CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

1,2-Dichloropropane (CAS Registry Number 78-87-5) is a colorless liquid belonging to a class of volatile organic compounds (VOCs). It has a chloroform-like odor and evaporates quickly at room temperature. 1,2-Dichloropropane is used in the United States as a chemical intermediate and in the manufacture of chlorinated and industrial solvents. A few consumer products contain 1,2-dichloropropane, including household stain removers and waxes and sealants for natural stone and other surfaces. Before the early 1980s, 1,2-dichloropropane was used in farming as a soil fumigant. Most of the 1,2-dichloropropane released into the environment ends up in the air or groundwater. The greatest potential for the general population to be exposed to 1,2-dichloropropane is through inhalation of contaminated ambient air and consumption of contaminated drinking water. The general population may also be exposed while using consumer products containing 1,2-dichloropropane. Occupational exposure to 1,2-dichloropropane may result during its production, use in chemical reactions, use as an industrial solvent, and disposal of processing wastes containing the chemical. Workers involved in cleaning up hazardous waste or spill sites that contain 1,2-dichloropropane may potentially be exposed.

1.2 SUMMARY OF HEALTH EFFECTS

Information on the noncancer toxicity of 1,2-dichloropropane comes primarily from studies in laboratory animals; however, several case reports in exposed humans contribute to the identification of primary toxicity targets. Eighty-six laboratory animal toxicity studies with health effects data have been identified: 51 inhalation, 32 oral, and 5 dermal.

As illustrated in Figures 1-1 and 1-2, sensitive targets in laboratory animals following inhalation or oral exposure include the upper respiratory tract (nasal) damage, liver damage, anemia, central nervous system (CNS) depression, and delayed ossification in fetuses. In general, the kidney does not appear to be a sensitive target in laboratory animals, but renal failure has been associated with high oral doses of 1,2-dichloropropane in human case reports. A systematic review of these endpoints resulted in the following hazard identification conclusions:

- Upper respiratory tract effects are a presumed health effect for humans following inhalation exposure.
- Hematological effects are a presumed health effect for humans.

- Hepatic effects are a presumed health effect for humans.
- CNS depression is a presumed health effect for humans.
- Developmental effects are a presumed health effect for humans.
- The data are inadequate to conclude whether renal effects will occur in humans.

