CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Chlorobenzene (C_6H_5Cl; CAS Number 108-90-7) is used as a solvent and as a chemical intermediate in industry, a portion of which is lost to the environment in water and air discharges. Chlorobenzene adsorbs moderately to soil and is biodegraded comparatively rapidly.

The most likely sources of potential exposure of the general population to chlorobenzene are from breathing air, drinking water, or eating food contaminated with chlorobenzene. However, chlorobenzene has been detected in only very small quantities in air, water, and limited food sources. In a study of urban volatile organic compound (VOC) concentrations in the United States between 1996 and 1997, the highest levels of chlorobenzene were <1 ppbv (<4.6 µg/m^3) at 13 monitoring stations (Mohamed et al. 2002). The potential for toxic exposure to chlorobenzene via the water supply may be somewhat limited by the relatively low solubility of chlorobenzene in water, as evidenced by the fact that environmental levels of chlorobenzene in groundwater and surface water are generally in the low ppb range (e.g., Van Wijk et al. 2004; USGS 2006).

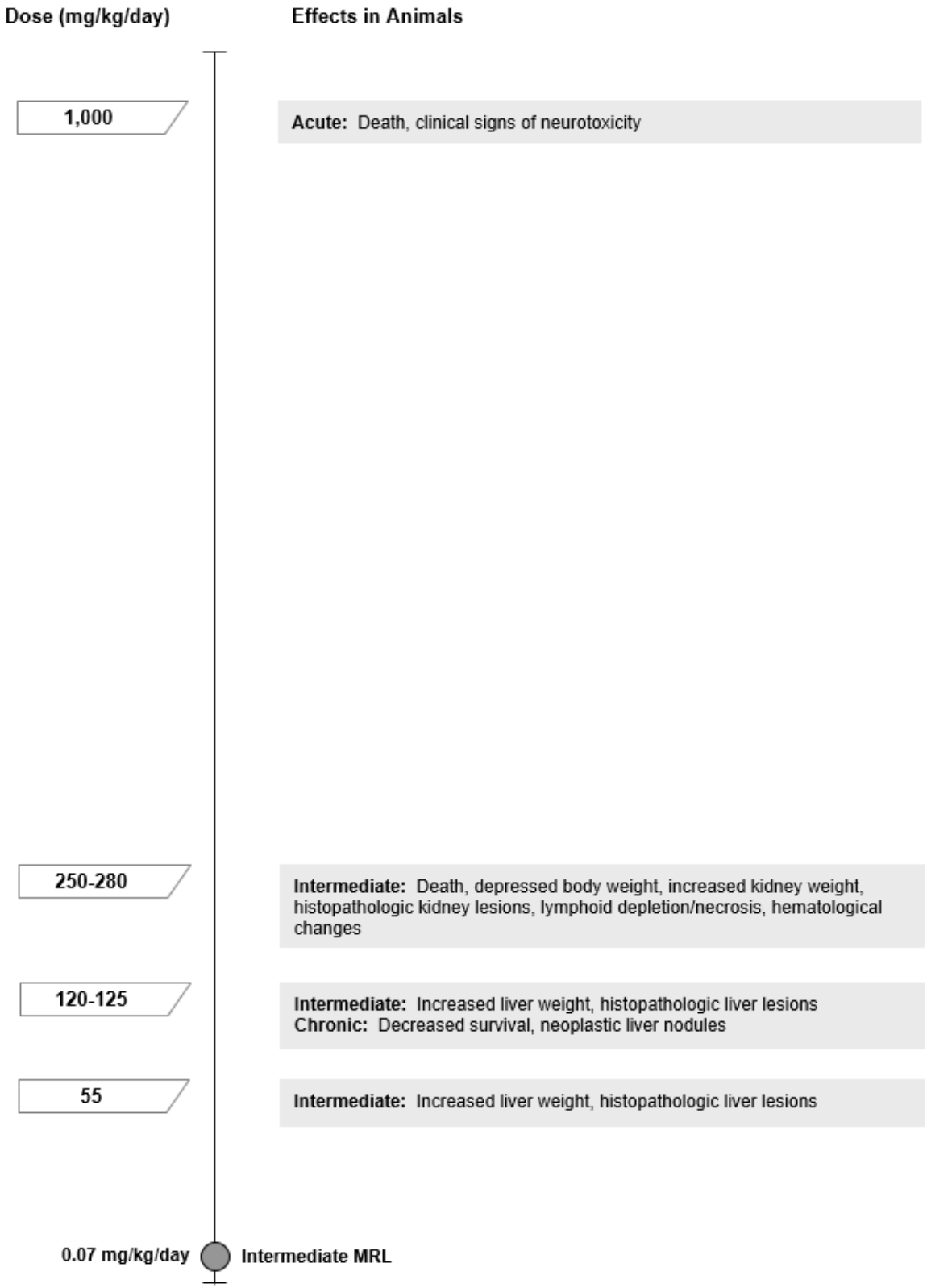
According to the results of the Centers for Disease Control and Prevention (CDC) National Health and Nutrition Examination Surveys conducted between 2003 and 2016, blood levels in the general public were undetectable at a limit of detection (LOD) of 0.011 ng/mL (CDC 2019).

