CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Chloroethane is a volatile, low molecular weight halogenated colorless gas. In the past, the single largest use of chloroethane was in the production of tetraethyl lead. Chloroethane is currently used in the production of ethyl cellulose and in miscellaneous applications including as a solvent and topical anesthetic, and in the manufacture of dyes, chemicals, foamed plastics, and pharmaceuticals.

When chloroethane is released to the environment, most will quickly partition to the atmosphere. Once in the atmosphere, it will break down by reactions with photochemically generated hydroxyl radicals. If released to soil or water, chloroethane is expected to volatilize rapidly but it may leach into groundwater since it is expected to possess high mobility in soil. It may undergo biodegradation under both aerobic and anaerobic conditions and may also be broken down by hydrolysis. Direct photolysis is not expected to be an important environmental fate process since chloroethane does not absorb photons of light in the environmental ultraviolet (UV) spectrum.

The general population may be exposed to chloroethane by inhalation of ambient air and possibly through the ingestion of drinking water. Dermal and inhalation exposure during domestic water use (e.g., showering or washing activities) may occur if the water contains chloroethane. Vapor intrusion of chloroethane into structures from contaminated soil and groundwater may result in indoor air levels of chloroethane in buildings and residences. Direct exposure may also occur when chloroethane is used as a topical anesthetic. Occupational exposure, inhalation or dermal, can occur at facilities were chloroethane is manufactured and used (e.g., printing and publishing, painting companies, and electric services). People have also been known to intentionally inhale chloroethane vapors from commercial products for its narcotic effects, which may result in unconsciousness or even death.

1.2 SUMMARY OF HEALTH EFFECTS

Information on the toxicity of chloroethane comes primarily from volunteer studies, case reports, and inhalation studies in animals. Most human studies have evaluated acute-duration inhalation exposure while animal studies have predominantly focused on acute- and intermediate-duration inhalation exposure. A limited number of oral animal studies were identified. Animal inhalation studies were located for most of the health endpoints evaluated in this profile.

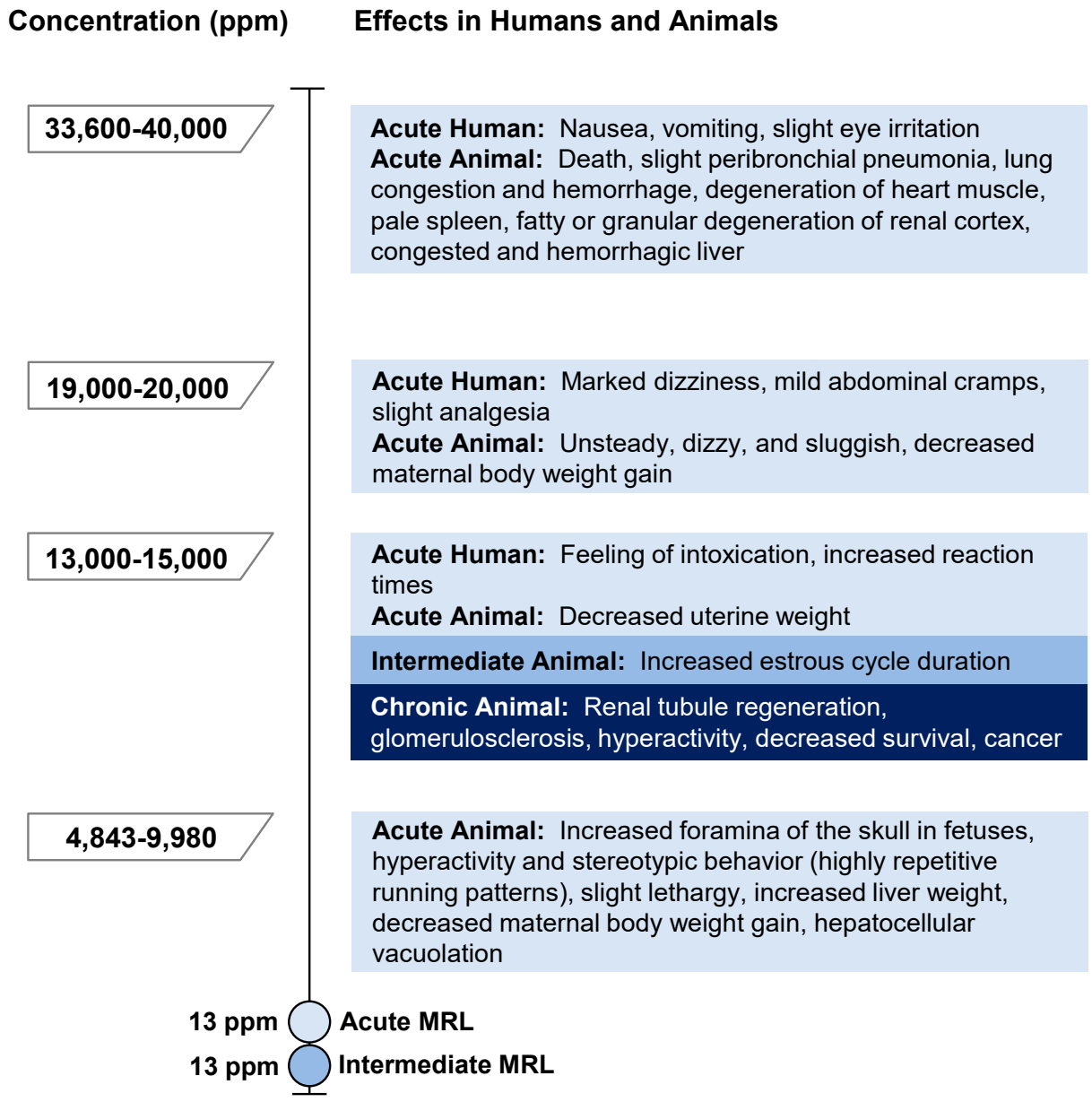
As shown in Figure 1-1, the most sensitive effects appear to affect the neurological, developmental, hepatic, and reproductive systems; decreased maternal body weight gain was also a sensitive effect. Hepatic and body weight effects were only observed in one or two studies and these changes were not reported in several other studies evaluating higher concentrations and/or longer durations (Figure 2-2). Therefore, only neurological, reproductive, and developmental effects were further considered as potential health hazards. A systematic review of these noncancer endpoints resulted in the following hazard identification conclusions:

- Neurological effects are a presumed health effect for humans.
- Reproductive effects are an unclassifiable health effect for humans.
- Developmental effects are an unclassifiable health effect for humans.

Due to the limited number of oral animal studies identified, no figure describing the health effects found in animals following oral exposure to chloroethane was created. The two acute-duration oral studies that exposed rats to chloroethane in drinking water at levels up to 662 mg/kg/day did not report any health effects.

Neurological Effects. Numerous human studies have reported neurological effects following inhalation of chloroethane. Volunteers who inhaled 13,000–20,000 ppm reported marked dizziness, increased reaction times, and a feeling of intoxication (Davidson 1925; USBM 1929). People who intentionally misused chloroethane experienced slurred speech, dizziness, and difficulty walking (Demarest et al. 2011; Hes et al. 1979; Senussi and Chalise 2015; Winkler et al. 2023; Young et al. 2023). In addition, some studies reported that individuals misusing chloroethane also experienced visual hallucinations, tremors, nausea, abdominal cramps, and an unsteady gait (Al-Ajmi et al. 2018; Kuthiah and Er 2019; Nordin et al. 1988; Young et al. 2023). Other symptoms associated with chloroethane misuse included sleep disorders, tachycardia, ataxia, confusion, dysdiadochokinesia (inability to perform rapid, repeated alternating movements) of the arm, and sluggish or brisk lower limb reflexes (Finch and Lobo 2005; Hager et al. 2021; Hes et al. 1979; Kuthiah and Er 2019; Nordin et al. 1988).

Figure 1-1. Health Effects Found Following Inhalation Exposure to Chloroethane



Neurological effects have also been observed in animals after inhalation in both acute- and chronic-duration studies in several species. Acute-duration inhalation exposure led to hyperactivity, stereotypic behavior, and/or loss of reflexes in mice (Dow 1985, 1995; Lazarew 1929); slight lethargy in rats (Landry et al. 1982); unsteadiness, dizziness, and sluggish behavior in guinea pigs (USBM 1929); and hyperactivity in dogs (Landry et al. 1982). In a 2-year inhalation study, female mice were hyperactive during the daily exposure (NTP 1989). Oral exposure to chloroethane via gavage led to female rats becoming unsteady 15–30 minutes after receiving chloroethane (Dow 1992); no effects were seen when chloroethane was administered in drinking water (Dow 1995).