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

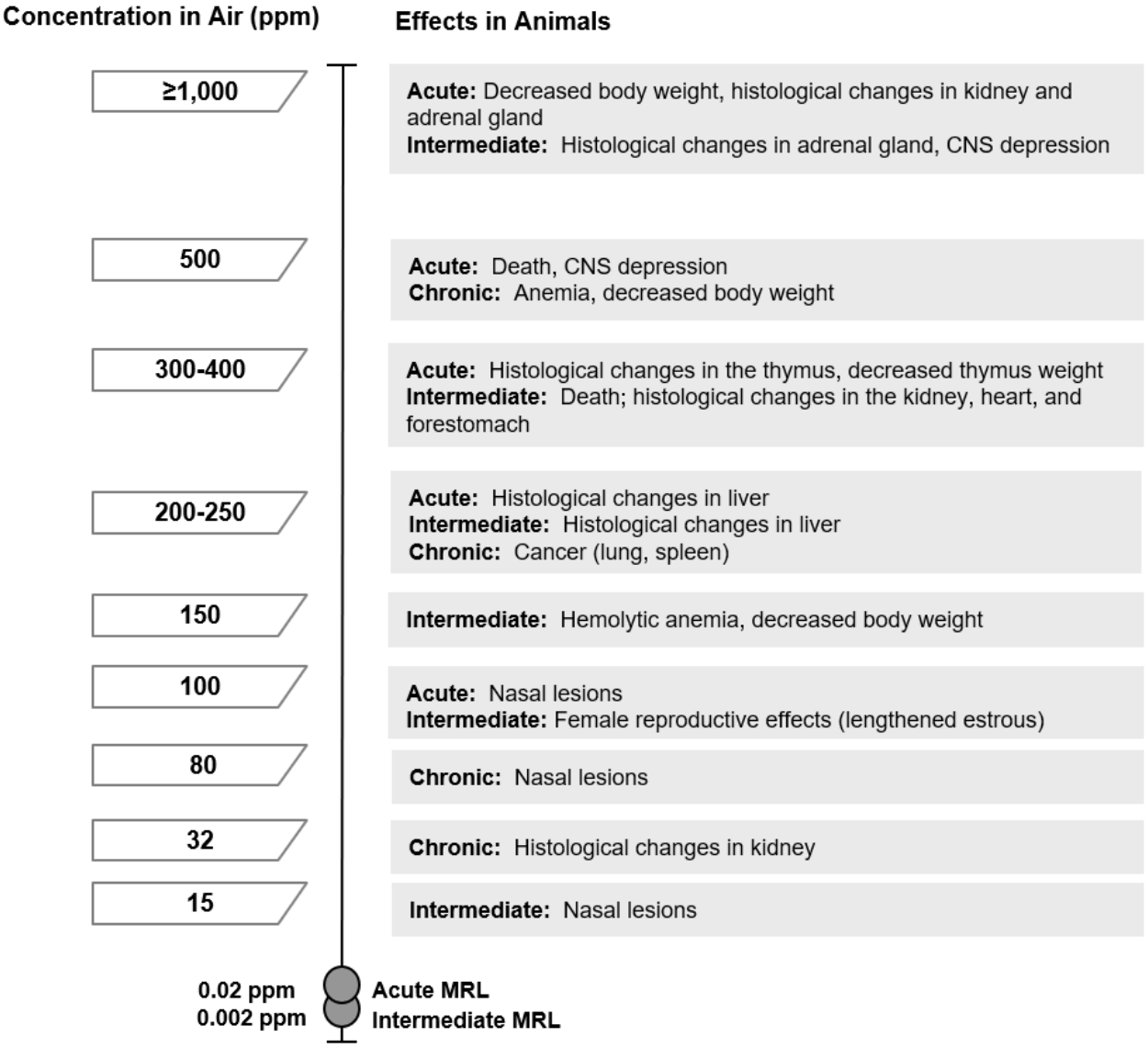
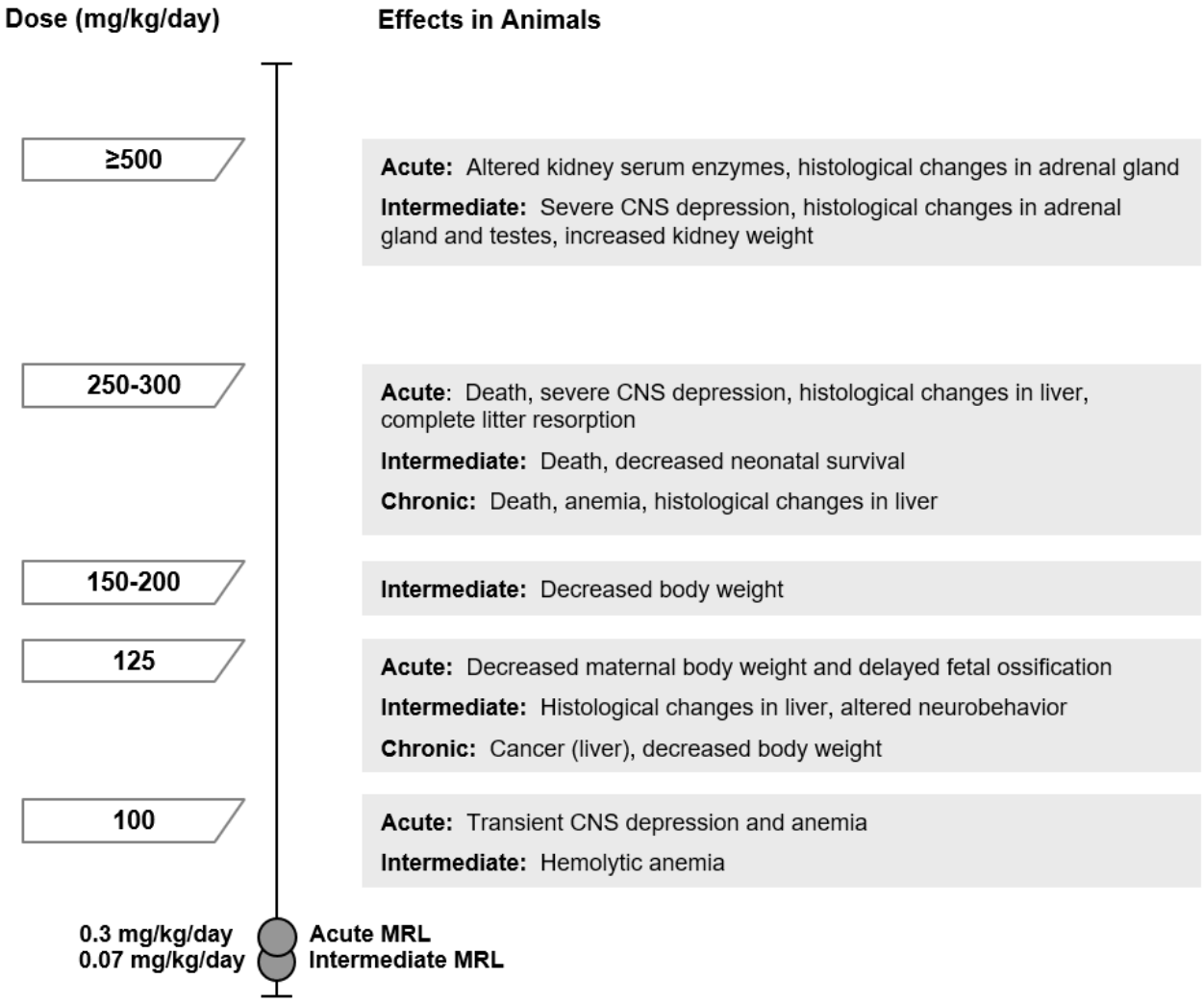


