# CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

## 1.1 OVERVIEW AND U.S. EXPOSURES

Hexachlorocyclohexane (HCH) is a mixture of eight isomers, four of which are of commercial significance: alpha (α)-HCH (Chemical Abstracts Service [CAS] Registry Number 319-84-6), beta (β)-HCH (CAS Registry Number 319-85-7), gamma (γ)-HCH (CAS Registry Number 58-89-9), and delta (δ)-HCH (CAS Registry Number 319-86-8). Technical (or technical-grade) HCH (CAS Registry Number 608-73-1) is not an isomer of HCH, but rather a mixture of several isomers; it consists of approximately 60–70% α-HCH, 5–12% β-HCH, 10–15% γ-HCH, 6–10% δ-HCH, and 3–4% ε-HCH (Kutz et al. 1991). The most well-studied isomer is γ-HCH (lindane), an organochlorine insecticide that was used for a broad range of agricultural applications in the United States and worldwide beginning in the 1940s. Its agricultural use began to be limited in the 1970s by the U.S. Environmental Protection Agency (EPA), citing human health concerns, and final registrations for products containing γ-HCH were cancelled in late 2006. Today, 1% γ-HCH prescription products, regulated by the U.S. Food and Drug Administration (FDA), are available for lice and scabies treatment. HCH isomers exist as white solids that can volatilize to the gas or particulate phase. HCH released to the environment can volatilize from, or partition to, soil and can leach to groundwater. The general population may be exposed to low amounts of HCH through inhalation of contaminated ambient air and ingestion of contaminated water (exposure in the range of parts per trillion) or contact with contaminated soils (exposure in the range of parts per billion). The highest exposures result from the use of γ-HCH pharmaceutical treatments. Workers who work at facilities that use or process γ-HCH and people who live near HCH-contaminated sites may have increased exposure.

## 1.2 SUMMARY OF HEALTH EFFECTS

The toxicological database for HCH includes human observational studies of pesticide workers and the general population and studies of animals exposed by inhalation, oral administration, and dermal application. In general, the studies of pesticide applicators with exposure to γ-HCH or technical HCH used qualitative measures of exposure. Most general population studies used blood or tissue concentrations of HCH isomers to assess exposure, and the samples were typically collected simultaneously with or after outcome assessment. As such, the temporal relationship between exposure and outcome is uncertain.

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Data pertaining to the effects in animals after inhalation or dermal exposure are limited to the γ-HCH isomer and technical HCH. In addition, the available data on effects in animals exposed by oral administration to α-, β-, or δ-HCH are relatively limited, compared to the information available for γ-HCH. Figures 1-1 through 1-5 show the most sensitive effects in animals after inhalation exposure to γ-HCH, oral exposure to α-HCH, oral exposure to β-HCH, oral exposure to γ-HCH, and oral exposure to technical-grade HCH, respectively. The available data on δ-HCH are not adequate to identify sensitive effects by any exposure route. As Figure 1-2 shows, the most sensitive effect of oral exposure to α-HCH is liver toxicity. A systematic review of this endpoint resulted in the following hazard identification conclusion:

- Hepatic effects are a presumed health effect for humans.

Figure 1-3 shows that the most sensitive effects of β-HCH in animals exposed orally are liver toxicity and neurological effects. A systematic review of these endpoints resulted in the following hazard identification conclusions:

- Hepatic effects are a presumed health effect for humans.
- Neurological effects are a presumed health effect for humans.

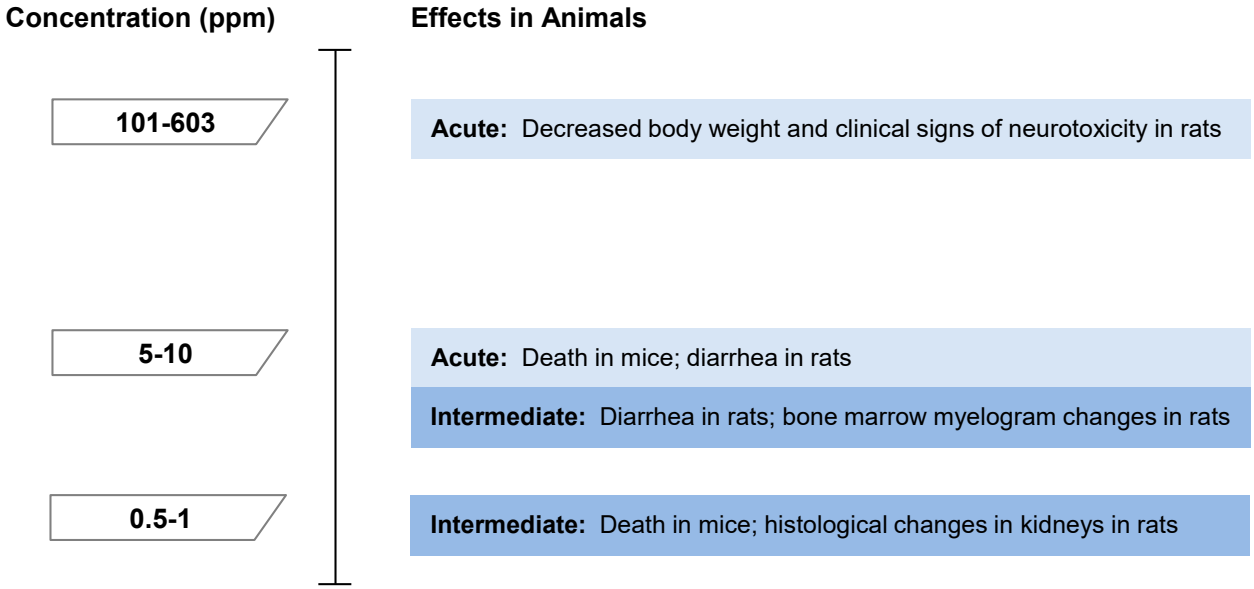
Figures 1-1 and 1-4 show that the most sensitive effects of γ-HCH in animals are developmental toxicity and immune system effects. A systematic review of these endpoints resulted in the following hazard identification conclusions:

- Developmental effects are a presumed health effect for humans.
- Immune system effects are a presumed health effect for humans.