1.2 SUMMARY OF HEALTH EFFECTS

- Available data, mostly from animal studies, identify the liver, kidney, and nervous system as principal targets of chlorobenzene, as illustrated in Figures 1-1 and 1-2 for inhalation and oral exposure, respectively.
- Results from oral studies in rats and mice indicate that the immunological system may be a target of chlorobenzene toxicity; however, tests of immune function in chlorobenzene-treated animals have not been performed.
- Results from limited animal studies suggest possible chlorobenzene-induced hematological effects.
- It is not clear whether chlorobenzene may cause cancer in humans.

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

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



Hematological Effects. Limited animal data suggest that chlorobenzene may exert adverse effects on red blood cell (RBC) parameters (NIOSH 1977) and cause leukopenia and lymphocytosis (Zub 1978). Decreases in hematocrit, hemoglobin, and/or RBC counts and changes in white blood cell (WBC) counts were noted in dogs administered chlorobenzene orally for 13 weeks (Monsanto Co. 1967a).

Hepatic Effects. Available information regarding the potential for chlorobenzene-induced hepatic effects in humans is limited to a single case report of severe liver necrosis in a suicidal male with a daily alcohol consumption of 200 g (Babany et al. 1991; Reygagne et al. 1992). The liver was identified as a target of chlorobenzene toxicity in laboratory animals following inhalation or oral exposure; effects included increased liver weight and histopathologic liver lesions (e.g., hepatocellular hypertrophy, vacuolation, degeneration/necrosis, bile duct hyperplasia) (Monsanto Co. 1967a, 1967b; Nair et al. 1987; NTP 1985).

Renal Effects. The kidney was identified as a target of chlorobenzene toxicity in laboratory animals following inhalation or oral exposure; effects included increased kidney weight and histopathologic kidney lesions (e.g., tubular dilatation, interstitial nephritis, degeneration/focal necrosis of proximal tubules, foci of regenerative epithelium) (Monsanto Co. 1967a; Nair et al. 1987; NTP 1985).

Immunological Effects. Results from 13-week studies of orally-exposed rats and mice suggest that chlorobenzene may affect the immune system; effects observed included myeloid and/or lymphoid depletion in bone marrow, spleen, and/or thymus (NTP 1985). However, no data were located regarding testing of immune function in animals exposed to chlorobenzene.

Neurological Effects. Case reports of humans demonstrated that chlorobenzene caused disturbances of the central nervous system, but there were no reports of changes in the structure of the brain or other parts of the nervous system. Neurological effects (e.g., headaches, dizziness, sleepiness) were observed in humans who inhaled vapors of chlorobenzene in the workplace for up to 2 years (Rozenbaum et al. 1947). However, quantitative exposure data were not available. Acute inhalation data from animals confirm the neurotoxicity of chlorobenzene at high exposure concentrations (Rozenbaum et al. 1947).

Cancer. No studies were found regarding the carcinogenicity of chlorobenzene in humans. In a chronic bioassay in animals, chlorobenzene (up to 120 mg/kg/day) did not produce increased tumor incidences in mice of either sex or in female rats (NTP 1985). High-dose (120 mg/kg/day) male rats exhibited statistically significantly increased incidence of neoplastic liver nodules. Based on available information from animal carcinogenicity studies and genotoxicity evaluations, the U.S. Environmental Protection

Agency (EPA) (IRIS 2003) assigned chlorobenzene to group D (not classifiable as to human carcinogenicity).

1.3 MINIMAL RISK LEVELS (MRLs)

As presented in Figure 1-3, available data have identified the liver and kidney as sensitive targets of chlorobenzene toxicity following inhalation exposure. No inhalation MRLs were derived for chlorobenzene due to insufficient data (see Appendix A). As presented in Figure 1-4, available data have identified the liver and kidney as sensitive targets of chlorobenzene toxicity following oral exposure. The oral database was considered adequate for derivation of an intermediate-duration oral MRL for chlorobenzene. The MRL value is summarized in Table 1-1 and discussed in detail in Appendix A. The database was not considered adequate for derivation of acute- or chronic-duration oral MRLs (see Appendix A).

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

The liver and kidney are the most sensitive targets of chlorobenzene inhalation exposure.
Numbers in circles are the lowest LOAELs for all health effects in animals; no human data were identified.

