CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Chloroform (also known as trichloromethane or methyl trichloride) is a volatile colorless liquid with a pleasant non-irritating odor and a slightly sweet taste. Chloroform is produced naturally via biological and physical processes. Most of the chloroform produced by industry in the United States is used as a chemical intermediate, specifically for producing refrigerants and polymers used for non-corrosive, waterproof, or nonstick liners. Additionally, chloroform may be used as a solvent in various industrial applications. Historically, chloroform was also used as an anesthetic during surgery, but it is no longer used for this purpose due to availability of safer alternatives.

Chloroform produced by industry can enter the environment from chemical companies' waste sites. Chloroform can also enter the environment as an unwanted disinfection byproduct that originates from the chlorination of drinking water. Chloroform is readily volatile and enters the air directly from factories that make or use it and by evaporating from water and soil that contain it. Chloroform enters water and soil when any wastewater containing chlorine is released into the environment and may migrate from soil to groundwater due to its low sorption. Since chloroform is produced naturally and is formed as a byproduct of chlorine in water, small amounts are likely to be found almost everywhere. Chloroform's half-life in the atmosphere is on the order of months and is persistent in aerobic environments; anaerobic biodegradation occurs more readily, especially at low chloroform concentrations.

Chloroform levels have been fairly well characterized in ambient and indoor air, food, and drinking water supplies. Detections are generally in the ppb range. Limited monitoring studies of surface water, groundwater, soil, and sediment were located. The general population is most likely to be exposed to chloroform through inhalation of indoor and outdoor air, ingestion of food or disinfected water, or dermal contact with disinfected water. Chloroform contamination of these media most likely results as a byproduct of disinfection of water by chlorine. Chloroform will readily volatize from treated water to indoor and outdoor air. Thus, low levels of chloroform vapor may be breathed in while using treated water during bathing or cleaning or during food preparation.

Populations with increased exposure to chloroform are expected to be people who work in industries that use or manufacture chloroform, or who work or reside near sources where chloroform may form as a disinfection byproduct. Limited occupational exposure data were available. Individuals who both work

in facilities that manufacture/use chloroform and live nearby (e.g., fence line communities) may have increased risk of higher cumulative exposure due to both occupational plus residential exposure. Other populations with increased risk of exposure include people who are around chlorinated water for extended periods of time, such as when swimming or cleaning, or are living near hazardous waste sites with chloroform contamination.

1.2 SUMMARY OF HEALTH EFFECTS

Information on the noncancer toxicity of chloroform in humans primarily comes from numerous case series and case reports following medical use as an anesthetic, intentional exposure (e.g., recreational, suicidal, or homicidal purposes), or accidental exposure. There are a limited number of occupational exposure studies informing noncancer toxicity of chloroform. Additionally, many epidemiological studies examine potential toxic effects following exposure to chloroform as a water disinfection byproduct. Further information on the noncancer toxicity of chloroform comes from numerous inhalation and oral studies in animals. Data following dermal exposure are very limited in humans and animals.

As illustrated in Figures 1-1 and 1-2, sensitive targets in laboratory animals following inhalation and/or oral exposure include the respiratory, hepatic, renal, and neurological systems, along with the developing organism.

A systematic review of these endpoints resulted in the following hazard identification conclusions:

- Respiratory effects are a presumed health effect for humans following inhalation exposure.
- Hepatic effects are a known health effect for humans.
- Renal effects are a presumed health effect for humans.
- Neurological effects are a known health effect for humans.
- Developmental effects are a suspected health effect for humans.

