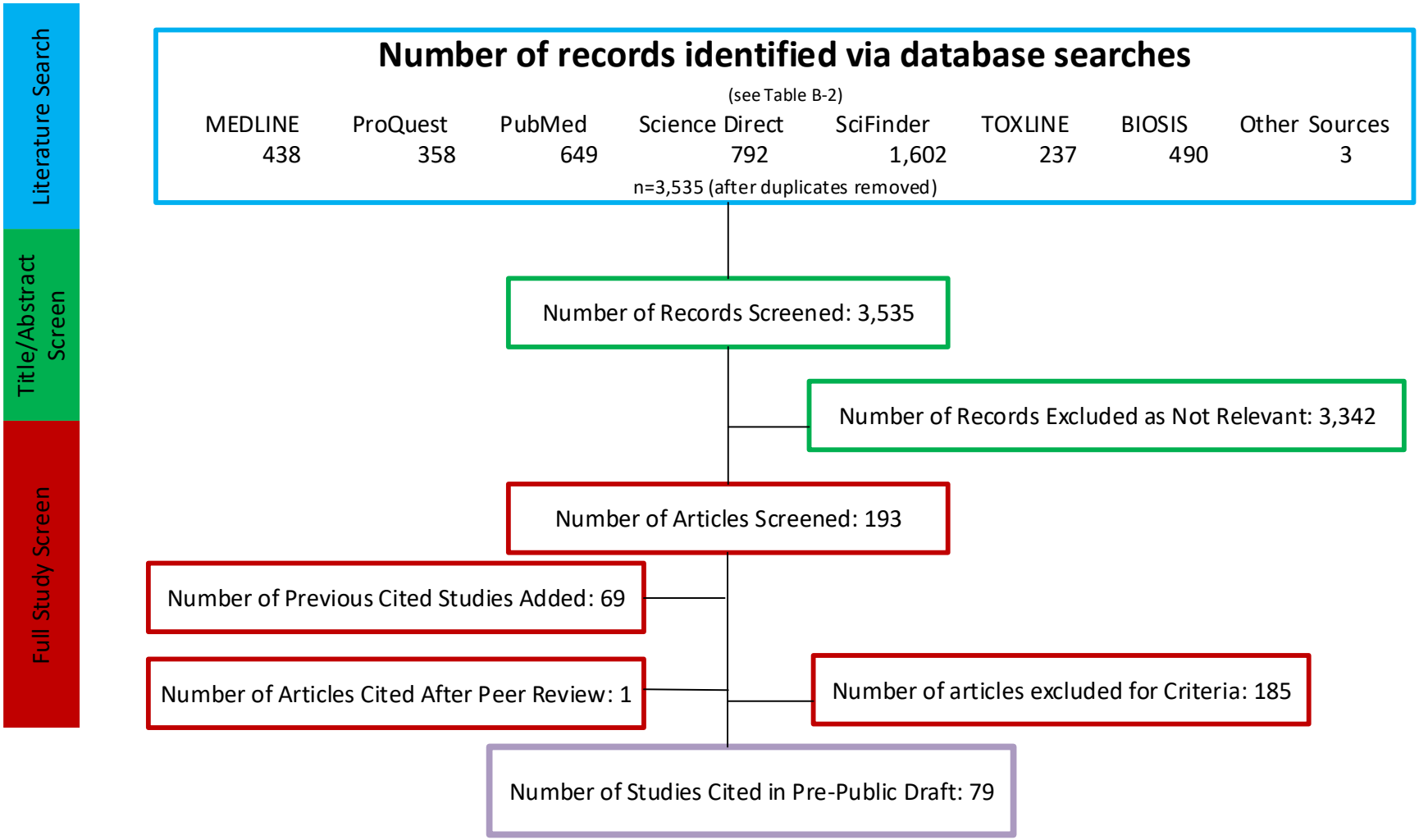
Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the Title and Abstract Screen step. Each of the 193 studies was reviewed to determine whether it met the inclusion criteria; however, the quality of the studies was not evaluated at this step of the process. Of the 193 studies, 9 were determined to be relevant to the human health endpoints evaluated in Chapter 2. In addition, after peer review we obtain access to one unpublished study which was relevant for profile development. These 10 studies were added to the 69 studies previously cited in the Health Effects sections of the 1998 profile, bringing the total number of health studies cited in the pre-public draft to 79.

- Number of studies that underwent full text review: 193
- Number of studies deemed relevant for chapter 2 after full text review: 9
- Number of studies cited in the Health Effects Section of the 1998 profile: 69
- Number of studies cited in the pre-public draft of the toxicological profile: 79

A summary of the results of the literature search and screening is presented in Figure B-1.

APPENDIX B

Figure B-1. Literature Search and Screen for Chloromethane Health Effect Studies



APPENDIX C. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF 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, and dermal exposure to chloromethane. The inclusion criteria used to identify relevant studies examining the health effects of chloromethane are presented in Table B-1 in the preceding section. 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.

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen were 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 literature search to update the existing toxicological profile for chloromethane (ATSDR 1998) was restricted to studies published between 1996 and 2019. See Appendix B for the databases searched and the strategy.

A total of 3,535 records relevant to the health effects section 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, 3,535 records were reviewed; 193 studies were considered to potentially meet the health effects inclusion criteria in Table C-1 and were 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 the 193 health effects studies identified in the Title and Abstract Screen was performed. 184 of these studies did not meet the inclusion criteria; some of the excluded studies were used as background information on toxicokinetics or mechanism of action or were relevant to other sections of the toxicological profile. Of the 69 studies included from Chapter 2 of the 1998 profile, 25 studies cited in the 1998 LSE tables were included in the systematic 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 ATSDR's EZTox Database (for toxicological studies and human controlled trials) and in Word tables (for human studies). A summary of the type of data extracted from each toxicological study is presented in Table C-2. Data extracted from epidemiological and human controlled trials included study population, outcomes assessed, confounders accounted for and the results of the assessment. For references that included more than one experiment or species, data extraction records were created for each experiment or species.

Overviews of the results of the inhalation, oral, dermal exposure studies are presented in Section 2.1of the profile and in the Levels Significant Exposures tables and in the Health Effects Evaluated in Humans Exposed to Chloromethane (Table 2-1, Table 2-2 and Table 2-3).

Table C-1. 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

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 Table C-4 and Table C-5, respectively. The human studies assessed for the systematic review examined a limited number of endpoints and reported cardiovascular, respiratory and neurological effects. Case studies were not included in the systematic review. Animal studies examined a comprehensive set of end points following inhalation, oral, or dermal exposure.

Evaluation of the literature indicated that sensitive endpoints associated with chloromethane exposure include cardiovascular, hepatic, renal, neurological, reproductive and developmental endpoints. Studies that were located in the current literature review or were listed in the 1998 Toxicological Profile's Level of Significant Exposure Table as assessing these potential outcomes were carried through to Steps 4-8 of the systematic review.

