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).

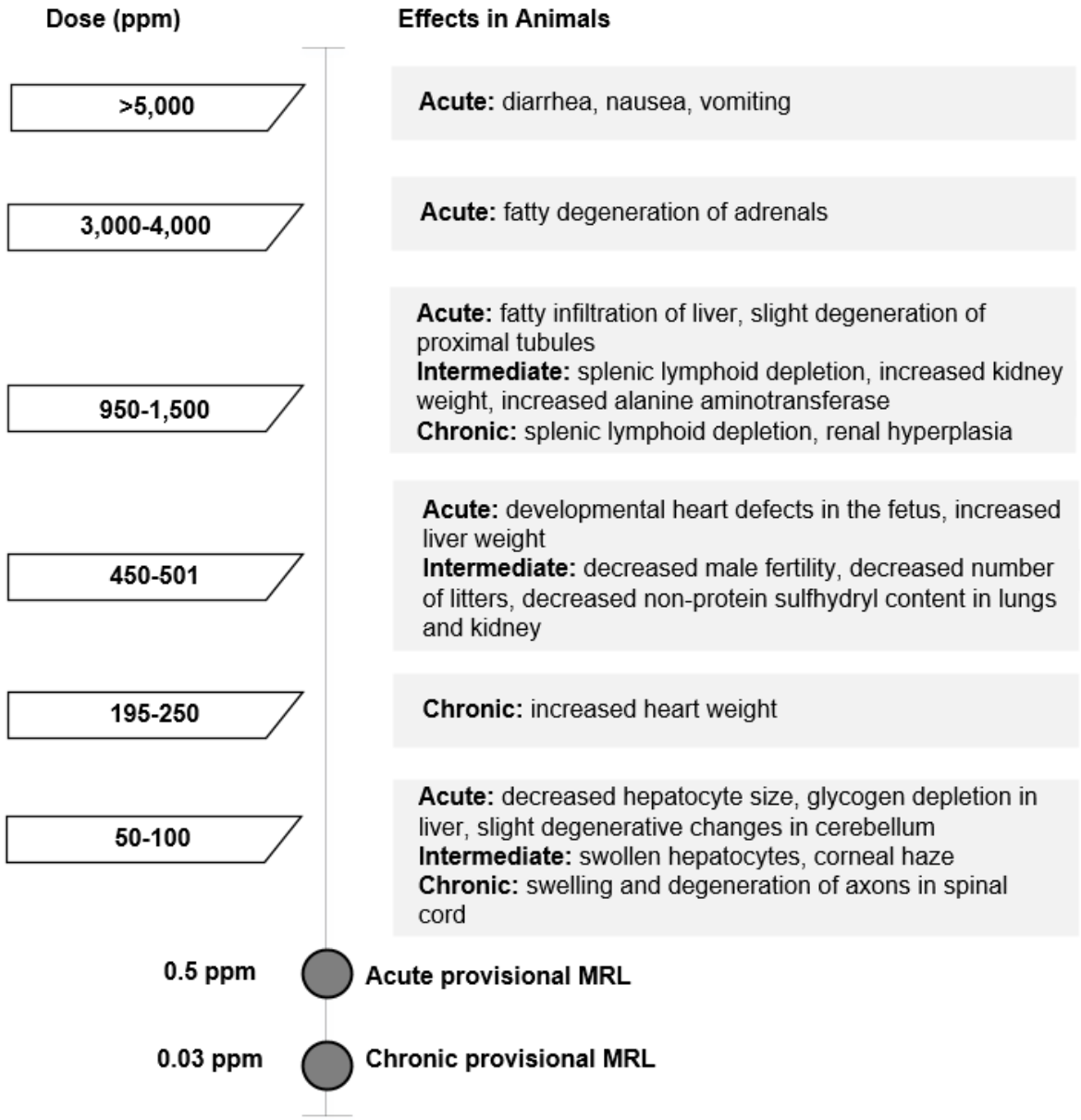
***Neurologic Effects*.** Numerous case studies of individuals who were highly exposed to chloromethane resulting from refrigeration system leaks consistently reported neurological effects, including fatigue, progressive drowsiness, staggering, headache, nausea, slurred speech, blurred and double vision, 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.