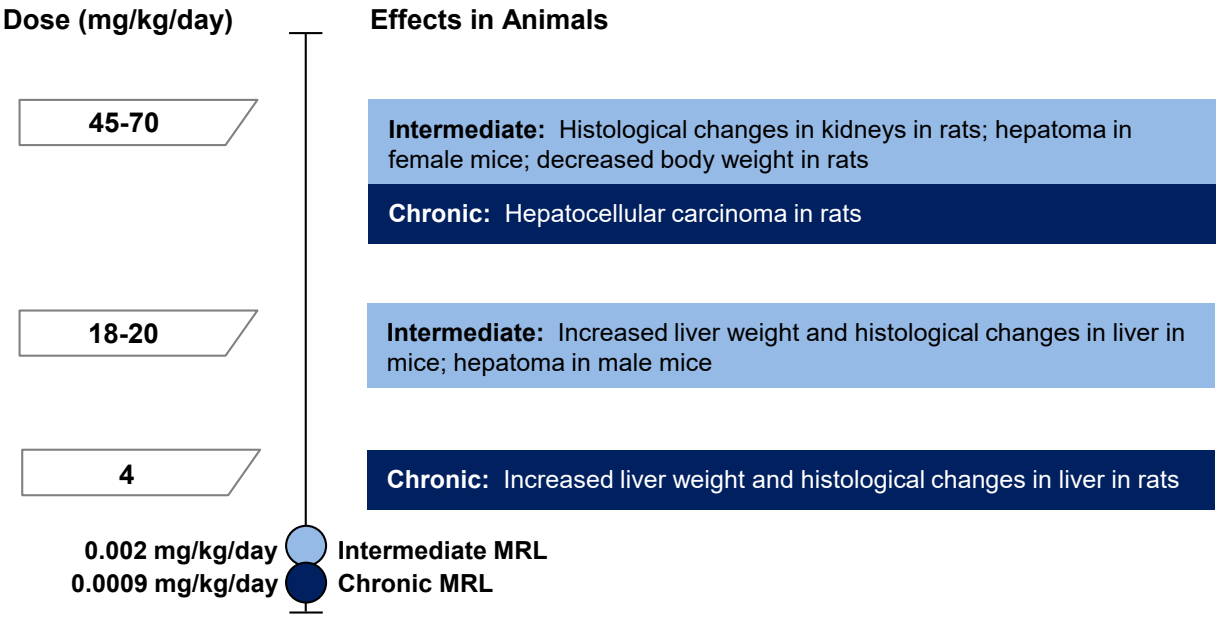
Figure 1-5 shows the most sensitive effects of technical-grade HCH (a mixture of isomers) or in studies that did not specify the HCH isomer(s). A systematic review was not conducted for the mixture.

***Hepatic Effects.*** Data on hepatic effects of HCH isomers in humans are inadequate for hazard identification, but studies in animals show similar liver effects induced by all the subject isomers of HCH after inhalation, oral, and dermal exposure. Hepatic effects consisting of increased absolute and/or relative liver weights, hepatocellular hypertrophy, necrosis, fatty degeneration, bile duct proliferation, and nodular hyperplasia have been observed in rats, mice, and hamsters exposed by oral administration of α-HCH for intermediate and chronic durations (Fitzhugh et al. 1950; Ito et al. 1975; Nagasaki et al. 1975; Sumida et al. 2007; Tryphonas and Iverson 1983). Dietary administration of β-HCH for intermediate and chronic durations has resulted in similar liver toxicity in rats and mice (Fitzhugh et al. 1950; Hanada et al.

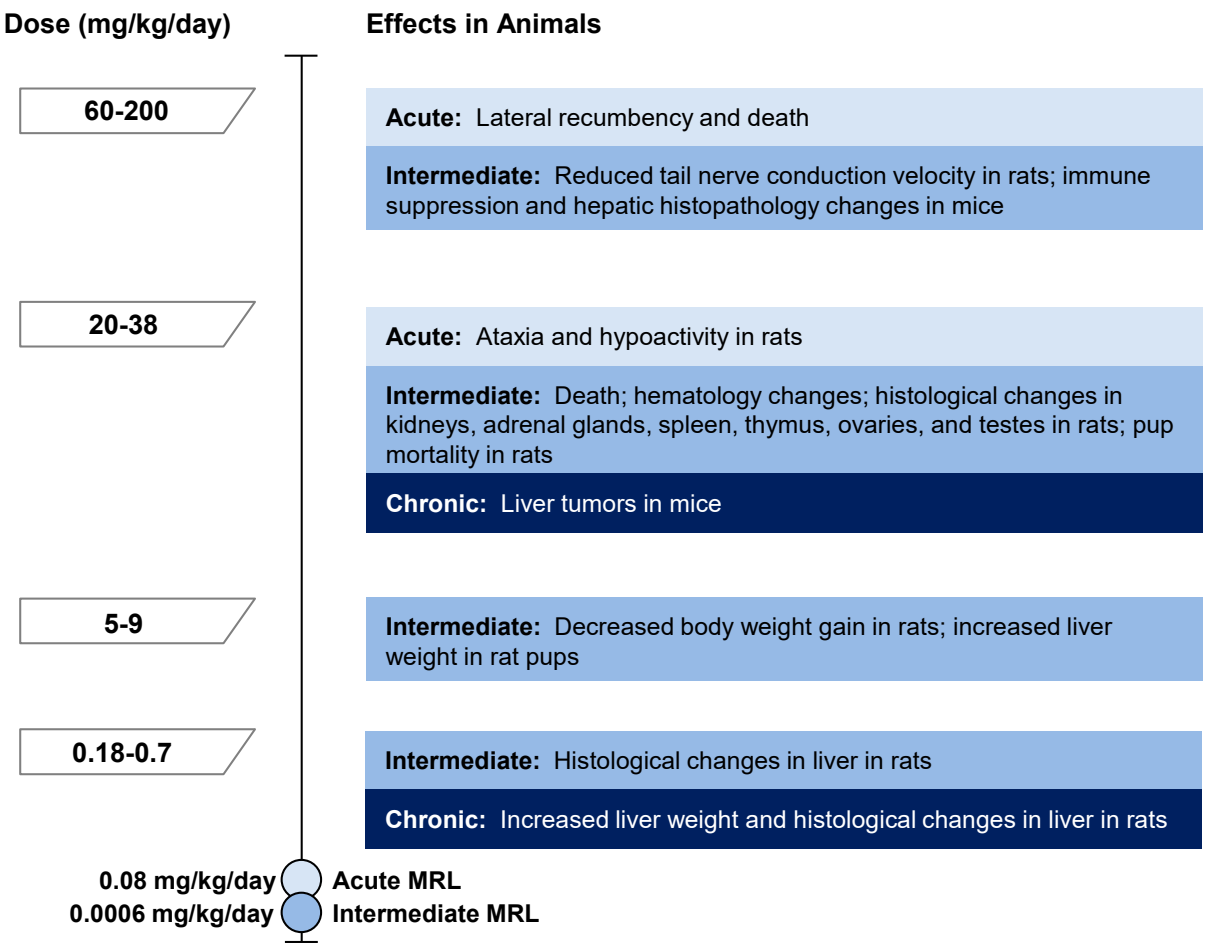
## Figure 1-1. Health Effects Found in Animals Following Inhalation Exposure to γ-Hexachlorocyclohexane