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

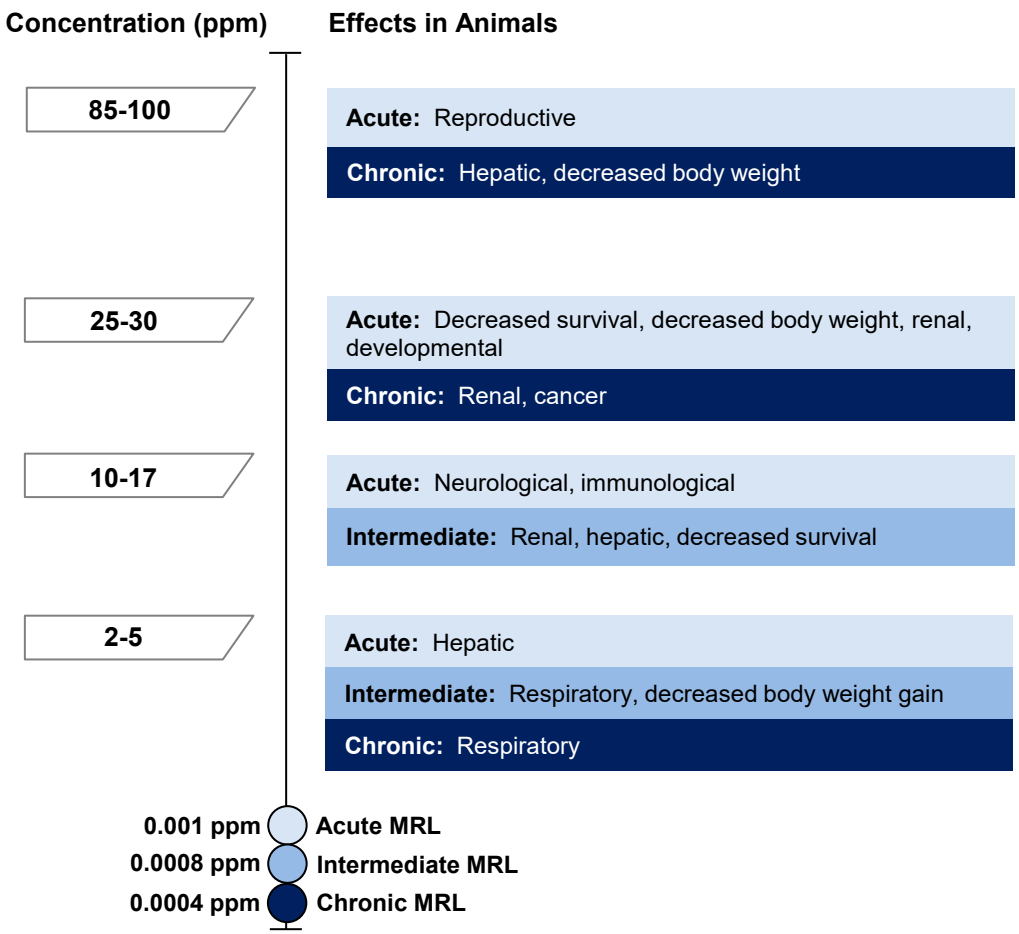
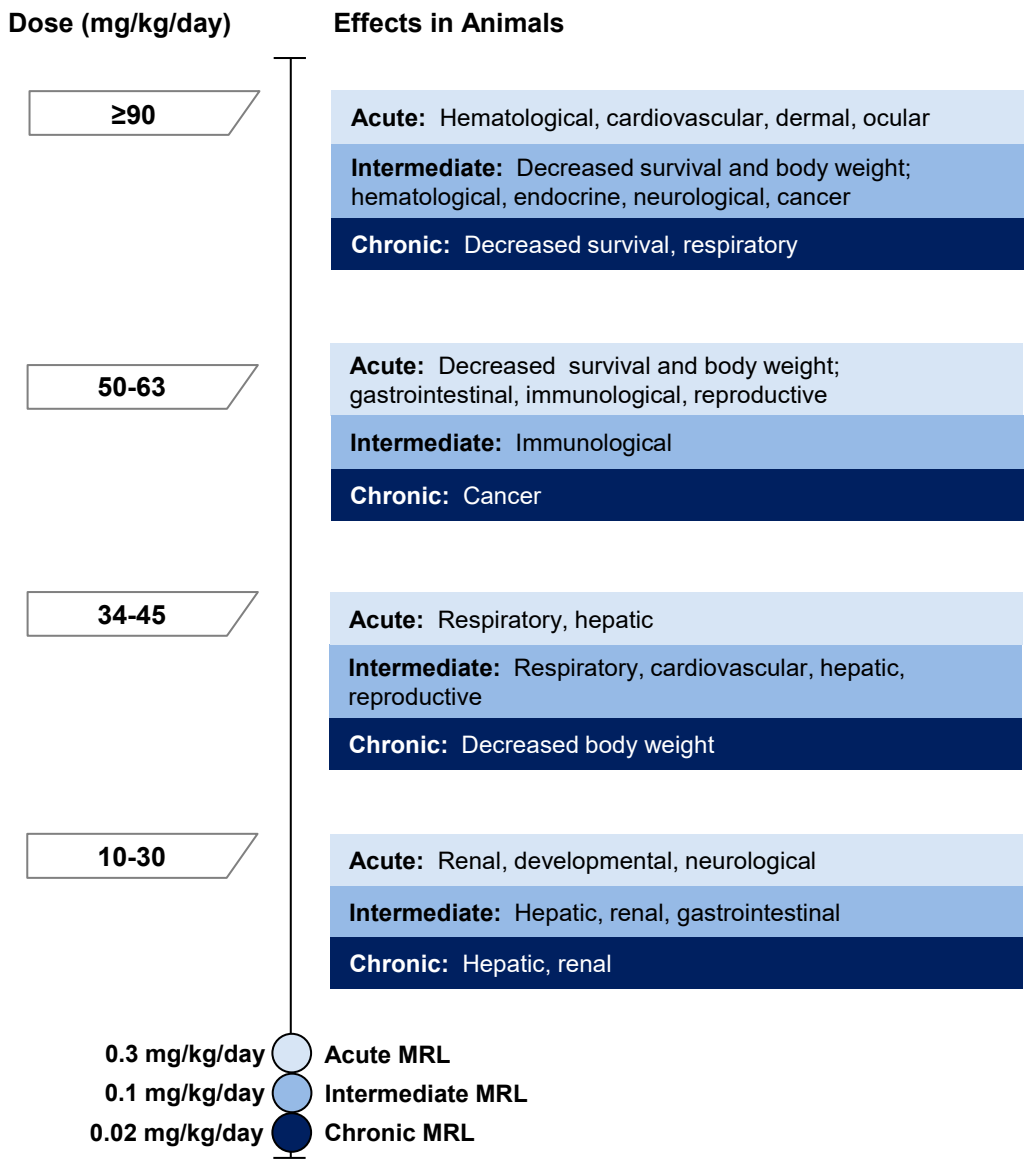