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to 1,2-Dichloropropane



Respiratory Effects. Limited data from chemical spill accident reports indicate that exposure to high concentrations of 1,2-dichloropropane can cause respiratory tract irritation in humans (ACGIH 2014; Rubin 1988). In laboratory animals, the upper respiratory tract is a sensitive target tissue following acute-, intermediate- and chronic-duration inhalation exposure (Matsumoto et al. 2013; Nitschke and Johnson 1983; Nitschke et al. 1988; Umeda et al. 2010). Rats are the most sensitive species, with degeneration of the olfactory mucosa observed at the lowest acute-duration concentration tested (100 ppm), hyperplasia of the nasal respiratory epithelium observed at the lowest intermediate-duration concentration tested (15 ppm), and atrophy of olfactory epithelium, inflammation of the respiratory epithelium, squamous cell metaplasia of respiratory epithelium, and hyperplasia of the transitional epithelium at the lowest chronic-duration concentration tested (80 ppm); additional effects observed at higher concentrations included squamous cell hyperplasia, degeneration of the olfactory epithelium, and inflammation and hyperplasia of the submucosal glands (Nitschke et al. 1988; Umeda et al. 2010). Similar nasal lesions were also observed in mice and rabbits following acute- or intermediate-duration exposure to concentrations ≥300 and 1,000 ppm, respectively (Nitschke and Johnson 1983; Nitschke et al. 1988), and in mice following chronic-duration exposure to concentrations ≥80 ppm (Matsumoto et al. 2013). The upper respiratory tract has not been assessed in animals following oral exposure to 1,2-dichloropropane.

