CHAPTER 6. ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of HCH is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of HCH.

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.1 EXISTING INFORMATION ON HEALTH EFFECTS

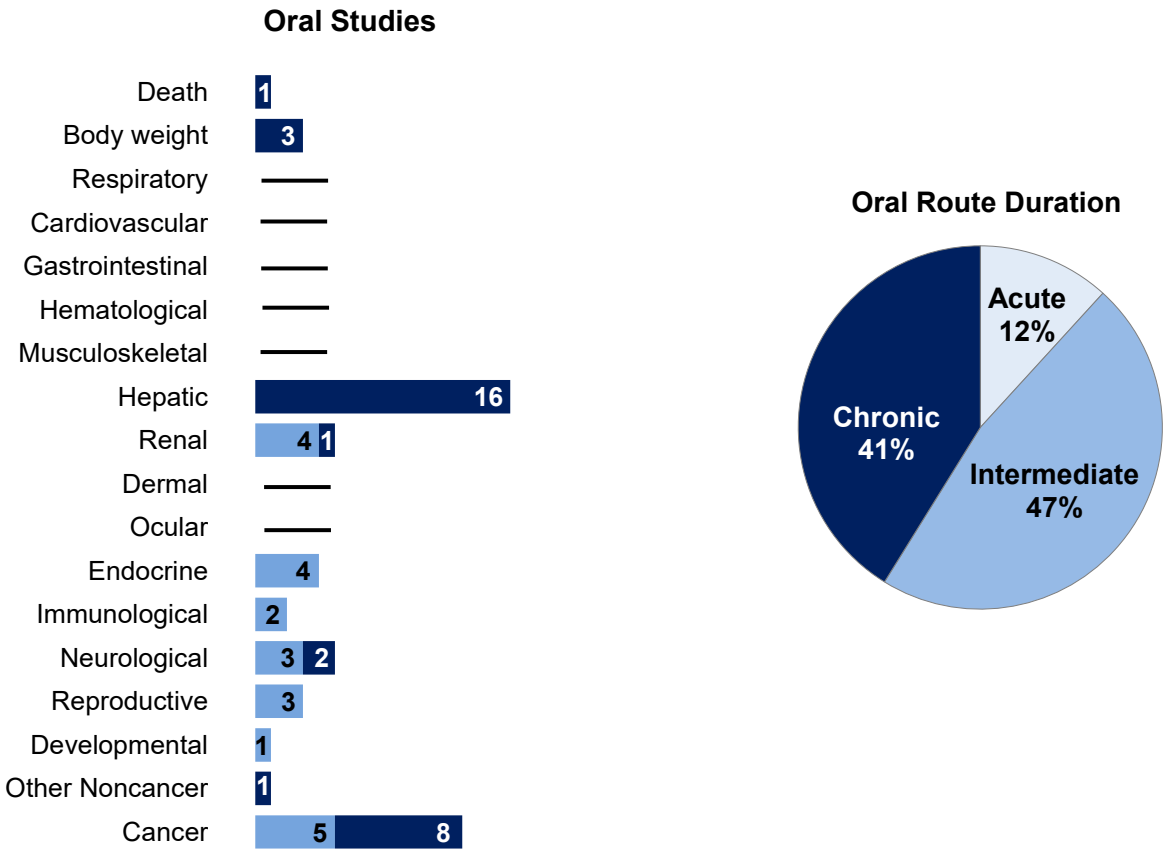
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to HCH that are discussed in Chapter 2 are summarized in Figures 6-1, 6-2, 6-3, and 6-4. The purpose of these figures is to illustrate the information concerning the health effects of HCH. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

6.2 IDENTIFICATION OF DATA NEEDS

Missing information in Figures 6-1, 6-2, 6-3, and 6-4 should not be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Figure 6-1. Summary of Existing Health Effects Studies on α-Hexachlorocyclohexane by Route and Endpoint*