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to Chloroform



Respiratory Effects. In humans, depression of respiratory rates and/or respiratory arrest have been reported in case reports of high-level exposure via inhalation (Jayaweera et al. 2017; Storms 1973; Whitaker and Jones 1965); these effects are likely secondary to central nervous system (CNS) depression. Lung damage has been reported in several fatal cases of inhalation or oral exposure (Section 2.4). In animals, the nasal epithelium and the underlying nasal bones are consistent targets of toxicity in rodents following acute-, intermediate-, and chronic-duration inhalation exposure (Constan et al. 1999; Kasai et al. 2002; Larson et al. 1994c, 1996; Mery et al. 1994; Templin et al. 1996b; Yamamoto et al. 2002) and acute- and intermediate-duration gavage exposure (Dorman et al. 1997; Larson et al. 1995b; Templin et al. 1996a).

Damage to the lower respiratory tract in animals was generally only observed at lethal exposure levels (Bowman et al. 1978; Kasai et al. 2002; NCI 1976). However, there is limited evidence of inflammatory responses in the lung at low inhalation exposure levels in mice (de Oliveira et al. 2015).

Hepatic Effects. There is some evidence of adverse hepatic effects with occupational exposure to chloroform, with effects reported in some studies (Bomski et al. 1967; Kang et al. 2014; Lin et al. 2005; Phoon et al. 1983) but not others (Callen et al. 1958; Li et al. 1993). However, the results of occupational studies should be interpreted with caution due to study limitations, including poor exposure characterization, small subject numbers, and lack of control for confounding factors (e.g., co-exposures). Despite limitations, findings reported in some workers are supported by numerous case series and case reports, which indicate that the liver is a clear target of toxicity in humans following inhalation exposure to high levels of chloroform (Giusti and Chiarotti 1981; Hwang and Kim 2022; Lionte 2010; Royston 1924; Townsend 1939). In fatal ingestion cases, acute liver failure and/or severe liver damage have also been found at autopsy (Dettling et al. 2016; Piersol et al. 1933). In numerous nonfatal cases of inhalation or ingestion, reversible clinical signs of hepatotoxicity manifest within 1–7 days of exposure (Section 2.9).

