Toxicological Profile for Hexachlorocyclohexane (HCH)

Draft for Public Comment

January 2023

U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

CS274127-A

DISCLAIMER

Use of trade names is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry, the Public Health Service, or the U.S. Department of Health and Human Services.

This information is distributed solely for the purpose of pre dissemination public comment under applicable information quality guidelines. It has not been formally disseminated by the Agency for Toxic Substances and Disease Registry. It does not represent and should not be construed to represent any agency determination or policy.

FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance and the associated acute, intermediate, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine the levels of exposure that present a significant risk to human health due to acute, intermediate, and chronic duration exposures; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. ATSDR plans to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Electronic comments may be submitted via: www.regulations.gov. Follow the on-line instructions for submitting comments.

Written comments may also be sent to: Agency for Toxic Substances and Disease Registry
Office of Innovation and Analytics
Toxicology Section
1600 Clifton Road, N.E.
Mail Stop S102-1
Atlanta, Georgia 30329-4027

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the NPL, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Patrick N. Breysse, Ph.D., CIH
Director, National Center for Environmental Health and
Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention

Christopher M. Reh, Ph.D.
Associate Director
Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention

VERSION HISTORY

Date	Description
January 2023	Draft for public comment toxicological profile released
August 2005	Final toxicological profile released
July 1999	Final toxicological profile released
May 1994	Final toxicological profile released
December 1989	Final toxicological profile released

CONTRIBUTORS & REVIEWERS

CHEMICAL MANAGER TEAM

Malcolm Williams, D.V.M., Ph.D. (Lead)
Melanie Buser, M.P.H.
Gaston Casillas, Ph.D.

ATSDR, Office of Innovation and Analytics, Toxicology Section, Atlanta, GA

Heather Carlson-Lynch, M.S., D.A.B.T.
Claire Heit, Ph.D.
Julie Melia, Ph.D., D.A.B.T.
Jennifer Rhoades, B.A.
Savannah Sierco, M.S.
SRC, Inc., North Syracuse, NY

REVIEWERS

Interagency Minimal Risk Level Workgroup:

Includes ATSDR; National Center for Environmental Health (NCEH); National Institute for Occupational Safety and Health (NIOSH); U.S. Environmental Protection Agency (EPA); National Toxicology Program (NTP).

Additional reviews for science and/or policy:

ATSDR, Office of Community Health and Hazard Assessment; ATSDR, Office of Capacity Development and Applied Prevention Science; ATSDR, Office of Science; NCEH, Division of Laboratory Science; NCEH, Division of Environmental Health Science and Practice.

PEER REVIEWERS

1. Lisa Kamendulis, Ph.D.; Department of Environmental and Occupational Health; Indiana University Bloomington; Bloomington, Indiana

2. Russell C. Cattley, VMD, Ph.D., Dipl. ACVP, Fellow IATP; Tyler & Frances Young Professor of Pathology; Greene Hall; College of Veterinary Medicine; Auburn University, Alabama

3. Stephen M. Roberts, Ph.D.; Director, Center for Environmental & Human Toxicology; Professor, College of Veterinary Medicine; College of Medicine, and College of Public Health and Health Professions; University of Florida; Gainesville, Florida

These experts collectively have knowledge of toxicology, chemistry, and/or health effects. All reviewers were selected in conformity with Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

ATSDR scientists review peer reviewers' comments and determine whether changes will be made to the profile based on comments. The peer reviewers' comments and responses to these comments are part of the administrative record for this compound.

The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

CONTENTS

LIST OF FIGURES

LIST OF TABLES

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 has the ability to 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. The vast majority of 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.

1. RELEVANCE TO PUBLIC HEALTH

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 of 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

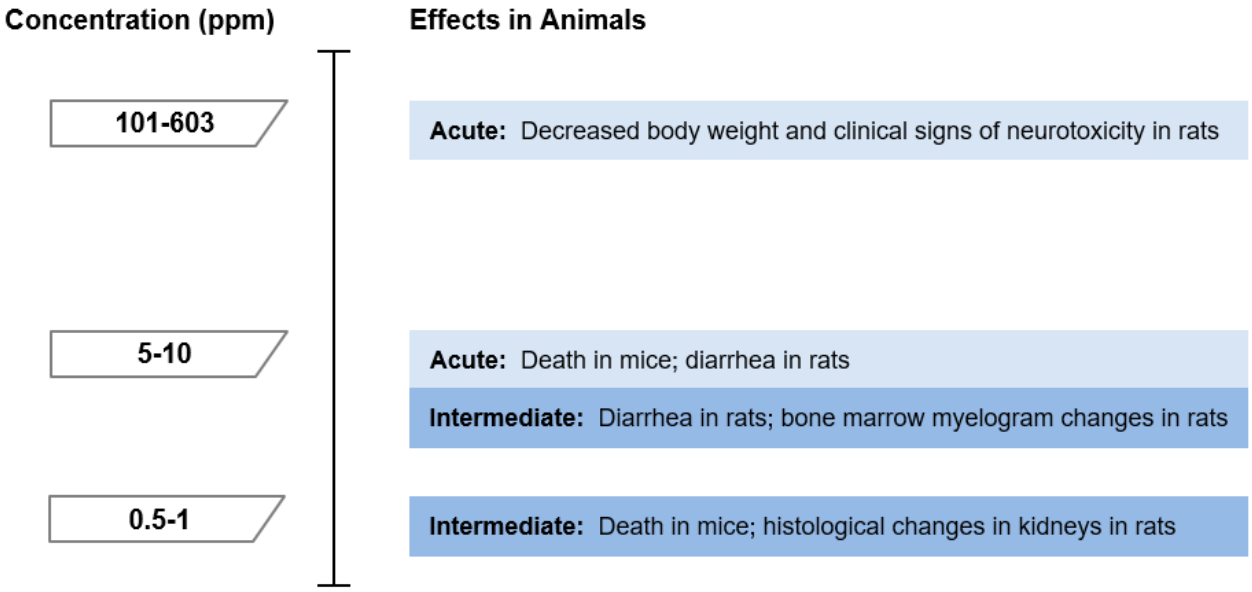


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to α-Hexachlorocyclohexane

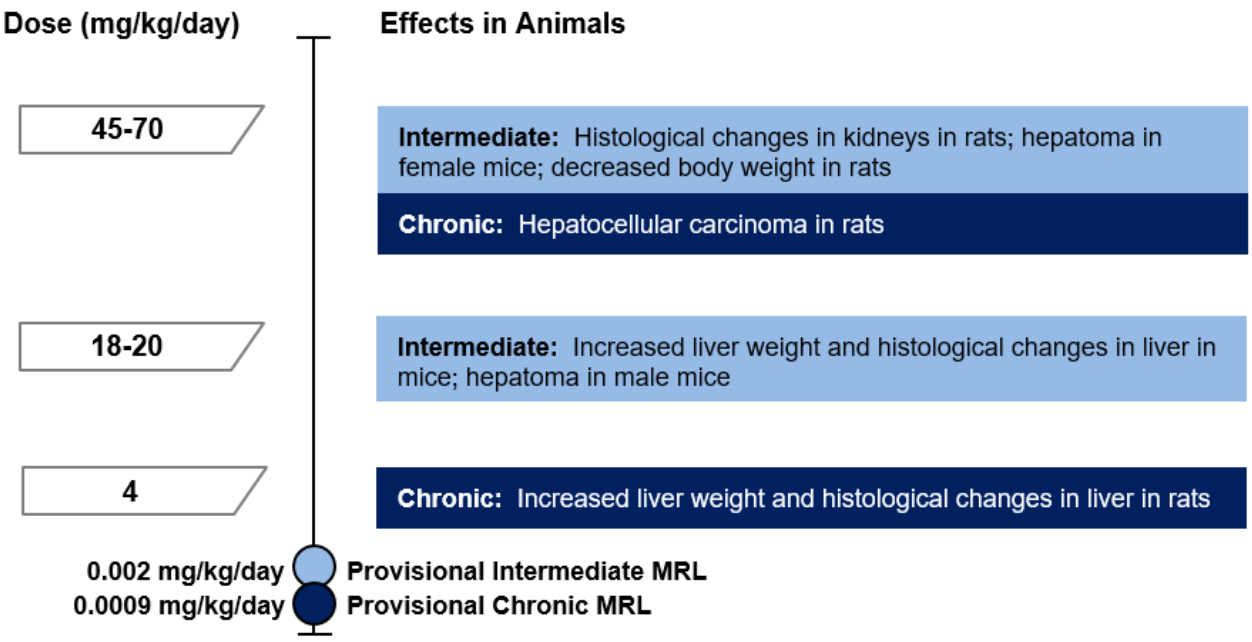


Figure 1-3. Health Effects Found in Animals Following Oral Exposure to β-Hexachlorocyclohexane

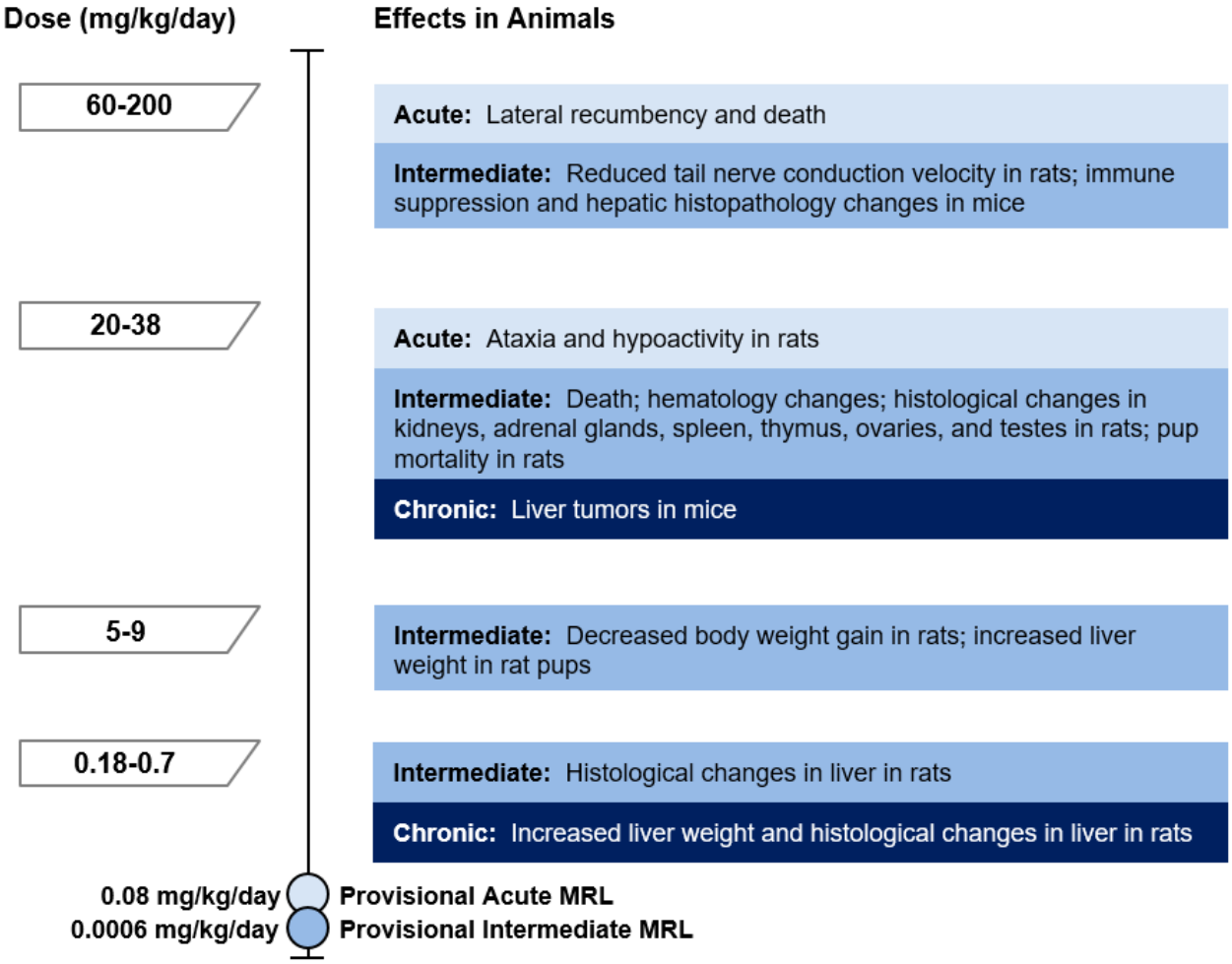


Figure 1-4. Health Effects Found in Animals Following Oral Exposure to γ-Hexachlorocyclohexane