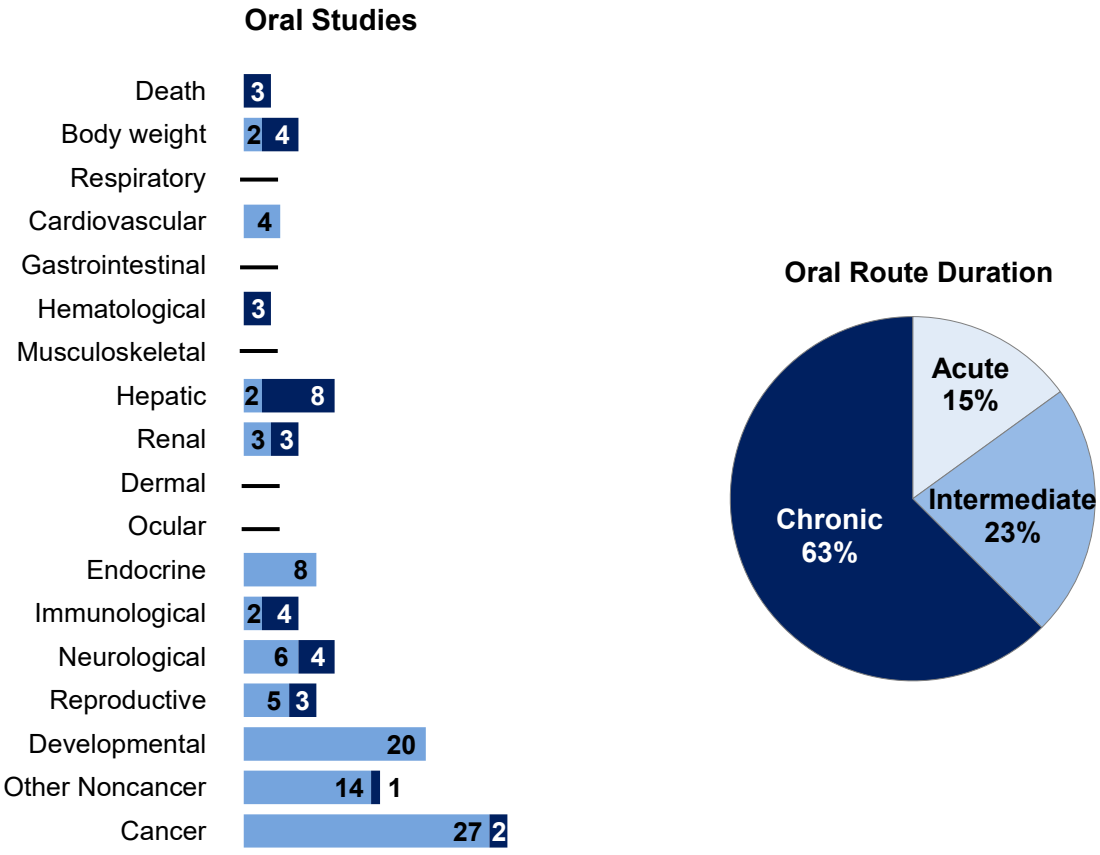
Potential body weight, liver, and cancer effects were the most studied endpoints
The majority of the studies examined oral exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. Most studies examined multiple endpoints. No inhalation or dermal studies in humans or animals were located. Human studies of unknown route and/or duration were classified as chronic oral studies for the purpose of this figure.

Figure 6-2. Summary of Existing Health Effects Studies on β-Hexachlorocyclohexane by Route and Endpoint*

Potential developmental, other noncancer, and cancer effects were the most studied endpoints
The majority of the studies examined exposure in **humans** (versus **animals**)

