CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

1,2,3-Trichloropropane ($C_3H_5Cl_3$; CAS number 96-18-4) is a man-made chemical that is present in the environment as a result of anthropogenic activity. It is primarily used in the production of other chemicals. In the past, it was used as a solvent and extractive agent. Exposure can occur through ingestion of contaminated food and water, inhalation, and dermal contact. Data regarding the concentrations of 1,2,3-trichloropropane in the environment are limited; low levels have been found in a few rivers and bays, drinking water, groundwater, and hazardous waste sites in the United States.

1.2 SUMMARY OF HEALTH EFFECTS

Information on the toxicity of 1,2,3-trichloropropane primarily comes from studies conducted in experimental animals. Three studies have evaluated the toxicity of 1,2,3-trichloropropane in humans. Approximately 30 experiments have been conducted in experimental animals, although there are less than 15 publications or unpublished studies. Approximately 50% of the studies are by the oral route, 30% by inhalation, and the remainder are dermal/ocular studies. As illustrated in Figures 1-1 and 1-2, the most sensitive effects appear to be liver damage, kidney damage, respiratory tract damage, hematological effects, heart damage, ocular effects, and cancer.

Respiratory Effects. Throat irritation was observed in humans exposed to 1,2,3-trichloropropane for 15 minutes (Silverman et al. 1946). The respiratory tract, specifically the nasal olfactory epithelium, is the most sensitive target of toxicity in experimental animals following inhalation exposure to 1,2,3-trichloropropane. The earliest sign of toxicity in the olfactory epithelium is a decrease in epithelial thickness; at higher concentrations, degeneration, inflammation, and fibrosis occur (Miller et al. 1986a, 1986b). Peribronchial hyperplasia has also been observed in rats following inhalation exposure (Johannsen et al. 1988). Oral exposure to relatively high doses of 1,2,3-trichloropropane also resulted in inflammation and necrotic lesions in the nasal cavity of rats and mice following acute- or intermediate-duration exposure (NTP 1993) and regenerative hyperplasia of bronchiolar epithelium in mice following chronic exposure (NTP 1993). Additionally, lung hemorrhages have resulted in rabbits administered a lethal dermal dose of 1,2,3-trichloropropane (Albert 1982; Union Carbide 1958).

Figure 1-1. Health Effects Found in Animals Following Inhalation Exposure to 1,2,3-Trichloropropane

