CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

1,1,2-Trichloroethane (CASRN 79-00-5) is predominantly a man-made chemical whose presence in the environment results from anthropogenic activity. This chemical is an intermediate in the biodegradation of 1,1,2,2-tetrachloroethane. It is made commercially by the chlorination of ethylene with chlorine or by the oxychlorination of ethylene with hydrogen chloride (HCl) and oxygen. It is primarily used as a captive intermediate in the production of 1,1-dichloroethene (vinylidene chloride), but may also be used as a solvent, especially in chlorinated rubber manufacture but also for fats, oils, waxes, and resins (Hawley 1981).

1,1,2-Trichloroethane is released into the air by vent gas and fugitive emissions from the production and use of 1,1,2-trichloroethane as well as volatilization from waste water and municipal treatment plants. Although 1,1,2-trichloroethane is found in the effluent from laundries and organic chemicals and mechanical products industries, exposure to 1,1,2-trichloroethane from contaminated drinking water is uncommon (Westrick et al. 1984). Few data with respect to the release of 1,1,2-trichloroethane to soil are available, but these releases are expected to involve the landfilling of sludge and process residues.

Because of 1,1,2-trichloroethane's short half-life in the body, it is difficult to describe exposure using traditional biomarkers. In the 2003–2004, 2005–2006, 2007–2008, 2009–2010, and 2011–2012 National Health and Nutrition Examination Survey (NHANES), levels of blood 1,1,2-trichloroethane were less than the limit of detection using participants' whole blood sample (CDC 2017). Levels below the limit of detection or trace amounts of 1,1,2-trichloroethane have been reported in exhaled air (Wallace et al. 1984). Low levels of 1,1,2-trichloroethane were likewise detected in the tissues of people exposed primarily via inhalation (Bauer 1981a, 1981b).

1.2 SUMMARY OF HEALTH EFFECTS

Studies in humans are confined to dermal irritation studies, and studies of occupational or residential exposures to 1,1,2-trichloroethane, all of which are confounded by exposure to other chemicals. Therefore, all implications of public health are derived from animal studies. Information on the toxicity of 1,1,2-trichloroethane comes primarily from acute-duration (up to 14 days in rats, mice, and dogs) and intermediate-duration (up to 13 weeks in rats and mice) oral studies and acute-duration inhalation studies. Several intermediate-duration and chronic-duration (78 weeks in rats and mice) oral toxicity studies in

animals are also available. Only one well-conducted intermediate-duration (13 weeks) inhalation toxicity study is available. Data integration involved evaluating all of the animal toxicity data, determining effects levels for the endpoints evaluated in these studies, and determining the effects that were observed at the lowest concentrations/doses. As illustrated in Figure 1-1 and Figure 1-2, the most sensitive effects appear to be respiratory effects, liver damage, impaired immune response, and neurological effects. A systematic review of these endpoints resulted in the following hazard identification conclusions (see also Appendix C, Section C.8):

- Respiratory effects following inhalation exposure are a presumed health effect for humans
- Hepatic effects are a presumed health effect for humans
- Neurological effects following acute exposure are a presumed health effect for humans
- Immunological effects are a suspected health effect for humans

Respiratory Effects. There were no studies in humans for this endpoint. In laboratory animals, acute- and intermediate-duration inhalation studies in rats and acute-, intermediate-, and/or chronic-duration studies in rats and mice were available. Rats exposed to 1,1,2-trichloroethane for 4 hours showed increased protein content in bronchoalveolar lavage at 1,473 ppm (males) and 840 ppm (females) and necrosis of the olfactory epithelium at ≥58 ppm; the incidence and severity of these lesions increased in an exposure-related manner (Kirkpatrick 2001). In the only intermediate-duration inhalation toxicity study available, rats exposed at ≥40 ppm for 13 weeks showed significantly increased incidences of lesions in the olfactory epithelium of the nasal turbinates, including atrophy, vacuolization and microcyst formation, and respiratory epithelial metaplasia compared to control rats (Kirkpatrick 2002). In oral studies, there were no effects on lung weight in mice exposed via gavage at up to 38 mg/kg/day for 14 days or 305 mg/kg/day (males) or 384 mg/kg/day (females) for 90 days (White et al. 1985). In 78-week studies, no non-neoplastic respiratory tract lesions were observed at up to 92 mg/kg/day (rats) or 390 mg/kg/day (mice) (NCI 1978). It is probable that respiratory effects (seen in animal inhalation toxicity studies that performed histological examinations) could also be produced in humans exposed to 1,1,2-trichloroethane, although there are no data currently available indicating respiratory effects in humans.