Table C-2. 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 Nonccancer	Cancer
Inhalation Studies																	
Cohort	0	2	4	0	0	0	0	0	0	0	0	0	1	0	0	0	3
Case Control	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	4
Population	0	1	1	0	1	0	0	0	0	0	0	0	3	0	0	0	0
Case Series	0	0	7	11	1	0	4	4	0	5	0	0	18	0	0	0	0
Oral Studies																	
Cohort	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Case Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Population	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Case Series	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Dermal Studies																	
Cohort	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Case Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Population	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Case Series	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Number of studies examining endpoint: 0, 1, 2, 3, 4, 5-9, ≥10

Table C-3. Overview of the Health Outcomes for Chloromethane Evaluated in Animal Studies

	Body Weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Cancer
Inhalation Studies																	
Acute Duration	8	7	3	2	3	1	11	10	1	3	3	2	12	12	2	1	0
Intermediate Duration	4	4	3	2	3	3	3	4	2	3	1	2	6	5	1	0	0
Chronic Duration	1	1	1	1	1	1	1	1	0	1	1	1	1	1	0	0	1
Oral Studies																	
Acute Duration	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Intermediate Duration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Chronic Duration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Dermal Studies																	
Acute Duration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Intermediate Duration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Chronic Duration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Number of studies examining endpoint	0	1	2	3	4	5-9	≥10

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 Table C-4, Table C-5, and Table C-6, 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-4. 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-5. 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?
Selective reporting bias
Were all measured outcomes reported?

Table C-6. 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?
Other bias
Did the study design or analysis account for important confounding and modifying variables?

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 epidemiological 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 epidemiological 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, human exposure, and animal experimental studies) are presented in Table C-7, Table C-8, Table C-9 respectively.

Table C-7. Summary of Risk of Bias Assessment for Chloromethane – Epidemiology Studies

Reference	Risk of bias criteria and ratings: 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							
Rafnsson and Gudmundsson 1997	++	-	+	-	++	++	Second
Rafnsson and Kristbjornsdottir 2014	++	-	+	-	++	++	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-8. Summary of Risk of Bias Assessment for Chloromethane – Human-Controlled Exposure Studies

Reference	Risk of bias criteria and ratings: Selection bias – Was administered dose or exposure level adequately randomized?	Selection bias – Was the allocation to study groups adequately concealed?	Performance bias – 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?	Detection bias – **Is there confidence in the outcome assessment?***	Selective reporting bias – Were all measured outcomes reported?	Risk of bias tier
Outcome: Respiratory								
Inhalation Acute Exposure								
Stewart et al. 1980	-	-	-	-	+	-	++	Third
Outcome: Cardiovascular								
Inhalation Acute Exposure								
Stewart et al. 1980	-	-	-	-	+	-	++	Third
Outcome: Neurologic								
Inhalation Acute Exposure								
Putz-Anderson (1981a)	-	-	-	– –	-	+	+	Second
Putz-Anderson (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-9. Risk of Bias Assessment for Select End Points for Chloromethane – Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: 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?	Detection bias: **Is there confidence in the outcome assessment?***	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
Outcome: Cardiovascular									
Inhalation acute exposure									
McKenna et al. 1981a (Beagle)	+	-	++	-	++	++	++	++	First
McKenna et al. 1981a (cat)	+	-	++	-	++	++	++	++	First
Inhalation intermediate exposure									
CIIT 1981 (6 mo., Rats)	++	++	+	-	++	++	++	++	First
CIIT 1981 (6mo, mouse)	++	++	+	-	+	-	++	++	First
CIIT 1981, (12 mo, rats)	++	++	+	-	++	++	++	++	First
CIIT 1981 (12 mo, mouse)	++	++	+	-	+	-	++	++	First
McKenna 1981b (rats)	++	-	++	-	+	++	+	+	First
McKenna 1981b (mouse)	++	-	++	-	+	++	+	+	First

Table C-9. Risk of Bias Assessment for Select End Points for Chloromethane – Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: 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?	Detection bias: **Is there confidence in the outcome assessment?***	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
McKenna 1981b (dog)	++	-	++	-	+	++	+	+	First
Mitchell et al. 1979 (rats)	++	-	+	-	++	++	-	+	Second
Mitchell et al. 1979 (mouse)	++	-	+	-	– –	++	-	+	Second
Inhalation chronic exposure									
CIIT 1981 (18 mo., Rats)	++	++	+	-	++	++	++	++	First
CIIT 1981 (18 mo., mouse)	++	++	+	-	+	-	++	++	First
CIIT 1981 (24 mo., rats)	++	++	+	-	++	++	++	++	First
CIIT 1981 (24 mo., mouse)	++	++	+	-	+	-	++	++	First
Outcome: Hepatic effects									
Inhalation acute exposure									
Burek et al. 1981 (rat)	++	-	++	-	++	++	+	++	First

Table C-9. Risk of Bias Assessment for Select End Points for Chloromethane – Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias — Was administered dose or exposure level adequately randomized?	Selection bias — Was the allocation to study groups adequately concealed?	Performance bias — Were experimental conditions identical across study groups?	Performance bias — 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?	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Were all measured outcomes reported?	Risk of bias tier
Chapin et al. 1984 (rat)	-	-	++	-	++	++	+	-	First
Chellman et al. 1986a	-	+	++	-	+	++	++	++	First
Chellman et al. 1986b (mouse)	-	+	++	-	-	+	+	+	First
Morgan KT et al. 1982 (mouse)	-	+	++	-	+	++	-	++	Second
Morgan KT et al. 1982 (rat)	-	+	++	-	+	++	-	++	Second
Landry et al. 1985 (mouse)	+	-	++	-	++	++	+	+	First
McKenna 1981a (beagle)	+	-	++	-	++	++	++	++	First
McKenna 1981a (cat)	+	-	++	-	++	++	++	++	First
Oral Acute exposure									
Reynolds and Yee 1967	-	-	+	-	-	-	+	++	Second

Table C-9. Risk of Bias Assessment for Select End Points for Chloromethane – Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: 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?	Detection bias: **Is there confidence in the outcome assessment?***	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
Inhalation intermediate exposure									
CIIT 1981 (6 mo., Rats)	++	++	+	-	++	++	++	++	First
CIIT 1981 (6 mo, mouse)	++	++	+	-	+	-	++	++	First
CIIT 1981 (12 mo, rats)	++	++	+	-	++	++	++	++	First
CIIT 1981 (12 mo, mouse)	++	++	+	-	+	-	++	++	First
McKenna 1981b (rats)	++	-	++	-	+	++	+	+	First
McKenna 1981b (mouse)	++	-	++	-	+	++	+	+	First
McKenna 1981b (dog)	++	-	++	-	+	++	+	+	First
Mitchell et al. 1979 (rats)	++	-	+	-	++	++	-	+	Second
Mitchell et al. 1979 (mouse)	++	-	+	-	– –	++	-	+	Second
Inhalation chronic exposure									