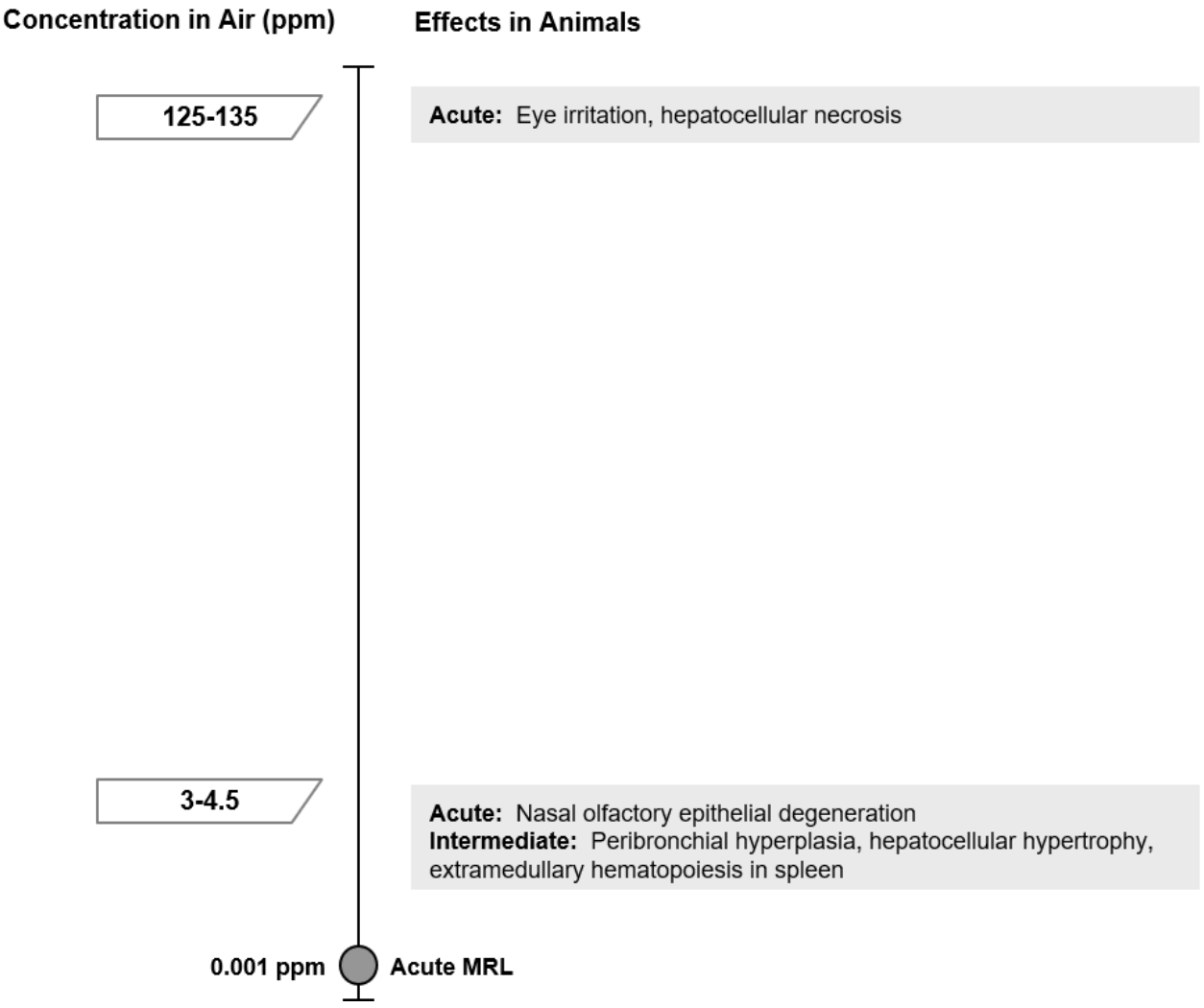
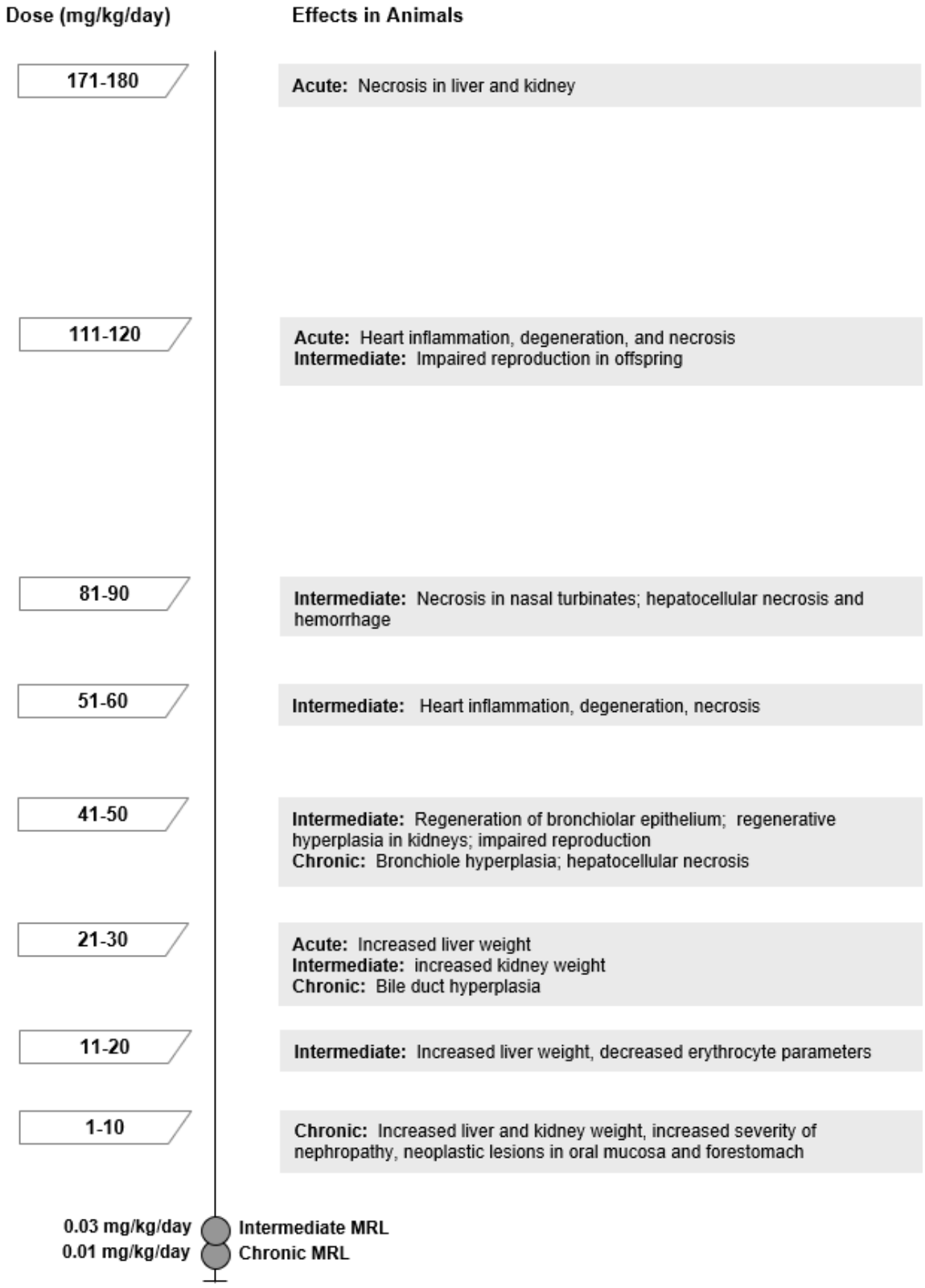