Figure 1-1. Health Effects Found in Animals Following Inhalation Exposure to 1,1,2-Trichloroethane

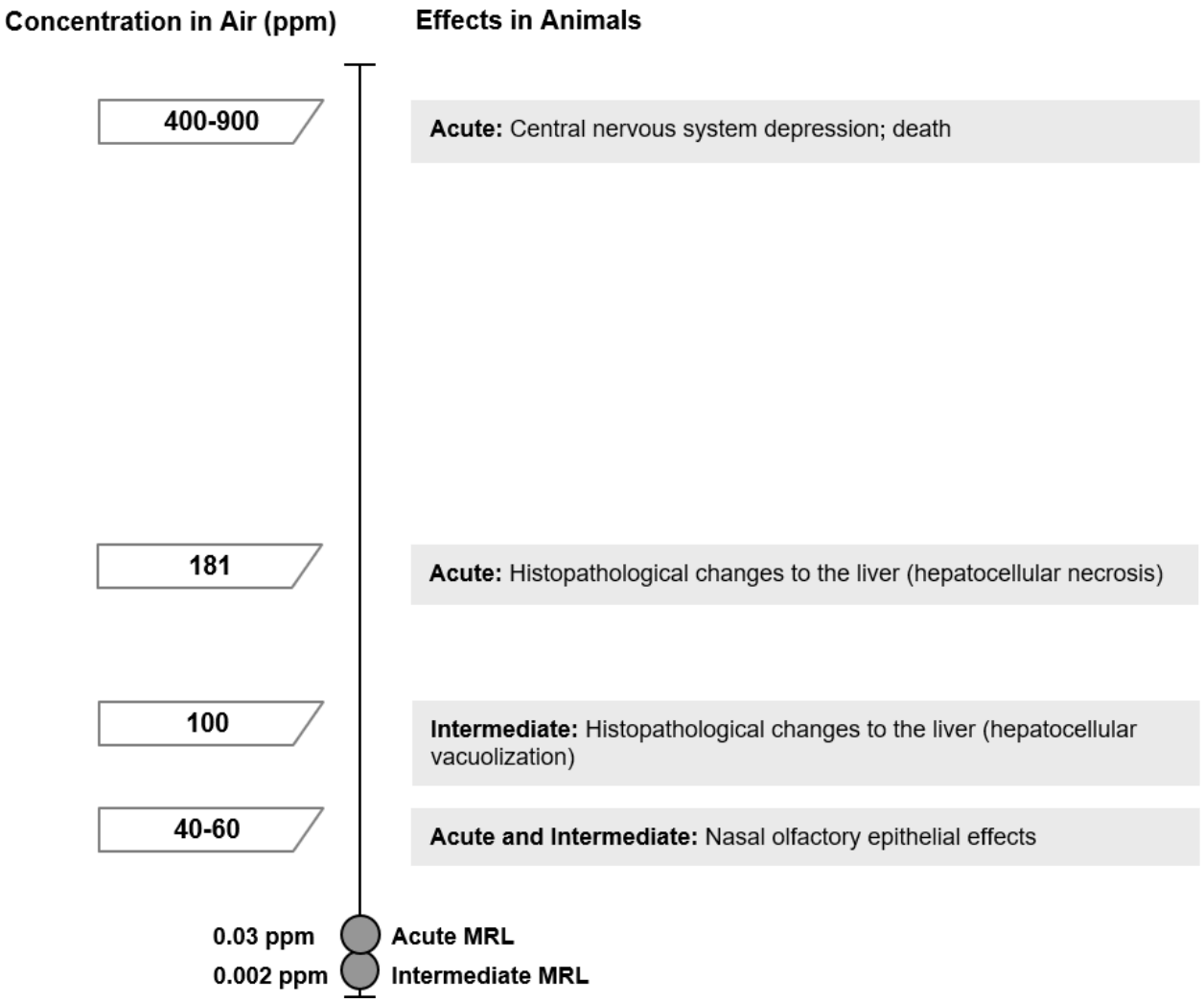
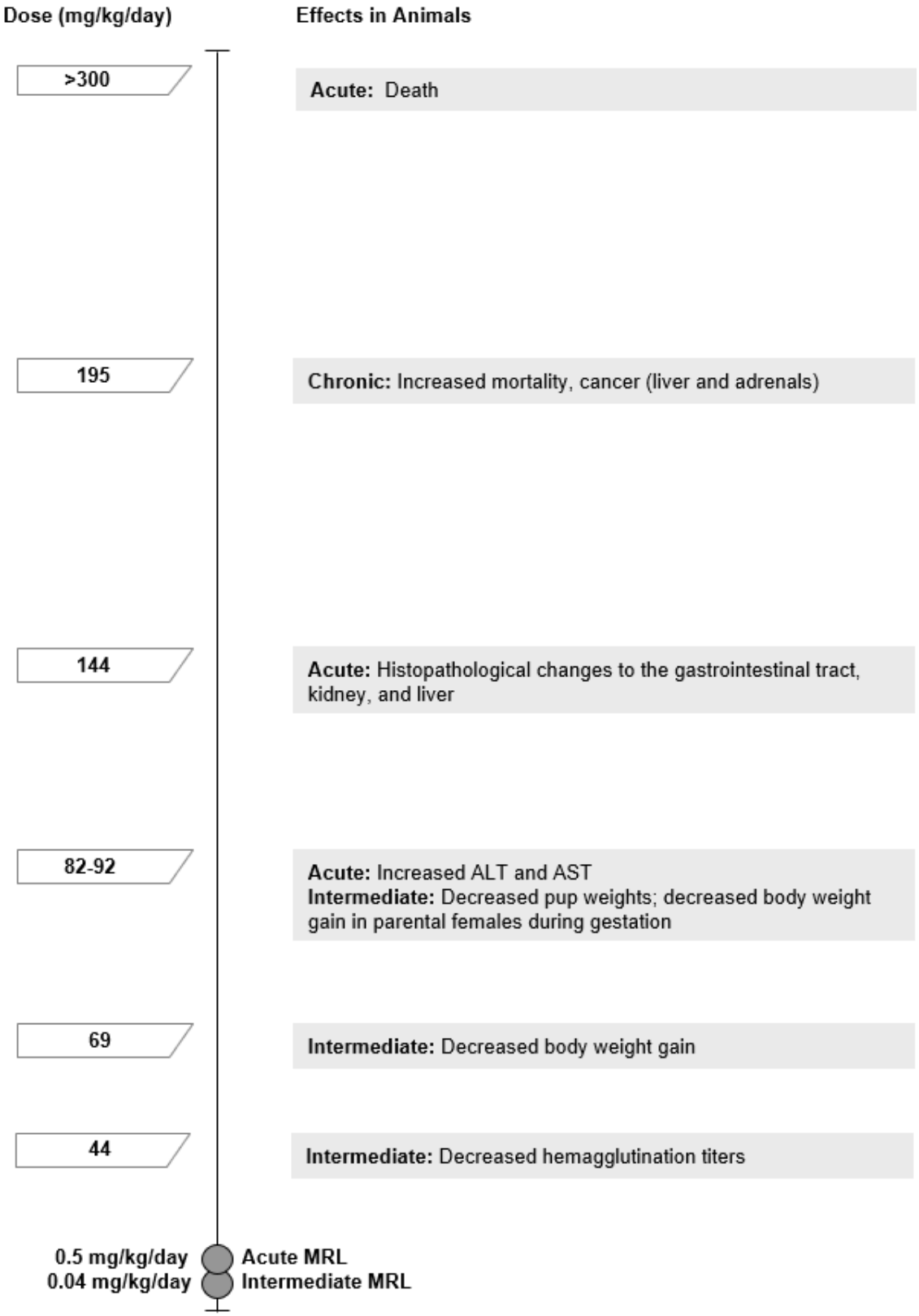