The liver is also a clear target of toxicity in animals. Hepatic lesions have been observed following acute-, intermediate-, and chronic-duration inhalation and oral exposure in rodents; intermediate- and chronic-duration oral exposure in dogs; and in an acute-duration oral exposure in rabbits (Section 2.9). Typical lesion progression begins with mild histopathological damage after low and/or brief exposures (e.g., lipid accumulation, cellular swelling and vacuolation, scattered necrosis, hepatocellular proliferation) and progresses to widespread and severe necrosis and degeneration with high level and/or

long-term exposure. In oral studies, rodents exposed via gavage were more susceptible to hepatotoxicity than those exposed via drinking water (Larson et al. 1994b, 1995a).

Renal Effects. Several case reports indicate that the kidney is a target of chloroform toxicity in humans following exposure to high levels via inhalation or oral routes. Fatal exposures have been associated with renal damage (Piersol et al. 1933; Royston 1924), while reversible changes in clinical chemistry and urinalysis have been reported in nonfatal cases (Dettling et al. 2016; Gosselink et al. 2012; Piersol et al. 1933; Schroeder 1965; Sridhar et al. 2011; Wallace 1950). The kidney is a clear target of toxicity in animals. Renal lesions have been observed following acute-, intermediate-, and chronic-duration inhalation and oral exposure in rodents; intermediate- and chronic-duration oral exposure in dogs; and acute-duration oral and dermal exposure in rabbits (Section 2.10). Typical lesion progression begins with mild histopathological damage after low and/or brief exposures (e.g., tubular dilation, single-cell necrosis, renal cell proliferation) and progresses to severe nephropathy characterized by widespread necrosis and degeneration with higher level and/or longer-term exposure. In oral studies, rodents exposed via gavage are more susceptible to renal toxicity than those exposed via drinking water.

Neurological Effects. Chloroform was previously utilized as a common general anesthetic, so it is a known CNS depressant at high exposure levels in both humans and animals (Section 2.15). There is limited evidence for neurological effects at exposure levels below those associated with frank CNS depression. One epidemiological study in humans reported neurobehavioral impairments at low occupational exposure levels (2.76–6.04 ppm), including impaired hand-eye coordination, slowed reaction time, and memory impairments (Li et al. 1993). Chloroform-exposed workers also had increased subjective complaints, including dizziness, fatigue, somnolence, insomnia, increased dreaming, anorexia, depression, and anger (Challen et al. 1958; Li et al. 1993). In animals, the only reported effects at concentrations below those associated with frank CNS depression included impaired operant conditioning and paired taste aversion (Balster and Borzelleca 1982; Landauer et al. 1982). The only histopathological change reported in the neurological system is olfactory nerve loss in rats following acute-duration inhalation exposure (Larson et al. 1994c; Mery et al. 1994); this finding is likely in response to degeneration of the nasal olfactory epithelial tissue observed at the same exposure levels.

Developmental Effects. Many epidemiological studies evaluated potential associations between developmental effects and exposure to disinfection byproducts in chlorinated water (Table 2-18). Some studies reported associations between chloroform exposure from tap water and measures of impaired growth, including low birth weight (Grazuleviciene et al. 2011; Wright et al. 2004), intrauterine growth

restriction (Kramer et al. 1992), small for gestational age (Summerhayes et al. 2012; Sun et al. 2020; Wright et al. 2004), and decreased postnatal weight gain (Botton et al. 2015). However, no associations were noted in several other studies (Bonou et al. 2017; Cao et al. 2016; Hinckley et al. 2005; Liu et al. 2021; Porter et al. 2005; Villanueva et al. 2011). No clear associations were observed between chloroform exposure and birth defects (Dodds and King 2001; Grazuleviciene et al. 2013; Kaufman et al. 2018, 2020; Zaganjor et al. 2020) or neurodevelopmental outcomes (Villanueva et al. 2018).