Reproductive Effects. Studies of reproductive effects in humans exposed to chloroethane were not identified. Several studies investigated female reproductive endpoints in animals after inhalation exposure. In acute-duration inhalation studies, chloroethane has been shown to decrease uterine glutathione (GSH) levels in both rats and mice (Fedtke et al. 1994b). In intermediate-duration studies, a small increase in the average duration of the estrous cycle was observed in mice exposed to high concentrations of chloroethane in the absence of any changes in serum estradiol and progesterone (Bucher et al. 1995). Decreased uterine motility and muscle tone were observed in dogs anesthetized with chloroethane (van Liere et al. 1966). The relevance of these uterine effects in animals to humans is not known.

Non-neoplastic lesions have not been observed in reproductive organs of rodents following inhalation exposure to acrolein. No histopathological effects were observed in reproductive organs of animals exposed to chloroethane for ≤2 or 13 weeks (Landry et al. 1982, 1987, 1989; NTP 1989). However, chloroethane produced uterine cancer in mice, but not rats, exposed to 15,000 ppm chloroethane for approximately 2 years (NTP 1989).

Developmental. No studies were located on developmental effects of chloroethane in humans. Two prenatal inhalation studies were located for chloroethane (Dow 1985; Scortichini et al. 1986). In a study of pregnant mice exposed to chloroethane for 6 hours/day on gestation days (GDs) 6–15, an increase in the incidence of delayed fetal foramina closure (DFFC) of the skull bones (developmental delay of ossification of small centers of unossified bone) was seen in the fetuses at 4,946 ppm (Scortichini et al. 1986). No significant treatment-related changes were observed in number of resorptions, number of live fetuses/litter, litter size, fetal sex ratio, fetal body weight, or incidence of external or visceral malformations in the fetuses at concentrations up to 4,946 ppm (Scortichini et al. 1986). No exposure-related changes in the number of resorptions, live fetuses/litter, or normal-appearing fetuses were

observed in pregnant mice up to 15,000 ppm of chloroethane for 6 hours/day on GDs 6–15 (Dow 1985). This study, however, did not examine fetuses for skeletal or visceral alterations.

Cancer. No studies were located regarding the carcinogenicity of chloroethane in humans. Animal cancer studies have observed specific carcinogenic outcomes but have not consistently identified a target organ across sexes or species. In a study by the National Toxicology Program (NTP 1989), 86% of female mice chronically exposed to chloroethane vapor developed highly malignant uterine carcinomas. Uterine tumors were not observed in any of the control mice. The incidence of hepatocellular carcinomas also increased significantly in female mice. Male mice had an increased incidence of alveolar and bronchiolar adenomas, but because male survival was substantially reduced toward the end of the study, these results are not conclusive. Male rats had marginally increased incidences of skin tumors, whereas female rats had marginally increased incidences of brain astrocytomas, providing evidence that chloroethane is carcinogenic in rats (NTP 1989).

Based on limited evidence of carcinogenicity in animals and no human data, the International Agency for Research on Cancer (IARC) considers chloroethane to be in Group 3, not classifiable as to carcinogenicity to humans (IARC 1999). The carcinogenicity of chloroethane has not been evaluated by the Department of Human Health Services (HHS) (NTP 2021). A provisional carcinogenicity assessment by the U.S. Environmental Protection Agency (EPA) determined that chloroethane was likely to be carcinogenic to humans (EPA 2007).

1.3 MINIMAL RISK LEVELS (MRLs)

Inhalation MRLs. As illustrated in Figure 1-2, available inhalation data for chloroethane suggest that the hepatic, developmental, neurological, body weight, reproductive, and renal systems are the most sensitive targets of toxicity; however, liver and body weight effects were not consistently observed, even at higher concentrations. The inhalation database was considered adequate for derivation of an acute- and intermediate-duration MRL. The MRL values are summarized in Table 1-1 and discussed in greater detail in Appendix A.