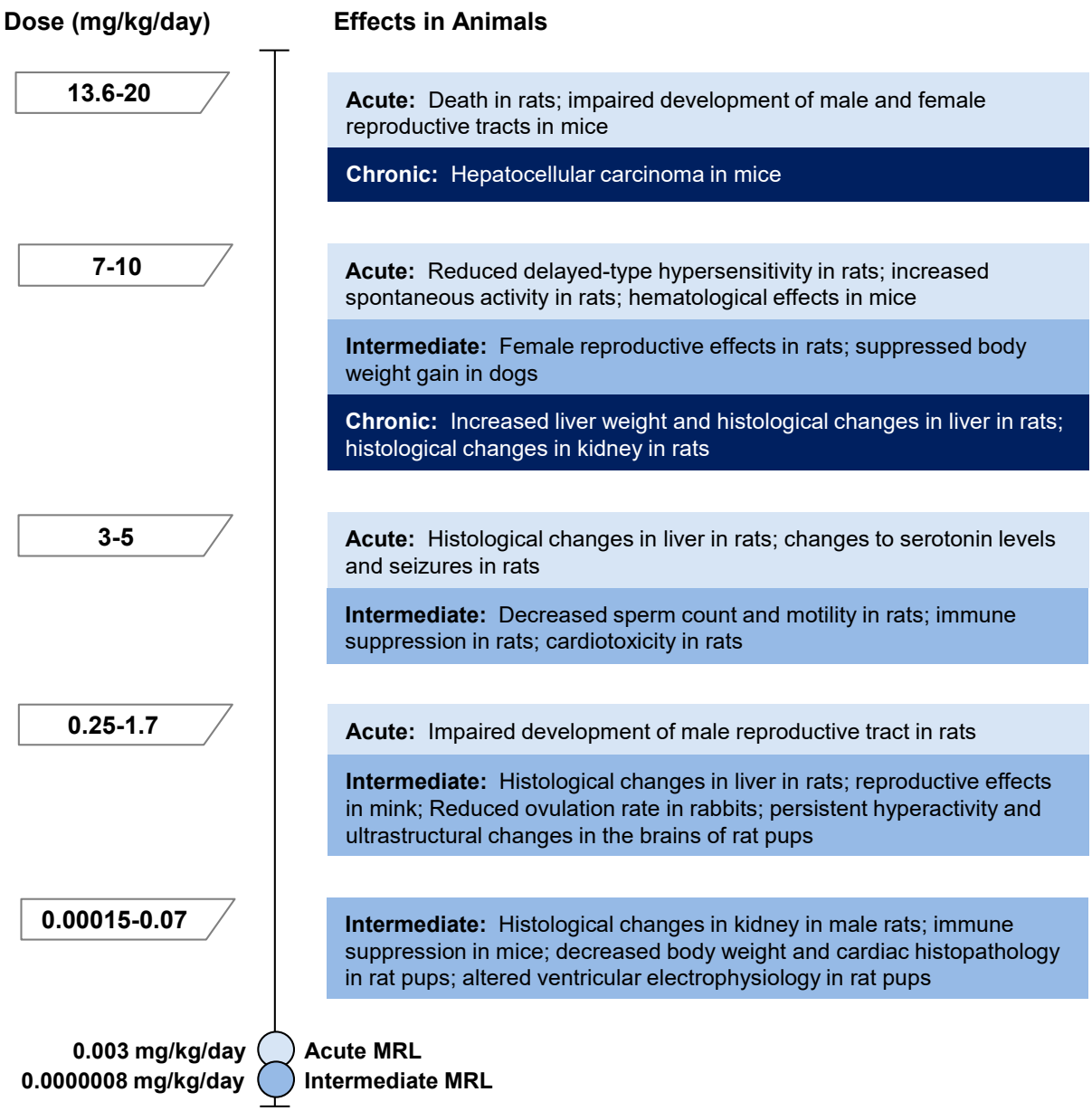

## Figure 1-2. Health Effects Found in Animals Following Oral Exposure to α-Hexachlorocyclohexane



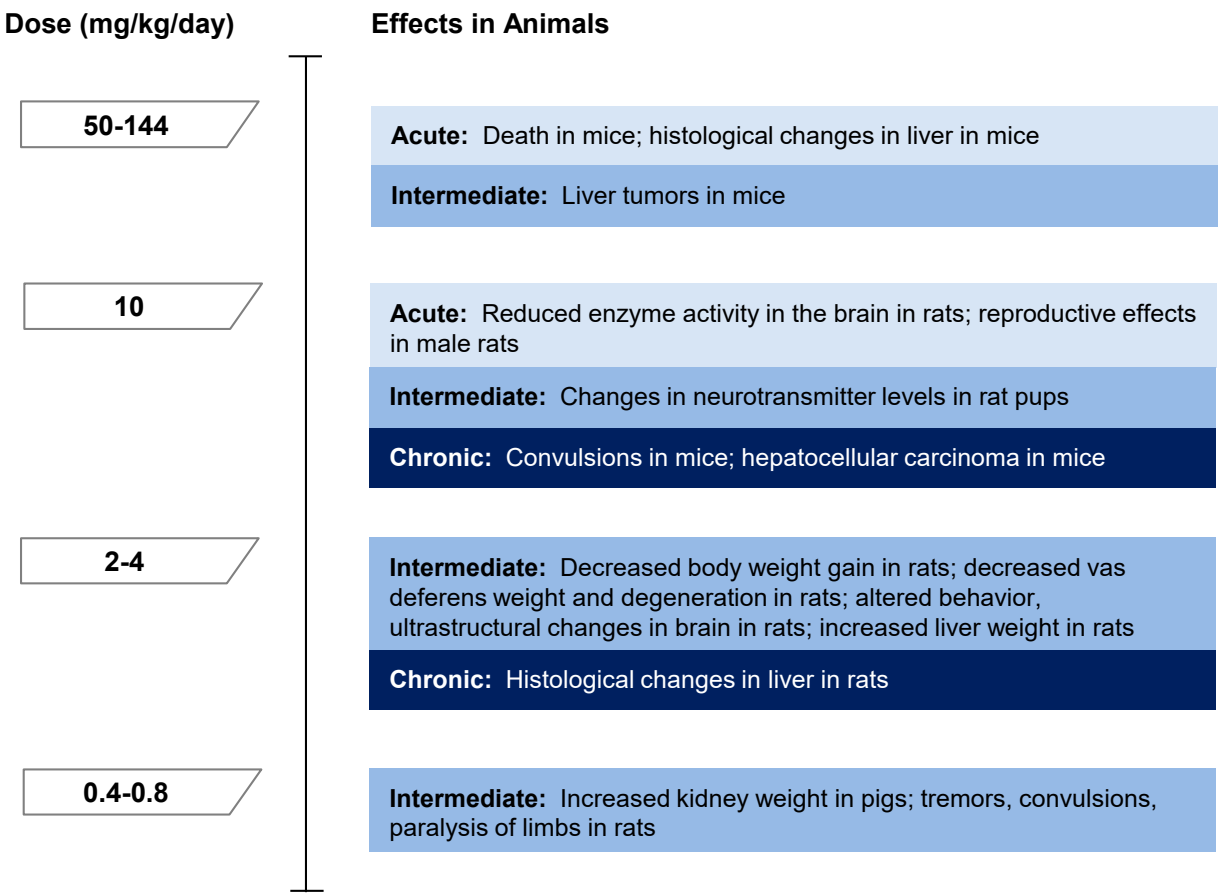
## Figure 1-3. Health Effects Found in Animals Following Oral Exposure to β-Hexachlorocyclohexane