Hematological Effects. Hemolytic anemia as well as incidences of disseminated intravascular coagulation have been reported in humans following accidental or intentional acute exposure to high levels of 1,2-dichloropropane via ingestion (Di Nucci et al. 1988; Perbellini et al. 1985), inhalation (Lucantoni et al. 1991, 1992; Pozzi et al. 1985), or dermal exposure (Fiaccadori et al. 2003), some of which were fatal. Exposure levels in these cases are unknown but are assumed to be high. Data from animal studies show that exposure to 1,2-dichloropropane at inhalation concentrations as low as 150 ppm or oral doses as low as 100 mg/kg/day result in hemolytic anemia in rats, mice, and rabbits (Berdasco et al. 1988; Bruckner et al. 1989; Imberti et al. 1990; Kirk et al. 1990, 1995; Matsumoto et al. 2013; Nitschke et al. 1988; Umeda et al. 2010).

Hepatic Effects. One of the principal target organs for the toxicity of 1,2-dichloropropane in both humans and animals is the liver. Numerous cases studies reported hepatic effects following occupational exposure, accidental or intentional ingestion, intentional inhalation abuse (“sniffing” or “huffing”), or prolonged dermal exposure to large amounts of mixtures containing 1,2-dichloropropane (Chiappino and Secchi 1968; Di Nucci et al. 1988; Fiaccadori et al. 2003; Larcan et al. 1977; Lucantoni et al. 1991, 1992; Kubo et al. 2015; Perbellini et al. 1985; Pozzi et al. 1985; Secchi and Alessio 1968; Thorel et al. 1986).

Observed effects in humans include altered serum liver enzymes, impaired liver function, toxic hepatitis, hepatic necrosis, and liver failure. In laboratory animals, hepatic lesions were consistently observed following exposure to 1,2-dichloropropane at inhalation concentrations of ≥250 ppm and oral doses ≥12 mg/kg/day (see Section 2.9 for references). Observed effects in animals were primarily fatty degeneration and necrosis.

Renal Effects. A few case reports of intentional or accidental 1,2-dichloropropane poisoning suggest that the kidney is a target organ of toxicity in humans (Di Nucci et al. 1988; Perbellini et al. 1985; Pozzi et al. 1985). Observed effects included impaired kidney function, tubular necrosis, and acute kidney failure. Exposure levels in these cases are unknown but are assumed to be high. However, the kidney does not appear to be a sensitive target of 1,2-dichloropropane in laboratory animals. Inconsistent findings of kidney damage were observed following inhalation exposure to 1,2-dichloropropane in laboratory animals, with most studies observing renal effects (fatty degeneration) only at concentrations ≥1,000 ppm (Heppel et al. 1946a, 1948; Highman and Heppel 1946); however, a chronic study in mice reported basophilic changes and cortical mineralization in males at concentrations ≥32 ppm (Matsumoto et al. 2013). No adverse renal effects were observed in laboratory animals in any available oral studies (Bruckner et al. 1989; Gi et al. 2015a; Gorzinski and Johnson 1989; Kirk et al. 1990; NTP 1986).

Neurological Effects. The CNS is a target for 1,2-dichloropropane toxicity in both humans and animals. Severe CNS depression and coma are associated with accidental or intentional ingestion or inhalation of large quantities of 1,2-dichloropropane (Larcan et al. 1977; Perbellini et al. 1985; see also reviews by ACGIH 2014; EPA 2016a; IARC 2017). 1,2-Dichloropropane is also a CNS depressant in animals exposed to inhalation concentrations ≥500 ppm and oral doses ≥100 mg/kg/day (Bruckner et al. 1989; Exxon 1981a; Gorzinski and Johnson 1989; Heppel et al. 1946b; Kirk et al. 1989; Nitschke and Johnson 1983; Shell Oil Co. 1982). Effects were generally transient unless observed at high exposure levels associated with lethality.

Developmental Effects. No human studies evaluating developmental toxicity were identified. In oral exposure studies in animals, delayed skull ossification was observed in rat and rabbit fetuses at gestational exposure doses ≥125 mg/kg/day, but findings may be secondary to maternal toxicity (clinical signs, decreased body weight) observed at the same dose in both species (Kirk et al. 1995). Similarly, decreased neonatal survival and reduced neonatal body weights were observed in a 2-generation study at drinking water exposure levels of 152–254 mg/kg/day, which corresponded to parental toxicity

(decreased body weight, maternal anemia, hepatic toxicity) (Kirk et al. 1990). No inhalation studies in laboratory animals were identified.