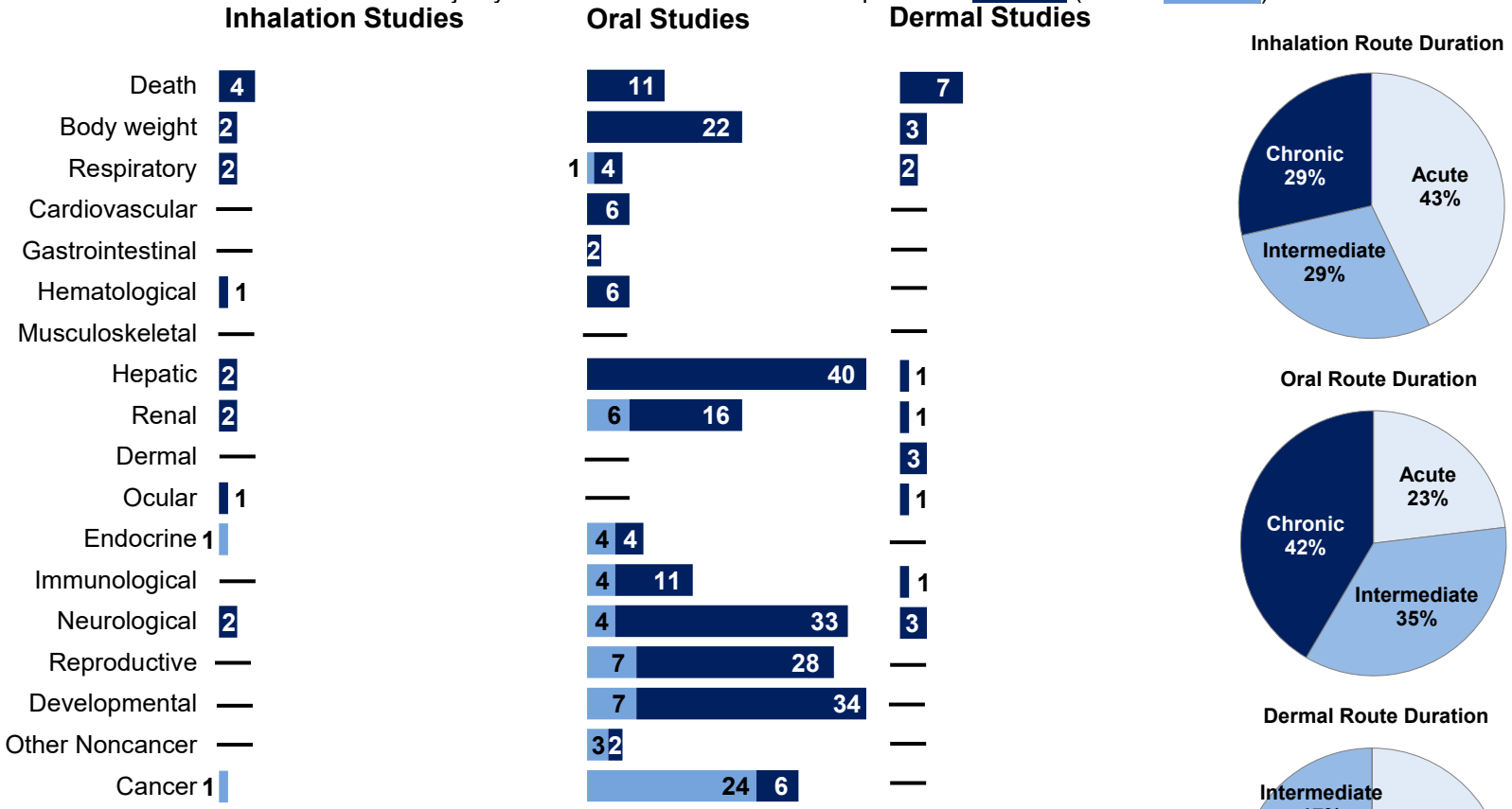


*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. Most studies examined multiple endpoints. No inhalation or dermal studies in humans or animals were located. Human studies of unknown route and/or duration were classified as chronic oral studies for the purpose of this figure.