There is also inconsistent evidence for fetal malformations or variations in animals following exposure to chloroform. There is limited evidence for missing ribs and acaudate fetuses with imperforate anus in rats (Schwetz et al. 1974) and cleft palate in mice (Murray et al. 1979) following maternal inhalation exposure during gestation. These defects were not observed in additional developmental studies in rats exposed via inhalation (Baeder and Hofmann 1988; EPA 1978) or rats or rabbits exposed orally (Ruddick et al. 1983; Thompson et al. 1974). Delayed ossification and decreased fetal growth were reported in many developmental studies after inhalation or oral exposure, generally only at levels associated with maternal toxicity (Section 2.17).

Cancer Effects. There is limited evidence of associations between chloroform exposure and cancer in humans. One occupational study reported an increased risk of pancreatic cancer in workers with "substantial" exposure to chloroform, but no association with a wide variety of other forms of cancer (Christensen et al. 2013). Additional occupational studies found no associations between chloroform exposure and several other forms of cancer (Section 2.19). Some epidemiological studies evaluating the potential risk of cancer and exposure to disinfection byproducts in chlorinated water reported associations between urinary bladder cancer, colon cancer, rectal cancer, melanoma, breast cancer, and childhood acute leukemia and chloroform exposure from tap water (Bove et al. 2007; Doyle et al. 1997; Font-Ribera et al. 2018; Gao et al. 2014; Jones et al. 2019). However, several other epidemiological studies did not observe associations with these or other forms of cancer (Section 2.19). In animals, chronic-duration inhalation exposure is associated with renal tumors in mice (Yamamoto et al. 2002) and chronic-duration oral exposure is associated with hepatic and renal tumors in rats (Jorgenson et al. 1985; NCI 1976; Tumasonis et al. 1985, 1987) and mice (Eschenbrenner and Miller 1945; NCI 1976; Roe et al. 1979).

The U.S. Environmental Protection Agency (EPA) determined that chloroform is likely to be carcinogenic to human by all routes of exposure under dose conditions that lead to cytotoxicity and regenerative hyperplasia in susceptible tissues; it is not likely to be carcinogenic by any route at dose levels that do not cause those effects (IRIS 2001). The International Agency for Research on Cancer

(IARC) determined that chloroform is possibly carcinogenic to humans based on inadequate evidence in humans and sufficient evidence in experimental animals (IARC 1999). The Department of Health and Human Services (HHS) determined that chloroform is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity in experimental animals (NTP 2021).

1.3 MINIMAL RISK LEVELS (MRLs)

The inhalation database was considered adequate for derivation of acute-, intermediate-, and chronic-duration inhalation MRLs for chloroform. As illustrated in Figure 1-3, the respiratory, hepatic, and neurological systems appear to be the most sensitive targets of chloroform toxicity following inhalation exposure. Immunological and body weight effects also have relatively low lowest-observed-adverse-effect level (LOAEL) values. The MRL values are summarized in Table 1-1 and discussed in greater detail in Appendix A.

The oral database was considered adequate for derivation of acute-, intermediate-, and chronic-duration oral MRLs for chloroform. As illustrated in Figure 1-4, the hepatic, renal, and developmental systems appear to be the most sensitive targets of chloroform toxicity following oral exposure. The MRL values are summarized in Table 1-1 and discussed in greater detail in Appendix A.

Figure 1-3. Summary of Sensitive Targets of Chloroform – Inhalation

Available data indicate that the respiratory, hepatic, and neurological systems are the most sensitive targets of chloroform inhalation exposure.

Numbers in triangles and circles are the lowest LOAELs (ppm) among health effects in humans and animals, respectively.

