CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Hexachlorobutadiene (C_4Cl_6; CAS No. 87-68-3) is a colorless liquid with a turpentine-like odor with an odor threshold of approximately 1 ppm. The main source of hexachlorobutadiene in the United States is its production as a byproduct of chlorinated hydrocarbon synthesis.

Low levels of hexachlorobutadiene can be detected in air, water, and sediment. Atmospheric levels of hexachlorobutadiene in rural and urban air samples typically range from 2 to 11 ppt, with a mean value of 2–3 ppt. Higher levels can be detected at areas near industrial and chemical waste disposal sites and production sites. Hexachlorobutadiene is infrequently detected in ambient waters, but has been detected in drinking water at levels of 2–3 ppt. Sediments contain higher levels of hexachlorobutadiene than the waters from which they were obtained. Foodstuffs generally do not contain detectable levels of hexachlorobutadiene, except for fish in which concentrations of 0.1–4.7 mg/kg have been reported. Thus, exposure can occur through ingestion of contaminated water or food or inhalation of contaminated air.

Hexachlorobutadiene has been detected in human adipose tissue and blood samples, although general population monitoring data are not available.

1.2 SUMMARY OF HEALTH EFFECTS

Information on the toxicity of hexachlorobutadiene primarily comes from studies in laboratory animals; only two epidemiology studies were identified. Both epidemiology studies were limited in scope examining either hepatic or renal endpoints. A wide range of potential endpoints were examined in the 24 experimental animal studies. Although hexachlorobutadiene toxicity has been more well-studied following oral exposure, the results of inhalation and dermal studies suggest similar targets.

As illustrated in Figures 1-1 and 1-2, the kidney is the most sensitive target of toxicity. Other targets include body weight gain, developmental toxicity, respiratory effects, hematological alterations, and hepatic toxicity; additionally, there is some evidence that chronic exposure can result in kidney tumors. Although body weight effects are also observed at lower doses, they are likely secondary to other effects. At higher doses, neurological effects, endocrine, ocular, and dermal effects (following direct contact exposure), and reproductive effects have been observed. The six sensitive targets of toxicity are discussed below.