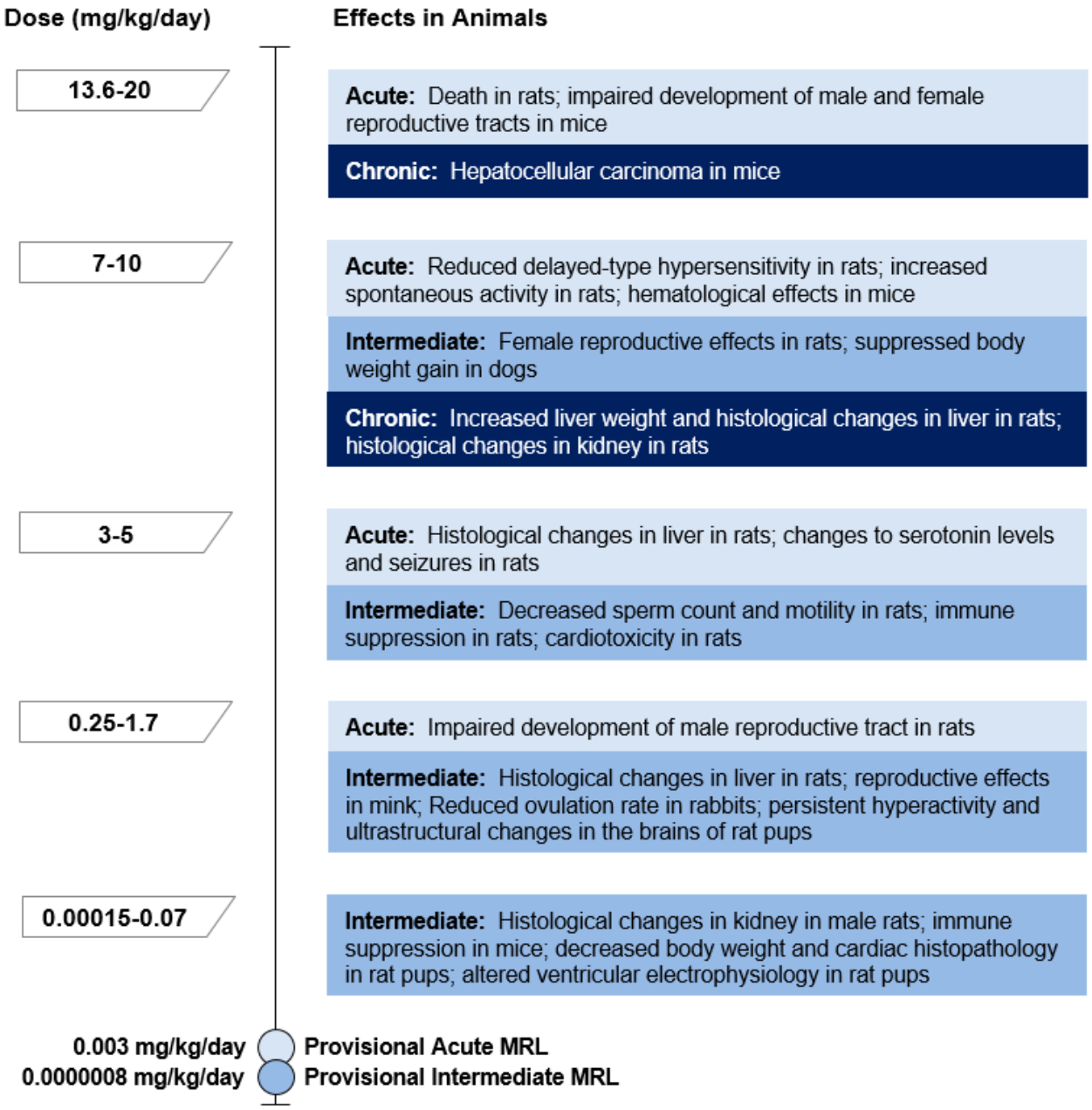
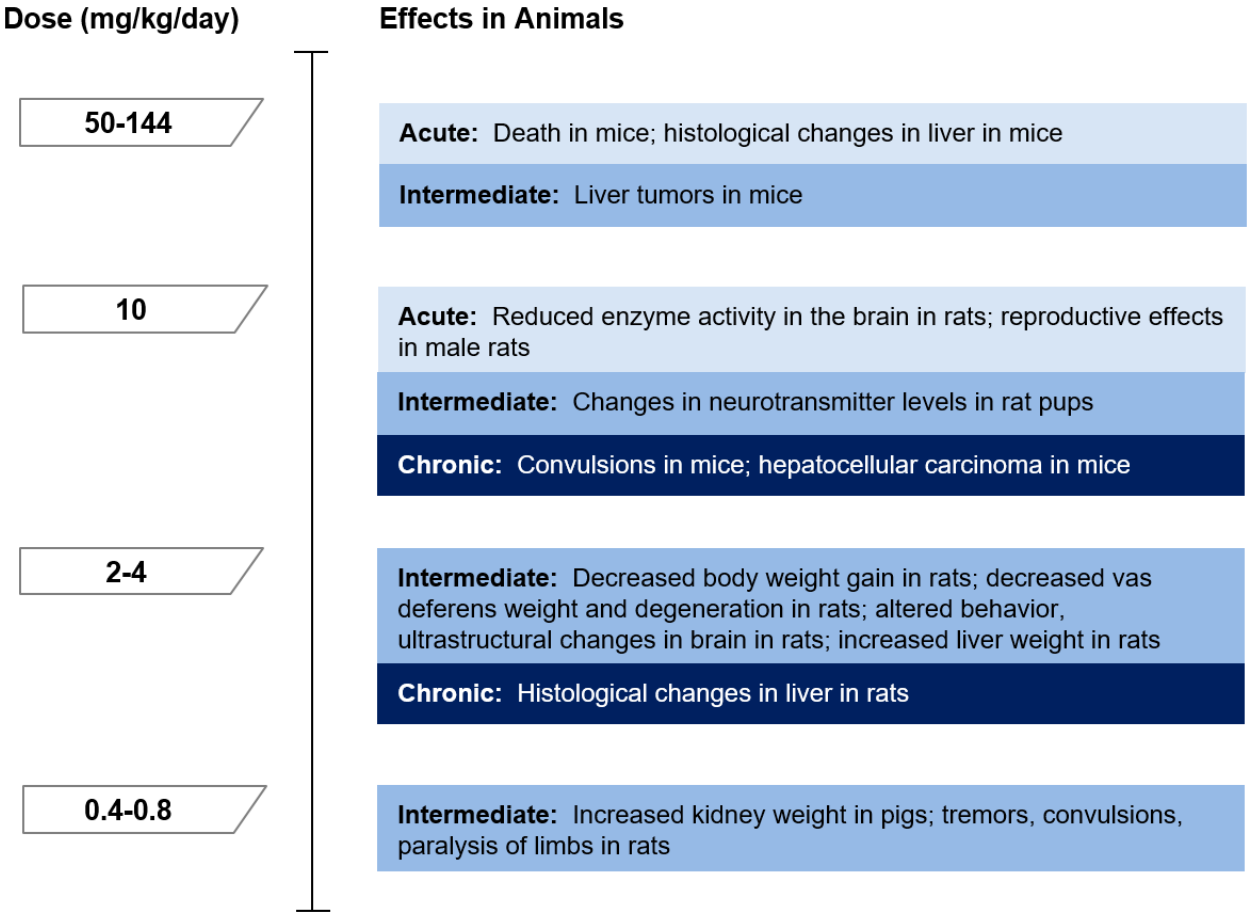


Figure 1-5. Health Effects Found in Animals Following Oral Exposure to Technical Hexachlorocyclohexane



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, and hepatocellular carcinoma (Arrebola et al. 2015a; Band et al. 2011; Lee et al. 2018a; Ibarluzea et al. 2004; Kumar et al. 2010; Purdue et al. 2007; Waliszewski et al. 2005; Weber et al. 2018; Xu et al. 2010; 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 2016). 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 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

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.

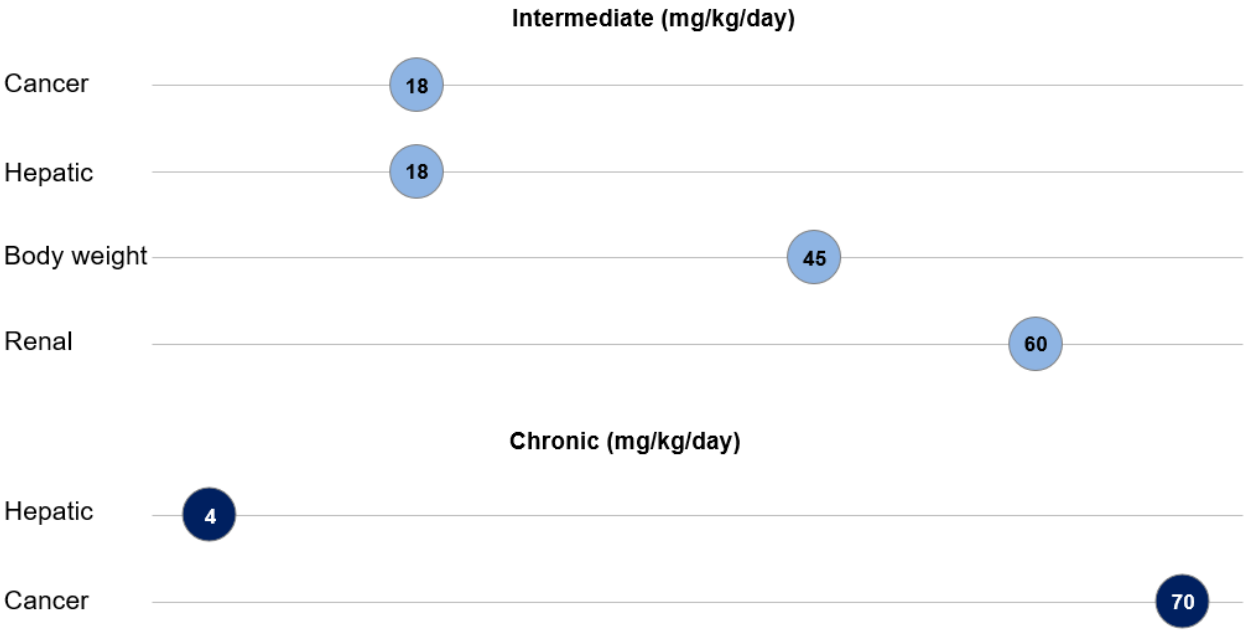


Figure 1-7. Summary of Sensitive Targets of β-Hexachlorocyclohexane (β-HCH) – Oral

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.

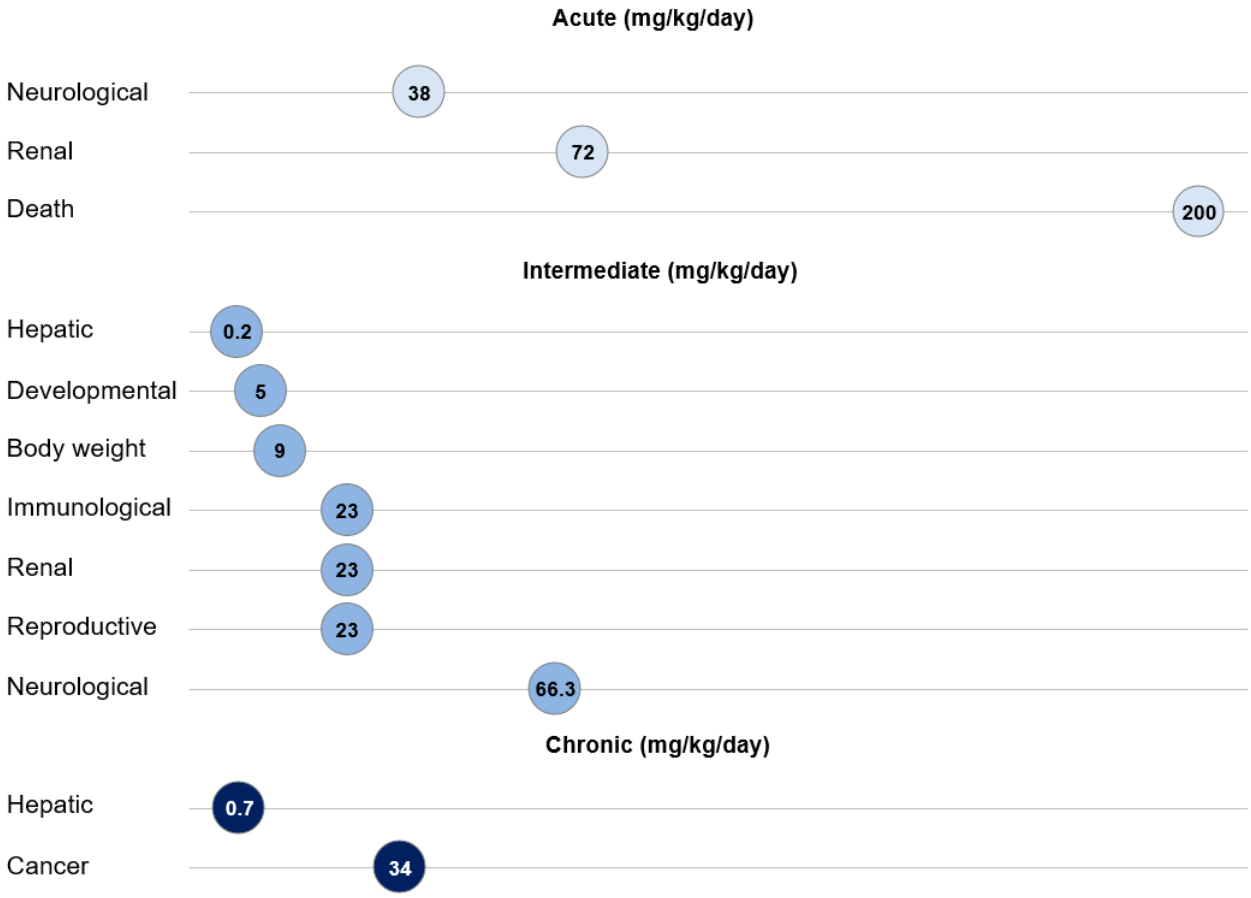


Figure 1-8. Summary of Sensitive Targets of γ-Hexachlorocyclohexane (γ-HCH) – Inhalation

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

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.

