CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

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

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

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

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

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

1.2 SUMMARY OF HEALTH EFFECTS

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

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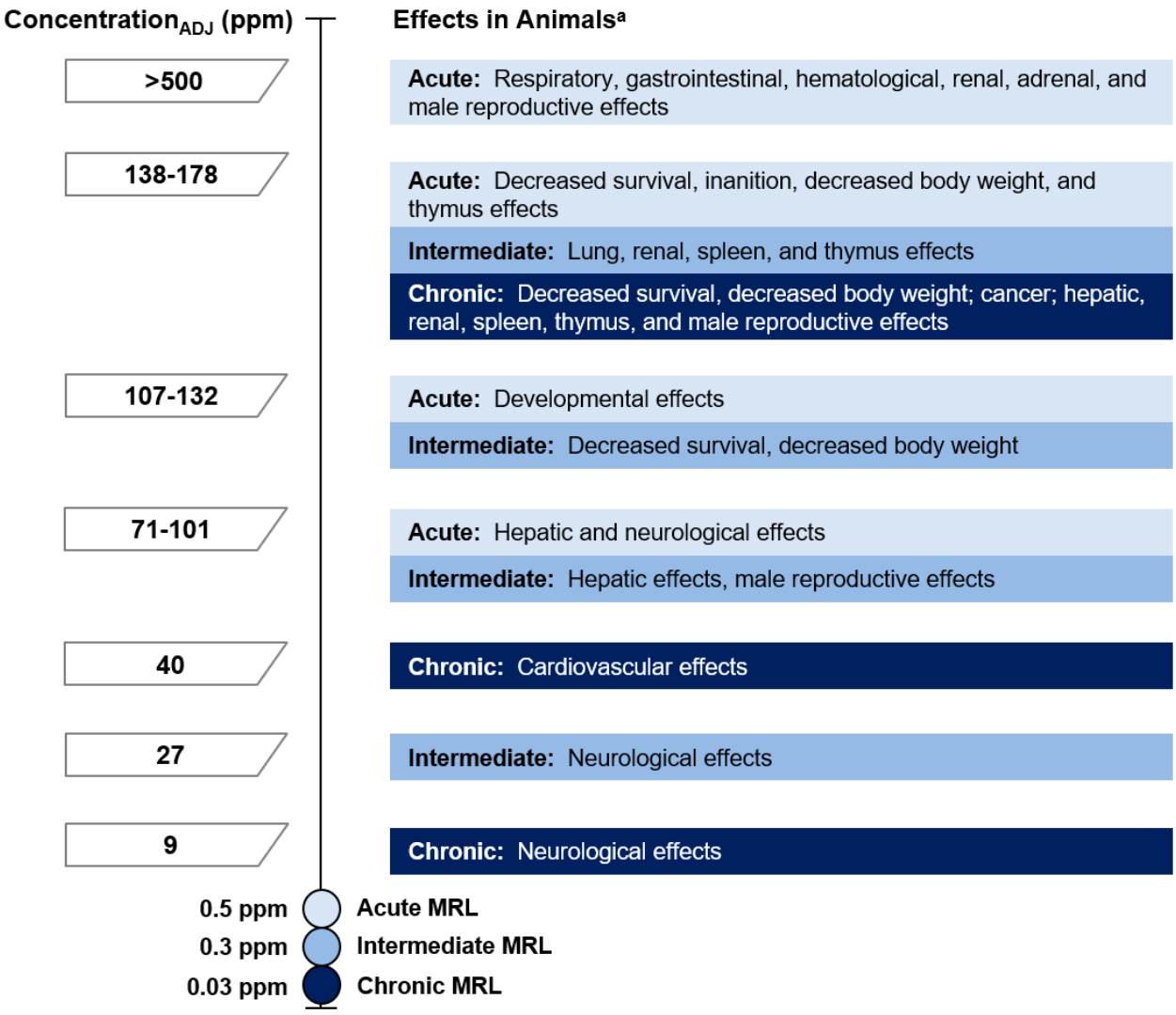
As illustrated in Figure 1-1, the neurological, hepatic, cardiovascular, developmental, and male reproductive systems appear to be sensitive to inhalation exposure to chloromethane. A systematic review of the available literature was conducted on these sensitive endpoints, including both human and animal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

- Neurological effects are a presumed health effect with inhalation exposure.
- Hepatic effects are a presumed health effect with inhalation exposure.
- Male reproductive effects are a presumed health effect with inhalation exposure.
- Cardiovascular effects are not classifiable with inhalation exposure.
- Developmental effects are not classifiable with inhalation exposure.

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

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



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

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

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

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

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

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

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

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

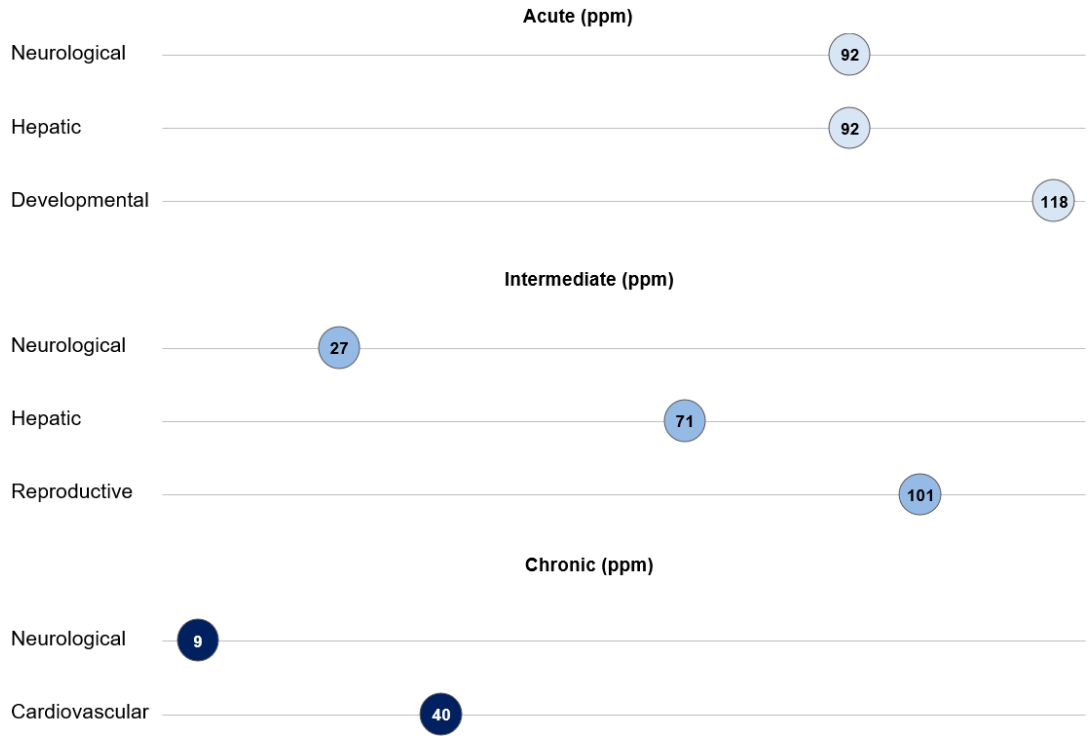
1.3 MINIMAL RISK LEVELS (MRLs)

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

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

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

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



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

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

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

[a]See Appendix A for additional information.

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