Table C-9. Risk of Bias Assessment for Select End Points for Chloromethane – Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: 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?	Detection bias: **Is there confidence in the outcome assessment?***	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
CIIT 1981 (18 mo., Rats)	++	++	+	-	++	++	++	++	First
CIIT 1981 (18 mo., mouse)	++	++	+	-	+	-	++	++	First
CIIT 1981 (24 mo., rats)	++	++	+	-	++	++	++	++	First
CIIT 1981 (24 mo., mouse)	++	++	+	-	+	-	++	++	First
Outcome: Renal effects									
Inhalation acute exposure									
Burek et al. 1981 (rat)	++	-	++	-	++	++	+	++	First
Chellman et al. 1986a (rat)	-	+	++	-	+	++	++	++	First
Chellman et al. 1986b (mouse)	-	+	++	-	-	+	+	+	First
Jiang et al. 1985	-	-	++	-	++	+	+	+	Second
Morgan KT et al. 1982 (mouse)	-	+	++	-	+	++	-	++	Second

Table C-9. Risk of Bias Assessment for Select End Points for Chloromethane – Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: 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?	Detection bias: **Is there confidence in the outcome assessment?***	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
Morgan KT et al. 1982 (Rat)	-	+	++	-	+	++	-	++	Second
Landry et al. 1985 (mouse)	+	-	++	-	++	++	+	+	First
McKenna 1981a (beagle)	+	-	++	-	++	++	++	++	First
McKenna 1981a (cat)	+	-	++	-	++	++	++	++	First
Inhalation intermediate exposure									
CIIT 1981 (6 mo., Rats)	++	++	+	-	++	++	++	++	First
CIIT 1981 (6 mo, mouse)	++	++	+	-	+	-	++	++	First
CIIT 1981 (12 mo, rats)	++	++	+	-	++	++	++	++	First
CIIT 1981 (12 mo, mouse)	++	++	+	-	+	-	++	++	First
McKenna 1981b (rats)	++	-	++	-	+	++	+	+	First

Table C-9. Risk of Bias Assessment for Select End Points for Chloromethane – Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: 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?	Detection bias: **Is there confidence in the outcome assessment?***	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
McKenna 1981b (mouse)	++	-	++	-	+	++	+	+	First
McKenna 1981b (dog)	++	-	++	-	+	++	+	+	First
Mitchell et al. 1979 (rats)	++	-	++	-	+	++	+	+	First
Mitchell et al. 1979 (mouse)	++	-	+	-	– –	++	-	+	Second
Inhalation chronic exposure									
CIIT 1981 (18 mo., Rats)	++	++	+	-	++	++	++	++	First
CIIT 1981 (18 mo., mouse)	++	++	+	-	+	-	++	++	First
CIIT 1981 (24 mo., rats)	++	++	+	-	++	++	++	++	First
CIIT 1981 (24 mo., mouse)	++	++	+	-	+	-	++	++	First
Outcome: Neurological									
Inhalation acute exposure									

Table C-9. Risk of Bias Assessment for Select End Points for Chloromethane – Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: 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?	Detection bias: **Is there confidence in the outcome assessment?***	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
Burek et al. 1981 (rat)	++	-	++	-	++	++	+	++	First
Chellman et al. 1986a (rat)	-	+	++	-	+	++	++	++	First
Chellman et al. 1986b (mouse)	-	+	++	-	-	+	+	+	First
Jiang et al. 1985	-	-	++	-	++	+	+	+	First
Morgan KT et al. 1982 (mouse)	-	+	++	-	+	++	-	++	Second
Morgan KT et al. 1982 (Rat)	-	+	++	-	+	++	-	++	Second
Landry et al. 1985 (mouse)	+	-	++	-	++	++	+	+	First
McKenna 1981a (beagle)	+	-	++	-	++	++	++	++	First
McKenna 1981a (cat)	+	-	++	-	++	++	++	++	First
Wolkowski-Tyl et al. 1983a (mouse)	-	-	++	-	+	++	-	++	Second

Table C-9. Risk of Bias Assessment for Select End Points for Chloromethane – Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias — Was administered dose or exposure level adequately randomized?	Selection bias — Was the allocation to study groups adequately concealed?	Performance bias — Were experimental conditions identical across study groups?	Performance bias — 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?	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Were all measured outcomes reported?	Risk of bias tier
Wolkowski-Tyl et al. 1983b (mouse)	+	-	+	-	++	++	-	++	Second
Inhalation intermediate exposure									
CIIT 1981 (6 mo., Rats)	++	++	+	-	++	++	++	++	First
CIIT 1981 (12 mo, rats)	++	++	+	-	+	-	++	++	First
McKenna 1981b (rats)	++	-	++	-	+	++	+	+	First
McKenna 1981b (mouse)	++	-	++	-	+	++	+	+	First
McKenna 1981b (dog)	++	-	++	-	+	++	+	+	First
Mitchell et al. 1979 (rats)	++	-	+	-	++	++	-	+	Second
Mitchell et al. 1979 (mouse)	++	-	+	-	– –	++	-	+	Second
Inhalation chronic exposure									
CIIT 1981 (18 mo., Rats)	++	++	+	-	++	++	++	++	First

Table C-9. Risk of Bias Assessment for Select End Points for Chloromethane – Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: 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?	Detection bias: **Is there confidence in the outcome assessment?***	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
CIIT 1981 (18 mo., mouse)	++	++	+	-	+	-	++	++	First
CIIT 1981 (24 mo., rats)	++	++	+	-	++	++	++	++	First
CIIT 1981 (24 mo., mouse)	++	++	+	-	+	-	++	++	First
Outcome: Reproductive									
Inhalation acute exposure									
Burek et al. 1981 (rat)	++	-	++	-	++	++	+	++	First
Chapin et al. 1984	-	-	++	-	++	++	+	++	First
Chellman et al. 1986a (rat)	-	+	++	-	+	+	++	++	First
Chellman et al. 1986b (mouse)	-	+	++	-	-	+	+	+	First
Chellman et al. 1987	+	+	++	-	+	++	+	+	First
Morgan KT et al. 1982 (Rat)	-	+	++	-	+	++	-	++	Second

Table C-9. Risk of Bias Assessment for Select End Points 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
McKenna 1981a (beagle)	+	-	++	-	++	++	++	++	First
McKenna 1981a (cat)	+	-	++	-	++	++	++	++	First
Wolkowski-Tyl et al. 1983a (mouse)	-	-	++	-	+	++	+	++	First
Wolkowshi-Tyl et al. 1983a (rat)	-	-	++	+	++	++	+	++	First
Wolkowski-Tyl et al. 1983b (mouse)	+	-	+	-	++	++	+	++	First
Working et al. 1985a	+	-	++	-	-	++	+	++	First
Working et al. 1985b	++	-	++	-	+	++	-	++	Second
Working and Bus 1986	+	-	+	-	+	+	+	++	First
Inhalation intermediate exposure									
CIIT 1981 (6 mo., Rats)	++	++	+	-	++	++	++	++	First