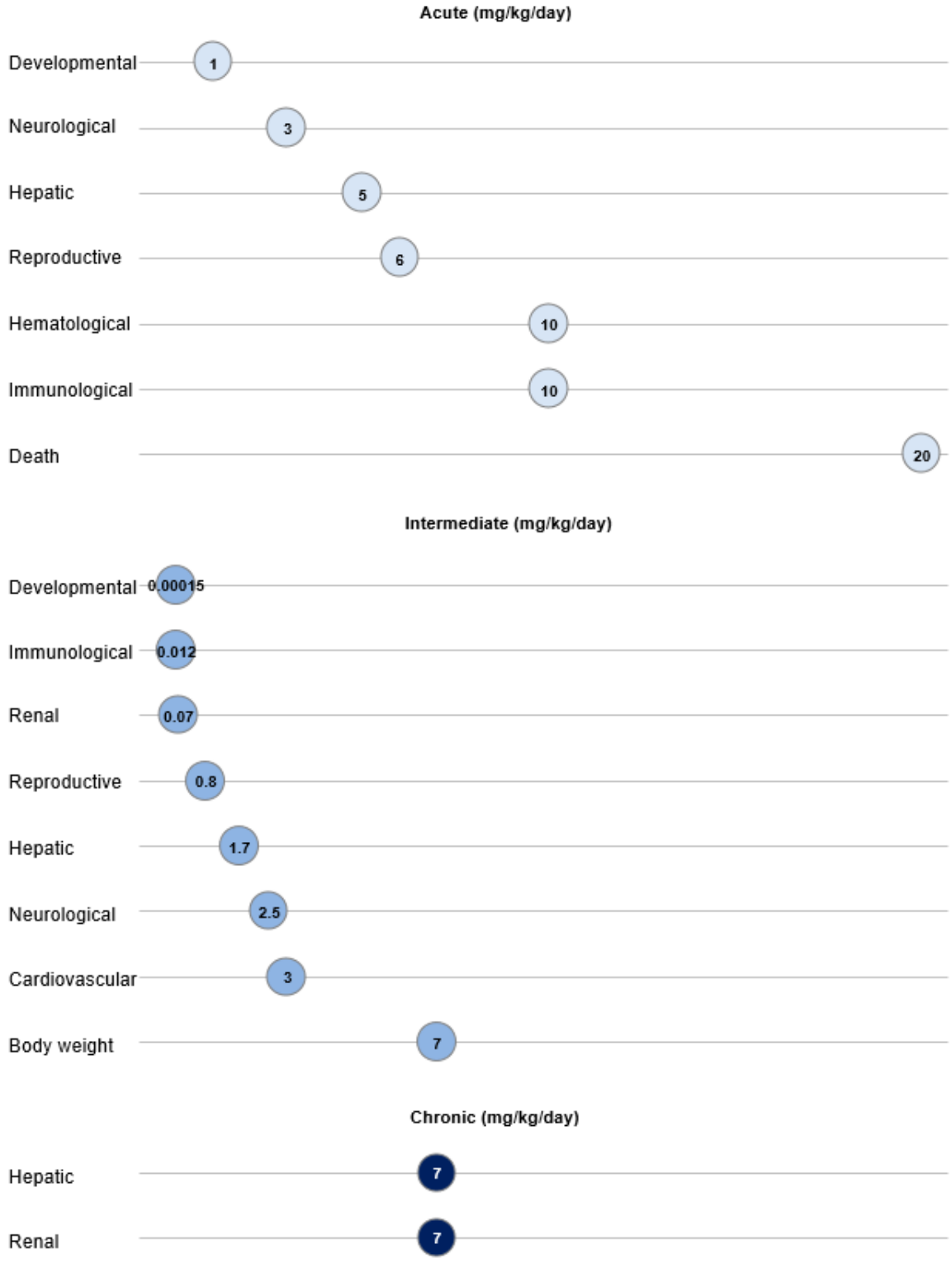
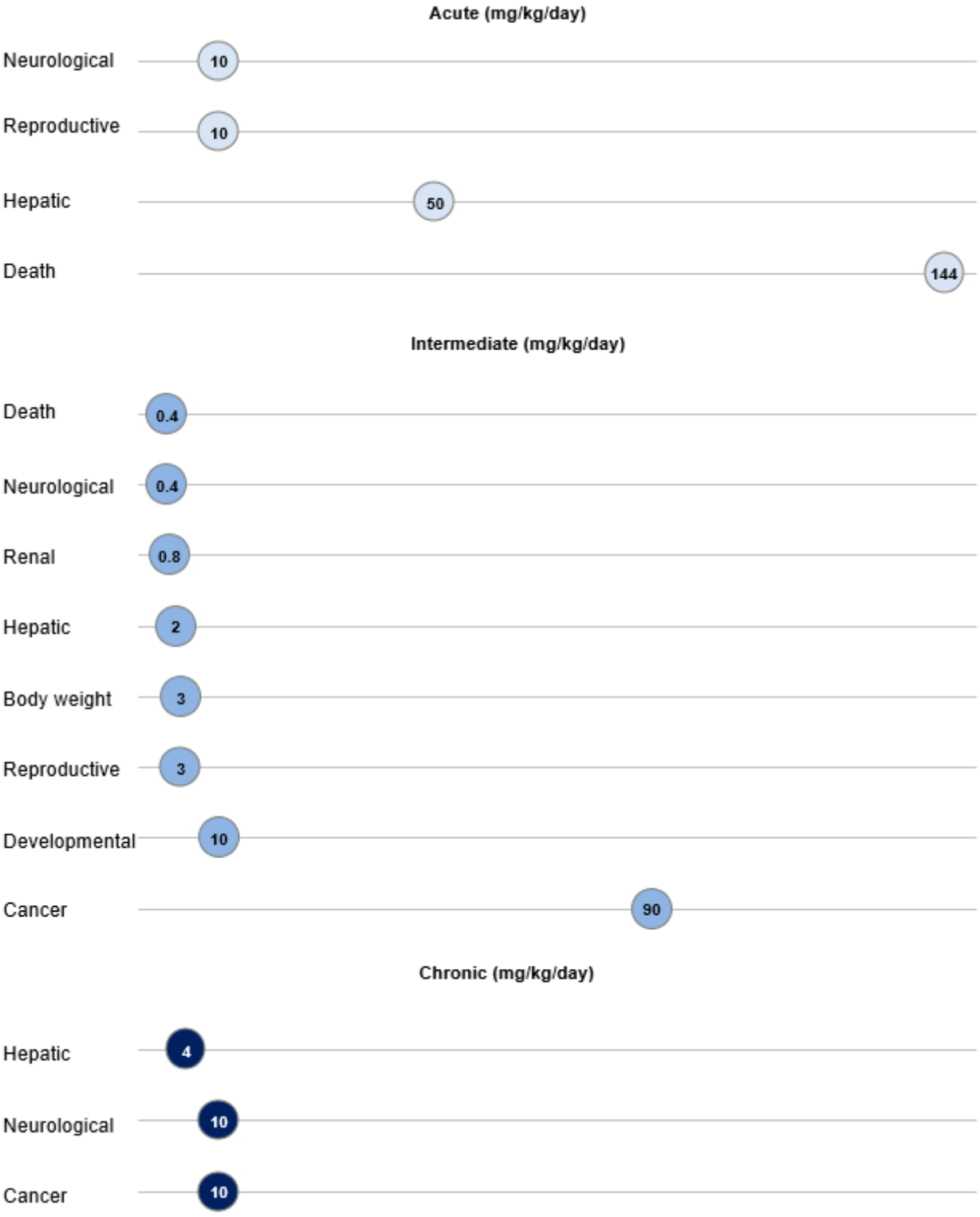


Figure 1-10. Summary of Sensitive Targets of Technical-Hexachlorocyclohexane (technical-HCH) – Oral

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 are summarized in Table 1-1 and discussed in greater detail in Appendix A.

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

Exposure duration	Provisional MRL	Critical effect	Point of departure/ Human equivalent concentration	Uncertainty/ modifying factor	Reference
Inhalation exposure (mg/m^3)					
Acute	Insufficient data for derivation of an MRL				
Inter-mediate	Insufficient data for derivation of an MRL				
Chronic	Insufficient data for derivation of an MRL				
Oral exposure (mg/kg/day)					
Acute	Insufficient data for derivation of an MRL				
Inter-mediate	**0.002** (2 µg/kg/day)	Increased liver weight and histopathology	NOAEL: 2	UF: 100 MF: 10	Sumida et al. 2007
Chronic	**0.0009** (0.9 µg/kg/day)	Increased liver weight and histopathology	NOAEL: 0.9	UF: 100 MF: 10	Fitzhugh et al. 1950

[a]See Appendix A for additional information.

LOAEL = lowest-observed-adverse-effect level; MF = modifying factor; NOAEL = no-observed-adverse-effect level; UF = uncertainty factor

The MRL values for β-HCH are summarized in Table 1-2 and discussed in greater detail in Appendix A.

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

Exposure duration	Provisional MRL	Critical effect	Point of departure/ Human equivalent concentration	Uncertainty/ modifying factor	Reference
Inhalation exposure (mg/m^3)					
Acute	Insufficient data for derivation of an MRL				
Inter-mediate	Insufficient data for derivation of an MRL				
Chronic	Insufficient data for derivation of an MRL				
Oral exposure (mg/kg/day)					
Acute	**0.08**	Clinical signs of neurotoxicity (ataxia, inactivity) at higher doses	NOAEL: 8	UF: 100	Van Velsen et al. 1986
Inter-mediate	**0.0006** (0.6 µg/kg/day)	Hyalinization of centrilobular liver cells	LOAEL: 0.18	UF: 300	Van Velsen et al. 1986

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

Exposure duration	Provisional MRL	Critical effect	Point of departure/ Human equivalent concentration	Uncertainty/ modifying factor	Reference
Chronic	Insufficient data for derivation of an MRL				

[a]See Appendix A for additional information.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; UF = uncertainty factor

The MRL values for γ-HCH are summarized in Table 1-3 and discussed in greater detail in Appendix A.

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

Exposure duration	Provisional MRL	Critical effect	Point of departure/ human equivalent concentration	Uncertainty/ modifying factor	Reference
Inhalation exposure (mg/m^3)					
Acute	Insufficient data for derivation of an MRL				
Inter-mediate	Insufficient data for derivation of an MRL				
Chronic	Insufficient data for derivation of an MRL				
Oral exposure (mg/kg/day)					
Acute	**0.003** (3 µg/kg/day)	Reduced reproductive organ weights, sperm numbers, serum testosterone, and increased intromission frequency in male offspring	LOAEL: 1	UF: 300	Dalsenter et al. 1997b
Inter-mediate	**0.0000008** (0.8 ng/kg/day)	Cardiac effects in offspring	NOAEL: 0.000076	UF: 100	Sauviat et al. 2005
Chronic	Insufficient data for derivation of an MRL				

[a]See Appendix A for additional information.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; UF = uncertainty factor

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of HCH. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figures 2-1, 2-2, and 2-3 provide an overview of the database of studies in humans or experimental animals for α-, β-, and γ-HCH included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to HCH, but may not be inclusive of the entire body of literature. A systematic review of the scientific evidence of the health effects associated with exposure to HCH was also conducted; the results of this review are presented in Appendix C.

Tabulated human studies of specific health endpoints are presented in the corresponding subsections of this Chapter. Animal inhalation studies of γ-HCH are presented in Table 2-1 and Figure 2-4. There were no inhalation studies of other HCH isomers or mixtures of isomers. Animal oral studies are presented in Table 2-2 and Figure 2-5 (α-HCH), Table 2-3 and Figure 2-6 (β-HCH), Table 2-4 and Figure 2-7 (γ-HCH), and Table 2-5 and Figure 2-8 (δ-HCH and technical-grade HCH or unspecified isomers). Animal dermal studies are presented in Table 2-6 (γ-HCH) and Table 2-7 (technical-grade or unspecified isomers). There were no dermal studies of other HCH isomers.

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects (SLOAELs) are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints (ATSDR 2018). ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health. Levels of oral exposure associated with cancer (Cancer Effect Levels, CELs) of HCH are indicated in Tables 2-2 through 2-5 and Figures 2-5 through 2-8.

A User's Guide has been provided at the end of this profile (see Appendix D). This guide should aid in the interpretation of the tables and figures for LSEs and MRLs.

The discussion of the available data for health effects in this chapter is organized into human and animal data, with isomer-specific subsections on the animal data provided in the following order: α-HCH, β-HCH, γ-HCH, δ-HCH, and technical-grade and mixtures of HCH isomers. Case reports of effects in humans are limited to γ-HCH and technical-grade HCH and are discussed under the isomer-specific subsections. If there are no case reports or animal data for a given isomer or for technical grade/mixtures, there is no corresponding subsection.

Effects of HCH isomers have been evaluated in epidemiological studies and in laboratory animals exposed under controlled conditions. A majority of the human epidemiological studies used measures of HCH isomers in blood or tissues to assess exposure, so the route is unknown; for the purpose of enumerations, these studies are considered to reflect oral exposure (e.g., through contaminated food). In

addition, there are a number of case reports of health effects in humans exposed by inhalation, oral, or dermal exposure to γ-HCH. The human data were not considered adequate for identification of sensitive target organs for any of the HCH isomers or mixtures.

As shown in Figure 2-1 (α-HCH), there were a small number of human studies examining a handful of endpoints; the largest number of studies were devoted to developmental endpoints. There were no inhalation or dermal animal studies of α-HCH, and few oral studies. The available animal studies primarily examined liver effects and cancer. Animal studies suggest that hepatic effects are a sensitive target of α-HCH toxicity.

- **Hepatic endpoints:** Hepatic toxicity is a presumed health effect for humans based on a high evidence level in animals showing increased liver weight and histopathological lesions after oral exposure to α-HCH. No information was located on hepatic effects in humans exposed to α-HCH.

Figure 2-2 provides an overview of the health effects data for β-HCH. For this isomer, human studies examined a wide range of outcomes, with more studies of endocrine endpoints (thyroid hormone levels) developmental outcomes, other noncancer endpoints (diabetes and metabolic perturbations), and cancer than other outcomes. Animal studies are limited to oral exposures, and the endpoints examined were largely focused on liver, kidney, body weight, nervous system, and cancer. Animal studies suggest that neurological and hepatic effects are sensitive targets of β-HCH toxicity after acute-duration exposures and intermediate- or chronic-duration exposures, respectively.

- **Neurological endpoints:** Neurotoxicity is a presumed health effect in humans based on human and animal studies. There is a moderate level of evidence in humans suggesting associations between serum β-HCH and risk of Parkinson disease, Alzheimer's disease, and cognitive deficits. There is a high level of evidence in animal studies of oral exposure showing clinical signs of neurotoxicity in rats and mice after acute durations and reduced nerve conduction velocity in rats after an intermediate duration. Clinical signs showed a dose-related increase in severity.

  Hepatic endpoints: Hepatic toxicity is a presumed health effect for humans based on a high level of evidence in animals showing increased liver weight and histopathology changes in rats and mice exposed by dietary administration for intermediate and chronic durations. In humans, there is a very low level of evidence for a minimal liver toxicity based on two cross-sectional studies reporting no association between serum or adipose levels of β-HCH and hepatic clinical chemistry endpoints except for increased serum bilirubin.

An overview of health effects data for γ-HCH is presented in Figure 2-3. Most of the human studies evaluated developmental, reproductive, renal, endocrine, or cancer endpoints. Studies of occupational exposure via pesticide application are considered to reflect primarily inhalation exposure. Most of the

animal studies used oral administration, and the available studies examined comprehensive noncancer and cancer endpoints. The effects seen at the lowest doses in the animal studies were developmental and immune system effects. Animal studies suggest that developmental and immune system effects are sensitive targets of γ-HCH toxicity after acute-duration exposures (developmental) and intermediate-duration exposures (developmental and immune system). Available studies of chronic-duration oral exposure to γ-HCH were limited, and identified effects on other systems (hepatic and renal) at much higher doses than those associated with developmental and immune system effects in acute- and intermediate-duration exposure studies.

- **Developmental endpoints:** Developmental toxicity is a presumed health effect in humans based on human and animal evidence. There is a low level of evidence in humans based on associations between γ-HCH in maternal or fetal blood (or tissue) and fetal growth retardation, preterm birth, and cryptorchidism or hypospadias. There is a high level of evidence in animals based on studies in a variety of species exposed orally to γ-HCH for acute or intermediate durations during gestation or postnatal development demonstrating adverse effects on a wide range of developmental endpoints, including birth outcomes and development of the male and female reproductive tracts, central nervous system, heart, thymus, and spleen.