Cancer. A series of case reports and retrospective cohort studies from Japanese printing companies indicate that exposure to high air levels of 1,2-dichloropropane (and/or other chlorinated solvents) may increase the risk of developing cholangiocarcinoma (CCA), a rare form of bile duct cancer (Kinoshita et al. 2019; Kubo et al. 2013, 2014a, 2014b; Kumagai 2014; Kumagai et al. 2013, 2014, 2016; Nakagawa et al. 2015; Ogawa et al. 2020; Sobue et al. 2015; Tomimaru et al. 2015; Yamada et al. 2014, 2015a, 2015b). Actual air levels of chlorinated solvents were not measured, but based on quantities of chemicals reportedly used, some studies estimated that print shop workers were exposed to 1,2-dichloropropane at concentrations ranging from 7 to 346 ppm (Kumagai et al. 2013, 2016; Yamada et al. 2014, 2015a, 2015b). Most workers were also exposed to other chlorinated solvents, including dichloromethane (15–360 ppm) and/or 1,1,1-trichloroethane (exposure levels not estimated). An excess of CCA has also been associated with employment in the printing and printing-related industries in Nordic and European countries; however, it is unclear if 1,2-dichloropropane was used in print shops in these countries (Ahrens et al. 2014; Vlaanderen et al. 2013).

1,2-Dichloropropane is carcinogenic in laboratory animals following both inhalation and oral exposure. There is evidence for respiratory tract cancer following inhalation exposure (nasal tumors in rats, lung tumors in mice) and some evidence for neoplastic lesions in the Harderian gland and spleen in male mice (Matsumoto et al. 2013; Umeda et al. 2010). Following oral exposure, the NTP (1986) concluded that there was equivocal evidence of mammary tumors in female rats and some evidence of liver tumors in male and female mice.