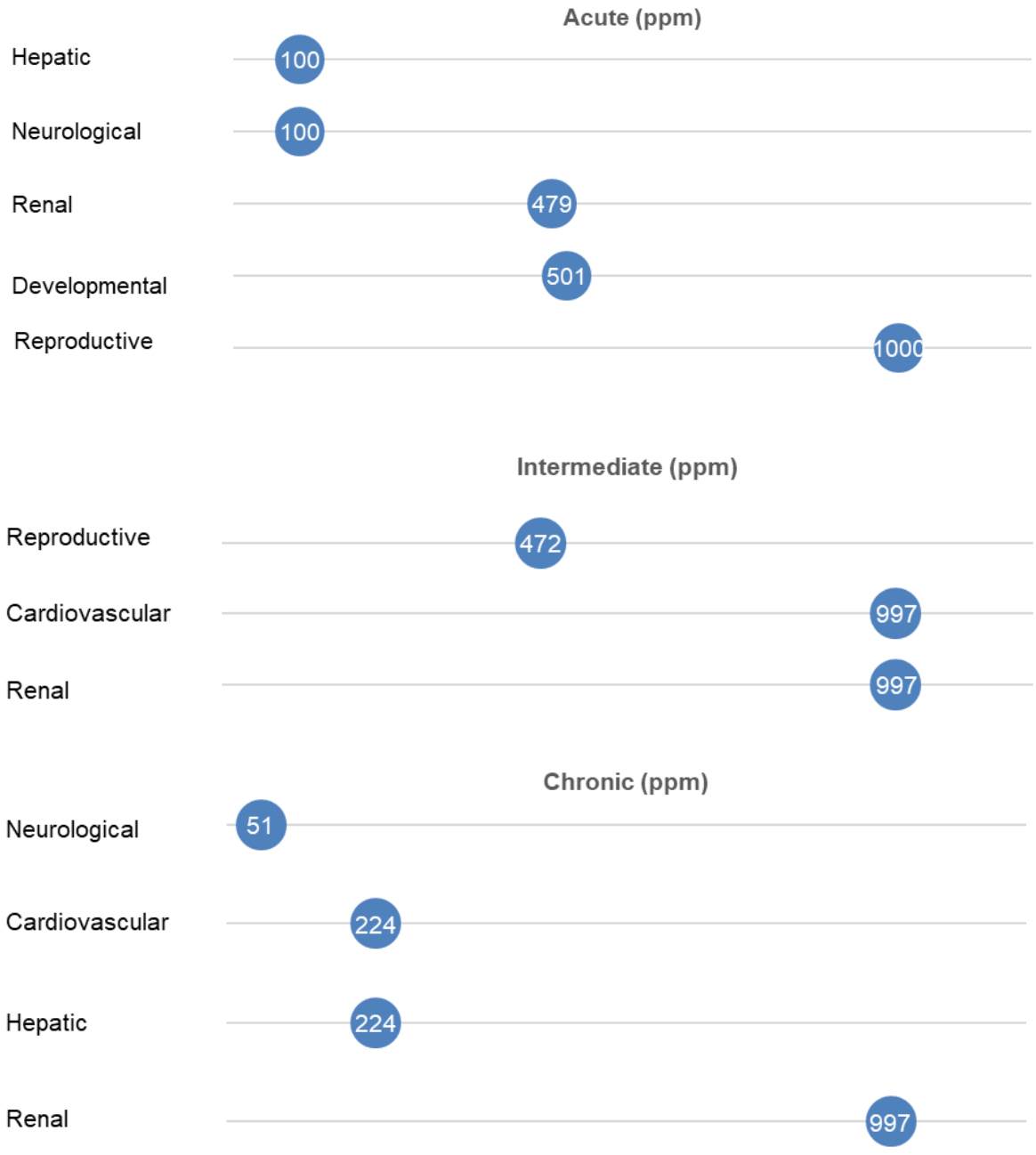


Table 1-1. Provisional Minimal Risk Levels for Chloromethane

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				