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to 1,1,2-Trichloroethane



Hepatic Effects. There were no studies in humans for this endpoint. In laboratory animals, acute- and intermediate-duration inhalation studies in rats and mice, and acute-, intermediate-, and/or chronic-duration studies in rats, mice, and dogs were available. Rats and mice acutely exposed to 1,1,2-trichloroethane (for 2–15 hours) showed increased alanine aminotransferase (ALT) levels at ≥2,080 ppm in rats and 800 ppm in mice (Carlson 1973; Gehring 1968; Takahara 1986a). Histopathological liver effects (hepatocellular vacuolization or necrosis) were also reported in rats exposed to 1,1,2-trichloroethane at ≥181 ppm for 4 hours (Kirkpatrick 2001) and in rats exposed at 100 ppm for 13 weeks (Kirkpatrick 2002). In oral studies, increased aspartate aminotransferase (AST) and ALT were among the most frequently observed effects in rats and mice following acute- (1–14 days of exposure at ≥~92 mg/kg/day) or intermediate-duration (90 days at 384 mg/kg/day) exposure to 1,1,2-trichloroethane (Moody and Smuckler 1986; Moody et al. 1981; Platt and Cockrill 1969; Tyson et al. 1983; Xia and Yu 1992). Histopathological changes (mild congestion, fatty acid degeneration, edema) were observed in dogs treated at a single dose of ≥144 mg/kg/day (Wright and Schaffer 1932), and increased liver weights were reported in female mice administered 384 mg/kg/day for 90 days (White et al. 1985). In the 90-day study by White et al. (1985), a sex difference in susceptibility to 1,1,2-trichloroethane was reported. Female mice, but not males, had a significant increase in ALT. Mechanistic data from *in vitro* and *ex vivo* studies suggest that the formation of free radicals may play a significant part in the mechanism of hepatotoxicity of 1,1,2-trichloroethane (Albano et al. 1985; Xia and Yu 1992). It is probable that hepatic effects (identified in numerous acute- and intermediate-duration animal toxicity studies) could also be produced in humans exposed to 1,1,2-trichloroethane, although there are no data currently available indicating hepatic effects in humans.

Immunological Effects. There were no studies in humans for this endpoint. In laboratory animals, acute- and intermediate-duration oral toxicity studies in mice were available. Studies of the effects of 1,1,2-trichloroethane on the immune system were performed by Sanders et al. (1985). In the acute-duration study, mice administered 1,1,2-trichloroethane by gavage at up to 38 mg/kg/day for 14 days showed no significant effects on humoral or cell-mediated immune endpoints; however, a limited number of evaluations were performed. A more comprehensive intermediate-duration (90 days) drinking water study identified a significant reduction in hemagglutination titers in male mice at ≥46 mg/kg/day and in female mice at ≥44 mg/kg/day. Macrophage phagocytic activity was also affected in males treated at higher doses, while endpoints evaluating the cell-mediated immune response in both sexes were unaffected by treatment. Chronic-duration (78 weeks) studies in mice and rats identified no-observed-adverse-effect levels (NOAELs) for immunological effects of 390 and 92 mg/kg/day, respectively, based on the absence of histological changes (to the spleen, thymus, bone marrow, or lymph nodes), but

immunological function was not evaluated. These data suggest that 1,1,2-trichloroethane may interfere with immune function in animals. The 90-day study by Sanders et al. (1985) also showed a sex difference in the response to 1,1,2-trichloroethane in mice. Male mice showed a decreased ability to phagocytize sheep red blood cells (sRBCs), whereas females showed increased vascular clearance of sRBCs by the fixed macrophages of the reticuloendothelial system. It is possible that immune effects (seen in a limited capacity in animal oral toxicity studies) could also be produced in humans exposed to 1,1,2-trichloroethane, although there are no data currently available indicating immune system effects in humans.