Table C-9. Risk of Bias Assessment for Select End Points for Chloromethane – Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias — Was administered dose or exposure level adequately randomized?	Selection bias — Was the allocation to study groups adequately concealed?	Performance bias — Were experimental conditions identical across study groups?	Performance bias — 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?	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Were all measured outcomes reported?	Risk of bias tier
CIIT 1981 (6 mo, mouse)	++	++	+	-	+	-	++	++	First
CIIT 1981 (12 mo, rats)	++	++	+	-	++	++	++	++	First
CIIT 1981 (12 mo, mouse)	++	++	+	-	+	-	++	++	First
Hamm et al. 1985 (20 wk)	+	-	-	-	-	+	+	++	Second
Hamm et al. 1985 (10 wk)	+	-	-	-	-	+	+	++	Second
McKenna 1981 b (rat)	++	-	++	-	+	++	+	+	First
McKenna 1981b (mouse)	++	-	++	-	+	++	+	+	First
McKenna 1981b (beagle)	++	-	++	-	+	++	+	+	First
Mitchell et al. 1979 (rat)	++	-	+	-	++	++	-	+	Second
Theuns-van Vliet et al. 2016 (rabbit)	-	– –	++	– –	++	++	-	+	Third

Inhalation chronic exposure

Table C-9. Risk of Bias Assessment for Select End Points for Chloromethane – Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: 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?	Detection bias: **Is there confidence in the outcome assessment?***	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
CIIT 1981 (18 mo., Rats)	++	++	+	-	++	++	++	++	First
CIIT 1981 (18 mo., mouse)	++	++	+	-	+	-	++	++	First
CIIT 1981 (24 mo., rats)	++	++	+	-	++	++	++	++	First
CIIT 1981 (24 mo., mouse)	++	++	+	-	+	-	++	++	First
Outcome: Developmental									
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 (20 wk)	+	-	-	-	-	+	+	++	Second

Table C-9. Risk of Bias Assessment for Select End Points 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
Theuns-van Vliet et al. 2016 (rabbit)	-	– –	++	– –	++	++	-	+	Third

++ = 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 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, observation epidemiology, human-controlled exposures and experimental animals. Unless there was a clear need for delineation in the confidence for a particular outcome, confidence assessments 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 study design features was determined for individual studies using four "yes or no" questions which were customized for observational 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 studies, and experimental animal studies are presented in Table C-10 Table C-11, Table C-12, 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-10. 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-11. 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 (i.e., 10 or more subjects)
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 (i.e., the statistical procedures used were presented in the paper and they were appropriate for the data)

Table C-12. Key Features of Study Design for Experimental Animal Studies

A concurrent control group was used
A sufficient number of animals per group were tested (i.e., 3 or more animals for acute exposure, 10-20 animals for intermediate exposure, 50 or more animals for chronic exposure)
Appropriate parameters used to assess a potential adverse effect (i.e., clinical, gross and histopathological outcomes were assessed. If an endpoint was not amendable to a clinical assessment then we did not downgrade the confidence in a study for not including it)
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis (i.e., the statistical procedures used were presented in the paper and they were appropriate for the data)

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 Table C-13 through Table C-15. 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 Table C-16.

Table C-13. 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						
Rafnsson and Gudmundsson 1997	no	yes	yes	yes	Moderate	
Rafnsson and Kristbjornsdottir 2014	no	yes	yes	yes	Moderate	

Table C-14. 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: Respiratory					
Inhalation Acute Exposure					
Stewart et al. 1980	yes	no	no	yes	Low
Outcome: Cardiovascular					
Inhalation Acute Exposure					
Stewart et al. 1980	yes	no	no	yes	Low
Outcome: Neurologic					
Inhalation Acute Exposure					
Putz-Anderson 1981a	yes	yes	yes	yes	High
Putz-Anderson 1981b	yes	yes	yes	yes	High
Stewart et al. 1980	yes	no	yes	yes	Moderate

Table C-15. 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					
Inhalation acute					
McKenna et al. 1981a (Beagle)	yes	no	yes	yes	Moderate
McKenna et al. 1981a (cat)	yes	no	yes	yes	Moderate
Inhalation intermediate exposure					
CIIT 1981 (6 mo., Rats)	yes	yes	yes	yes	High
CIIT 1981 (6mo, mouse)	yes	yes	yes	yes	High
CIIT 1981 (12 mo, rats)	yes	yes	yes	yes	High
CIIT 1981 (12 mo, mouse)	yes	yes	yes	yes	High
McKenna 1981b (rats)	yes	yes	yes	yes	High
McKenna 1981b (mouse)	yes	yes	yes	yes	High
McKenna 1981b (dog)	yes	yes	no	yes	Moderate
Mitchell et al. 1979 (rats)	yes	yes	yes	yes	High
Mitchell et al. 1979 (mouse)	yes	yes	yes	yes	High
Inhalation chronic exposure					
CIIT 1981 (18 mo., Rats)	yes	yes	yes	yes	High
CIIT 1981 (18 mo., mouse)	yes	yes	yes	yes	High
CIIT 1981 (24 mo., rats)	yes	yes	yes	yes	High
CIIT 1981 (24 mo., mouse)	yes	yes	yes	yes	High
Outcome: hepatic effects					
Inhalation acute					
Burek et al. 1981 (rat)	yes	yes	yes	yes	High
Chapin et al. 1984 (rat)	yes	yes	no	yes	Moderate
Chellman et al. 1986a	yes	yes	yes	yes	High
Chellman et al. 1986b (mouse)	yes	yes	yes	yes	High
Morgan KT et al. 1982 (mouse)	yes	yes	yes	yes	High

Table C-15. 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
Morgan KT et al. 1982 (Rat)	yes	yes	yes	yes	High
Landry et al. 1985 (mouse)	yes	yes	yes	yes	High
McKenna 1981a (beagle)	yes	no	yes	yes	Moderate
McKenna 1981a (cat)	yes	no	yes	yes	Moderate
Oral acute exposure					
Reynolds and Yee 1967	yes	no	yes	no	Low
Inhalation intermediate exposure					
CIIT 1981 (6 mo., Rats)	yes	yes	yes	yes	High
CIIT 1981 (6mo, mouse)	yes	yes	yes	yes	High
CIIT 1981 (12 mo, rats)	yes	yes	yes	yes	High
CIIT 1981 (12 mo, mouse)	yes	yes	yes	yes	High
McKenna 1981b (rats)	yes	yes	yes	yes	High
McKenna 1981b (mouse)	yes	yes	yes	yes	High
McKenna 1981b (dog)	yes	yes	no	yes	Moderate
Mitchell et al. 1979 (rats)	yes	yes	yes	yes	High
Mitchell et al. 1979 (mouse)	yes	yes	yes	yes	High
Inhalation chronic exposure					
CIIT 1981 (18 mo., Rats)	yes	yes	yes	yes	High
CIIT 1981 (18 mo., mouse)	yes	yes	yes	yes	High
CIIT 1981 (24 mo., rats)	yes	yes	yes	yes	High
CIIT 1981 (24 mo., mouse)	yes	yes	yes	yes	High
Outcome: Renal 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