Figure 6-3. Summary of Existing Health Effects Studies on γ-Hexachlorocyclohexane by Route and Endpoint*

Potential body weight, liver, and neurological effects were the most studied endpoints

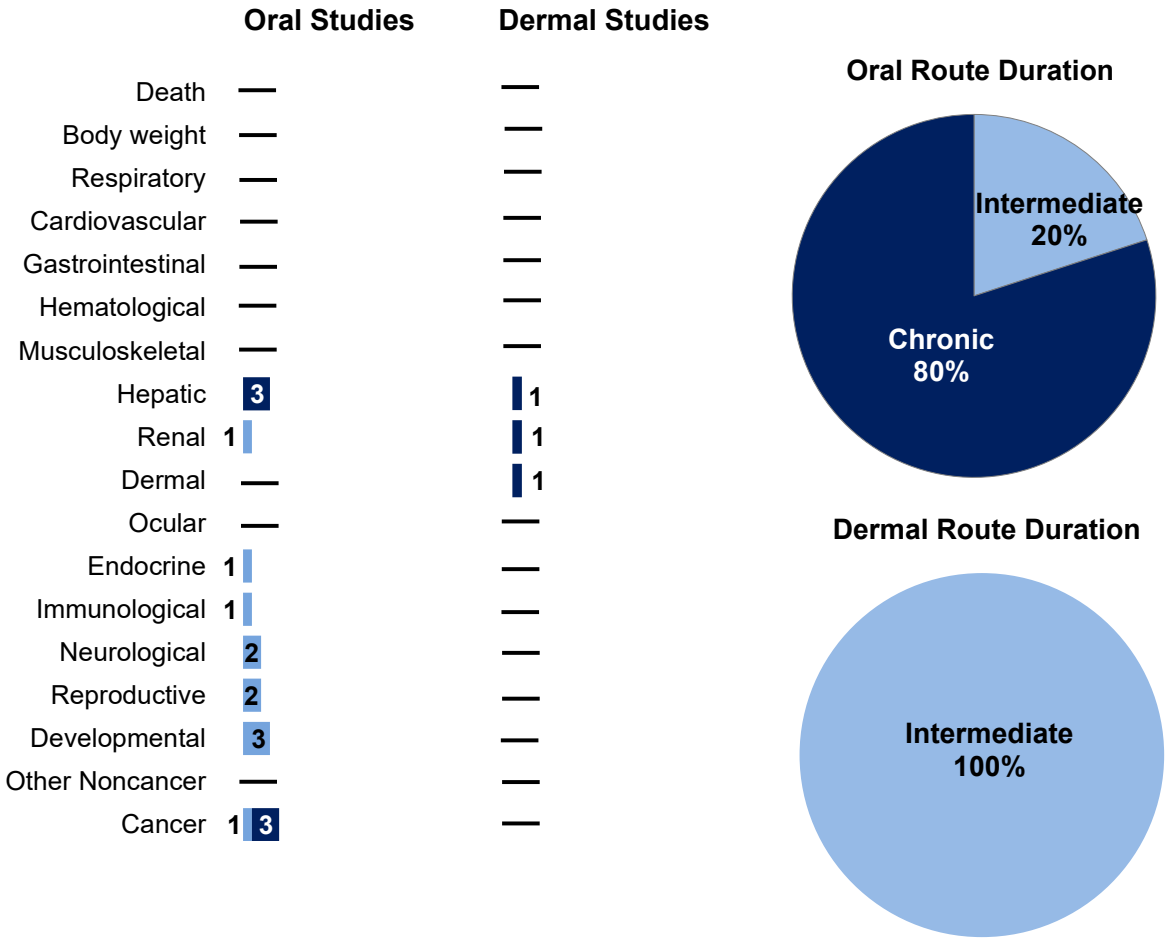
The majority of the studies examined oral exposure in animals (versus humans)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. Most studies examined multiple endpoints. Human studies of unknown route and/or duration were classified as chronic oral studies for the purpose of this figure.