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to 1,2,3-Trichloropropane



Cardiovascular Effects. Heart inflammation, degeneration, and necrosis have been observed in rats administered 1,2,3-trichloropropane for an acute- or intermediate-duration exposure (Merrick et al. 1991). However, other oral studies and inhalation studies have not found histological alterations in the heart (Johannsen et al. 1988; Miller et al. 1986a; NTP 1993; Villeneuve et al. 1985).

Hematological Effects. Decreases in hematocrit, hemoglobin, and erythrocyte levels have been observed in rats following intermediate-duration oral exposure (NTP 1993); the resulting anemia appeared to be due to depressed erythropoiesis. Similar decreases in hematological parameters were also observed in rats and mice following chronic oral exposure, but this may have been due to blood loss associated with tumors (NTP 1993). In addition to the alterations in hematological parameters, splenic extramedullary hematopoiesis has been observed following inhalation (Johannsen et al. 1988) and oral (NTP 1993) exposures.

Liver Effects. Human data on the hepatotoxicity of 1,2,3-trichloropropane is limited to a case report of an individual with rapid progressive degeneration of liver function after ingesting 1,2,3-trichloropropane (Han 2010). Evidence of liver damage has been observed in rats and mice following inhalation or oral exposure. Observed effects include increases in liver weight, often observed at lower doses than those associated with histological damage; clinical chemistry alterations including alterations in serum enzymes, increases in serum bilirubin, and decreases in pseudocholinesterase levels; hepatocellular vacuolization; hepatocellular necrosis; and bile duct hyperplasia (Johannsen et al. 1988; Merrick et al. 1991; NTP 1993; Villeneuve et al. 1985). Following oral exposure, liver damage is one of the most sensitive effects.

Kidney Effects. The kidney is one of the most sensitive targets of toxicity following oral exposure. Increases in kidney weight were observed at lower doses; at higher doses, regenerative hyperplasia, tubular necrosis, and increases in the severity of chronic nephropathy have been observed (NTP 1993; Villeneuve et al. 1985). In contrast, renal effects have not been observed following inhalation exposure (Johannsen et al. 1988; Miller et al. 1986a).

Ocular Effects. Exposure to 1,2,3-trichloropropane has resulted in eye irritation in humans (Silverman et al. 1946), rats (Gushow and Quast 1984; Johannsen et al. 1988), and mice (Gushow and Quast 1984). The kidney is one of the most sensitive targets of toxicity following oral exposure. Eye irritation has also been reported in rabbits following direct ocular application (Albert 1982; Clark 1977).