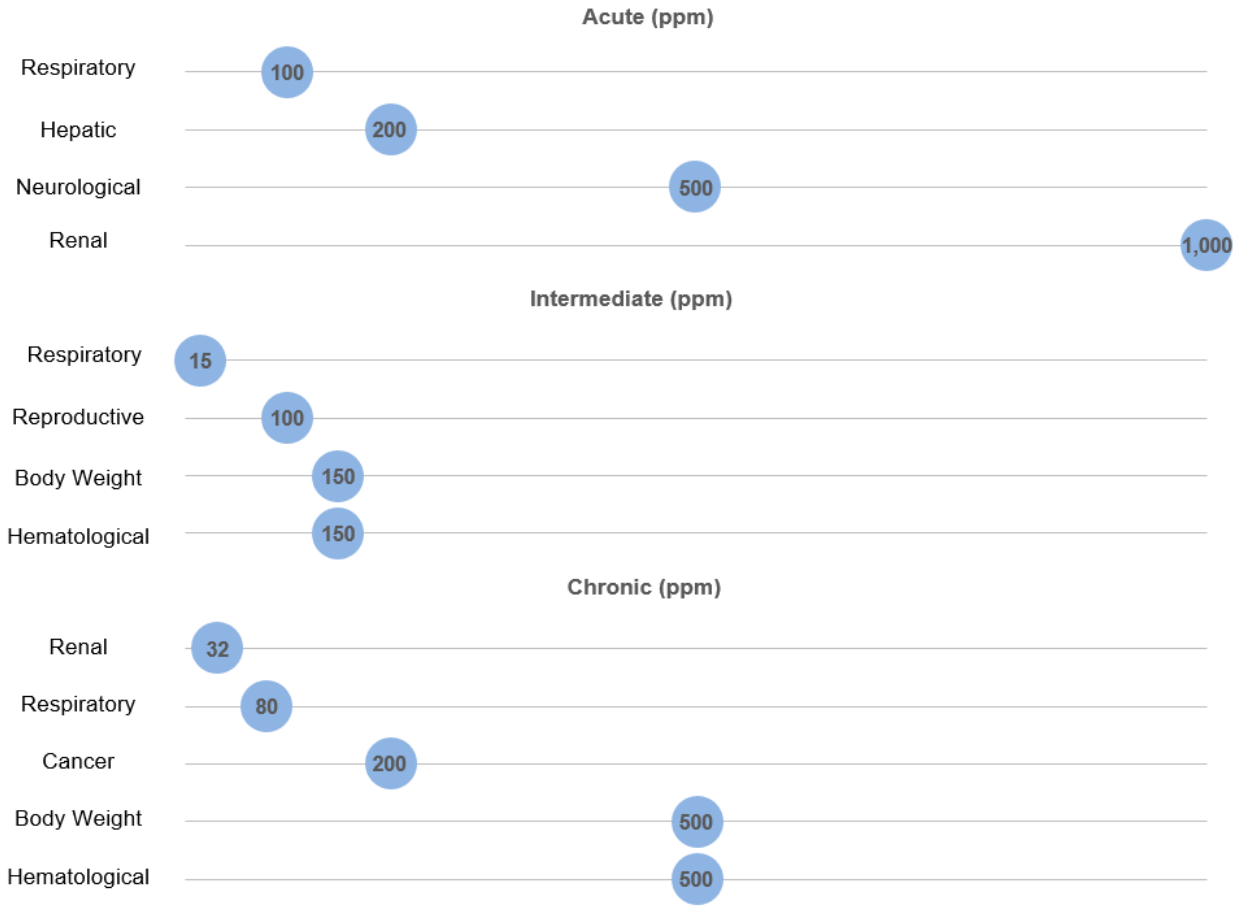
The International Agency for Research on Cancer (IARC 2017) concluded that 1,2-dichloropropane is carcinogenic to humans (Group 1) based on evidence that 1,2-dichloropropane exposure causes cancer of the biliary tract (CCA) in occupationally exposed workers and supporting mechanistic data. The EPA Peer-Reviewed Provisional Toxicity Value (PPRTV) program determined that 1,2-dichloropropane is likely to be carcinogenic to humans based on evidence of a potential correlation between occupational exposure to 1,2-dichloropropane and CCA cancer and adequate evidence in laboratory animals (EPA 2016a).

1.3 MINIMAL RISK LEVELS (MRLs)

The inhalation database was considered adequate for deriving acute- and intermediate-duration MRLs but inadequate for derivation of a chronic-duration MRL. As presented in Figure 1-3, the available inhalation data for 1,2-dichloropropane suggest that the upper respiratory tract is the most sensitive target of toxicity in laboratory animals.

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

The upper respiratory system is the most sensitive target of 1,2-dichloropropane.
Numbers in circles are the lowest LOAELs for all health effects in animals; no reliable dose-response data were available for humans.