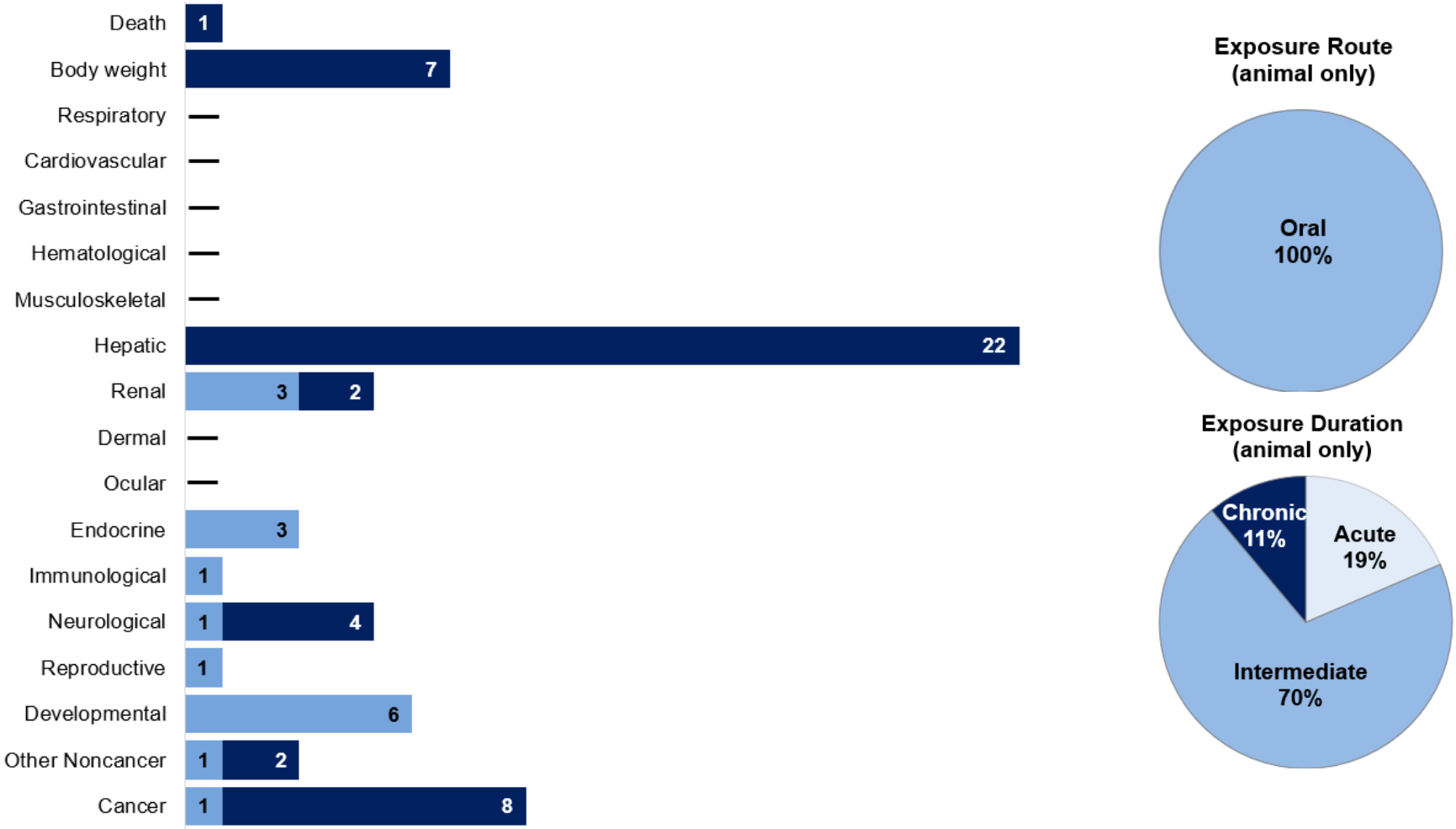
- **Immune system endpoints:** Immunotoxicity is a presumed health effect in humans based primarily on animal evidence. There is a low level of evidence in humans based on an observed association between asthma and plasma levels of γ-HCH in children and no evidence for increased prevalence of monoclonal gammopathy of undetermined significance in male pesticide applicators. There is a high level of evidence in animals based on acute- and intermediate-duration studies of γ-HCH administered orally to rats, mice, rabbits, and sheep showing suppression of the immune system and effects on thymus, spleen, and lymph node weights or histology.

Available studies of δ-HCH are not adequate to identify target organs.

Figure 2-1. Overview of the Number of Studies Examining α-Hexachlorocyclohexane (α-HCH) Health Effects*

Most studies examined the potential body weight, hepatic, and cancer effects of α-HCH

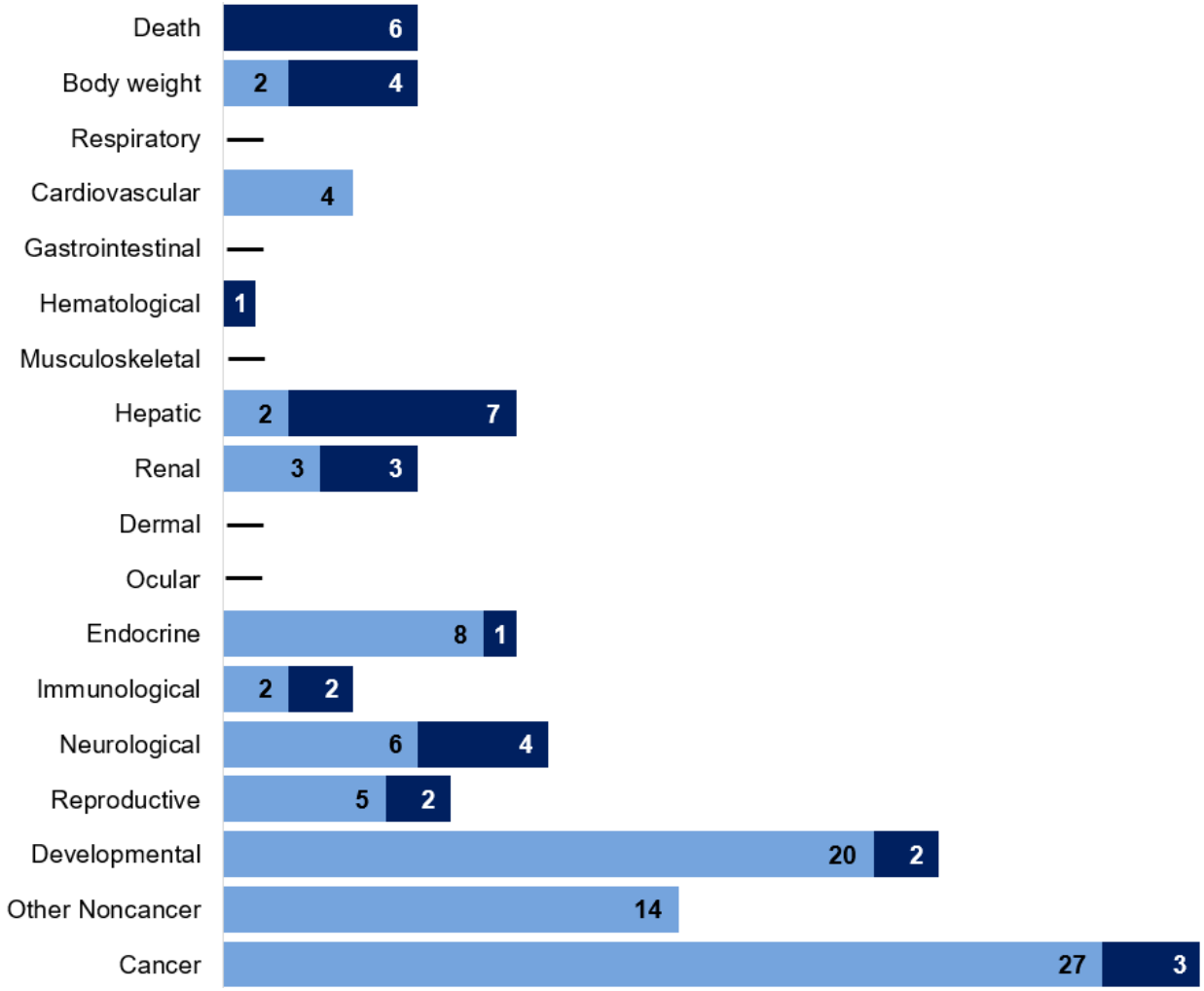
Fewer studies evaluated health effects in humans than animals (counts represent studies examining endpoint)

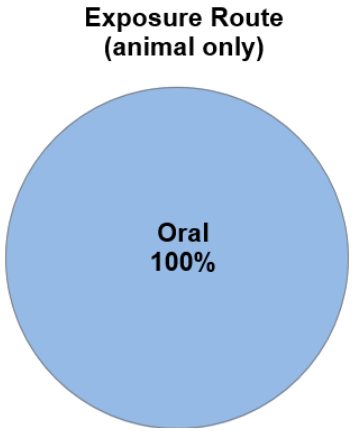


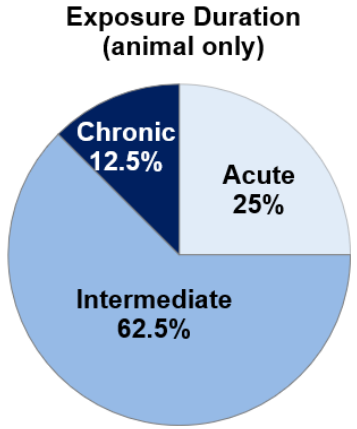
*Includes studies discussed in Chapter 2. A total of 40 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Figure 2-2. Overview of the Number of Studies Examining β-Hexachlorocyclohexane (β-HCH) Health Effects*

Most studies examined the potential developmental, other noncancer, and cancer effects of β-HCH
More studies evaluated health effects in humans than animals (counts represent studies examining endpoint)



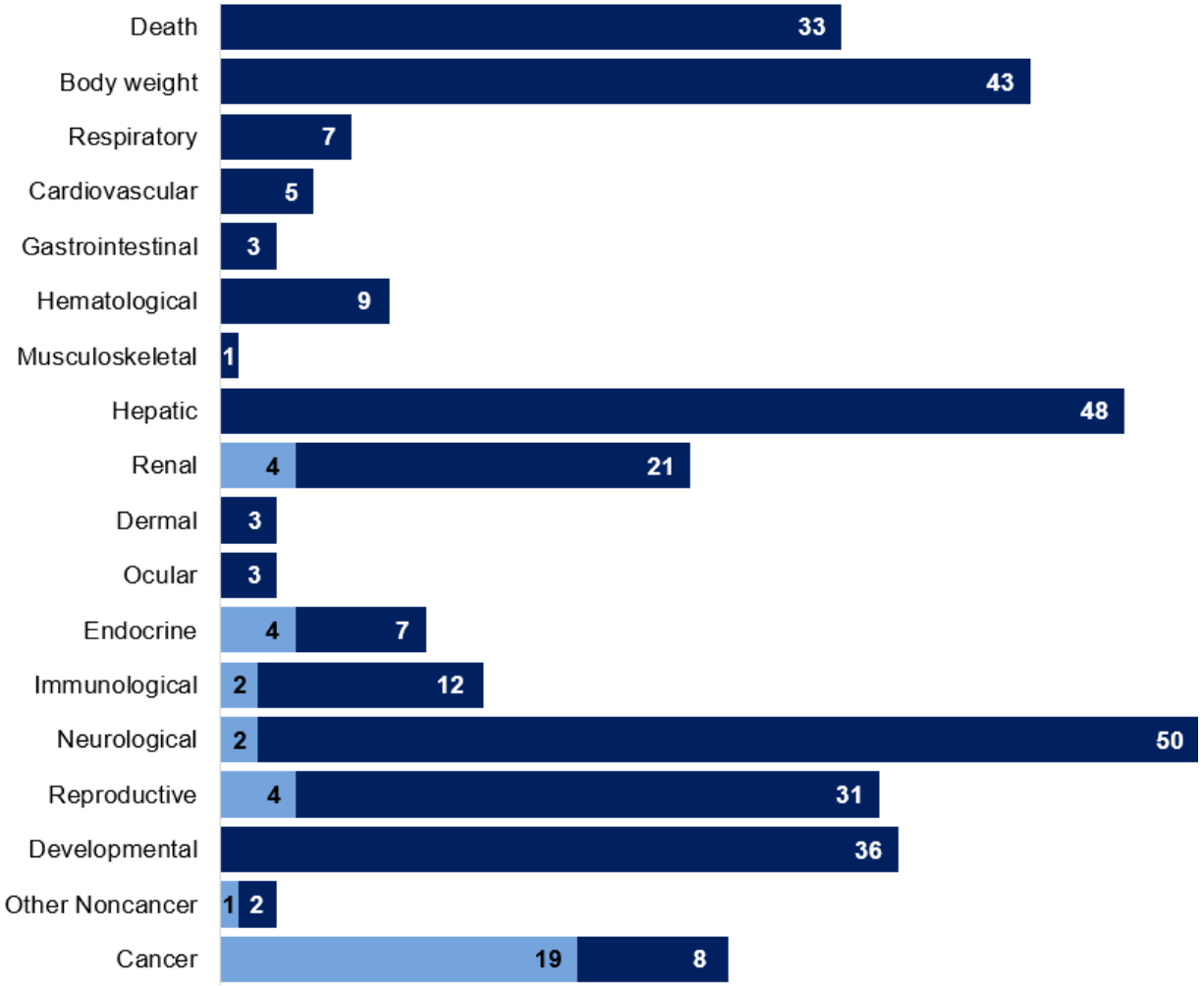


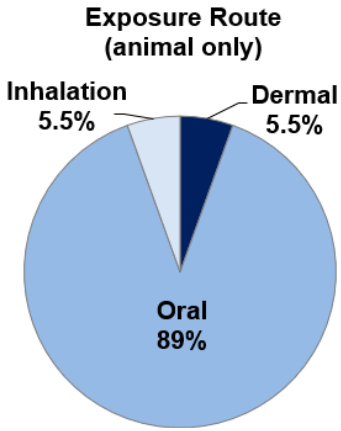


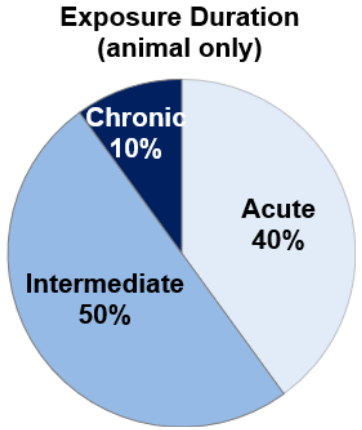
*Includes studies discussed in Chapter 2. A total of 41 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Figure 2-3. Overview of the Number of Studies Examining γ-Hexachlorocyclohexane (γ-HCH) Health Effects*

Most studies examined the potential body weight, hepatic, and neurological effects of γ-HCH
Fewer studies evaluated health effects in humans than animals (counts represent studies examining endpoint)







*Includes studies discussed in Chapter 2. A total of 158 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Table 2-1. Levels of Significant Exposure to γ-Hexachlorocyclohexane – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
ACUTE EXPOSURE									
Oldiges et al. 1980									
1	Rat (Wistar) 5 M, 5 F	4 hours	0, 273, 603	LE, CS, GN, OW	Bd wt		603 F		Body weight loss in females during first week of observation
					Neuro		273	603	LOAEL: clinical signs of restlessness, hyperactivity Serious LOAEL: marked somnolence
Ullmann 1986b									
2	Rat (Wistar) 5 M, 5 F	4 hours	0, 101, 378, 642, 2,104	LE, CS, BW, GN	Death			378	20% of rats died (LC_{50}: 1,560 mg/m^3)
					Neuro		101		Clinical signs (sedation, curved body position)
Klonne and Kintigh 1988									
3	Mouse (CD-1) 45 M, 45 F	1 week 5 days/week 6 hours/day	0, 0.3, 1, 5, 10	LE, CS	Death			10	12/45 females and 2/45 males died during first week of 13-week study
INTERMEDIATE EXPOSURE									
Oldiges et al. 1983									
4	Rat (Wistar) 12 M, 12 F	90 days 7 days/week 6 hours/day	0, 0.02, 0.1, 0.5, 5	LE, CS, BW, FI, WI, HE, UR, OW, HP	Bd wt	5			
					Resp	5			
					Cardio	5			
					Gastro	0.5	5		Diarrhea
					Hemato	0.5	5		Bone marrow myelogram changes (increased reticulocytes, stem cells and myeloblasts; decreased lymphocytes)
					Hepatic	5			
					Renal	5 F	0.5 M		Dilated tubules with protein-containing contents; proliferated tubules
					Endocr	5			

Table 2-1. Levels of Significant Exposure to γ-Hexachlorocyclohexane – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
					Neuro	5			
					Repro	5			
Klonne and Kintigh 1988									
5	Mouse (CD-1) 45 M, 45 F	14 weeks 5 days/week 6 hours/day	0, 0.3, 1.0, 5	LE, CS, BW, FI, WI, HE, BC, UR, GN, OW, HP	Death			1	1/45 males and 1/45 females died at 1 mg/m^3; 5/45 males and 15/45 females died at 5 mg/m^3
					Bd wt	5			
					Resp	5			
					Cardio	5			
					Gastro	5			
					Hemato	5			
					Hepatic	5			
					Renal	5			
					Endocr	5			
					Repro	5			No histopathology changes in reproductive organs

[a]The number corresponds to entries in Figure 2-4; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-4. Where such differences exist, only the levels of effect for the most sensitive sex are presented.