## Figure 1-4. Health Effects Found in Animals Following Oral Exposure to γ-Hexachlorocyclohexane



## Figure 1-5. Health Effects Found in Animals Following Oral Exposure to Technical Hexachlorocyclohexane



1973; Ito et al. 1973, 1975; Van Velsen et al. 1986). In intermediate-duration studies of rats exposed to γ-HCH aerosol, increased liver weights were seen without histology changes (Oldiges et al. 1983). After oral exposure to γ-HCH for acute, intermediate, and chronic durations, liver effects in rats, mice, and rabbits have included increased serum enzymes indicative of hepatocellular injury, increased serum lipids, increased liver weight, hepatocellular hypertrophy, vacuolar degeneration, necrosis, and congestion (Ali and Shakoori 1998; Amyes 1990; Attia et al. 2011; Boll et al. 1995; Cerón et al. 1995; EPA 1991a, 2000a; Fatih Fidan et al. 2008; Fitzhugh et al. 1950; Grabarczyk et al. 1990; Hfaiedh et al. 2012; Kamal El-Dein et al. 2016; Kopec-Szlezak et al. 1989; Matsuura et al. 2005; Parmar et al. 2003; Singh and Sharma 2011; Sumida et al. 2007; Suter 1983; Vijaya Padma et al. 2011). Centrilobular hepatocellular hypertrophy was also reported in rats exposed to γ-HCH for 13 weeks by dermal application (EPA 1988a). In intermediate-duration studies of rats and mice exposed to δ-HCH, increased liver weight and/or centrilobular hypertrophy were reported (Ito et al. 1973, 1975). Studies of animals exposed to technical-grade HCH by oral or dermal administration (e.g., Dikshith et al. 1978, 1989b, 1991a, 1991c; Fitzhugh et al. 1950; Philip et al. 1989; Trivedi et al. 2007, 2009) provide supporting evidence for hepatic effects of HCH isomers.

***Developmental Effects.*** Epidemiological studies examining relationships between birth outcomes and maternal or fetal blood or tissue levels of β-HCH have reported associations with decreased birth weight (Anand and Taneja 2020; Callan et al. 2016; Fang et al. 2019a, 2019b; Guo et al. 2014; Lopez-Espinosa et al. 2011; Yang et al. 2020) and fetal growth restriction (Sharma et al. 2012). Studies using α- or γ-HCH levels in maternal or fetal tissues to assess the relationship between HCH exposure and developmental outcomes in humans have not shown consistent results and are limited by the relatively short half-life of these isomers in the human body (see details in Section 3.1.4). No developmental toxicity studies of animals exposed to α-HCH were located. Developmental toxicity data for β-HCH are very limited but show increased perinatal mortality and increased liver weight of pups after exposure during gestation and lactation or lactation only (Srinivasan et al. 1991). After oral administration of technical-grade HCH during gestation, mice exhibited increased fetal resorptions (Dikshith et al. 1990; Srivastava and Raizada 2000) and rats have shown altered neurotransmitter levels in the brain (Nagaraja and Desiraju 1994).

Studies in a variety of species exposed to γ-HCH for acute or intermediate durations during gestation or postnatal development have demonstrated effects on a wide range of endpoints, including birth outcomes and development of the male and female reproductive tracts, central nervous system, heart, liver, thymus, and spleen. Increased stillbirths, reduced neonatal viability, and decreased pup weights have been reported in rats, mice, and mink (Beard et al. 1997; EPA 1991a, 1999c; Hassoun and Stohs 1996a;

Matsuura et al. 2005; Sauviat et al. 2005). In male offspring of rats and mice exposed to γ-HCH via oral administration during gestation and/or postnatal development, effects on preputial separation, serum hormone levels, spermatogenesis, reproductive organ weights, and testicular histopathology have been reported (Agrahari et al. 2019; Dalsenter et al. 1997a, 1997b; Di Consiglio et al. 2009; La Sala et al. 2009; Traina et al. 2003). Female offspring of rats and mice exposed similarly exhibited effects on vaginal opening, oogenesis, and uterine weight (La Sala et al. 2009; Maranghi et al. 2007; Matsuura et al. 2005). Oral exposure of maternal rats and mice to γ-HCH has resulted in significant decreases in thymus and spleen weights in the offspring (Hassoun et al. 1996; Matsuura et al. 2005), increases in pup liver weight (Srinivasan et al. 1991), and cardiac electrophysiology and histopathology changes in pups (Sauviat et al. 2005). Developmental neurotoxicity findings in animals orally exposed to γ-HCH *in utero* or during development included seizures and convulsions (Albertson et al. 1985; Johri et al. 2008); effects on motor activity, learning, and memory (EPA 1999c; Johri et al. 2007; Rivera et al. 1998; Srivastava et al. 2019); changes in neurotransmitter levels (Rivera et al. 1991, 1998); altered brain wave activity (Breton et al. 2005); and ultrastructural changes in the brain (Srivastava et al. 2019).

***Immune System Effects.*** There are inadequate data on effects of HCH isomers on the immune system of humans. No studies of immune endpoints in animals exposed to α-HCH by inhalation, oral, or dermal routes were located. Information on immune effects of β-HCH includes a report of decreased lympho-proliferative responses to mitogens in mice exposed via diet for 30 days (Cornacoff et al. 1988) and a report of thymic and splenic histopathology changes (atrophy of the thymus and depletion of splenic lymphoid tissue) in rats at doses associated with humane sacrifice due to moribund condition (Van Velsen et al. 1986). Suppression of the immune system has been demonstrated in a small number of acute- and intermediate-duration studies of γ-HCH administered orally to rats, mice, rabbits, and sheep. Effects seen in these studies include reduced delayed-type hypersensitivity response (Khurana et al. 1999; Mediratta et al. 2008) and decreased antibody titers in response to antigens (Banerjee et al. 1996; Desi et al. 1978; Dewan et al. 1980; Koner et al. 1998; Meera et al. 1992). Decreased spleen and thymus weights and histopathology changes in the thymus, lymph nodes, and spleen have also been seen in animals exposed to γ-HCH (Hong and Boorman 1993; Meera et al. 1992).