Table C-15. 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
Jiang et al. 1985	yes	yes	no	no	Low
Morgan KT et al. 1982 (mouse)	yes	yes	yes	yes	High
Morgan KT et al. 1982 (Rat)	yes	yes	yes	yes	High
Landry et al. 1985 (mouse)	yes	yes	yes	yes	High
McKenna 1981a (beagle)	yes	no	yes	yes	Moderate
McKenna 1981a (cat)	yes	no	yes	yes	Moderate
Inhalation intermediate exposure					
CIIT 1981 (6 mo., Rats)	yes	yes	yes	yes	High
CIIT 1981 (6mo, mouse)	yes	yes	yes	yes	High
CIIT 1981 (12 mo, rats)	yes	yes	yes	yes	High
CIIT 1981 (12 mo, mouse)	yes	yes	yes	yes	High
McKenna 1981b (rats)	yes	yes	yes	yes	High
McKenna 1981b (mouse)	yes	yes	yes	yes	High
McKenna 1981b (dog)	yes	yes	no	yes	Moderate
Mitchell et al. 1979 (rats)	yes	yes	yes	yes	High
Mitchell et al. 1979 (mouse)	yes	yes	yes	yes	High
Inhalation chronic exposure					
CIIT 1981 (18 mo., Rats)	yes	yes	yes	yes	High
CIIT 1981 (18 mo., mouse)	yes	yes	yes	yes	High
CIIT 1981 (24 mo., rats)	yes	yes	yes	yes	High
CIIT 1981 (24 mo., mouse)	yes	yes	yes	yes	High
Outcome: Neurological					
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)	yes	yes	yes	yes	Moderate

Table C-15. 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
Jiang et al. 1985	yes	yes	yes	no	Moderate
Morgan KT et al. 1982 (mouse)	yes	yes	yes	yes	High
Morgan KT et al. 1982 (Rat)	yes	yes	yes	yes	High
Landry et al. 1985 (mouse)	yes	yes	yes	yes	High
McKenna 1981a (beagle)	yes	no	yes	yes	Moderate
McKenna 1981a (cat)	yes	no	yes	yes	Moderate
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 mo., Rats)	yes	yes	no	yes	Moderate
CIIT 1981 (12 mo, rats)	yes	yes	no	yes	Moderate
CIIT 1981 (6 mo., mouse)	yes	yes	no	yes	Moderate
CIIT 1981 (12 mo, mouse)	yes	yes	no	yes	Moderate
McKenna 1981b (rats)	yes	yes	yes	yes	High
McKenna 1981b (mouse)	yes	yes	yes	yes	High
McKenna 1981b (dog)	yes	yes	no	yes	Moderate
Mitchell et al. 1979 (rats)	yes	yes	yes	yes	High
Mitchell et al. 1979 (mouse)	yes	yes	yes	yes	High
Inhalation chronic exposure					
CIIT 1981 (18 mo., Rats)	yes	yes	yes	yes	High
CIIT 1981 (18 mo., mouse)	yes	yes	yes	yes	High
CIIT 1981 (24 mo., rats)	yes	yes	yes	yes	High
CIIT 1981 (24 mo., mouse)	yes	yes	yes	yes	High
Outcome: Reproductive					
Inhalation acute exposure					
Burek et al. 1981 (rat)	yes	yes	yes	yes	High

Table C-15. 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
Chapin et al. 1984	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
Chellman et al. 1987	yes	yes	yes	yes	High
Morgan KT et al. 1982 (Rat)	yes	yes	yes	yes	High
McKenna 1981a (beagle)	yes	no	yes	yes	Moderate
McKenna 1981a (cat)	yes	no	yes	yes	Moderate
Wolkowski-Tyl et al. 1983a (mouse)	yes	yes	yes	yes	High
Wolkowshi-Tyl et al. 1983a (rat)	yes	yes	yes	yes	High
Wolkowski-Tyl et al. 1983b (mouse)	yes	yes	yes	yes	High
Working et al. 1985a	yes	yes	yes	yes	High
Working et al. 1985b	yes	yes	yes	yes	High
Working and Bus 1986	yes	yes	yes	yes	High
Inhalation intermediate exposure					
CIIT 1981 (6 mo., Rats)	yes	yes	yes	yes	High
CIIT 1981 (6mo, mouse)	yes	yes	yes	yes	High
CIIT 1981 (12 mo, rats)	yes	yes	yes	yes	High
CIIT 1981 (12 mo, mouse)	yes	yes	yes	yes	High
Hamm et al. 1985 (20 wk)	yes	yes	yes	yes	High
Hamm et al. 1985 (10 wk)	yes	yes	yes	yes	High
McKenna 1981 b (rat)	yes	yes	yes	yes	High
McKenna 1981b (mouse)	yes	yes	yes	yes	High
McKenna 1981b (beagle)	yes	no	yes	yes	Moderate
Mitchell et al. 1979 (rat)	yes	yes	yes	yes	High
Theuns-van Vliet et al. 2016 (rabbit)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					

Table C-15. 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
CIIT 1981 (18 mo., Rats)	yes	yes	yes	yes	High
CIIT 1981 (18 mo., mouse)	yes	yes	yes	yes	High
CIIT 1981 (24 mo., rats)	yes	yes	yes	yes	High
CIIT 1981 (24 mo., mouse)	yes	yes	yes	yes	High
Outcome: Developmental					
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 (20 wk)	yes	yes	yes	yes	High
Theuns-van Vliet et al. 2016 (rabbit)	yes	yes	yes	yes	High

Table C-16. Initial Confidence Rating for Chloromethane Health Effects Studies

	Initial Study Confidence	Initial Confidence Rating
Outcome: Cardiovascular		
Inhalation acute		
Animal Studies		
McKenna et al. 1981a (Beagle)	Moderate	Moderate
McKenna et al. 1981a (cat)	Moderate	
Human Studies		
Stewart 1980	Low	Moderate
Rafnsson and Gudmundsson 1997	Moderate	
Rafnsson and Kristbjornsdottir 2014	Moderate	
Inhalation intermediate exposure		
Animal Studies		
CIIT 1981 (6 mo., Rats)	High	High
CIIT 1981 (6mo, mouse)	High	
CIIT 1981 (12 mo, rats)	High	
CIIT 1981 (12 mo, mouse)	High	
McKenna 1981b (rats)	High	
McKenna 1981b (mouse)	High	
McKenna 1981b (dog)	Moderate	
Mitchell et al. 1979 (rats)	High	
Mitchell et al. 1979 (mouse)	Moderate	
Inhalation chronic exposure		
Animal Studies		
CIIT 1981 (18 mo., Rats)	High	High
CIIT 1981 (18 mo., mouse)	High	
CIIT 1981 (24 mo., rats)	High	
CIIT 1981 (24 mo., mouse)	High	
Outcome: hepatic effects		
Inhalation acute exposure		
Animal studies		
Burek et al. 1981 (rat)	High	High
Chapin et al. 1984 (rat)	Moderate	
Chellman et al. 1986a	High	
Chellman et al. 1986b (mouse)	High	