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

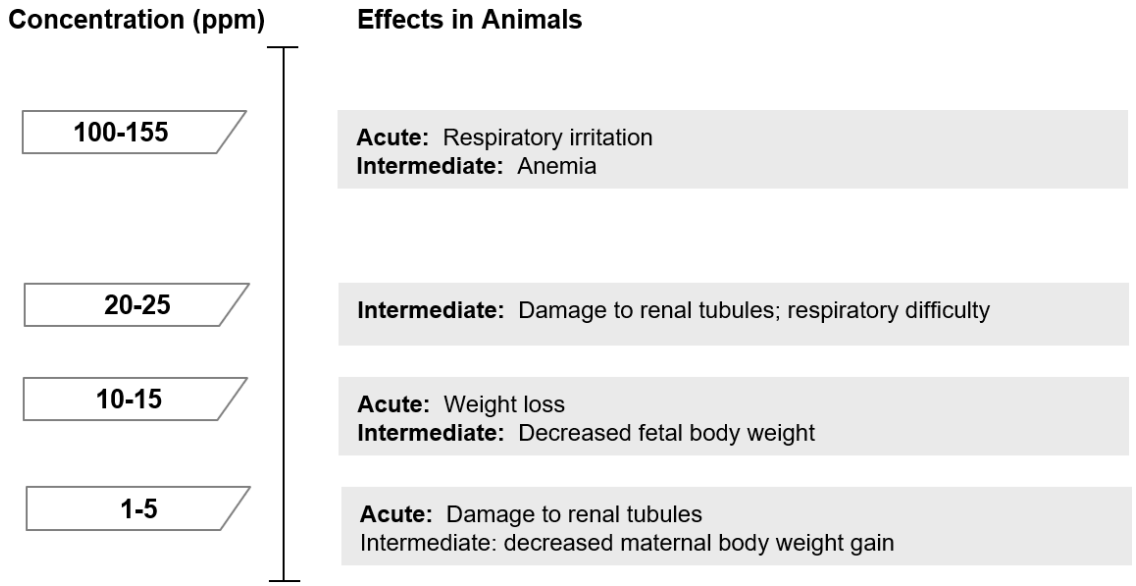
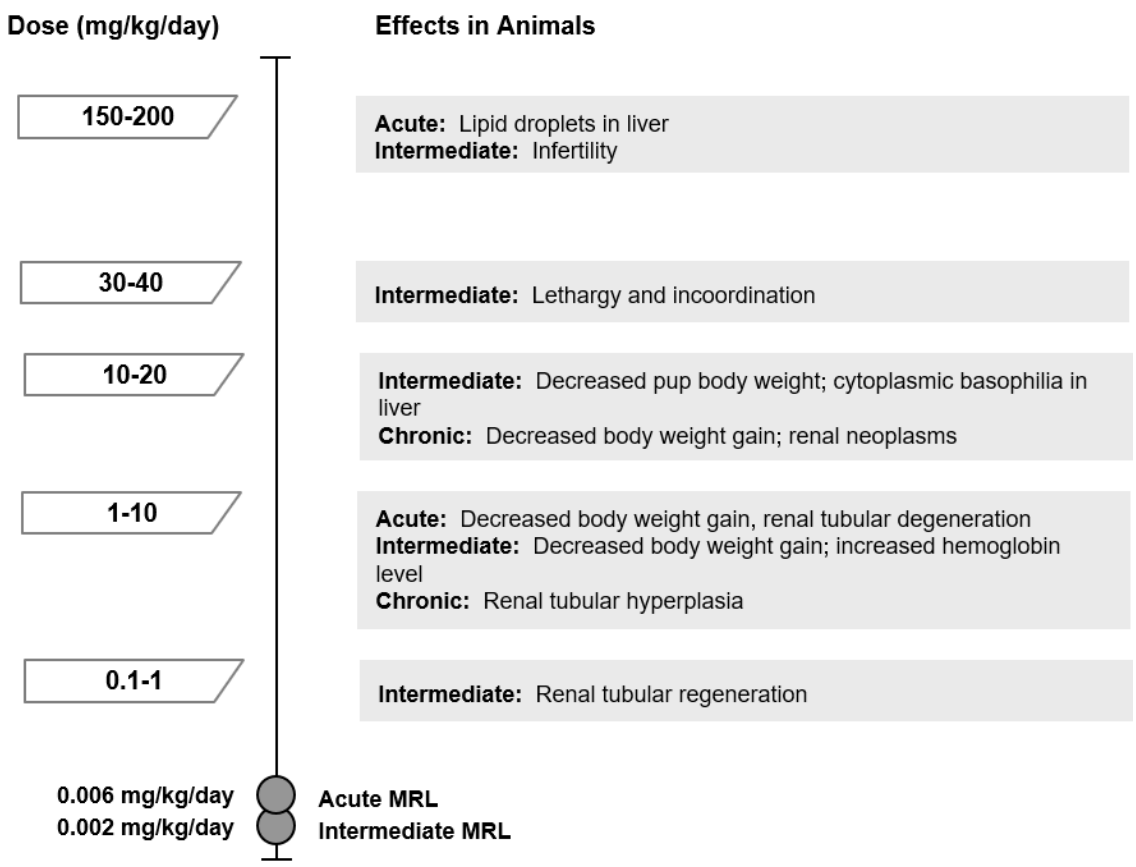


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to Hexachlorobutadiene



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Renal Effects. An epidemiology study found alterations in several biomarkers of renal toxicity (α-glutathione-S-transferase, γ-glutamyltransferase, leucine aminopeptidase, and π-glutathione-S-transferase) among residents living in homes contaminated with hexachlorobutadiene (Staples et al. 2003). The biomarkers returned to normal levels in most of the subjects 10 months after exposure termination, suggesting that the effects may be reversible. In experimental animals, renal toxicity, characterized as histological damage and alterations in biomarkers of impaired renal function, has been observed following inhalation, oral, dermal, and parenteral exposures and has been observed in single and repeated exposure studies. The histological damage was typically found in the pars recta region of the proximal tubules, although the S1/S2 regions have also been affected. The lesions included epithelial degeneration (Gage 1970; Harleman and Seinen 1979; Kociba et al. 1971; NTP 1991; Schwetz et al. 1977), epithelial regeneration (Schwetz et al. 1977; NTP 1991), hyperplasia (Kociba et al. 1977), and necrosis at higher concentrations/doses (Birner et al. 1995; Harleman and Seinen 1979; Jonker et al. 1993a; Kociba et al. 1971; NTP 1991). Several urinary biomarkers of renal function have been altered by hexachlorobutadiene exposure including increases in N-acetyl-β-glucosaminidase, protein, and glucose levels, increases in volume, and decreases in urine concentrating ability (Harleman and Seinen 1979; Jonker et al. 1993a).

Developmental Effects. Inhalation and oral exposure studies in rats have consistently reported decreases in fetal or pup body weights (Harleman and Seinen 1979; Saillenfait et al. 1989; Schwetz et al. 1977); decreases in maternal body weight gain were typically observed at the same dose level. No other developmental effects including fetal loss, resorptions, pup survival, or occurrence of anomalies or malformations were observed.