Oral MRLs. The oral database was considered inadequate for derivation of acute-, intermediate-, and chronic-duration MRLs. Since no adverse effects were noted in the limited number of oral studies identified, a figure depicting sensitive targets following oral exposure to chloroethane could not be

generated. The MRL findings are summarized in Table 1-1 and discussed in greater detail in Appendix A.

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

Available data indicate that the hepatic, developmental, renal, neurological, body weight, reproductive, and renal systems appear to be the most sensitive targets of chloroethane inhalation exposure; however, liver and body weight effects were not consistently observed, even at higher concentrations.

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

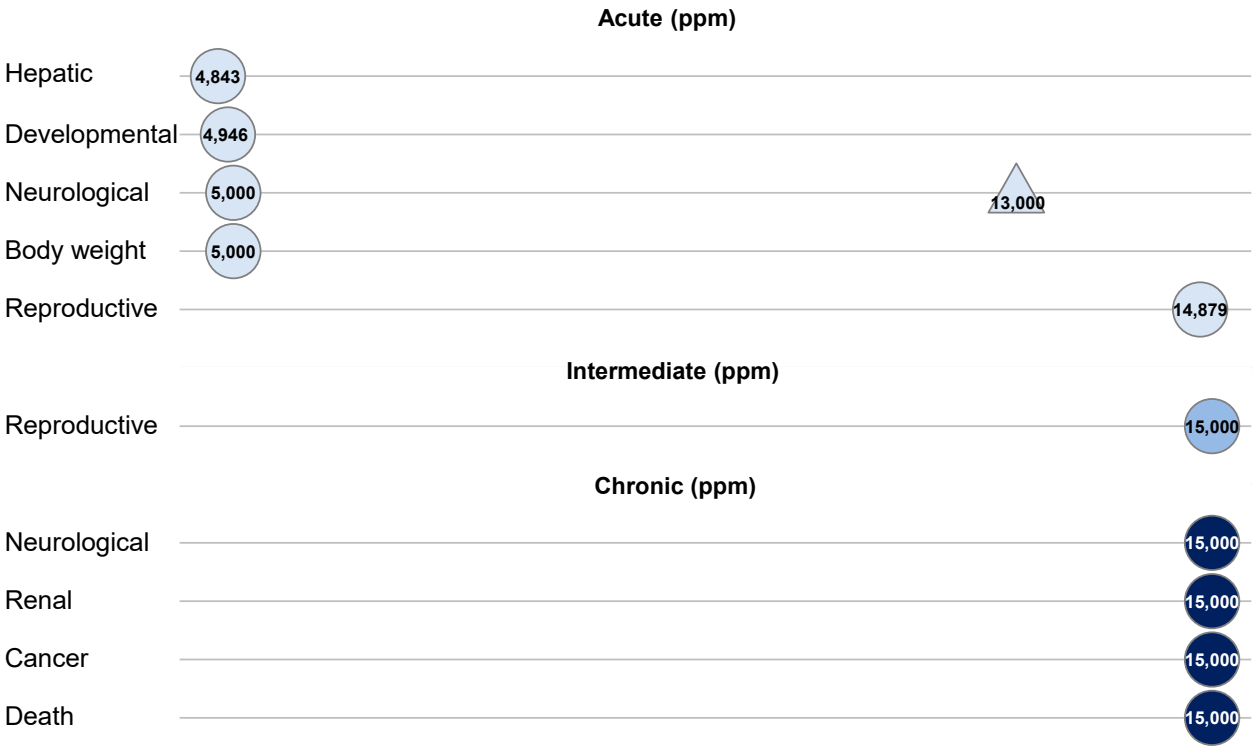


Table 1-1. Minimal Risk Levels (MRLs) for Chloroethane[a]

Exposure route	Exposure duration	MRL	Critical effect	POD type	POD value	Uncertainty/ modifying factor	Reference
Inhalation	Acute	**13 ppm** (34 mg/m^3)	Increased incidence of delayed fetal foramina closure (DFFC) of the skull bones; developmental delay of ossification of small centers of unossified bone of the skull in mice.	$NOAEL_{HEC}$	376.0 ppm	UF: 30	Scortichini et al. 1986
	Intermediate	**13 ppm** (34 mg/m^3)	Increased estrous cycle in mice	$LOAEL_{HEC}$	3,750 ppm	UF: 300	Bucher et al. 1995
	Chronic	None	–	–	–	–	–
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