***Neurological Effects.*** The available epidemiological data on neurological effects of HCH isomers are generally inadequate for hazard identification, but case reports support a relationship between oral and dermal exposure to γ-HCH and seizures or convulsions in humans of all ages (Aks et al. 1995; Boffa et al. 1995; CDC 2005; Davies et al. 1983; Fischer 1994; Forrester et al. 2004; Hall and Hall 1999; Harris et al. 1969; Lee and Groth 1977; Lifshitz and Gavrilov 2002; Matsuoka 1981; Munk and Nantel 1977; Nordt

and Chew 2000; Powell 1980; Ramabhatta et al. 2014; Ramchander et al. 1991; Solomon et al. 1995; Starr and Clifford 1972; Storen 1955; Sudakin 2007; Wheeler 1977; Telch and Jarvis 1982; Tenenbein 1991; Wiles et al. 2015). Information on neurotoxicity of α-HCH in animals is limited to a single study showing no effect on nerve conduction velocity in rats exposed for 30 days (Muller et al. 1981). In addition, few data on this endpoint are available for β-HCH. Studies include reports of clinical signs of neurotoxicity after acute durations (ataxia and hypoactivity progressing in some cases to coma) (Cornacoff et al. 1988; Van Velsen et al. 1986) and reduced nerve conduction velocity in the tail of rats in the isomer comparison study by Muller et al. (1981).

Neurological effects have been observed in rats and/or mice exposed to γ-HCH by inhalation, oral, and dermal exposure routes. Inhalation exposure of rats for acute durations resulted in central nervous system depression or restlessness, excitation, and ataxia, with spasms observed at higher concentrations (Oldiges et al. 1980; Ullmann 1986b). In rats exposed by gavage or dietary administration of γ-HCH, seizures and convulsions have been observed (Amyes 1990; EPA 1999a; Fitzhugh et al. 1950; Gilbert and Mack 1995; Johri et al. 2008; Joy et al. 1982; Martinez and Martinez-Conde 1995; Martinez et al. 1991; Matsuura et al. 2005; Parmar et al. 2003; Tusell et al. 1988; Vendrell et al. 1992a, 1992b; Woolley and Griffith 1989). Altered neurotransmitter levels in the brain were noted in rats exposed orally for acute or intermediate durations (Attia et al. 1991; Martinez and Martinez-Conde 1995). Clinical signs of toxicity in orally-dosed rats have included decreased motor activity, decreased grooming behavior, increased rearing, altered gait, and hypersensitivity to touch (EPA 1999a, 1999b). Effects on motor activity, anxiety, cognition, and memory were demonstrated in neurobehavioral testing of rats after acute- and intermediate-duration oral exposures to γ-HCH (Desi 1974; EPA 1999a; Llorens et al. 1990; Sahaya et al. 2007; Srivastava et al. 2019; Tilson et al. 1987); in one study, the behavioral changes were accompanied by ultrastructural changes in the hippocampus and substantia nigra of the rats (Srivastava et al. 2019). Clinical signs of neurotoxicity, including seizures, convulsions, hyperactivity, ataxia, and/or sedation were reported in rats and rabbits after single or repeated dermal applications of γ-HCH (EPA 1988a; Hanig et al. 1976; Ullmann 1986a).

***Cancer.*** Human epidemiological data provide evidence for an association between exposure to HCH isomers and non-Hodgkin's lymphoma (NHL). The strongest evidence is derived from a prospective cohort study of pesticide applicators in Iowa and North Carolina, which showed that NHL incidence increased with duration and intensity of exposure to γ-HCH (Alavanja et al. 2014). A large, pooled case-control study reported similar findings. Kachuri et al. (2020) pooled data across three population-based, case-control studies in the United States and Canada (North American Pooled Project). The odds of NHL

were increased with self-reported exposure to γ-HCH in analyses of 1,690 cases and 5,131 controls (Kachuri et al. 2020). Additional support for the association with NHL comes from a case-control study nested within three large prospective cohorts in Shanghai and Singapore. Bassig et al. (2020) observed a positive association between incident NHL and blood levels of β-HCH measured approximately 7 years prior to diagnosis. Nested case-control studies that reported no association between NHL and blood or tissue levels of β-HCH (Brauner et al. 2012; Cantor et al. 2003) generally reported lower exposure levels than the study by Bassig et al. (2020).

Other epidemiological studies reported positive associations between β- or γ-HCH in blood or qualitative exposure to γ-HCH and multiple myeloma, leukemia, colorectal cancer, female breast cancer, prostate cancer, lung cancer, thyroid cancer, brain cancer, and hepatocellular carcinoma (Arrebola et al. 2015a; Band et al. 2011; Lee et al. 2018a; Lerro et al. 2021; Ibarluzea et al. 2004; Kumar et al. 2010; Miao et al. 2021; Purdue et al. 2007; Salimi et al. 2023; Waliszewski et al. 2005; Weber et al. 2018; Xu et al. 2010; Yousefi et al. 2022; Zhao et al. 2012). However, the evidence for an association between HCH isomer exposure and these cancer types is much weaker than that for NHL.

Studies in rats and mice exposed to α-, β-, γ-, and technical HCH by dietary administration have shown increased incidences of liver tumors (Bhatt and Bano 2009; Bhatt and Nagda 2012; Hanada et al. 1973; Ito et al. 1973, 1975, 1976; Karnik et al. 1981; Kashyap et al. 1979; Munir et al. 1983; Nagasaki et al. 1975; NCI 1977; Thakore et al. 1981; Thorpe and Walker 1973; Trivedi et al. 2007, 2009; Tryphonas and Iverson 1983; Tsukada et al. 1979; Wolff et al. 1987). In addition, chronic dermal exposure to technical-grade HCH resulted in liver tumors in mice (Kashyap et al. 1979). γ-HCH has been reported to induce increased incidences of bronchiolar-alveolar adenomas and carcinomas in female mice exposed via diet (EPA 2000a; Wolff et al. 1987).

The EPA (IRIS 1987a) listed α-HCH as a probable human carcinogen based on sufficient evidence of carcinogenicity in animals and inadequate data in humans. The Integrated Risk Information System (IRIS 1987b) listed β-HCH as a possible human carcinogen based on evidence for benign liver tumors in exposed mice and inadequate data in humans. Data on δ-HCH were considered inadequate to classify the potential human carcinogenicity (IRIS 1987d). Although the IRIS (1987c) program did not evaluate the carcinogenicity of γ-HCH, EPA's Office of Pesticide Programs (EPA 2001, 2002) classified γ-HCH into the category "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential." The Department of Health and Human Services (HHS) National Toxicology Program (NTP) determined that γ-HCH and other HCH isomers may reasonably be anticipated to cause cancer in humans

(NTP 2021). In 2018, the International Agency for Research on Cancer (IARC) determined that there was sufficient evidence in both humans and animals for the carcinogenicity of γ-HCH, assigning it to Group 1 (carcinogenic to humans). IARC (2018) concluded that γ-HCH causes NHL in humans.