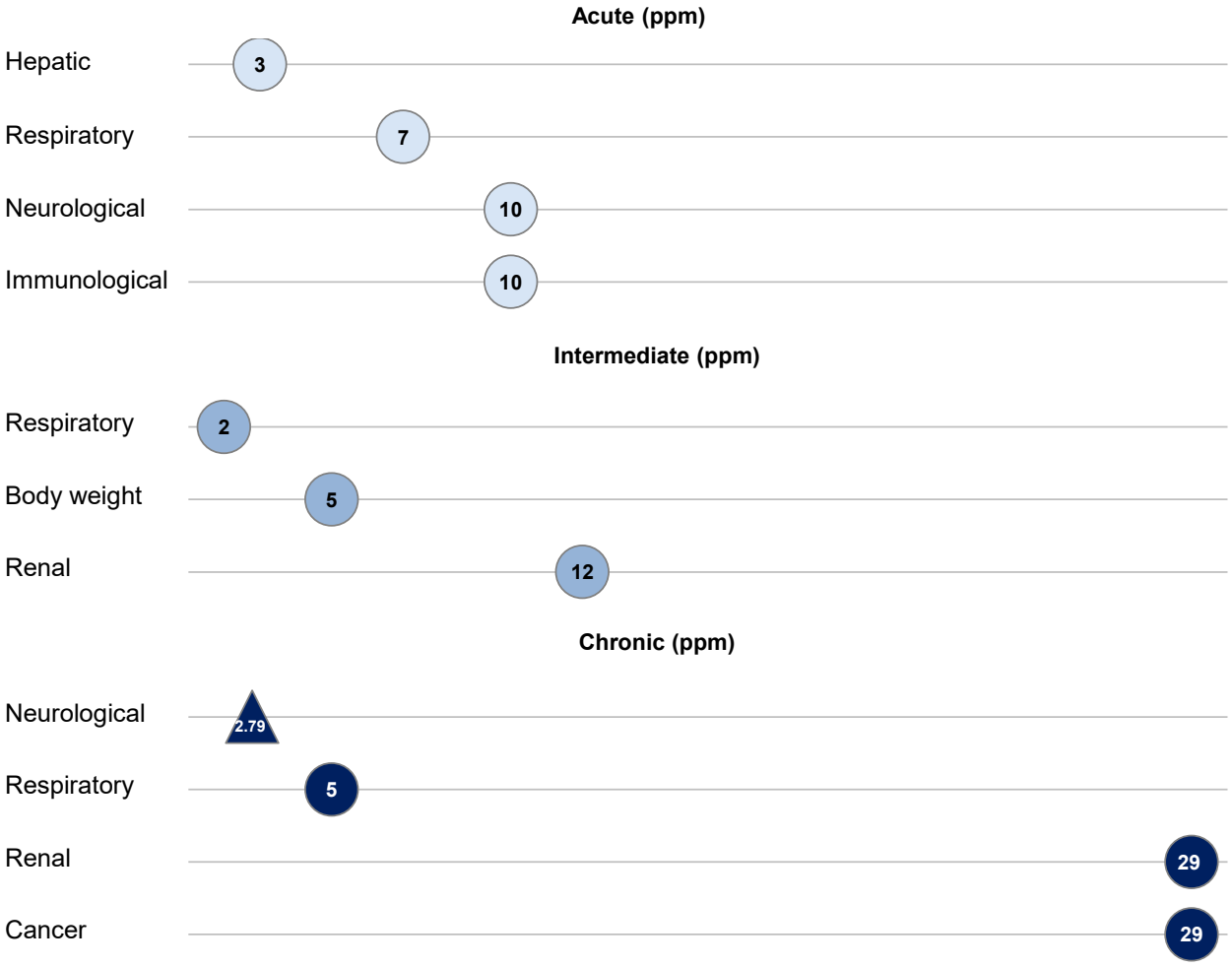


Figure 1-4. Summary of Sensitive Targets of Chloroform – Oral

Available data indicate that the hepatic, renal, and developmental systems are the most sensitive targets of chloroform oral exposure.

Numbers in circles are the lowest LOAELs for all health effects in animals; no reliable dose response data were available for humans.