Table C-16. Initial Confidence Rating for Chloromethane Health Effects Studies

	Initial Study Confidence	Initial Confidence Rating
Morgan KT et al. 1982 (mouse)	High	
Morgan KT et al. 1982 (Rat)	High	
Landry et al. 1985 (mouse)	High	
McKenna 1981a (beagle)	Moderate	
McKenna 1981a (cat)	Moderate	
Oral acute exposure		
Animal Studies		
Reynolds and Yee 1967	Low	Low
Inhalation intermediate exposure		
CIIT 1981 (6 mo., Rats)	High	
CIIT 1981 (6mo, mouse)	High	
CIIT 1981 (12 mo, rats)	High	
CIIT 1981 (12 mo, mouse)	High	
McKenna 1981b (rats)	High	High
McKenna 1981b (mouse)	High	
McKenna 1981b (dog)	Moderate	
Mitchell et al. 1979 (rats)	High	
Mitchell et al. 1979 (mouse)	Moderate	
Inhalation chronic exposure		
Animal Studies		
CIIT 1981 (18 mo., Rats)	High	
CIIT 1981 (18 mo., mouse)	High	High
CIIT 1981 (24 mo., rats)	High	
CIIT 1981 (24 mo., mouse)	High	
Outcome: Renal effects		
Inhalation acute exposure		
Animal Studies		
Burek et al. 1981 (rat)	High	
Chellman et al. 1986a (rat)	High	
Chellman et al. 1986b (mouse)	High	
Jiang et al. 1985	Low	High
Morgan KT et al. 1982 (mouse)	High	
Morgan KT et al. 1982 (Rat)	High	
Landry et al. 1985 (mouse)	High	

Table C-16. Initial Confidence Rating for Chloromethane Health Effects Studies

	Initial Study Confidence	Initial Confidence Rating
McKenna 1981a (beagle)	Moderate	
McKenna 1981a (cat)	Moderate	
Inhalation intermediate exposure		
Animal Studies		
CIIT 1981 (6 mo., Rats)	High	
CIIT 1981 (6mo, mouse)	High	
CIIT 1981 (12 mo, rats)	High	
CIIT 1981 (12 mo, mouse)	High	
McKenna 1981b (rats)	High	High
McKenna 1981b (mouse)	High	
McKenna 1981b (dog)	Moderate	
Mitchell et al. 1979 (rats)	High	
Mitchell et al. 1979 (mouse)	Moderate	
Inhalation chronic exposure		
Animal Studies		
CIIT 1981 (18 mo., Rats)	High	
CIIT 1981 (18 mo., mouse)	High	High
CIIT 1981 (24 mo., rats)	High	
CIIT 1981 (24 mo., mouse)	High	
Outcome: Neurological		
Inhalation acute exposure		
Animal Studies		
Burek et al. 1981 (rat)	Low	
Chellman et al. 1986a (rat)	High	
Chellman et al. 1986b (mouse)	Moderate	
Jiang et al. 1985	Moderate	
Morgan KT et al. 1982 (mouse)	High	
Morgan KT et al. 1982 (Rat)	High	High
Landry et al. 1985 (mouse)	High	
McKenna 1981a (beagle)	Moderate	
McKenna 1981a (cat)	Moderate	
Wolkowski-Tyl et al. 1983a (mouse)	High	
Wolkowski-Tyl et al. 1983b (mouse)	Low	
Human studies		

Table C-16. Initial Confidence Rating for Chloromethane Health Effects Studies

	Initial Study Confidence	Initial Confidence Rating
Putz-Anderson (1981a)	High	
Putz-Anderson (1981b)	High	High
Stewart et al. 1980	Moderate	
Inhalation intermediate exposure		
Animal Studies		
CIIT 1981 (6 mo., Rats)	Moderate	
CIIT 1981 (12 mo, rats)	Moderate	
CIIT 1981 (6 mo., mouse)	Moderate	
CIIT 1981 (12 mo, mouse)	Moderate	
McKenna 1981b (rats)	High	High
McKenna 1981b (mouse)	High	
McKenna 1981b (dog)	Moderate	
Mitchell et al. 1979 (rats)	High	
Mitchell et al. 1979 (mouse)	Moderate	
Inhalation chronic exposure		
Animal Studies		
CIIT 1981 (18 mo., Rats)	High	
CIIT 1981 (18 mo., mouse)	High	High
CIIT 1981 (24 mo., rats)	High	
CIIT 1981 (24 mo., mouse)	High	
Outcome: Reproductive		
Inhalation acute exposure		
Animal Studies		
Burek et al. 1981 (rat)	High	
Chapin et al. 1984	High	
Chellman et al. 1986a (rat)	High	
Chellman et al. 1986b (mouse)	High	
Chellman et al. 1987	High	
Morgan KT et al. 1982 (Rat)	High	High
McKenna 1981a (beagle)	Moderate	
McKenna 1981a (cat)	Moderate	
Wolkowski-Tyl et al. 1983a (mouse)	High	
Wolkowshi-Tyl et al. 1983a (rat)	High	
Wolkowski-Tyl et al. 1983b (mouse)	High	

Table C-16. Initial Confidence Rating for Chloromethane Health Effects Studies

	Initial Study Confidence	Initial Confidence Rating
Working et al. 1985a	High	
Working et al. 1985b	High	
Working and Bus 1986	High	
Inhalation intermediate exposure		
Animal Studies		
CIIT 1981 (6 mo., Rats)	High	
CIIT 1981 (6mo, mouse)	High	
CIIT 1981 (12 mo, rats)	High	
CIIT 1981 (12 mo, mouse)	High	
Hamm et al. 1985 (20 wk)	High	
Hamm et al. 1985 (10 wk)	High	High
McKenna 1981 b (rat)	High	
McKenna 1981b (mouse)	High	
McKenna 1981b (beagle)	Moderate	
Mitchell et al. 1979 (rat)	High	
Theuns-van Vliet 2016 (rabbit)	High	
Inhalation chronic exposure		
Animal Studies		
CIIT 1981 (18 mo., Rats)	High	
CIIT 1981 (18 mo., mouse)	High	
CIIT 1981 (24 mo., rats)	High	High
CIIT 1981 (24 mo., mouse)	High	
Outcome: Developmental		
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 (20 wk)	High	High
Theuns-van Vliet et al. 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 are presented in Table C-15. 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.

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 (Table C-4, Table C-5, Table C-6). 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 end points 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

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.

  - 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:

  - Upgrade one confidence level for evidence of a monotonic dose-response gradient
  - 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:

- 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:

  - Upgrade one confidence level if there is a high degree of consistency in the database

The results of this assessment are presented in Table C-17. with the final confidence in the body of literature by endpoint presented in Table C-18.

Table C-17. 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	Low
Animal studies	Moderate	None	Moderate
Outcome: Hepatic Effects			
Animal studies (Inhalation)	High	+1 Large magnitude of effect	High
Animal studies (Oral)	Low	-2 risk of bias	Very Low
Outcome: Renal Effects:			
Animal Studies	High	-1 unexplained inconsistency	Moderate
Outcome: Neurological Effects			
Human Studies	High	-1 risk of bias	Moderate
Animal Studies	High	None	High
Outcome: Reproductive Effects			
Animal Studies	High	-1 Unexplained inconsistency	Moderate
Outcome: Developmental Effects			
Animal Studies	High	-1 Indirectness - 1 Unexplained inconsistency	Low

Table C-18. Confidence in the Body of Evidence for Chloromethane

Outcome	Confidence in Body of Evidence	
	Human Studies	Animal Studies
Cardiovascular	Low	Moderate
Hepatic	No Data	High (Inhalation)
		Very Low (Oral)
Renal	No Data	Moderate
Neurological	Moderate	High
Reproductive	No Data	Moderate
Developmental	No Data	Low

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-19.