Neurological Effects. There were no studies in humans for this endpoint. In laboratory animals, acute-duration oral and inhalation toxicity studies were available. Signs of central nervous system depression (anesthesia, sedation, and sleepiness) have been reported following acute-duration inhalation (2–15 hours) exposure to 1,1,2-trichloroethane in rats (at ≥840 ppm) and mice (at ≥418 ppm) (Bonnet et al. 1980; de Ceaurriz et al. 1981; Gehring 1968; Kirkpatrick 2001; Lazarew 1929). These types of effects were also observed after acute-duration oral exposure at ≥450 mg/kg in mice and 289–722 mg/kg in dogs (White et al. 1985; Wright and Schaffer 1932). One study identified gait impairment in rats administered a single gavage dose of 1,1,2-trichloroethane (in 10 mL/kg corn oil) at 200 mg/kg (Beck 2004); motor impairment was noted in mice given 1,1,2-trichloroethane by gavage at 128 mg/kg (Borzelleca 1983). Taste aversion, which represents a conditioned avoidance response following repetitive conditioning trials, was another neurological effect produced by 7 days of exposure to 1,1,2-trichloroethane at 100 mg/kg/day (Kallman et al. 1983). No data on neurological effects of 1,1,2-trichloroethane in humans were located, but the evidence in animals (from numerous acute-duration inhalation toxicity studies in rats and mice) suggests that this compound may have central nervous depressant effects in humans as well.

Cancer. With respect to studies in humans, a study by Dosemeci et al. (1999) contained data for this endpoint. This study evaluated the risks of renal cell carcinoma (RCC) caused by occupational exposures to various solvents and found no significant differences in RCC risk from exposure to 1,1,2-trichloroethane compared to control population (RCC risk was significantly increased from exposure to chlorinated solvents in general). The study is limited by a small sample size (687 respondents, including only 23 with any exposure to 1,1,2-trichloroethane), and indirect measures of exposure. In laboratory animals, chronic-duration oral and dermal toxicity studies were available in rats and mice. Among animals, 1,1,2-trichloroethane was carcinogenic in mice, but not rats. 1,1,2-Trichloroethane induced increased incidences of hepatocellular carcinomas and adrenal pheochromocytomas (not specified as benign or malignant) in mice after exposure for 78 weeks (NCI 1978). Data from a subcutaneous carcinogenicity study in Sprague-Dawley rats conducted by Norpoth et al. (1988) found that treatment

with 15.37 or 46.77 µmol 1,1,2-trichloroethane (approximately 2.05 or 6.24 mg) once per week for 2 years had no significant effect on the incidence of benign mesenchymal and epithelial tumors at any site. Although there was a dose-related increased incidence of sarcomas in treated rats of both sexes compared to untreated controls, no sarcomas were observed in untreated controls (based on data for 35 males and 50 females), and this effect was not significant based on comparison to vehicle-only (dimethyl sulfoxide [DMSO]) controls. Based on references cited in the study report, the spontaneous incidence of sarcomas in this strain of rats ranges between 1/16 and 2/4 in males and 4/36 and 2/13 for females. A cancer initiation and promotion study in rats was also negative (Story et al. 1986). The mechanism of 1,1,2-trichloroethane carcinogenicity in mice is not known; however, free radicals and aryl chlorides (including chloroacetic acid) generated from P-450-mediated metabolism of 1,1,2-trichloroethane and deoxyribonucleic acid (DNA) adduct formation may play a role in tumor formation (Mazzullo et al. 1986; Yllner 1971). From the limited evidence in mice, 1,1,2-trichloroethane has been classified in Group C as a possible carcinogen (EPA 1988a). The International Agency for Research on Cancer (IARC 1999) classified the chemical as Group 3, not classifiable as to carcinogenicity in humans.

1.3 MINIMAL RISK LEVELS (MRLs)

As presented in Figure 1-3, limited inhalation data from animals indicate respiratory, hepatic, and neurological systems as particularly sensitive targets of 1,1,2-trichloroethane toxicity. The MRLs for acute- and intermediate-duration inhalation exposure to 1,1,2-trichloroethane are summarized in Table 1-1 and discussed in greater detail in Appendix A. No chronic inhalation studies were identified. As presented in Figure 1-4, available oral data in animals identify hepatic, immunological, and neurological systems as the most sensitive targets of 1,1,2-trichloroethane toxicity. The MRL values for acute- and intermediate-duration oral exposure to 1,1,2-trichloroethane are summarized in Table 1-1 and discussed in greater detail in Appendix A. The available data were not considered adequate for derivation of a chronic-duration oral MRL.