BC = serum (blood) chemistry; Bd wt or BW = body weight; Cardio = cardiovascular; CS = clinical signs; Endocr = endocrine; F = female(s); FI = food intake; Gastro = gastrointestinal; GN = gross necropsy; HE = hematology; Hemato = hematological; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Neuro = neurological; NOAEL = no-observed-adverse-effect level; OW = organ weight; Repro = reproductive; Resp = respiratory; UR = urinalysis; WI = water intake

Figure 2-4. Levels of Significant Exposure to γ-Hexachlorocyclohexane (Lindane) – Inhalation
Acute (≤14 days)

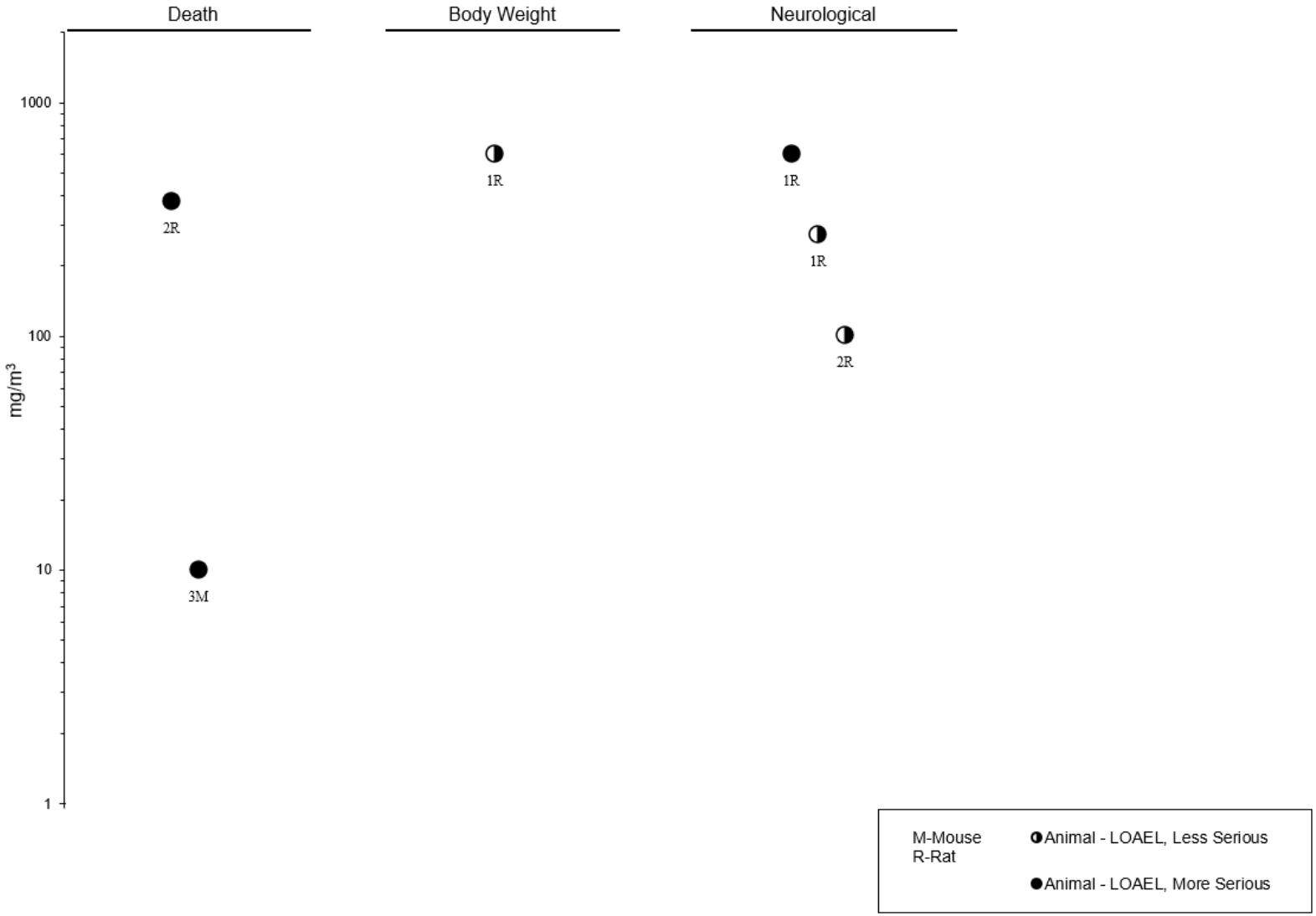


Figure 2-4. Levels of Significant Exposure to γ-Hexachlorocyclohexane (Lindane) – Inhalation
Intermediate (15-364 days)

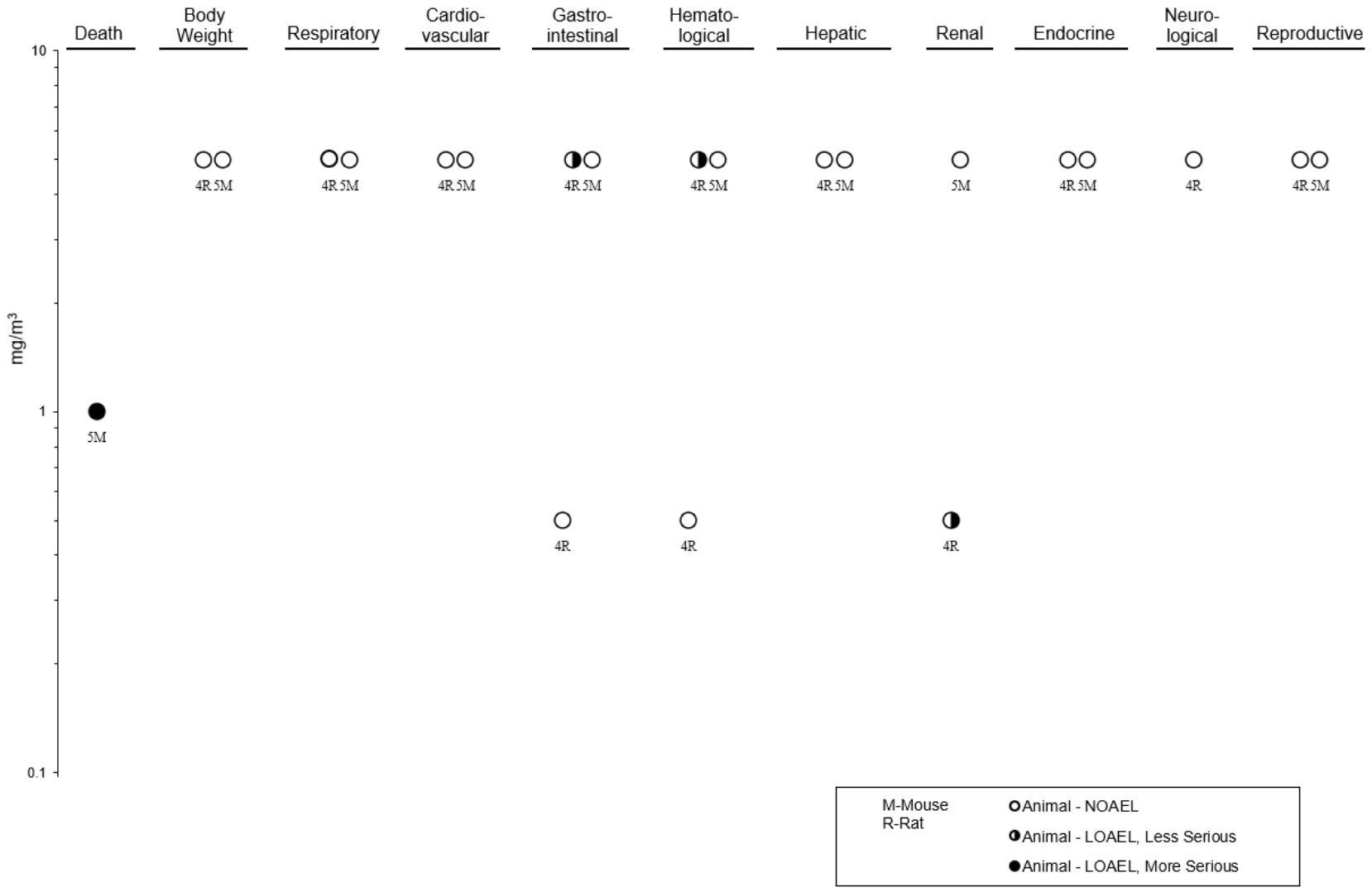


Table 2-2. Levels of Significant Exposure to α-Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
ACUTE EXPOSURE									
Sumida et al. 2007									
1	Rat (Fischer-344) 4 M	1, 3, 7, or 14 d (GO)	0, 2, 20	BW, BC, OW	Bd wt	20			
					Hepatic	2	20		24% increase in relative liver weight
INTERMEDIATE EXPOSURE									
Fitzhugh et al. 1950									
2	Rat (Wistar) 10 F, 10 M	6–9 months (F)	Males: 0, 60 Females: 0, 70	LE, BW, FI, GN, OW, HP	Death			60 M 70 F	Mean survival was 35.9 weeks versus 58.3 weeks in controls
					Bd wt		60 M 70 F		11–15% decrease in body weight gain
					Resp	60 M 70 F			
					Cardio	60 M 70 F			
					Gastro	60 M 70 F			
					Hemato	60 M 70 F			
					Musc/skel	60 M 70 F			
					Hepatic		60 M 70 F		Moderate histopathology changes (focal necrosis, fatty degeneration); >2-fold increase in liver weight
					Renal		60 M 70 F		Slight to moderate histopathology changes including tubular dilatation, hyaline tubular casts, glomerular fibrosis or atrophy, pigment deposition

Table 2-2. Levels of Significant Exposure to α-Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Endo	60 M 70 F			
					Repro	60 M 70 F			
Ito et al. 1975									
3	Rat (W strain) 18–24 M	48 weeks (F)	0, 35, 70	BW, OW, HP	Hepatic		35		Hepatocellular hypertrophy
					Cancer			70	CEL: liver tumors after 48 weeks
Muller et al. 1981									
4	Rat (Wistar) 15 M	30 days (F)	0, 5.1, 54.2, 106.2	NX	Neuro	106.2			No reduction in motor conduction velocity
Nagasaki et al. 1975									
5	Rat (Wistar) 8 M	24 weeks (F)	0, 45	BW, OW, HP	Bd wt		45		15% decrease in terminal body weight
					Hepatic		45		Mild hypertrophy; ~2-fold increase in absolute and relative liver weight
Sumida et al. 2007									
6	Rat (Fischer-344) 4 M	28 days (GO)	0, 2, 20	BW, BC, OW, HP	Bd wt	20			
					Hepatic	2[b]	20		Increased relative liver weight (25%); centrilobular hepatocellular hypertrophy
Hanada et al. 1973									
7	Mouse (dd) 10–11 M, 10–11 F	32 weeks (F)	M: 0, 18, 54, 108 F: 0, 20, 60, 120	BC, GN, HP	Cancer			18 M 60 F	CEL: hepatoma

Table 2-2. Levels of Significant Exposure to α-Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Ito et al. 1973									
8	Mouse (dd) 20–40 M	24 weeks (F)	0, 18, 45, 90	BW, OW, GN, HP	Bd wt	90			
					Hepatic		18		Increased relative liver weight (33%); hepatocellular hypertrophy
					Cancer			45	CEL: hepatocellular carcinoma
Ito et al. 1976									
9	Mouse (DDY) 13–20 M	16–36 weeks (F)	0, 90	BW, OW, HP	Cancer			90	CEL: hepatocellular carcinoma
Nagasaki et al. 1975									
10	Mouse (DDY, ICR, DBA/2, C57BL/6, C3H/He) 20 M, 20 F	24 weeks (F)	Males: 0, 90 Females: 0, 100	BW, OW, HP	Bd wt		90 M		17% decrease in terminal body weight of male C57BL/6 mice
					Hepatic		90 M 100 F		Parenchymal cell hypertrophy, bile duct proliferation, oval cells; nodular hyperplasia; 2-fold increase in liver weight
					Cancer			90 M 100 F	CEL: hepatocellular carcinomas
Tryphonas and Iverson 1983									
11	Mouse (HPB) 75 M	50 weeks (F)	0, 90	BW, GN, OW, HP	Hepatic		90		Hepatomegaly; megalocytosis
					Cancer			90	CEL: neoplastic nodules of the liver after 21 weeks
Tsukada et al. 1979									
12	Mouse (DD) 6 M	16–36 weeks (F)	0, 90	GN HP	Cancer			90	CEL: hepatomas after 28 weeks

Table 2-2. Levels of Significant Exposure to α-Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Nagasaki et al. 1975									
13	Hamster (Golden Syrian) 6–10 M	24 weeks (F)	0, 45	BW, OW, HP	Bd wt		45		14% decrease in terminal body weight
					Hepatic		45		20–38% increase in liver weight; liver cell hypertrophy
CHRONIC EXPOSURE									
Fitzhugh et al. 1950									
14	Rat (Wistar) 10 F, 10 M	107 weeks (F)	M: 0, 0.7, 4, 7 F: 0, 0.9, 4, 9	LE, BW, FI, GN, OW, HP	Resp	9 F 7 M			
					Cardio	9 F 7 M			
					Gastro	9 F 7 M			
					Hemato	9 F 7 M			
					Musc/skel	9 F 7 M			
					Hepatic	0.7 M 0.9[c] F	4		32% increase in relative liver weight and very slight to slight microscopic damage
					Renal	9 F 7 M			
					Endo	9 F 7 M			
					Repro	9 F 7 M			

Table 2-2. Levels of Significant Exposure to α-Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Ito et al. 1975									
15	Rat (W strain) 18–24 M	72 weeks (F)	0, 70, 105	BW, OW, HP	Cancer			70	CEL: hepatocellular carcinoma

[a]The number corresponds to entries in Figure 2-5; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-5. Where such differences exist, only the levels of effect for the most sensitive sex are presented.
[b]Used to derive a provisional acute-duration oral minimal risk level (MRL). The NOAEL of 2 mg/kg/day was divided by an uncertainty factor of 100 (10 for human variability and 10 for animal to human extrapolation) and modifying factor of 10 (for lack of data on developmental toxicity, immunotoxicity, and neurotoxicity), resulting in a provisional MRL of 0.002 mg/kg/day ($2x10^{-3}$ mg/kg/day).
[c]Used to derive a provisional chronic-duration oral MRL. The NOAEL of 0.9 mg/kg/day was divided by an uncertainty factor of 100 (10 for human variability and 10 for animal to human extrapolation) and modifying factor of 10 (for lack of data on immunotoxicity and neurotoxicity), resulting in a provisional MRL of 0.0009 mg/kg/day ($9x10^{-4}$ mg/kg/day).