## 1.3 MINIMAL RISK LEVELS (MRLs)

***α-HCH.*** The inhalation database was considered inadequate for derivation of acute-, intermediate-, or chronic-duration inhalation MRLs for α-HCH. The oral database for α-HCH was considered inadequate for derivation of an acute-duration oral MRL, but data were adequate for derivation of intermediate- and chronic-duration oral MRLs. As shown in Figure 1-6, hepatic effects are the most sensitive targets of toxicity in animals exposed orally to α-HCH.

***β-HCH.*** The inhalation database was considered inadequate for derivation of acute-, intermediate-, or chronic-duration inhalation MRLs for β-HCH. The oral database for β-HCH was considered adequate for derivation of acute- and intermediate-duration oral MRLs, but not for a chronic-duration oral MRL. As shown in Figure 1-7, neurological and hepatic effects are the most sensitive targets of toxicity in animals exposed orally to β-HCH.

***γ-HCH (Lindane).*** The inhalation database was considered inadequate for derivation of acute-, intermediate-, or chronic-duration inhalation MRLs for γ-HCH. Figure 1-8 shows that death and renal and gastrointestinal effects were seen at the lowest concentrations of γ-HCH in available inhalation studies. The oral database for γ-HCH was considered adequate for derivation of acute- and intermediate-duration oral MRLs, but not for a chronic-duration oral MRL. As shown in Figure 1-9, developmental and immune system effects are the most sensitive targets of toxicity in animals exposed orally to γ-HCH.

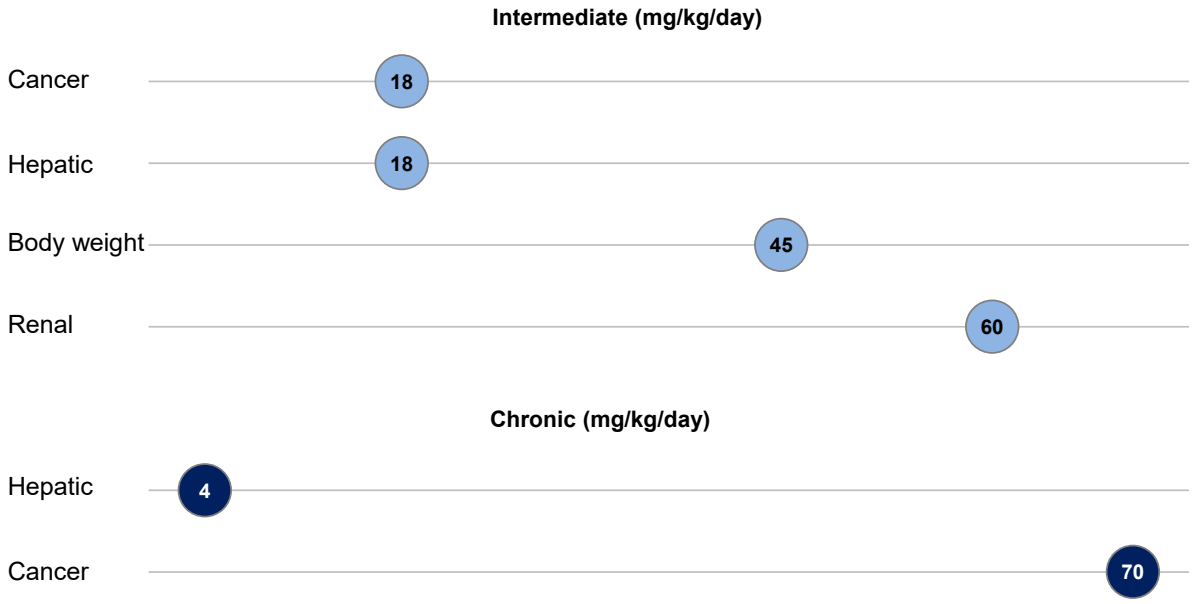
***δ-HCH.*** The inhalation and oral databases were considered inadequate for derivation of acute-, intermediate-, or chronic-duration inhalation or oral MRLs for δ-HCH.

***Technical HCH or Unspecified Isomers of HCH.*** MRLs were not derived for technical-grade HCH due to the wide variation in isomer composition of technical HCH. Figure 1-10 shows the sensitive targets in studies of technical-grade HCH or unspecified HCH isomers.

## Figure 1-6. Summary of Sensitive Targets of α-Hexachlorocyclohexane (α-HCH) – Oral

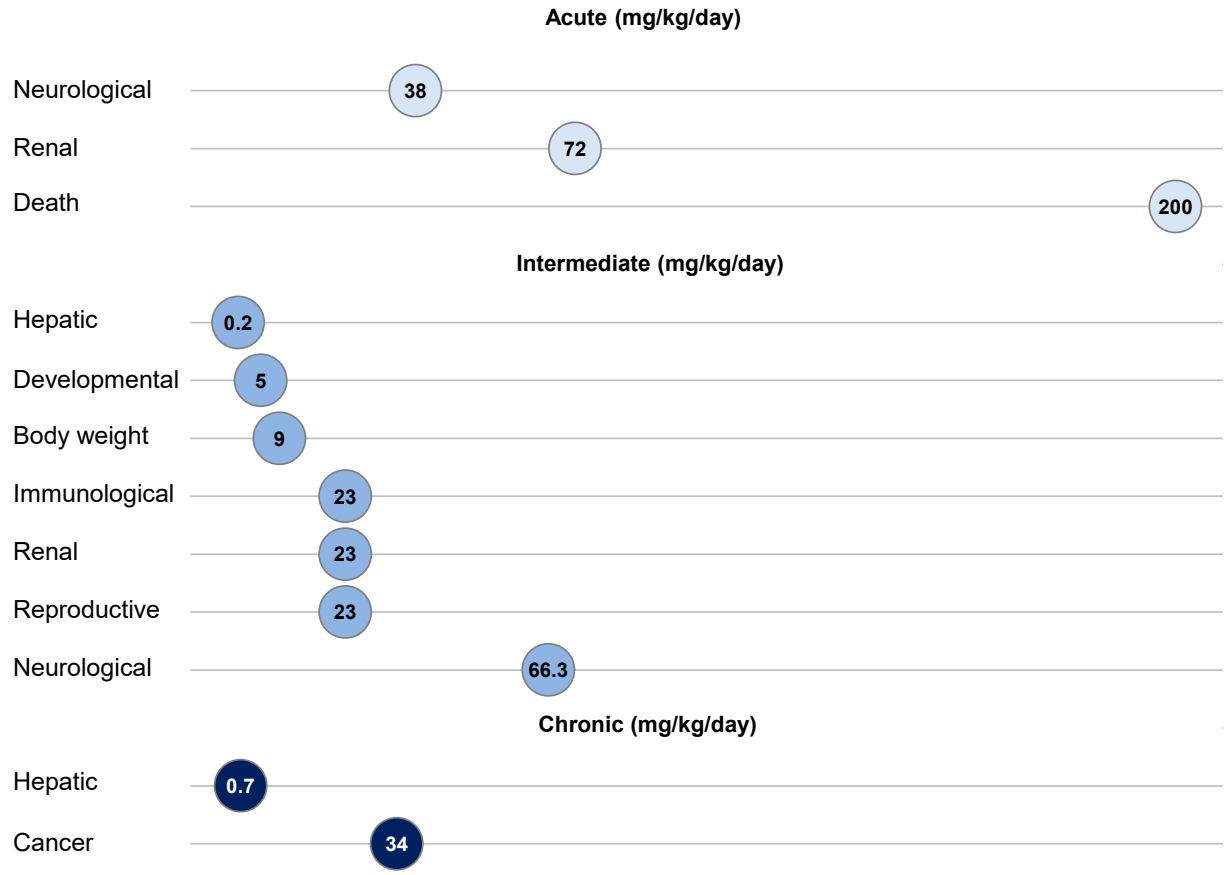
**Available data indicate that the liver, and liver cancers, are the most sensitive targets of α-HCH oral exposure.**