Cancer Effects. The carcinogenicity of 1,2,3-trichloropropane was evaluated in rats and mice in a chronic gavage study (NTP 1993). In both species, forestomach squamous cell papillomas or carcinomas were observed at the lowest doses tested. Other sites with neoplastic lesions included the oral mucosa, liver, renal tubules, clitoral gland, mammary gland, preputial gland, harderian gland, and Zymbal's gland.

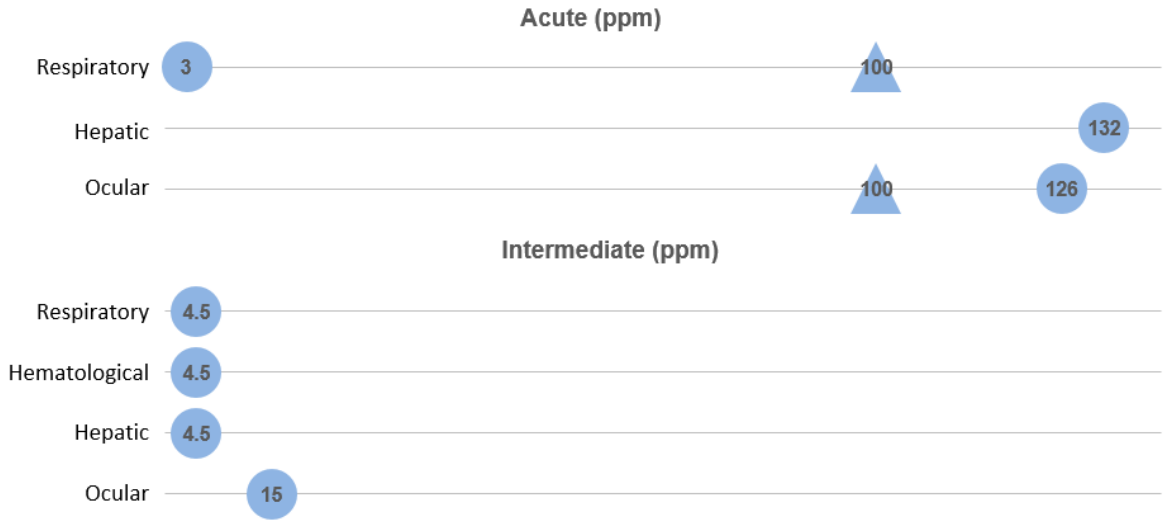
The U.S. Department of Health and Human Services (HHS) categorized 1,2,3-trichloropropane as reasonably anticipated to be a human carcinogen (NTP 2016), the U.S. Environmental Protection Agency (EPA) categorized it as likely to be carcinogenic to humans (EPA 2009a), and the International Agency for Research on Cancer (IARC) categorized it as probably carcinogenic to humans (IARC 1995).

1.3 MINIMAL RISK LEVELS (MRLs)

The inhalation database was considered adequate for derivation of an acute-duration inhalation MRL for 1,2,3-trichloropropane. The data were not considered adequate for derivation of an intermediate-duration inhalation MRL and no chronic inhalation studies were identified. As presented in Figure 1-3, the available inhalation data for 1,2,3-trichloropropane suggest that the respiratory tract, hematological erythrocyte, liver, and eyes are sensitive targets of toxicity.

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

The respiratory tract, liver, erythrocyte, and eye are the most sensitive targets of 1,2,3-trichloropropane.
Numbers in triangles and circles are the lowest LOAELs among health effects in humans and animals, respectively.



The oral database was considered adequate for derivation of an intermediate-duration oral MRL and a chronic-duration oral MRL for 1,2,3-trichloropropane. The liver, kidney, erythrocytes, and cancer are sensitive targets following oral exposure to 1,2,3-trichloropropane. Reproductive and cardiovascular endpoints also have relatively low lowest-observed-adverse-effect level (LOAEL) values, as illustrated in Figure 1-4. The MRL values are summarized in Table 1-1 and discussed in greater detail in Appendix A.

Figure 1-4. Summary of Sensitive Targets of 1,2,3-Trichloropropane – Oral

The liver, erythrocyte, kidney, and cancer are the most sensitive targets of 1,2,3-trichloropropane. Numbers in circles are the lowest LOAELs for all health effects in animals; no reliable dose-response data were available for humans.