Figure 6-4. Summary of Existing Health Effects Studies on δ-Hexachlorocyclohexane and Unspecified Hexachlorocyclohexanes by Route and Endpoint*

Potential hepatic and cancer effects were the most studied endpoints
The majority of the studies examined exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. Most studies examined multiple endpoints. No inhalation or dermal studies in humans or inhalation studies in animals were located. Human studies of unknown route and/or duration were classified as chronic oral studies for the purpose of this figure.

Acute-Duration MRLs. The inhalation database is inadequate to derive acute-duration inhalation MRLs for any HCH isomer. The oral database is adequate to derive acute-duration oral MRLs for β- and γ-HCH, but not for α- or δ-HCH. Acute oral studies providing data on effects of α- and δ-HCH at low doses are needed.

Intermediate-Duration MRLs. The inhalation database is inadequate to derive intermediate-duration inhalation MRLs for any HCH isomer. The oral database is adequate to derive intermediate-duration oral MRLs for α-, β-, and γ-HCH, but not for δ-HCH. Intermediate oral studies providing data on effects of δ-HCH at low doses are needed.

Chronic-Duration MRLs. The inhalation database is inadequate to derive chronic-duration inhalation MRLs for any HCH isomer. The oral database is adequate to derive a chronic-duration oral MRL for α-HCH, but not for β-, γ-, or δ-HCH. Chronic-duration oral studies providing data on effects of β-, γ-, and δ-HCH at low doses are needed.

Health Effects.

Hepatic. Available animal studies provide abundant evidence for hepatic effects after oral exposure to α- and β-HCH for intermediate and chronic durations, and to γ-HCH for all exposure durations. Very limited data are available for liver effects in animals exposed chronically to δ-HCH by oral administration. Additional studies examining sensitive liver endpoints after acute-duration oral exposure to α- and β-HCH, all durations of oral exposure to δ-HCH, and inhalation exposure of all durations to all HCH isomers would complete the database for this health effect.

Neurotoxicity. Studies examining sensitive neurological and neurobehavioral effects in animals exposed to α-, β-, and δ-HCH by oral and inhalation exposure are needed, as studies of γ-HCH have shown neurotoxicity after inhalation, oral, and dermal exposure of animals and case-reports have demonstrated severe neurological effects in exposed humans. For γ-HCH, specialized neurotoxicity studies of inhalation exposure (all durations) are needed.

Developmental. There are no data on the developmental effects of α- or δ-HCH and very limited data on the developmental effects of β-HCH. One epidemiological study in children under 4 years of age suggested that β-HCH in serum may be associated with deficits in cochlear function, but the findings varied by age at blood sampling; further assessment of the potential

ototoxicity of β-HCH in humans or animals is needed to enable conclusions regarding this health effect. Data in animals exposed via oral administration of γ-HCH demonstrate a wide variety of serious effects on the developing organism, including effects on birth outcomes, reproductive tract development, and the development of the central nervous system and heart. Therefore, the lack of information on potential developmental toxicity of the other isomers represents a significant data gap. In addition, there are no studies of these endpoints in animals exposed to any HCH isomer by inhalation; availability of such information is needed to provide adequate data for derivation of inhalation MRLs.

Immunotoxicity. There are no data on the effects of α- or δ-HCH on the immune system of animals exposed by any route, and very limited data on the effects of β-HCH after oral exposure. Data in animals exposed via oral administration of γ-HCH demonstrate immune suppression in a variety of species after acute- and intermediate-durations. Specialized studies examining the functioning of the immune system in animals exposed orally to α-, β-, and δ-HCH are needed, as are studies of immunotoxicity in animals exposed by inhalation to the HCH isomers.

For the key health outcomes, especially those shown above, data on the mechanisms by which HCH isomers induce toxicity are limited. Additional mechanistic studies may improve the understanding of the human relevance of toxic effects observed in animals.