Respiratory Effects. Respiratory irritation, characterized as nasal irritation, decreases in respiratory rate, and breathing difficulties have been observed in rats and mice exposed to hexachlorobutadiene vapor (de Ceaurriz et al. 1988; Gage 1970). Histological examinations were not conducted in the inhalation studies, and oral studies have not found evidence of lung damage.

Hematological Effects. Two studies reported altered hematological parameters (Gage 1970; Kociba et al. 1971); however, the results were not consistent with each other or with other studies that found no alterations (Harleman and Seinen 1979; Kociba et al. 1977; Schwetz et al. 1977). An inhalation study reported anemia (Gage 1970) and an oral study reported increases in hemoglobin levels (Kociba et al. 1971). The inconsistency of the results makes it difficult to evaluate the relevance of this effect to humans.

Hepatic Effects. An increase in serum bile acids was reported in a study of workers exposed to hexachlorobutadiene, along with other solvents such as carbon tetrachloride and tetrachloroethylene (Driscoll et al. 1992); the study does not allow for an interpretation of whether these effects were due to hexachlorobutadiene exposure or to the other solvents that are known hepatotoxicants. Some oral exposure animal studies have reported hepatic effects (Birner et al. 1995; Harleman and Seinen 1979; Kociba et al. 1971), whereas other studies have not found histological alterations (Harleman and Seinen 1979; Kociba et al. 1977; NTP 1991; Schwetz et al. 1977). Observed effects included cytoplasmic lipid droplets (Birner et al. 1995), cytoplasmic basophilia (Harleman and Seinen 1979), and hepatocellular swelling (Kociba et al. 1971).

Cancer Effects. Increases in the incidence of renal neoplasms were observed in male and female rats orally exposed to hexachlorobutadiene for 2 years (Kociba et al. 1977). No increases in tumor incidences were observed in mice dermally exposed for 1.2–1.6 years (Van Duuren et al. 1979). Based on the results of the Kociba et al. (1977) study, EPA classified hexachlorobutadiene as a possible human carcinogen (Group C) (IRIS 1993). IARC categorized hexachlorobutadiene as not classifiable as to its carcinogenicity in humans (Group 3) (IARC 1999).

1.3 MINIMAL RISK LEVELS (MRLs)

The inhalation database was not considered adequate for deriving inhalation MRLs. As presented in Figure 1-3, the available inhalation data for hexachlorobutadiene suggest that sensitive targets include the kidney, respiratory tract, and developing organisms (fetal body weight); body weight effects have also been observed at low concentrations.

The oral database was considered adequate for derivation of acute- and intermediate-duration MRLs for hexachlorobutadiene; but was not considered adequate for derivation of a chronic-duration MRL. The kidney is the most sensitive target following acute, intermediate, or chronic duration exposure. As illustrated in Figure 1-4, body weight, hematological, and developmental effects are also observed at low doses. The oral MRLs for hexachlorobutadiene are summarized in Table 1-1 and discussed in greater detail in Appendix A.

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

The kidney is the most sensitive target of hexachlorobutadiene.
Numbers in circles are the lowest LOAELs (ppm) for all health effects in animals; no reliable concentration-response is available for humans.