Table C-19. 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	Low	Health Effect	Low
Hepatic	No data		No data
Renal	No data		No data
Neurologic	Moderate	Health Effect	Moderate
Reproductive	No data		No data
Developmental	No data		No data
Animal Studies			
Cardiovascular	Moderate	No Health Effect	Inadequate
Hepatic	High (Inhalation)	Health Effect	High (Inhalation)
	Very Low (Oral)	No Health Effect	Inadequate
Renal	Moderate	Health Effect	Moderate
Neurological	High	Health Effect	High
Reproductive	Moderate	Health Effect	Moderate
Developmental	Low	Health Effect	Inadequate

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:

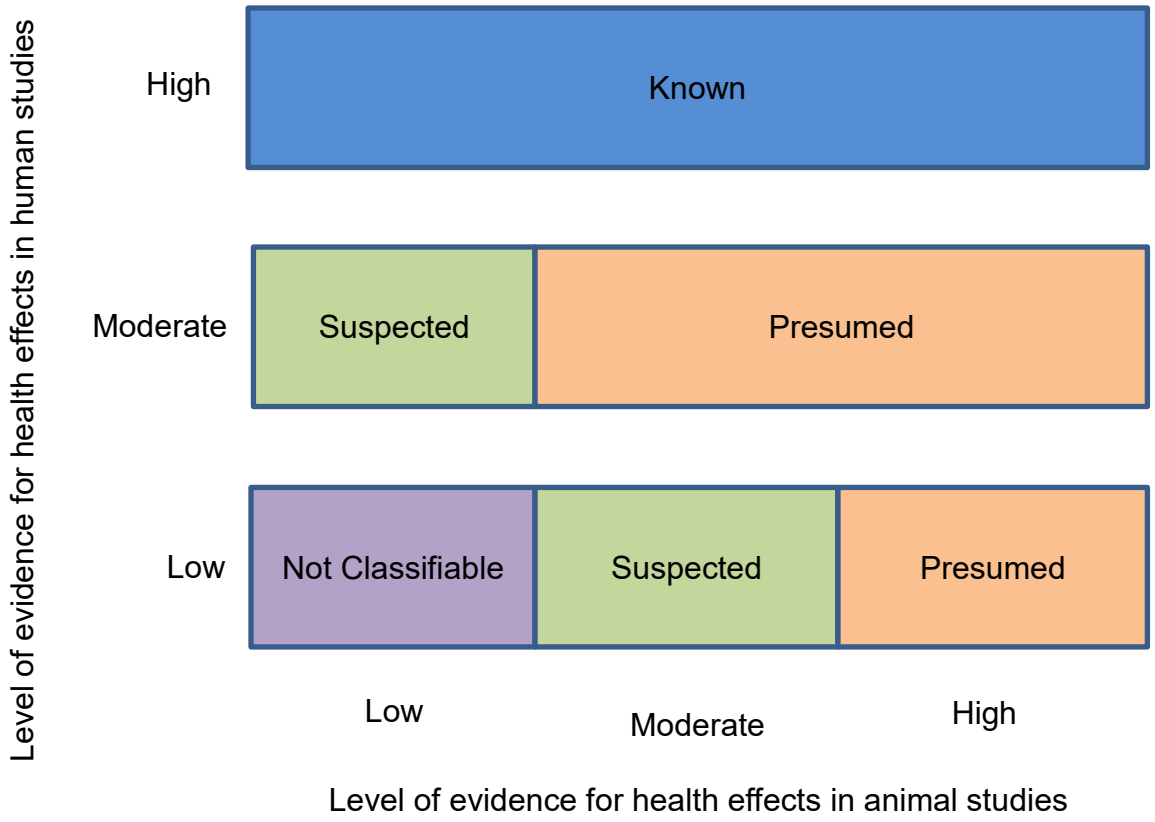
- Known to be a hazard to humans
- Presumed to be a hazard to humans
- Suspected to be a hazard to humans
- Not classifiable as to the hazard to humans

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.

The hazard identification conclusions for chloromethane are listed below and summarized in Table C-20.

Presumed Health Effects

- Hepatic effects following inhalation exposure
    - No evidence from human studies was evaluated in the systematic review.
    - There is a high level of evidence from experimental animal studies, and mice are deemed more susceptible than rats. Acute, intermediate, or chronic exposure of mice to approximately 1,000-l,500 ppm generally resulted in necrosis and degeneration of the liver (Chellman et al. 1986a, Chellman et al. 1986b; CIIT 1981; Landry et al. 1985; Mitchell et al. 1979; Morgan KT et al. 1982). Additionally, chloromethane exposure in rats was associated with changes in enzyme levels (Chapin et al. 1984; Dodd et al. 1982).

- Neurologic effects following inhalation exposure
    - Human controlled trials did not show significant nervous system effects with low levels of exposure to chloromethane (Putz-Anderson et al. 1981a; 1981b; Stewart et al. 1980).
    - Experimental animal studies show a high level of evidence for a range of neurological impacts due to acute, intermediate, and chronic duration exposure. The nervous system impacts range from observable changes in outcomes such as behavior, gait, ataxia, and tremors to histopathological lesions in the brain and axonal swelling (Chellman et al. 1986a, Chellman et al. 1986b; CIIT 1981; Jiang et al. 1985; Landry et al. 1985; McKenna 1981a, 1981b; Morgan KT et al. 1982; Wolkowski-Tyl et al. 1983a, 1983b). The impacts have been seen following acute, intermediate, and chronic exposure.

Suspected Health Effects

- Renal
    - No evidence from human studies was evaluated in the systematic review.
    - Experimental rodent studies provide moderate evidence of an association between chloromethane exposure and renal health effects. Effects to the kidneys range from changes in serum enzymes (Dodd et al. 1982), to histopathological lesions (Chellman et al. 1986a; CIIT 1981), to kidney failure (Burek et al. 1981).

- Reproductive
    - No evidence from human studies was evaluated in the systematic review.
    - Experimental animal studies provide moderate evidence of an association between chloromethane exposure and reproductive health effects. The reproductive endpoints are mainly seen in male rodents and consist of testicular and epididymal lesions (Burek et al. 1981; Hamm et al. 1985; Chellman et al. 1987; Working et al. 1985b), incomplete or ineffective spermatogenesis (Burek et al. 1981; Chapin et al. 1984; Chellman et al. 1987; Working et al. 1985b), and corresponding decreases in fertility via pre- and post-implantation loss (Working et al. 1985a). Decreased fertility is thought to be primarily attributable to male

exposures to chloromethane and resulting damage to sperm. The impacts have been seen following acute, intermediate, and chronic exposure.