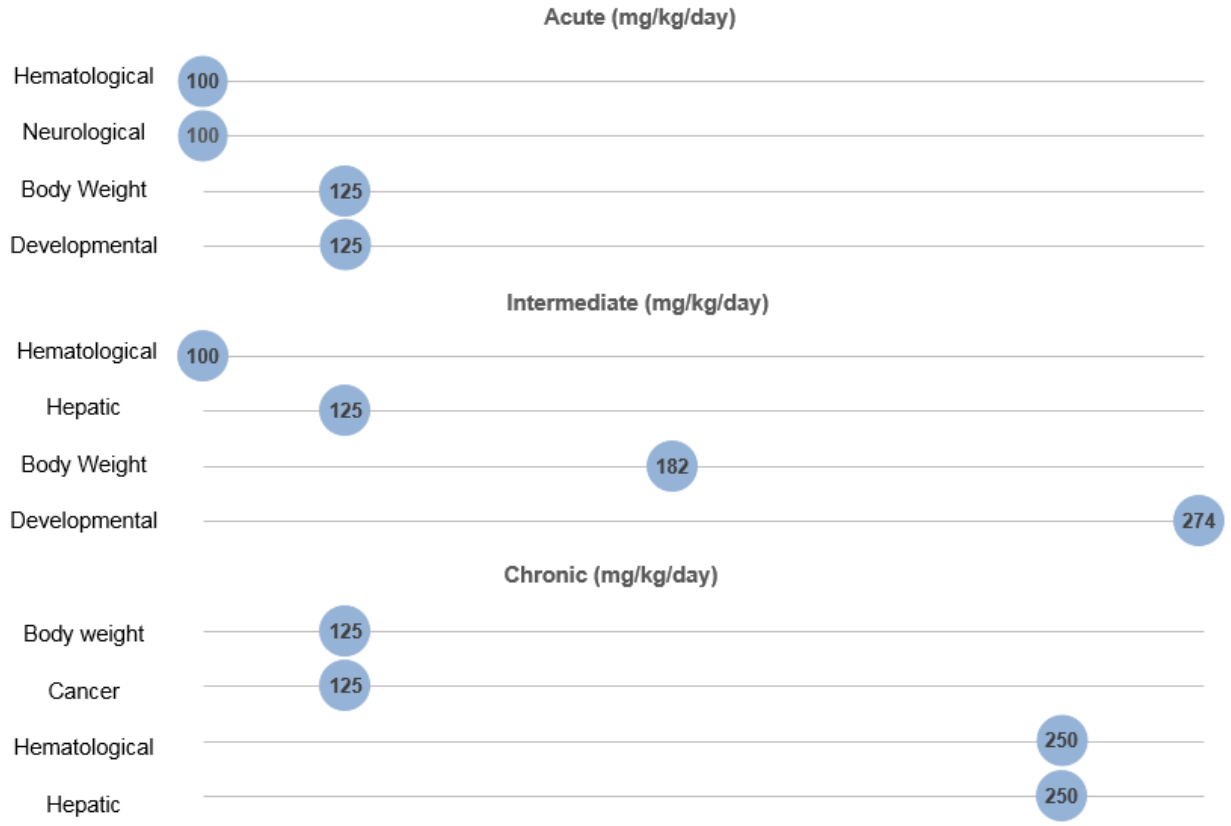


The oral database was considered adequate for deriving acute- and intermediate-duration MRLs. The oral database was inadequate for derivation of a chronic-duration MRL. As presented in Figure 1-4, the available oral data for 1,2-dichloropropane suggest that the CNS, liver, hematological system, developing fetus, and cancer are the most sensitive targets of toxicity in laboratory animals.

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

The CNS, liver, hematological system, developing fetus, and cancer are the most sensitive targets of 1,2-dichloropropane.

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



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

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

Exposure duration	MRL	Critical effect	Point of departure/ human equivalent concentration	Uncertainty factor	Reference
Inhalation exposure (ppm)					
Acute	0.02	Slight degeneration of the olfactory mucosa in rats	LOAEL: 100 ($LOAEL_{HEC}$: 1.8)	90	Nitschke and Johnson 1983
Intermediate	0.002	Very slight hyperplasia of the nasal respiratory epithelium in rats	$BMCL_{10}$: 2.38 ($BMCL_{10[HEC]}$:0.05)	30	Nitschke et al. 1988
Chronic	Insufficient data for MRL derivation				
Oral exposure (mg/kg/day)					
Acute	0.3	Maternal anemia in rabbits	$BMDL_{1SD}$: 30	100	Berdasco et al. 1988; Kirk et al. 1995
Intermediate	0.07	Hemolytic anemia in rats	LOAEL: 100 $LOAEL_{ADJ}$: 71	1,000	Bruckner et al. 1989
Chronic	Insufficient data for MRL derivation				

[a]See Appendix A for additional information.

ADJ = adjusted for continuous exposure; BMDL/BMCL= 95% lower confidence limit on the benchmark dose/concentration (subscripts denote benchmark response: exposure level associated with 10% extra risk or 1 SD change in endpoint); HEC = human equivalency concentration; LOAEL = lowest-observed-adverse-effect level; SD = standard deviation