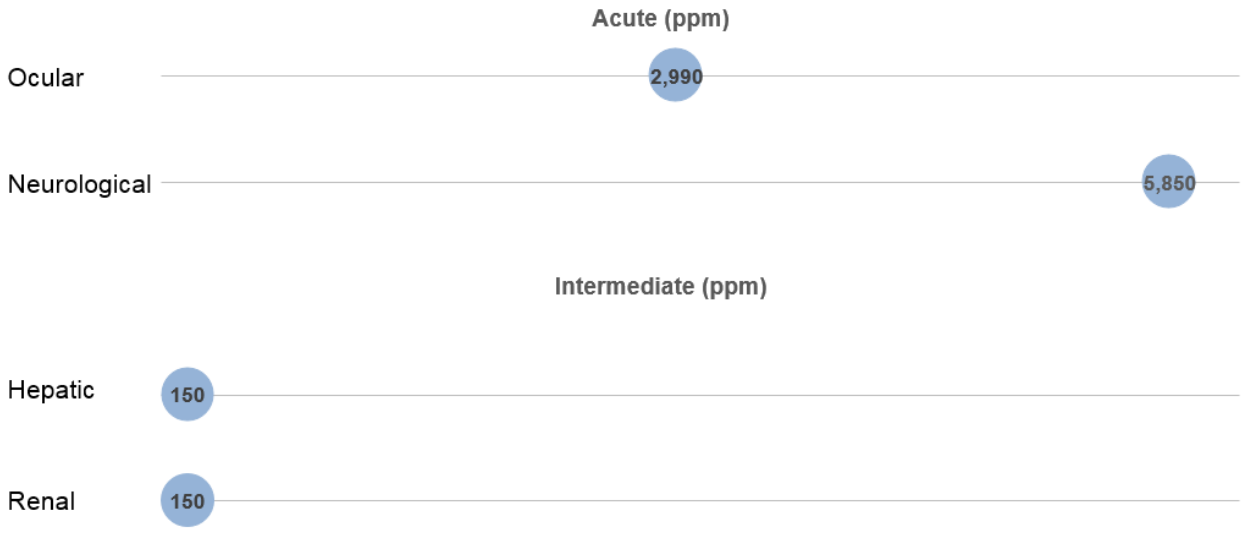


Figure 1-4. Summary of Sensitive Targets of Chlorobenzene – Oral

The liver is the most sensitive target of chlorobenzene oral exposure.
Numbers in circles are the lowest LOAELs for all health effects in animals.
No reliable dose response data were available for humans.

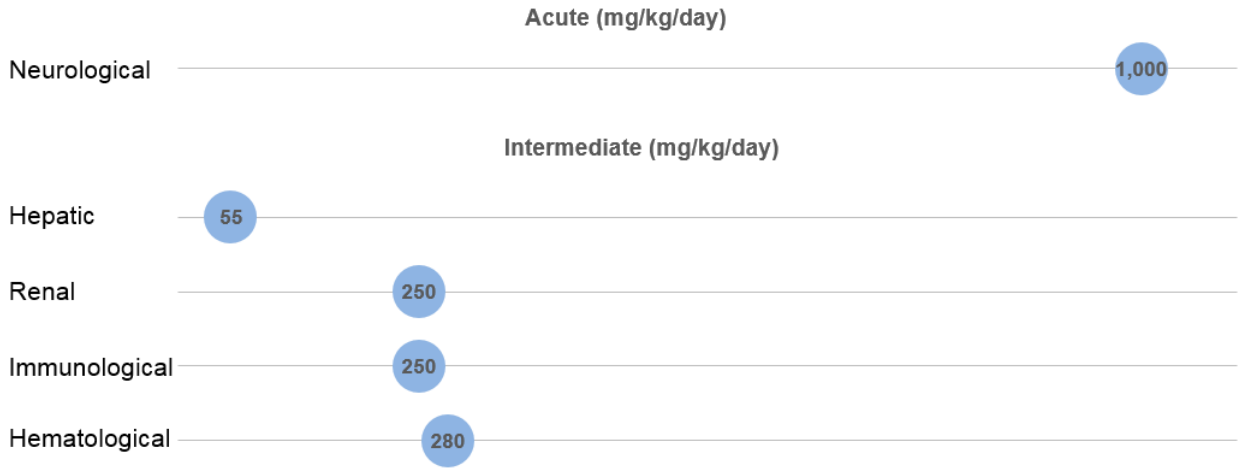


Table 1-1. Minimal Risk Levels (MRLs) for Chlorobenzene[a]

Exposure duration	MRL	Critical effect	Point of departure	Uncertainty and modifying factors	Reference
Inhalation exposure (ppm)					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic	Insufficient data for MRL derivation				
Oral exposure (mg/kg/day)					
Acute	Insufficient data for MRL derivation				
Intermediate	0.07	Bile duct hyperplasia	$BMDL_{10}$: 9.59 mg/kg ($BMDL_{ADJ}$: 6.85)	UF: 100	Monsanto Co. 1967a
Chronic	Insufficient data for MRL derivation				

[a]See Appendix A for additional information.

ADJ = duration-adjusted; $BMDL_{10}$ = 95% lower confidence limit on the benchmark dose with a benchmark response of 10% of extra risk; UF = uncertainty factor