Numbers in circles are the lowest LOAELs for all health effects in animals; no human data were identified.



## Figure 1-7. Summary of Sensitive Targets of β-Hexachlorocyclohexane (β-HCH) – Oral

**Available data indicate that the liver is the most sensitive target of β-HCH oral exposure.**
Numbers in circles are the lowest LOAELs for all health effects in animals.
No reliable dose-response data were available for humans.



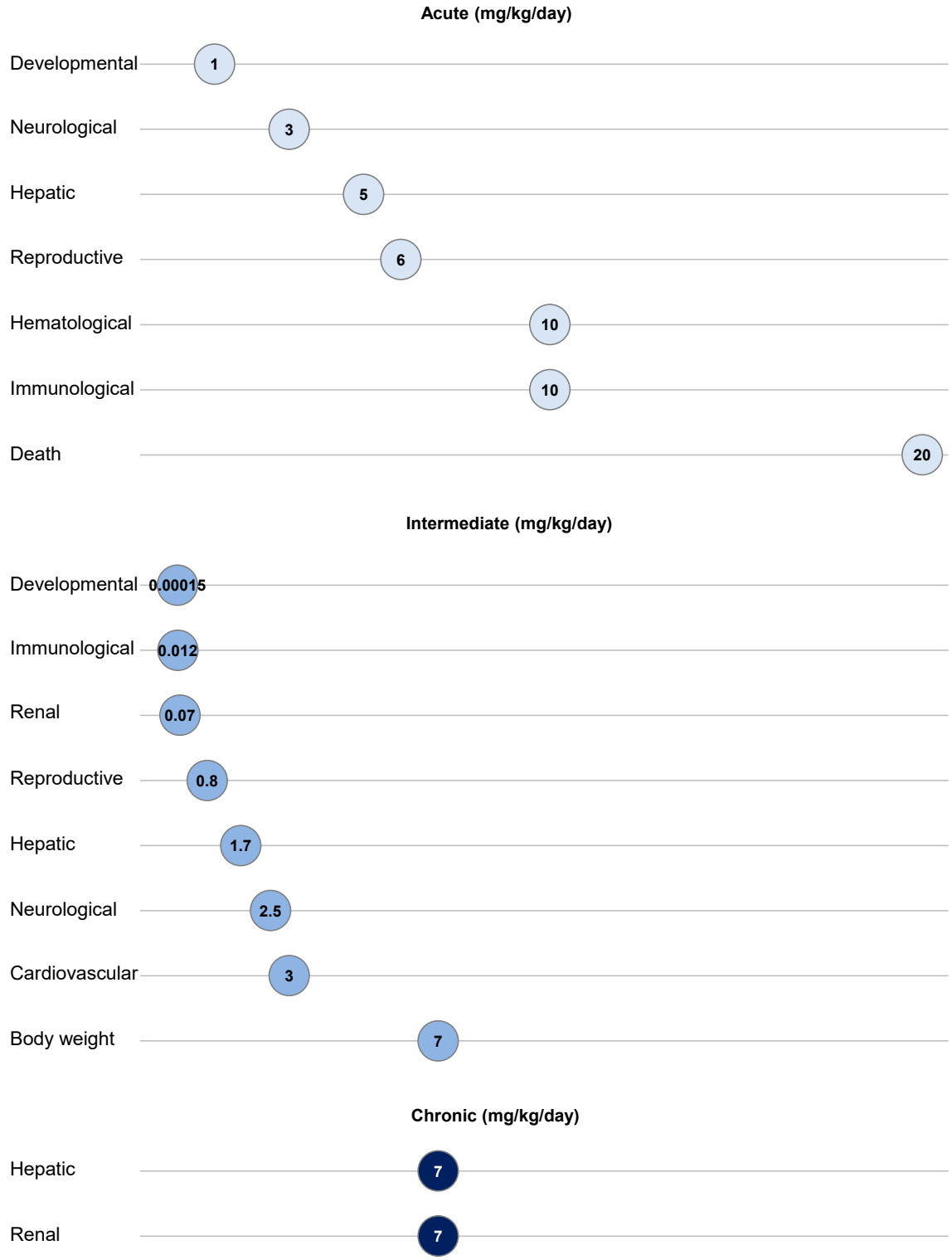
## Figure 1-8. Summary of Sensitive Targets of γ-Hexachlorocyclohexane (γ-HCH) – Inhalation

**Available data indicate that the kidney is the most sensitive target of γ-HCH inhalation exposure.**
Numbers in circles are the lowest LOAELs for all health effects in animals; no human data were identified.