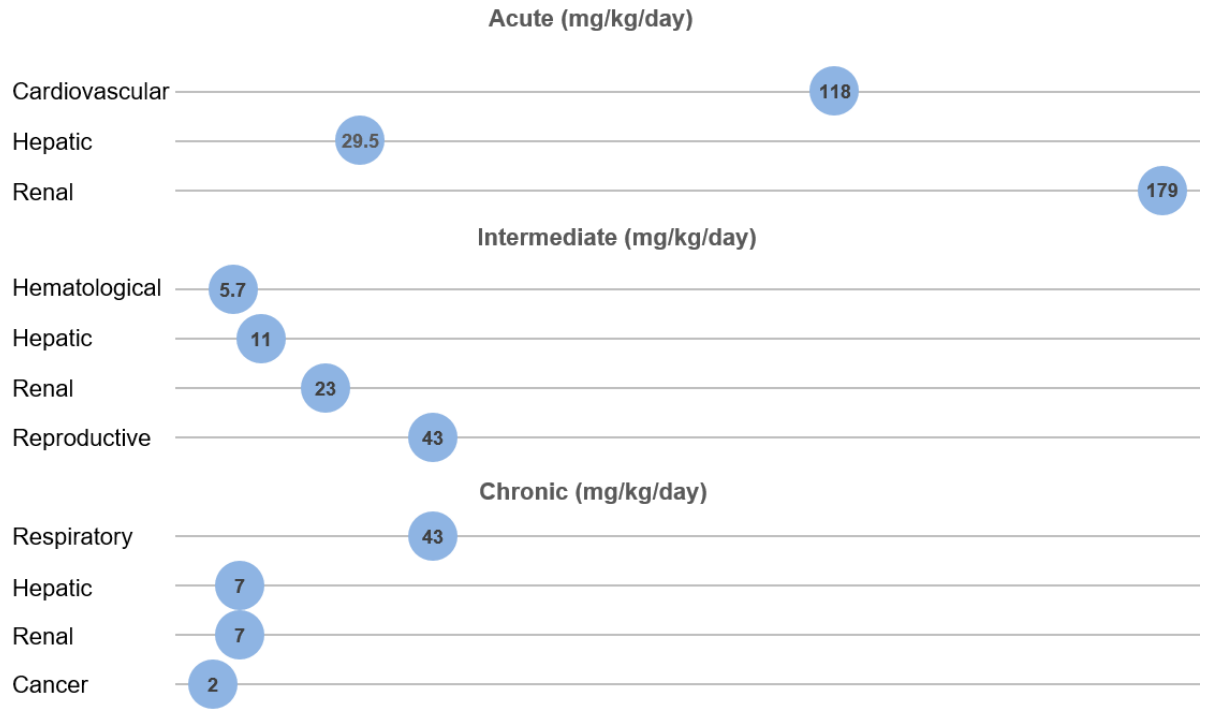


Table 1-1. Minimal Risk Levels (MRLs) for 1,2,3-Trichloropropane[a]

Exposure duration	MRL	Critical effect	Point of departure/ human equivalent concentration	Uncertainty factor	Reference
Inhalation exposure (ppm)					
Acute	0.001	Decreased thickness of nasal olfactory epithelium	NOAEL: 1 ($NOAEL_{HEC}$: 0.03)	30	Miller et al. 1986b
Intermediate	Insufficient data for MRL derivation				
Chronic	Insufficient data for MRL derivation				
Oral exposure (mg/kg/day)					
Acute	Insufficient data for MRL derivation				
Intermediate	0.03	Decreased hematocrit levels	$BMDL_{1SD}$: 4.03 mg/kg ($BMDL_{ADJ}$: 2.9)	100	NTP 1993
Chronic	0.01	Bile duct hyperplasia	$BMDL_{10}$: 1.94 mg/kg ($BMDL_{ADJ}$: 1.38)	100	NTP 1993

[a]See Appendix A for additional information.

ADJ = adjusted; BMDL = benchmark dose, 95% lower confidence limit; HEC = human equivalent concentration; NOAEL = no-observed-adverse-effect level; SD = standard deviation