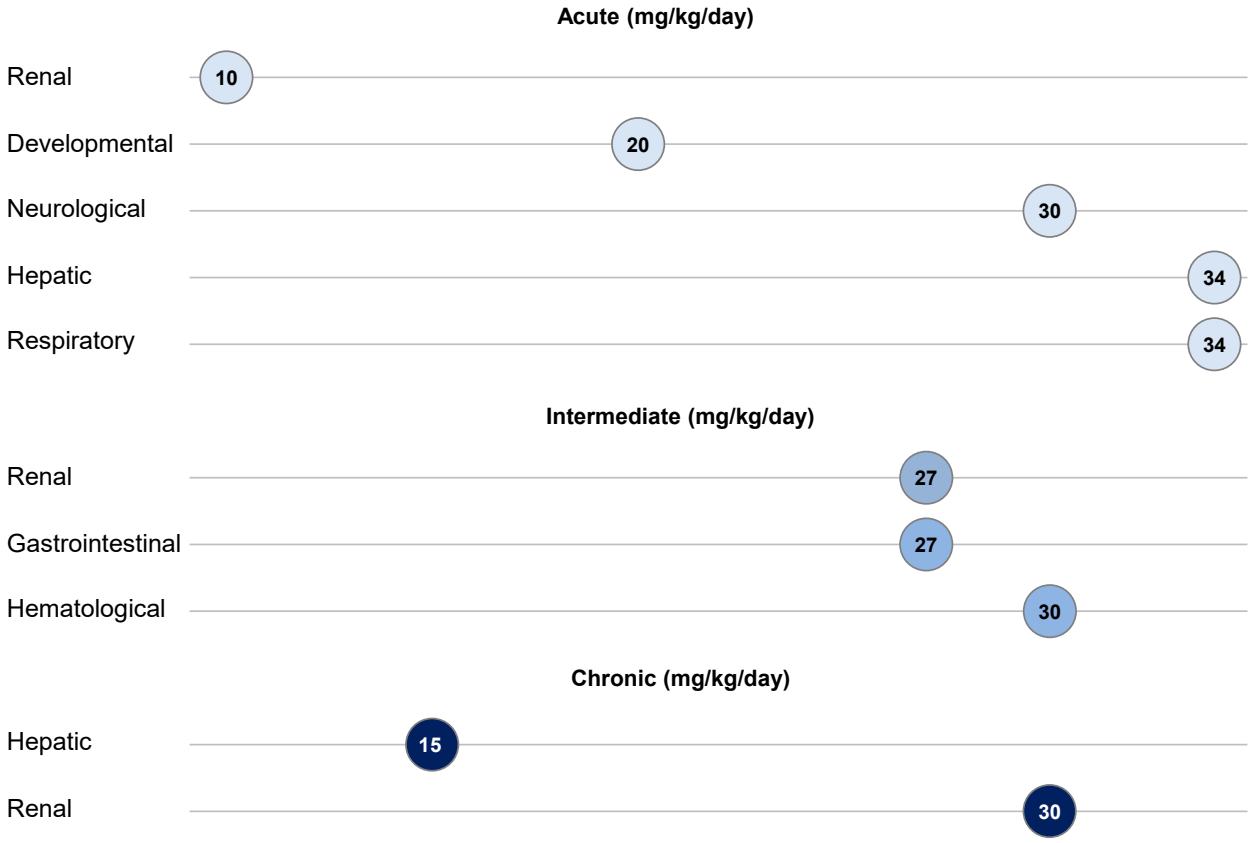


Table 1-1. Minimal Risk Levels (MRLs) for Chloroform[a]

Exposure route	Exposure duration	MRL	Critical effect	POD type	POD value	Uncertainty/ modifying factor	Reference
Inhalation	**Acute**	**0.001 ppm** (0.005 mg/m^3)	Nasal lesions	$NOAEL_{HEC}$	0.04 ppm	30	Larson et al. 1996; Templin et al. 1996b
	Intermediate	**0.0008 ppm** (0.004 mg/m^3)	Nasal lesions	$LOAEL_{HEC}$	0.07 ppm	90	Templin et al. 1996b
	Chronic	**0.0004 ppm** (0.002 mg/m^3)	Nasal lesions	$LOAEL_{HEC}$	0.11 ppm	300	Yamamoto et al. 2002
Oral	**Acute**	**0.3 mg/kg/day**	Hepatic lesions	NOAEL	26 mg/kg/day	100	Larson et al. 1994b
	Intermediate	**0.1 mg/kg/day**	Increased serum ALT (~2-fold)	$NOAEL_{ADJ}$	13 mg/kg/day	100	Heywood et al. 1979
	Chronic	**0.02 mg/kg/day**	Hepatic lesions	$BMDL_{ADJ}$	1.84 mg/kg/day	100	Heywood et al. 1979

[a]See Appendix A for additional information.

ADJ = adjusted for continuous/daily exposure; ALT = alanine aminotransferase; BMDL = benchmark dose lower confidence limit; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level