Epidemiology and Human Dosimetry Studies. In the United States, γ-HCH and technical HCH are no longer used for agricultural purposes, and HCH is not produced in the United States. Currently authorized uses are limited to prescription shampoos or lotions containing 1% γ-HCH for treatment of lice and scabies. As a result of the limited current exposures to HCH isomers, additional follow-up of occupational cohorts established previously may be the most useful approach to obtaining additional human data. Other epidemiological studies have used blood or tissue levels of HCH isomers in the general population to evaluate past exposure, an approach that is viable for the more persistent β-HCH isomer, but not for the isomers with shorter half-lives.

Biomarkers of Exposure and Effect. Methods exist for the analysis of HCH isomers in blood (normalized by lipid content) and hair and for HCH metabolites in urine. Serum measurements of γ-HCH represent short-term exposure because γ-HCH is metabolized and excreted rapidly. Due to its high lipid solubility and persistence, β-HCH levels represent longer-term exposures. However, reported blood levels of HCH have not been quantitatively correlated with ambient HCH levels or past exposure.

Methods that measure the levels of HCH metabolites in urine are not specific enough to detect exposure to HCH alone. More information could be provided by studies designed to correlate biomarkers of exposure with exposure levels. No biomarkers of effect, specific for HCH isomers, have been identified in the literature. Several studies have demonstrated increases in lipid peroxidation and depletion of antioxidants in the central nervous system, liver, male reproductive tract, and maternal or fetal tissues in animals exposed to γ-HCH; however, these are nonspecific effects induced by a wide range of compounds. Additional studies designed to assess mechanisms of action and/or adverse outcome pathways may serve to identify specific biomarkers of effect for health outcomes of concern for HCH isomers (e.g., liver, neurological, developmental, and immune system effects).

Absorption, Distribution, Metabolism, and Excretion. Information is available to evaluate the toxicokinetics of HCH isomers following oral and dermal exposure in animals and humans. Studies evaluating toxicokinetic properties following inhalation exposure would be helpful. Limited information suggests differences in the metabolism of the HCH isomers. Additional data on metabolism of the α-, β-, and δ-HCH isomers would be beneficial, especially if such information was linked to differences in specific health outcomes. *In vitro* studies using rat liver microsomes have demonstrated the formation of a reactive epoxide metabolite; however, investigations have not been conducted to examine the epoxide formation *in vivo* or its role in inducing mutagenic and carcinogenic effects. Further information on the possible role of epoxide formation in carcinogenesis *in vivo*, as well as its rate of formation under various conditions, would be useful.

Comparative Toxicokinetics. The development and validation of additional PBPK models that compare predictions against observations in humans could provide valuable information in extrapolating animal toxicity data to humans.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects are discussed in detail in the Developmental Toxicity subsection above. Limited data are available on the toxicokinetics or health effects of α- and β-HCH isomers on exposed children. Further, additional animal studies evaluating potential early life susceptibility to neurotoxicity and/or cancer after exposure to γ-HCH would be useful.

Physical and Chemical Properties. Sufficient information is available on the physical and chemical properties of γ-HCH and the other HCH isomers (see Chapter 4) to permit an assessment of the environmental fate of these compounds. No additional studies are warranted at this time.

Production, Import/Export, Use, Release, and Disposal. Production methods for HCH are well described in the literature (IARC 1979). γ-HCH is used as an insecticide and as a therapeutic scabicide and pediculicide for treatment of ectoparasites in humans and animals (Budavari et al. 1989). The production and use of γ-HCH as a pesticide has been restricted in the United States, and the use of γ-HCH was voluntarily canceled in 2006 (EPA 2006b). Recent data suggest that the uses and import/export volumes of γ-HCH are decreasing (EPA 2012, 2016; Hauzenberger et al. 2002). Release of γ-HCH to environmental media has been primarily from its use as a pesticide. Wastes containing γ-HCH must be contained, incinerated, and disposed of in landfills (EPA 1975). Carbon absorption or flocculation are useful treatment methods for the removal of HCH from aqueous effluent streams, except when methanol is also contained in the effluents (NLM 2021). Disposal methods are currently subject to revision under EPA guidance.