Not Classifiable Health Effects

- Hepatic effects following oral exposure
    - 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). No liver necrosis was found in the rats given chloromethane.
- Cardiovascular
    - Human studies provide a low level of evidence of an association between chloromethane exposure and cardiovascular outcomes. Specifically, epidemiologic studies (Rafnsson and Gudmundsson 1997; Rafnsson and Kristbjornsdottir 2014) have noted increases in cardiovascular effects in human populations; these studies are limited in that the levels of exposure that occurred are not available. Additionally, the inability to account for residual confounding increases the risk of bias of the studies (Rafnsson and Gudmundsson 1997; Rafnsson and Kristbjornsdottir 2014).
    - Animal studies noted changes in cardiovascular outcomes; however, these were deemed likely secondary to neurologic effects (von Oettingen et al. 1949, 1950). No histopathologic lesions were noted in animal studies after exposure to chloromethane with intermediate and chronic exposure durations (McKenna et al. 1981a; 1981b; Mitchell et al. 1979, CIIT 1981).
- Developmental
    - No evidence from human studies was evaluated in this systematic review for developmental endpoints.
    - Experimental animal studies provide low evidence of an association between chloromethane exposure and adverse developmental outcomes. The fetal effects consisted of reduced fetal body weight and crown-rump length, and reduced ossification in the metatarsals and phalanges, the centra of the thoracic vertebrae, the pubis of the pelvic girdle, and the metatarsals of the hind limbs (Wolkowski-Tyl et al. 1983a). However, this delayed ossification occurred in rats at doses which were maternally toxic, and was not observed in mice. Additionally, heart malformations were observed in experimental B6C3F1 mice exposed to chloromethane during gestation (Wolkowski-Tyl et al. 1983a, 1983b). The same malformations were not observed in rats (Wolkowski-Tyl et al. 1981a; 1983a). The findings from Wolkowski-Tyl et al. (1981a,b; 1983 a,b) related to cardiac heart malformations were questioned by John-Green et al. (1985) as potentially due to the sectioning technique used. However, their argument was based on a lack of observed malformations with a vastly different exposure protocol (lower doses and shorter exposure durations). In an unpublished study by Theuns-van Vliet et al. (2016), exposure to chloromethane up to 1012 ppm did not result in any cardiac malformations in New Zealand White Rabbits. This brings into question whether the effects seen in the mice were specific to that species; and whether there is human health relevance from the Wolkowski-Tyl et al. (1981 a,b; 1983a,b) cardiac malformation findings.

Table C-20. Hazard Identification Conclusions for Chloromethane

Outcome	Hazard identification
Cardiovascular	Not Classifiable
Hepatic	Presumed (Inhalation) Not Classifiable (Oral)
Renal	Suspected
Neurologic	Presumed
Reproductive	Suspected
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 CHEMICALS, 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 C-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 C-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.

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
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 (10)									
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									

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

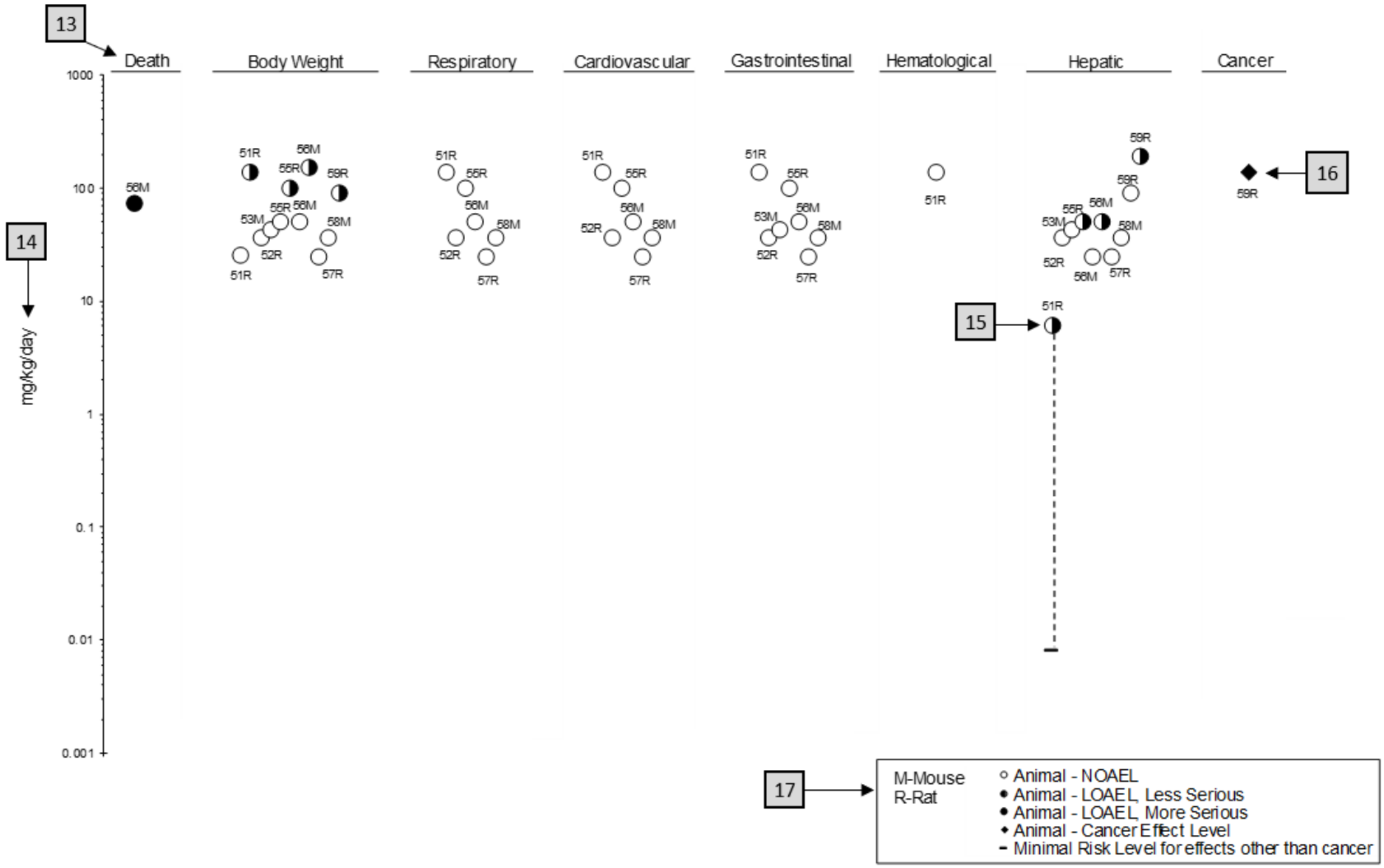
(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[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).

APPENDIX D

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral

12 → Chronic (≥365 days)



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

The following additional materials are available online:

Case Studies in Environmental Medicine are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see https://www.atsdr.cdc.gov/csem/csem.html).

Managing Hazardous Materials Incidents is a three-volume 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.asp). Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

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.

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.

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/m3 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.

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
DHHS	Department of Health and Human Services
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	lactic 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
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 level/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
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
q1*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result