BC = serum (blood) chemistry; Bd wt or BW = body weight; CEL = cancer effect level; (F) = feed; F = female(s); FI = food intake; GN = gross necropsy; (GO) = gavage in oil; HP = histopathology; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = muscular/skeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NX = neurotoxicity; OW = organ weight; (W) = drinking water

Figure 2-5. Levels of Significant Exposure to α-Hexachlorocyclohexane – Oral
Acute (≤14 days)

Figure 2-5. Levels of Significant Exposure to α-Hexachlorocyclohexane – Oral
Intermediate (15-364 days)

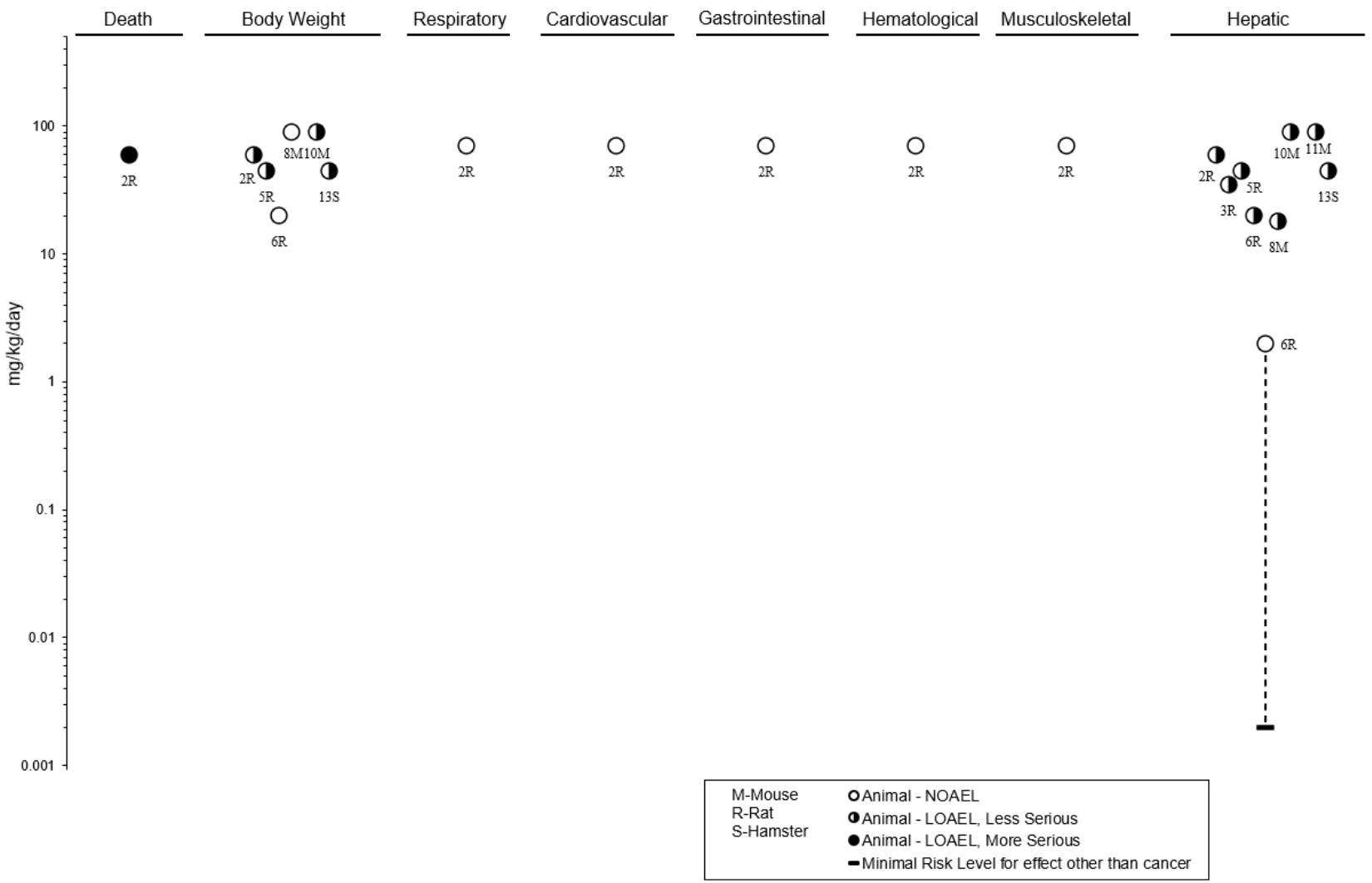


Figure 2-5. Levels of Significant Exposure to α-Hexachlorocyclohexane – Oral
Intermediate (15-364 days)

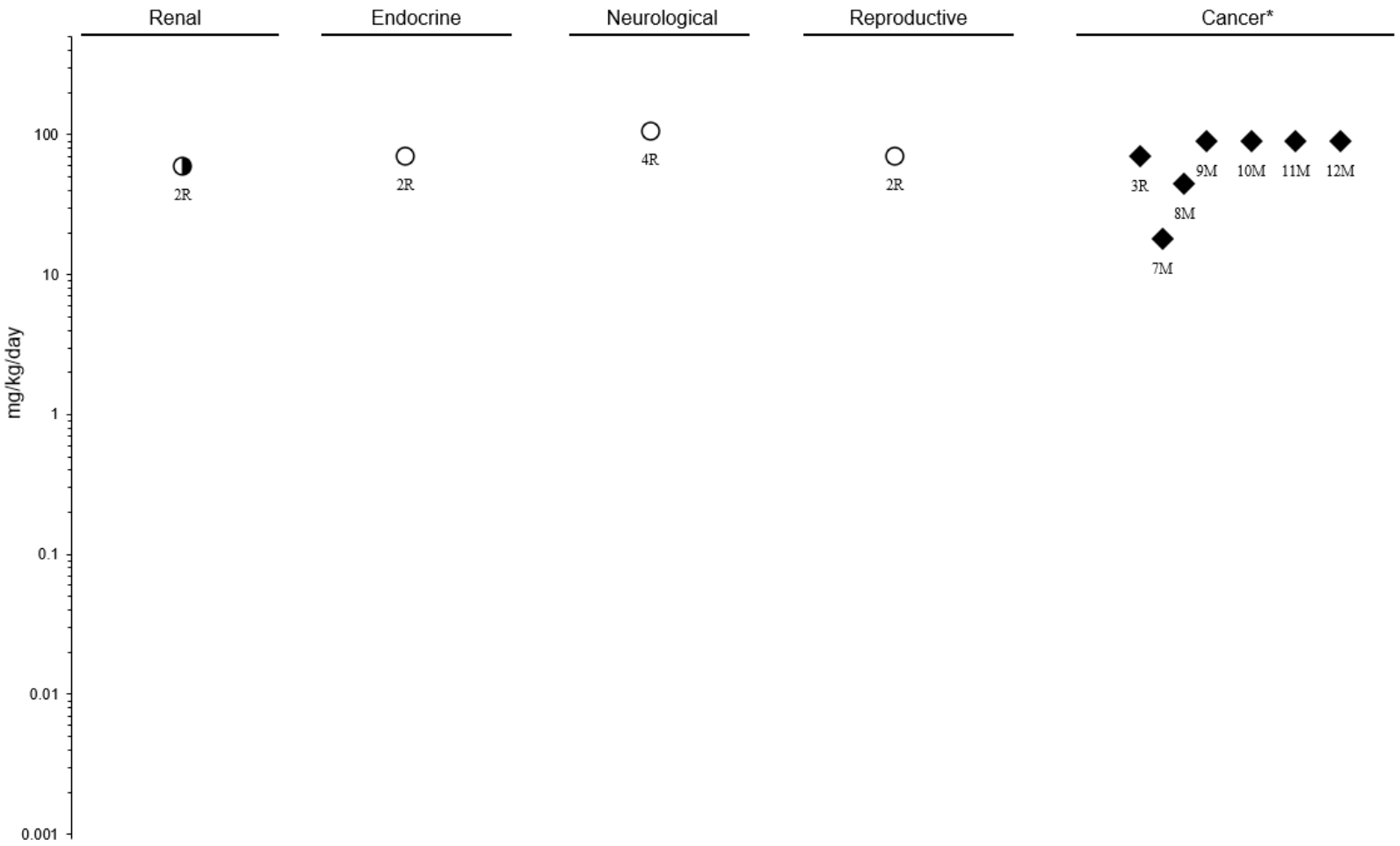


Figure 2-5. Levels of Significant Exposure to α-Hexachlorocyclohexane – Oral

Chronic (≥365 days)

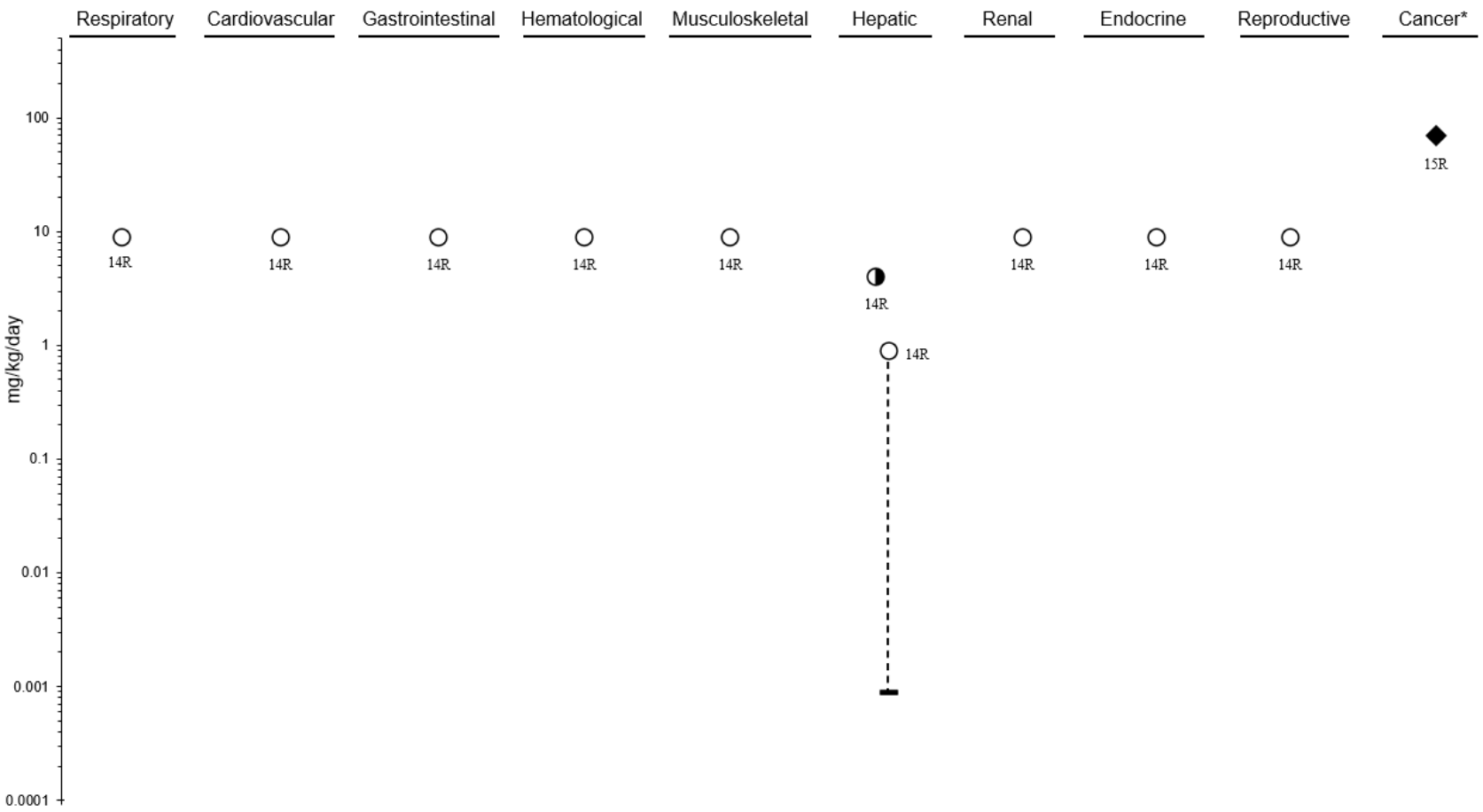


Table 2-3. Levels of Significant Exposure to β-Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
ACUTE EXPOSURE									
Srinivasan et al. 1984									
1	Rat (Wistar) 6 M	2 weeks (F)	0, 72	BW, BC, UR, HP	Renal		72		Tubular degeneration, distention of glomeruli, swelling of tubular epithelia, 22% increase in kidney weight, glucosuria, increased urinary excretion of urea and creatinine, decreased excretion of protein
Van Velsen et al. 1986									
2	Rat (Wistar) 10 F, 10 M	2 weeks (F)	0, 8, 38	CS	Neuro	8[b]		38	Ataxia, hypoactivity
Cornacoff et al. 1988									
3	Mouse (B6C3F1) 6 F	1 weeks (F)	0, 20, 60, 200	CS	Death			200	Lateral recumbency leading to humane sacrifice in 80% of mice
					Neuro	20	60		Ataxia resolving within a few days
INTERMEDIATE EXPOSURE									
Fitzhugh et al. 1950									
4	Rat (Wistar) 10 F, 10 M	10 weeks (F)	Males: 0, 60 Females: 0, 70	LE, BW, FI, GN, OW, HP	Death			70 F 60 M	All animals died by 10 weeks of exposure; mean age at death was 4.4 weeks
					Resp	70 F 60 M			
					Cardio	70 F 60 M			
					Gastro	70 F 60 M			