Environmental Fate. HCH released to the environment partitions to the atmosphere, soils, and sediments (Atkins and Eggleton 1971; Lewis and Lee 1976; Melancon et al. 1986; Saleh et al. 1982; Stanley et al. 1971). HCH is transported in the atmosphere, surface water, and groundwater (Mackay and Leinonen 1975; Nordmeyer et al. 1992; Stanley et al. 1971). HCH is transformed via biodegradation in soils and surface waters (Govind et al. 1991; Kar and Singh 1979b; Kennedy et al. 1990; Macholz and Kujawa 1985; Sharom et al. 1980; Tu 1976). Wet and dry deposition are significant removal processes for HCH in the atmosphere (Atkins and Eggleton 1971; Hamada et al. 1981; Wiberg et al. 2001). Additional information on the transport, transformation, and persistence of the individual isomers in soils and groundwater, particularly at hazardous waste sites, are needed to identify the most important routes of human exposure to HCH. There is information regarding the half-lives for γ-HCH in water (3–30, 30–300, and >300 days for river, lake, and groundwater, respectively) (Zoeteman et al. 1980). Reported half-lives determined in groundwater of a contaminated site were 223, 62–287, and 120–632 days for α-, β-, and δ-HCH isomers, respectively (Bashir et al. 2015). Hydrolysis occurs slowly under most environmental conditions, but the rate is much more rapid under alkaline conditions. At 25°C, hydrolysis half-lives of 92, 648, and 771 hours were observed for γ-HCH at pH 9.3, 7.8, and 7.3, respectively (Saleh et al. 1982). The alkaline hydrolysis (pH 9.78) half-life of α-HCH was calculated at 1,083 hours (Zhang et al. 2014). The degradation of HCH in the atmosphere occurs through the reaction with photochemically generated hydroxyl radicals, and half-lives of γ- and α-HCH are around 100 days, but can be much longer based upon environmental conditions (Brubaker and Hites 1998).

Bioavailability from Environmental Media. Evidence of absorption following inhalation and dermal exposure is available for workers involved in the formulation of pesticide products containing HCH isomers and in the use of γ-HCH (Baumann et al. 1980; Grey et al. 1983). Dietary intake is not a major route of exposure for the general population (FDA 2020a, 2020b). Additional information on the absorption of γ-HCH, following ingestion of or contact with media containing residues of the compound, would be helpful. As mentioned in Section 6.3.1, Duff and Kissel (1996) showed that bioavailability of γ-HCH via dermal exposure depended upon levels of soil loading. Dermal absorption ranged from 0.45 to 2.35%. For populations living in the vicinity of hazardous waste sites, additional information on absorption following dermal contact with, or ingestion of, contaminated soil is needed, given the expected strong sorption of the compound to soil particulates. Because of the potential of HCH to contaminate air, drinking water, and soil, further information on the bioavailability of the HCH isomers from these environmental media are needed for assessing possible health concerns for humans.

Food Chain Bioaccumulation. γ-HCH in surface waters and soils is taken up and bioconcentrated by terrestrial and aquatic organisms (Just et al. 1990; Matsumura and Benezet 1973; Ramamoorthy 1985; Schimmel et al. 1977; Verma and Pillai 1991; Viswanathan et al. 1988). Uptake from soils and bioconcentration by plants and terrestrial organisms appears to be limited (Chen et al. 2013; Šmídová et al. 2015; Verma and Pillai 1991; Wild and Jones 1992). Plant uptake from air may be greater (Yang et al. 2007). Limited information suggests that the compound is not biomagnified in terrestrial food chains because of its metabolism by terrestrial organisms (Schmitt et al. 1985). Trophic level transfer of γ-HCH has been observed (Bemy et al. 2003). Bioconcentration values in zebra fish for α- and β-HCH have been reported (Butte et al. 1991). Among the HCH isomers, β-HCH accumulates the most in the food chain (Szokolay et al. 1977). Additional information on the potential bioaccumulation of α-, β-, and δ-HCH isomers in terrestrial and aquatic food chains is needed.