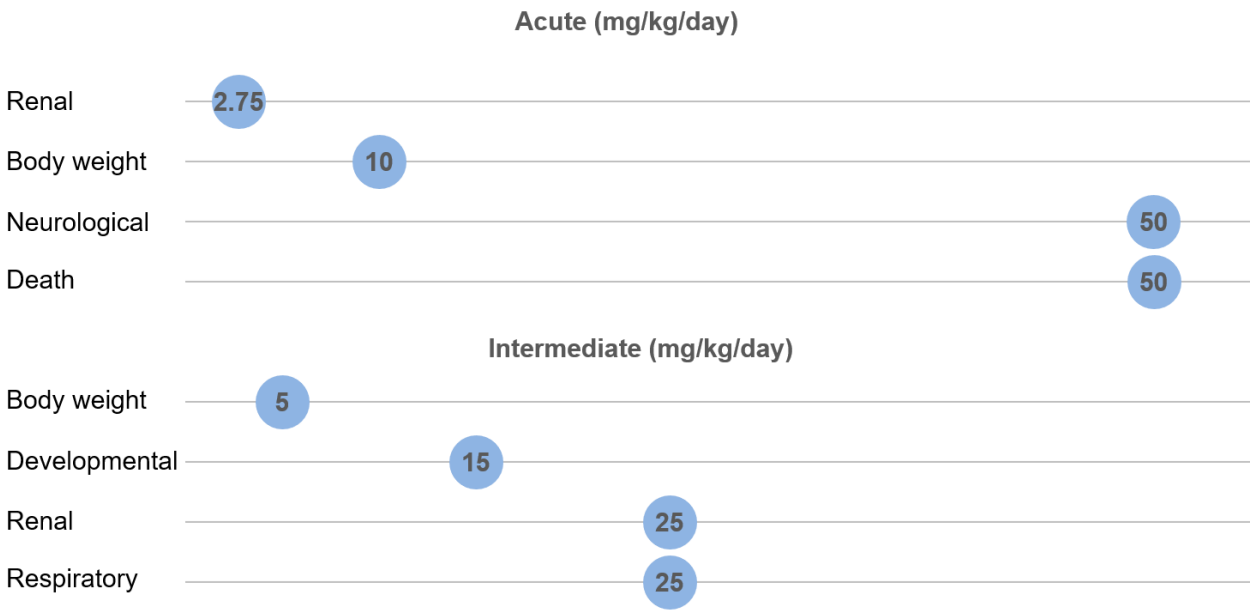

Figure 1-4. Summary of Sensitive Targets of Hexachlorobutadiene – Oral

The kidney is the most sensitive target of hexachlorobutadiene.
Numbers in circles are the lowest LOAELs (mg/kg/day) for all health effects in animals; no human data were identified.

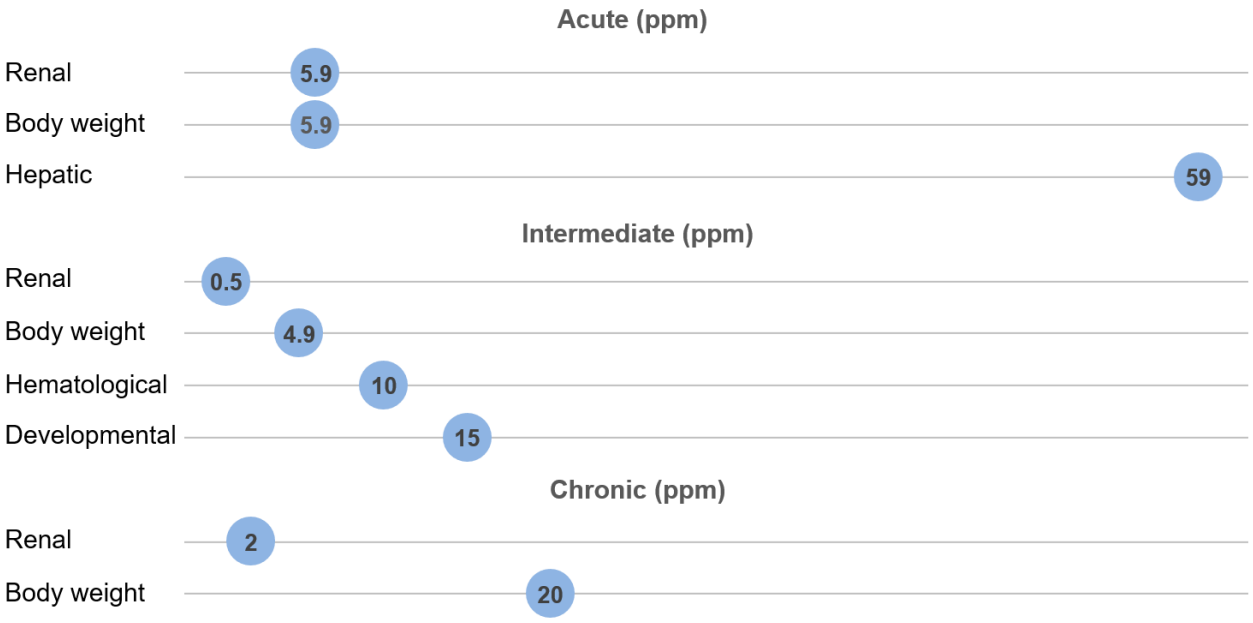

Table 1-1. Minimal Risk Levels (MRLs) for Hexachlorobutadiene[a]

Exposure duration	MRL	Critical effect	Point of departure	Modifying and uncertainty 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	0.006	Renal proximal tubule degeneration	5.9 (LOAEL)	1,000	Harleman and Seinen 1979
Intermediate	0.002	Renal proximal tubule regeneration	0.2 (NOAEL)	100	NTP 1991
Chronic	Insufficient data for MRL derivation				

[a]See Appendix A for additional information.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level