Table 2-3. Levels of Significant Exposure to β-Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Hemato	70 F 60 M			
					Musc/skel	70 F 60 M			
					Hepatic			70 F 60 M	Moderate to marked liver damage including fatty degeneration and focal necrosis
					Renal		70 F 60 M		Very slight nephritis; basal vacuolation
					Endo	70 F 60 M			
					Repro	70 F 60 M			
Fitzhugh et al. 1950									
5	Rat (Wistar) 10 M, 10 F	6 months (F)	M: 0, 7 F: 0, 9	BW	Bd wt	7 M	9 F		11% decrease in body weight gain among females
Ito et al. 1975									
6	Rat (W strain) 18–24 M	48 weeks (F)	0, 35, 70	BW, OW, HP	Hepatic		35		Hepatocellular hypertrophy
Muller et al. 1981									
7	Rat (Wistar) 15 M	30 days (F)	0, 66.3, 270.6	NX	Neuro		66.3		Reduced tail nerve conduction velocity
Srinivasan et al. 1991									
8	Rat (Wistar) 6 F	GDs 0–21 (F)	0, 5, 20, 40, 80	DX	Death			80	None of the dams survived 3 weeks of treatment
					Develop	5		20	48% pup mortality before PND 5

Table 2-3. Levels of Significant Exposure to β-Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Srinivasan et al. 1991									
9	Rat (Wistar) 6 F	GDs 0–21 and LDs 1–28 or LDs 1–28 only (F)	0, 5, 25	RX, DX	Develop		5	25	LOAEL: increased liver weight in pups at 28 days of age Serious LOAEL: 100% mortality before PND 5 in pups exposed *in utero*
Van Velsen et al. 1986									
10	Rat (Wistar) 10 F, 10 M	13 weeks (F)	Males: 0, 0.18, 0.9, 4.5, 22.5 Females: 0, 0.2, 1.0, 5, 25	CS, BW FI, HE, BC, BI, OW, HP	Death			22.5 M 25 F	50% of animals were moribund and sacrificed humanely
					Bd wt	5 F 4.5 M	25 F 22.5 M		≥10% decrease in body weight
					Hemato	5 F 4.5 M	25 F 22.5 M		Decreased red blood cells, leukocytes, and hemoglobin concentrations
					Hepatic	ND M 1 F	0.18[c] M 5 F		Hyalinization of centrilobular cells in males; increased mitoses in females
					Renal	4.5 M	22.5 M		Renal medullary calcinosis
					Endo	5 F 4.5 M	25 F 22.5 M		Adrenal cortical hypertrophy
					Immuno	5 F 4.5 M	25 F 22.5 M		Depletion of splenic lymphoid tissue; thymic cortical atrophy
					Repro	5 F 4.5 M		25 F 22.5 M	Atrophy of testes and ovaries

Table 2-3. Levels of Significant Exposure to β-Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Cornacoff et al. 1988									
11	Mouse (B6C3F1) 6 F	30 days (F)	0, 20, 60	CS, BW, HE, OW, HP, NX	Bd wt	60			
					Immuno	20	60		Decreased lymphoproliferative responses to T-cell mitogens, decreased natural killer cell activity
					Repro	60			No changes in ovarian or uterine histology
Hanada et al. 1973									
12	Mouse (dd) 10–11 M, 10–11 F	32 weeks (F)	Males: 0, 20, 50, 100 Females: 0, 20, 60, 100	GN, HP	Hepatic	20	60 F 50 M		Nuclear irregularities in foci of enlarged hepatocytes
Ito et al. 1973									
13	Mouse (dd) 20–40 M	24 weeks (F)	0, 18, 45, 90	BW, OW, HP	Bd wt	90			
					Hepatic		18		18% increase in relative liver weight with histopathology changes (liver cell hypertrophy) at higher doses
Thorpe and Walker 1973									
14	Mouse CF1 30 M, 30 F	3 months (F)	0, 34	LE	Death			34	12% of males and 25% of females died during the first 3 months of a chronic study
CHRONIC EXPOSURE									
Fitzhugh et al. 1950									
15	Rat (Wistar) 10 F, 10 M	107 weeks (F)	M: 0, 0.7, 7 F: 0, 0.9, 9	LE, BW, FI, GN, OW, HP	Resp	7 M 9 F			
					Cardio	7 M 9 F			

Table 2-3. Levels of Significant Exposure to β-Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Gastro	7 M 9 F			
					Hemato	7 M 9 F			
					Musc/skel	7 M 9 F			
					Hepatic		0.7 M 0.9 F		34% increase in relative liver weight; very slight histopathology changes
					Renal	7 M 9 F			
					Endo	7 M 9 F			
					Repro	0.7 M 9 F		7 M	Slight testicular atrophy
Thorpe and Walker 1973									
16	Mouse (CF1) 30 M, 30 F	104 weeks (F)	0, 34	CS, GN, HP	Cancer			34	CEL: liver tumors in males; unspecified tumors in females.

[a]The number corresponds to entries in Figure 2-6; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-6. Where such differences exist, only the levels of effect for the most sensitive sex are presented.
[b]Used to derive a provisional acute-duration oral minimal risk level (MRL). The NOAEL of 8 mg/kg/day was divided by an uncertainty factor of 100 (10 for human variability and 10 for animal to human extrapolation) resulting in a provisional MRL of 0.08 mg/kg/day ($8x10^{-2}$ mg/kg/day).
[c]Used to derive an intermediate-duration oral MRL. The LOAEL of 0.18 mg/kg/day was divided by an uncertainty factor of 300 (10 for human variability, 10 for animal to human extrapolation, and 3 for use of a minimal LOAEL) resulting in a provisional MRL of 0.0006 mg/kg/day ($6x10^{-4}$ mg/kg/day).

Bd wt or BW = body weight; CEL = cancer effect level; CS = clinical signs; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; (F) = feed; F = female(s); FI = food intake; GD = gestation day; GN = gross necropsy; Hemato = hematological; HP = histopathology; Immuno = immunological; LD = lactation day; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = muscular/skeletal; ND = not determined; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NX = neurotoxicity; OW = organ weight; PND = postnatal day; Repro = reproductive; RX = reproductive toxicity; UR = urinalysis

Figure 2-6. Levels of Significant Exposure to β-Hexachlorocyclohexane – Oral
Acute (≤14 days)

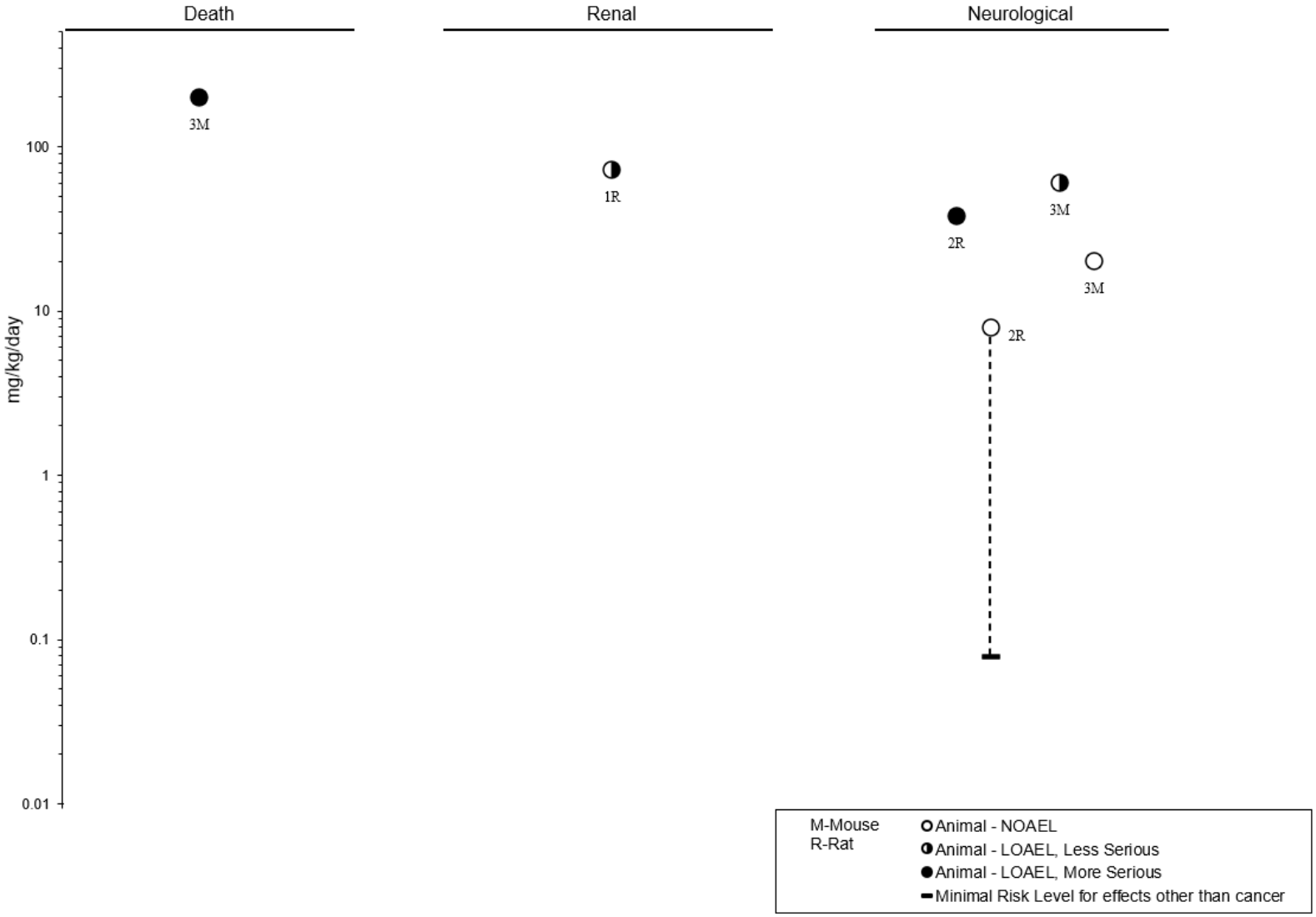


Figure 2-6. Levels of Significant Exposure to β-Hexachlorocyclohexane – Oral
Intermediate (15-364 days)

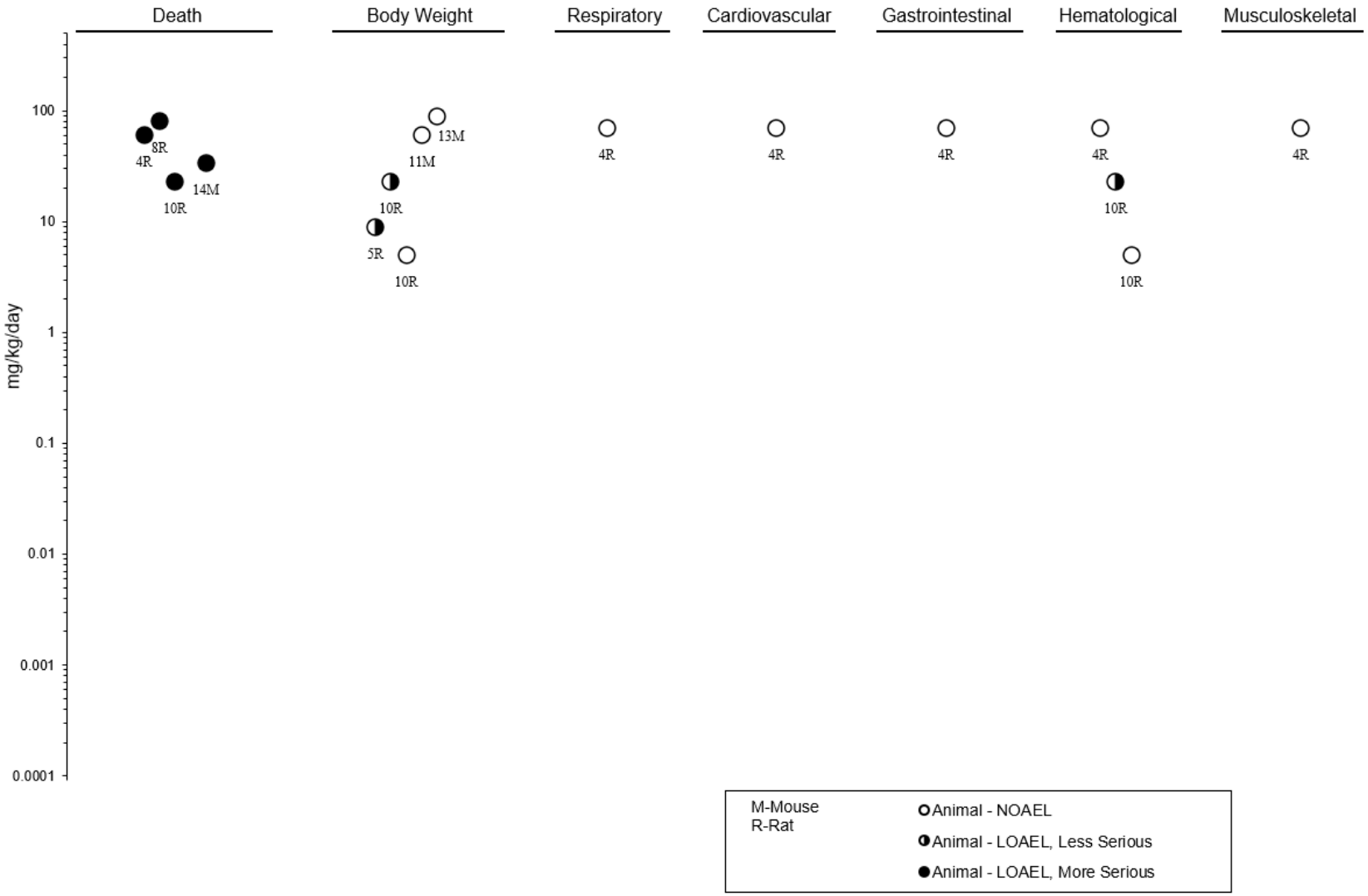


Figure 2-6. Levels of Significant Exposure to β-Hexachlorocyclohexane – Oral
Intermediate (15-364 days)