## Figure 1-9. Summary of Sensitive Targets of γ-Hexachlorocyclohexane (γ-HCH) – Oral

**Available data indicate that the developing organism is the most sensitive target of γ-HCH oral exposure.**

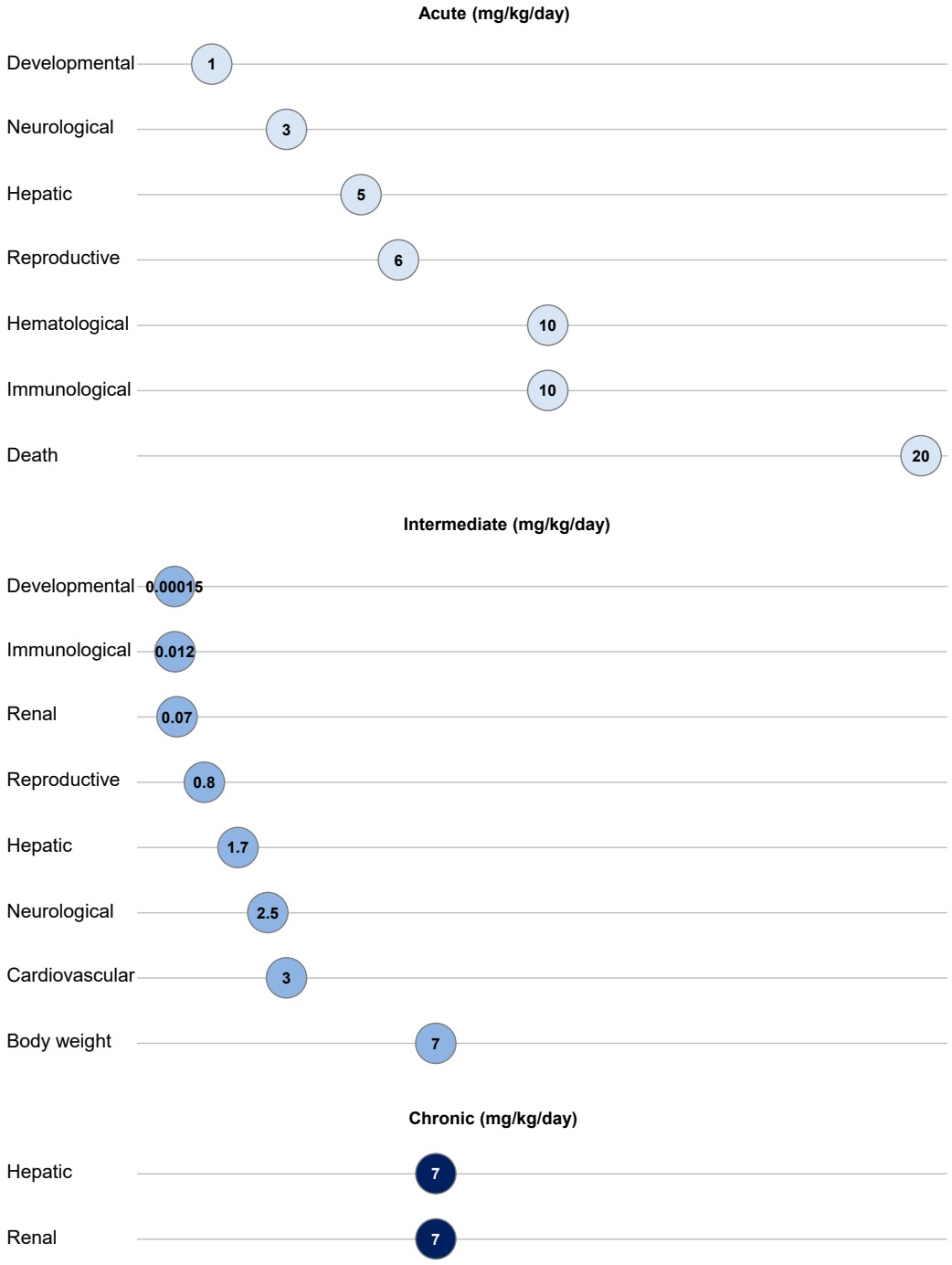
Numbers in circles are the lowest LOAELs for all health effects in animals; no human data were identified.



## Figure 1-10. Summary of Sensitive Targets of Technical-Hexachlorocyclohexane (technical-HCH) – Oral

**Available data indicate that the central nervous system is the most sensitive target of technical-HCH oral exposure.**

Numbers in circles are the lowest LOAELs for all health effects in animals; no human data were identified.




The MRL values for α-HCH, β-HCH, and γ-HCH are summarized in Tables 1-1, 1-2, and 1-3, respectively, and discussed in greater detail in Appendix A.

## Table 1-1. Minimal Risk Levels (MRLs) for α-Hexachlorocyclohexane[a]

| Exposure route | Exposure duration | MRL | Critical effect | POD type | POD value | Uncertainty/ modifying factor | Reference |
|---|---|---|---|---|---|---|---|
| Inhalation | **No inhalation MRLs were derived for any duration.** | | | | | | |
| Oral | Acute | None | – | – | – | – | – |
| | Intermediate | **0.002 mg/kg/day** | Increased liver weight and histopathology | NOAEL | 2 mg/kg/day | UF: 100<br>MF: 10 | Sumida et al. 2007 |
| | Chronic | **$9x10^{-4}$ mg/kg/day** | Increased liver weight and histopathology | NOAEL | 0.9 mg/kg/day | UF: 100<br>MF: 10 | Fitzhugh et al. 1950 |

[a]See Appendix A for additional information.

MF = modifying factor; NOAEL = no-observed-adverse-effect level; POD = point of departure; UF = uncertainty factor

## Table 1-2. Minimal Risk Levels (MRLs) for β-Hexachlorocyclohexane[a]

| Exposure route | Exposure duration | MRL | Critical effect | POD type | POD value | Uncertainty/ modifying factor | Reference |
|---|---|---|---|---|---|---|---|
| Inhalation | **No inhalation MRLs were derived for any duration.** | | | | | | |
| Oral | Acute | **0.08 mg/kg/day** | Clinical signs of neurotoxicity (ataxia, inactivity) at higher doses | NOAEL | 8 mg/kg/day | UF: 100 | Van Velsen et al. 1986 |
| | Intermediate | **$6x10^{-4}$ mg/kg/day** | Hyalinization of centrilobular liver cells | LOAEL | 0.18 mg/kg/day | UF: 300 | Van Velsen et al. 1986 |
| | Chronic | None | – | – | – | – | – |

[a]See Appendix A for additional information.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; UF = uncertainty factor

**Table 1-3. Minimal Risk Levels (MRLs) for γ-Hexachlorocyclohexane[a]**

| Exposure route | Exposure duration | MRL | Critical effect | POD type | POD value | Uncertainty/ modifying factor | Reference |
|---|---|---|---|---|---|---|---|
| Inhalation | **No inhalation MRLs were derived for any duration.** | | | | | | |
| Oral | Acute | **0.003 mg/kg/day** | Reduced reproductive organ weights, sperm numbers, serum testosterone, and increased intromission frequency in male offspring | LOAEL | 1 mg/kg/day | UF: 300 | Dalsenter et al. 1997b |
| | Intermediate | **$8x10^{-7}$ mg/kg/day** | Cardiac effects in offspring | NOAEL | $7.6x10^{-5}$ mg/kg/day | UF: 100 | Sauviat et al. 2005 |
| | Chronic | None | – | – | – | – | – |

[a]See Appendix A for additional information.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; UF = uncertainty factor