Figure 1-3. Summary of Sensitive Targets of 1,1,2-Trichloroethane – Inhalation

The respiratory system is the most sensitive target of 1,1,2-trichloroethane inhalation exposure.
Numbers in circles are the lowest LOAELs for all health effects in animals; no human data were identified.

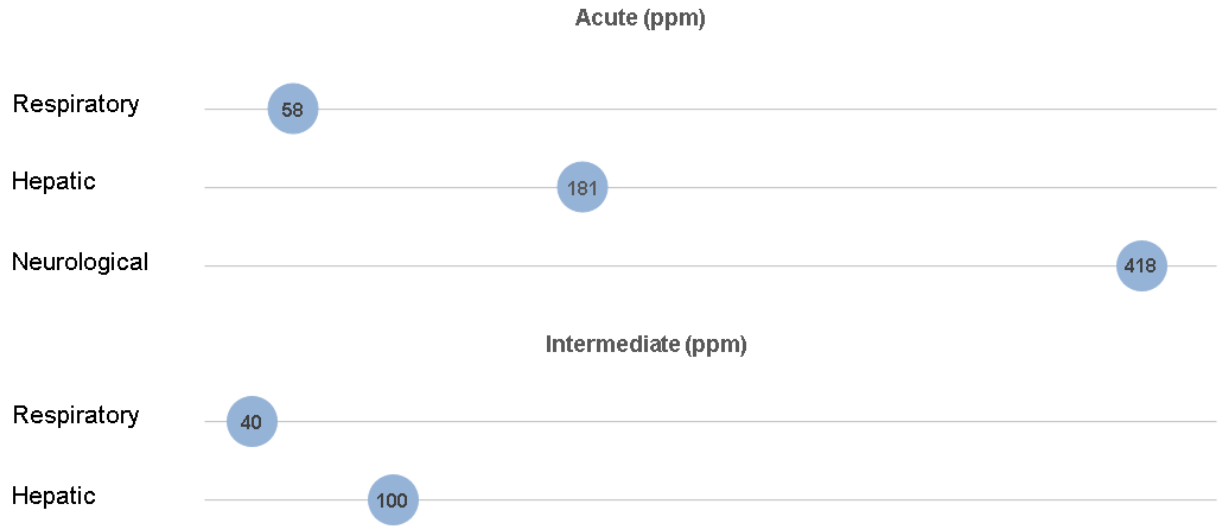


Table 1-1. Minimal Risk Levels (MRLs) for 1,1,2-Trichloroethane[a]

Exposure duration	MRL	Critical effect	Point of departure/ human equivalent concentration	Uncertainty and modifying factors	Reference
Inhalation exposure (ppm)					
Acute	**0.03**	Necrosis of the olfactory epithelium	LOAEL: 58 ($LOAEL_{HEC}$: 7.5)	UF: 90 MF: 3	Kirkpatrick 2001
Intermediate	**0.002**	Lesions of the olfactory epithelium	$BMCL_{10}$: 3.15 ($BMCL_{HEC}$: 0.07)	UF: 30	Kirkpatrick 2002
Chronic	Insufficient data for MRL derivation				
Oral exposure (mg/kg/day)					
Acute	**0.5**	Increased ALT and AST	NOAEL: 46	UF: 100	Tyson et al. 1983
Intermediate	**0.04**	Decreased hemagglutination titers	NOAEL: 3.9	UF: 100	Sanders et al. 1985
Chronic	Insufficient data for MRL derivation				

[a]See Appendix A for additional information.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMCL = lower confidence limit on the benchmark concentration; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; MF = modifying factor; NOAEL = no-observed-adverse-effect level; UF = uncertainty factor

Figure 1-4. Summary of Sensitive Targets of 1,1,2-Trichloroethane – Oral

The immunological and hepatic systems are the most sensitive targets of 1,1,2-trichloroethane oral exposure.

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