Exposure Levels in Environmental Media. γ-HCH has been detected in air, surface water and groundwater, sediment, soil, and food. A gradual decrease of α- and γ-HCH air has been seen across the decades (Atlas and Giam 1988; Cortes and Hites 2000; WQP 2021), and there is evidence of decreases of α- and β-HCH in surface water and groundwater although the data have a large range (WQP 2021). Trends for soil, reflecting varying land uses, are not as clear for the isomers. Although the use of γ-HCH as a pesticide was voluntarily canceled in 2006 (EPA 2006b), it is uncertain whether new environmental measurements will show considerably lower levels of HCH since there are remaining impacts from importing and processing HCH, and evidence of persistency of the isomers. For example, a study of a pesticide reformulating and packaging facility reported groundwater contamination at the site (Chartrand

et al. 2015). Therefore, additional information on the levels of γ-, α-, β-, and δ-HCH isomers would be beneficial to determine current potential human exposure to the chemicals from environmental media, particularly near hazardous waste sites.

Exposure Levels in Humans. HCH can be detected in the blood (Baumann et al. 1980; Bradman et al. 2007; Griffith and Blanke 1975; Hao et al. 2020; Murphy and Harvey 1985; Whitehead et al. 2015), urine (Murphy and Harvey 1985), adipose tissue (Baumann et al. 1980; EPA 1986), breast milk (Takahashi et al. 1981), hair (Smith-Baker and Saleh 2011), and semen (Stachel et al. 1989) of exposed individuals. Most of the data on the body burden of HCH in adipose tissue and breast milk are prior to the 2006 voluntary cancellation of γ-HCH for agricultural use. Additional information after this time point would be helpful to assess current population body burdens. Additionally, most of the data on the body burden of HCH are from adipose tissue and blood serum analyses conducted postmortem or on occupationally exposed individuals. The disadvantage of using postmortem blood is that the HCH concentration may change after death. The occupational studies often do not report environmental levels; therefore, it is not possible to correlate body HCH levels with environmental levels. The results of the NHATS conducted in 1982 showed that β-HCH, the most prevalent isomer in fatty tissue, was detected most often in postmortem samples collected from individuals from the southern United States. Samples of human milk that were collected over the years in certain populations and used to monitor other contaminants (e.g., polychlorinated biphenyls) could be tested for HCHs content. Additional information is needed on exposure to γ-, α-, β-, and δ-HCH isomers in populations living in the vicinity of hazardous waste sites.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Prenatal exposure of children to HCH has been demonstrated; it is well documented that placental transfer of HCH occurs, and HCH levels have been measured in placenta and cord blood in humans (Morello-Frosch et al. 2016; Nair et al. 1996; Saxena et al. 1981b) and in amniotic fluid and fetal tissues in mice (Srivastava and Raizada 1993). Infants have previously also been exposed via ingestion of breast milk and cow's milk. Exposure may also occur via ingestion of water containing HCH and possibly through incidental ingestion of household dust; exposure is less likely from food and animal products. It has been demonstrated that household dust can be an important source of environmental HCH (Starr et al. 1974). This occurs especially if the parents work in facilities that process or use HCH and can bring home residues of HCH via their work clothes, skin, hair, tools, or other objects removed from the workplace. A take-home exposure study on pesticide applicators might be

useful if such occupational exposure settings occur. Limited studies conducted on exposure of infants and children to γ-HCH from application of 1% γ-HCH lotion as scabicide indicated dermal absorption occurred (Ginsburg et al. 1977). Adipose tissue is a major storage depot for HCH. Although data from a national human adipose tissue survey exist (EPA 1986), no quantitative data are currently available on the body burden of HCH in children. These studies are needed because unique exposure pathways for children exist, and children may be different from adults in their weight-adjusted intake of HCH because of their higher surface area to volume ratio and higher ingestion rate of household dust.

6.3 ONGOING STUDIES

No ongoing studies were identified in the National Institutes of Health (NIH) RePORTER (2023) database, which tracks projects funded by NIH.