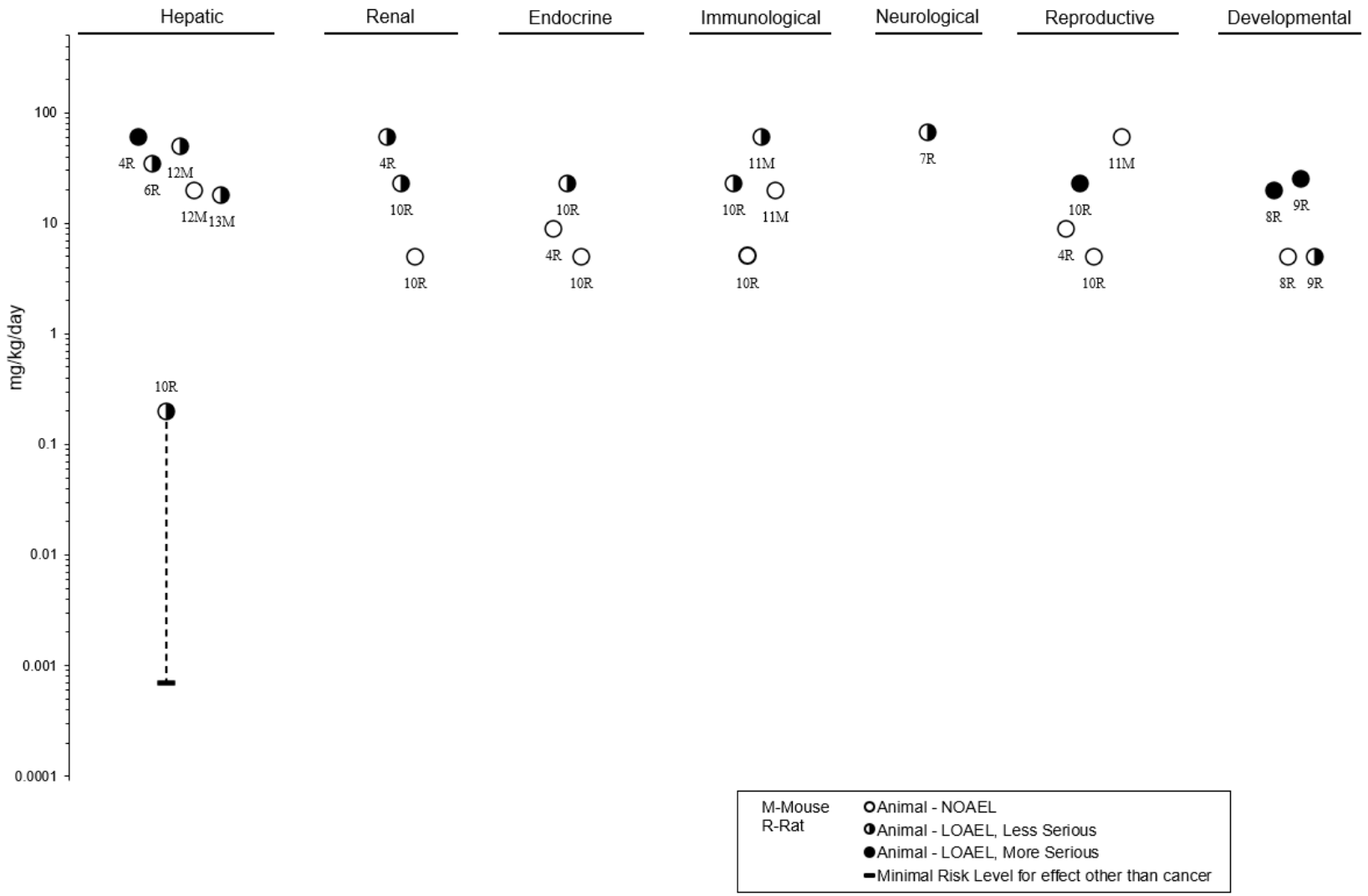


Figure 2-6. Levels of Significant Exposure to β-Hexachlorocyclohexane – Oral

Chronic (≥365 days)

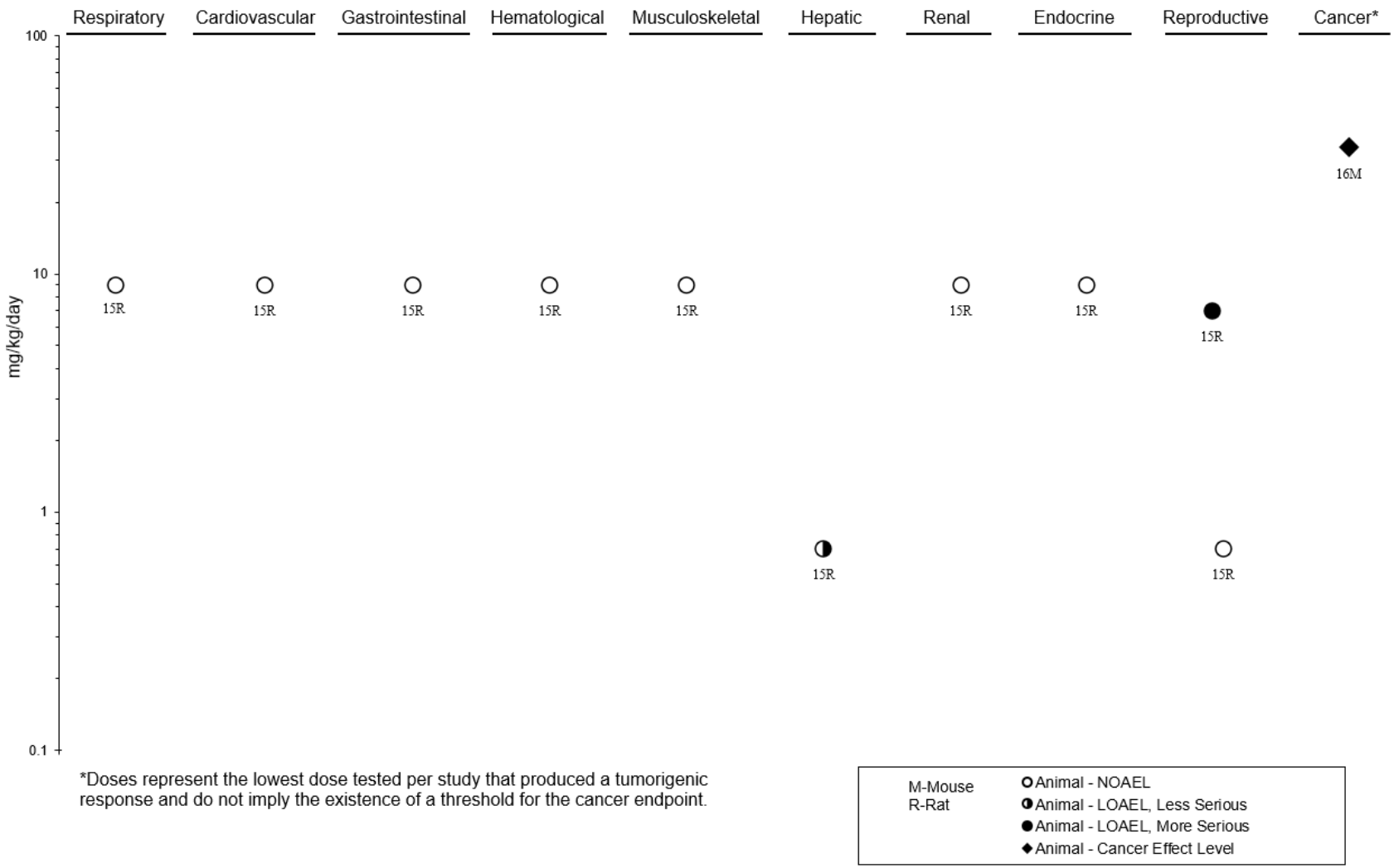


Table 2-4. Levels of Significant Exposure to γ-Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
ACUTE EXPOSURE									
Ali and Shakoori 1998									
1	Rat (Sprague-Dawley) 3–5, NS	2 days (F)	0, 30	HP	Hepatic		30		Reduced number of cells per field; increased cell, nucleus, and nucleolus size; slight cellular disorganization
Attia et al. 1991									
2	Rat (Sprague-Dawley) 9 M	6 days (GO)	0, 3	BI	Neuro		3		Increased pineal N-acetyl-transferase, decreased serotonin levels
Dalsenter et al. 1996									
3	Rat (Wistar) 15 M	1–5 days	0, 6, 30	RX	Repro		6		Decreased number of spermatids per epididymis
Dalsenter et al. 1997a									
4	Rat (Wistar) 15 M	GDs 15 once (GO)	0, 30	DX	Develop		30		Reduced serum testosterone in adult offspring
Dalsenter et al. 1997b									
5	Rat (BOR) 9 F	LD 9 or 14 once (GO)	0, 6	CS, BI, OW, HP, NX, RX	Develop		6		In male pups, reduced relative testicular and epididymis weight (~10%), spermatid and sperm counts (~8–10%), testosterone levels (~30–50%), Leydig cell numbers, and spermatogenesis at maturity, with no effect on fertility

Table 2-4. Levels of Significant Exposure to γ-Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Dalsenter et al. 1997b									
6	Rat (BOR) 9 F	LDs 9–14 (GO)	0, 1	CS, BI, OW, HP, NX, RX	Develop		1[b]		In male pups, reduced relative testicular and epididymis weight (~10%), spermatid and sperm counts (~10%), and testosterone levels (30–50%) at maturity, with no effect on fertility
EPA 1999a									
7	Rat (CD) 10 M, 10 F	Once (G)	0, 6, 20, 60		Neuro	6 F 20 M	20 F	60 M	LOAEL: decreased motor activity and grooming behavior, increased forelimb grip strength in females Serious LOAEL: tremors and convulsions in one male
Gaines 1960									
8	Rat (Sherman) 89 M, 69 F	Once (GO)	NS	LE, CS	Death			91 F 88 M	LD_{50} LD_{50}
Gilbert 1995									
9	Rat (Long-Evans) 15–16 M	10 days 3 days/week (GO)	0, 10	CS	Neuro			10	Myoclonic jerks and clonic seizures
Gilbert and Mack 1995									
10	Rat (Long-Evans) 14 M	once (GO)	0, 5, 10, 20	CS	Neuro			5	Myoclonic jerks and single clonic seizure in naive animals

Table 2-4. Levels of Significant Exposure to γ-Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Hfaiedh et al. 2012									
11	Rat (Wistar) 6 M	3 days (GO)	0, 5	BC, BI, HP	Hepatic		5		Fatty degeneration, vacuolation, and necrosis of the liver
Johri et al. 2008									
12	Rat (Wistar) 10 M	Once (GO)	0, 30	CS	Neuro			30	Convulsions in 5/10 animals
Joy et al. 1982									
13	Rat (Sprague-Dawley) 7–14 M	4 days (GO)	0, 1, 3, 10	CS, BW, BC, OW, HP, NX	Neuro	1	3	10	LOAEL: increased kindling acquisition Serious LOAEL: seizures
Khera et al. 1979									
14	Rat (Wistar) 20 F	GDs 6–15 (GO)	0, 6.25, 12.5, 25	DX	Develop	25			No teratogenic effects
Llorens et al. 1989									
15	Rat (Wistar) 9 M	Once (GO)	0, 10, 15, 30	CS, NX	Neuro		10		Increased spontaneous motor behavior
Llorens et al. 1990									
16	Rat (Wistar) 9 M	Once (GO)	0, 20	CS, NX	Neuro		20		Increased anxiety
Martinez and Martinez-Conde 1995									
17	Rat (Wistar) 8 M, 8 F	Once (GO)	0, 60	CS, NX	Neuro			60	Convulsions
Martinez et al. 1991									
18	Rat (Wistar) 7 M	Once (GO)	0, 60	LE, CS, NX	Death			60	1/7 died
					Neuro			60	Tonic-clonic seizures

Table 2-4. Levels of Significant Exposure to γ-Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Mediratta et al. 2008									
19	Rat (Wistar) 8 M	14 days (NS)	0, 10	IX	Immuno		10		Reduced delayed-type hypersensitivity (43% decrease in foot pad thickness)
Palmer et al. 1978									
20	Rat (CFY) 20 F	GDs 6–16 (G)	0, 5, 10, 20	DX	Develop	20			
Parmar et al. 2003									
21	Rat (Wistar) 10 M	Once (GO)	0, 35	CS	Neuro			35	Convulsions in 4/10 rats
Parmar et al. 2003									
22	Rat (Wistar) 10 M	5 days (GO)	0, 2.5, 5, 10, 15	CS, BW, BI, OW	Bd wt	15			
Rivera et al. 1991									
23	Rat (Wistar) 4 M, 4 F	Once (GO)	0, 20	CS, BI, NX	Develop		20		Regional changes in brain noradrenaline, serotonin, and dopamine metabolite levels in suckling rats
Rivera et al. 1998									
24	Rat (Wistar) NS M, F	PND 15 once (G)	0, 20	DX	Develop		20		Altered acquisition of a passive avoidance task, decreased motor activity, altered neurotransmitter levels in brain
Rivera et al. 1998									
25	Rat (Wistar) NS M, F	PNDs 8–14 (G)	0, 10	DX	Develop		10		Altered acquisition of a passive avoidance task, increased motor activity, altered neurotransmitter levels in brain

Table 2-4. Levels of Significant Exposure to γ-Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Serrano et al. 1990									
26	Rat (Wistar) 5 M, 5 F	PNDs 8–10 (GO)	0, 5, 10, 15, 20	BW, BI	Develop			5	Decreased myelin in developing brain
Sharma and Singh 2010									
27	Rat (Wistar) 6 M	14 days (GO)	0, 30	RX	Repro			30	Markedly decreased epididymis (27%) and testes (68%) weights; substantial and persistent reductions (≥85% less than controls) in sperm head count, motility, and percent live sperm; marked and persistent increases (4-fold) in percent abnormal sperm
Singh and Sharma 2011									
28	Rat (Wistar) NS M	1 day (G)	0, 60	BI, HP	Hepatic			60	Marked centrilobular necrosis
Sinha and Shukla 2003									
29	Rat (Druckrey) 8 M	3 days (GO)	0, 8.8	BW, OW	Bd wt	8.8			
Srinivasan et al. 1984									
30	Rat (Wistar) 6 M	2 weeks (F)	0, 72	BW, BC, UR, OW, HP	Renal		72		10% increase in kidney weight, distention of glomeruli, swelling of tubular epithelia, glucosuria, increased excretion of urea and creatinine, decreased excretion of protein

Table 2-4. Levels of Significant Exposure to γ-Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Sumida et al. 2007									
31	Rat (Fischer-344) 4 M	1, 3, 7, or 14 days (GO)	0, 1, 10	BW, BC, OW	Bd wt	10			
					Hepatic	10			
Tusell et al. 1988									
32	Rat (Wistar) 4 M	3–12 days	0, 5, 12, 20	LE, CS	Death			20	2/18 died on 3rd day
					Neuro	5		12	Convulsions after 3 days
Uphouse and Williams 1989									
33	Rat (CDF-F344) 8–11 F	Once (G)	0, 12.5, 25, 33, 50	RX	Repro		25		Increased length of estrous cycle
Woolley and Griffith 1989									
34	Rat (Sprague-Dawley) 7 M	Once (GO)	0, 30, 40, 50	CS, NX	Neuro			30	Seizures
Di Consiglio et al. 2009									
35	Mouse (CD-1) 2–10 F	GDs 9–16 (GO)	0, 25	LE, CS, BW, BI, OW, HP, DX	Bd wt	25			
					Develop		25		Decreased sperm concentration (20%) and count (27%) in F1 males at PNDs 65–69

Table 2-4. Levels of Significant Exposure to γ-Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Hassoun and Stohs 1996a									
36	Mouse (C57BL/6J and DBA/2J) NS F	GD 12 once (GO)	0, 30, 45	LE, DX	Death			30	14% of dams died at 30 mg/kg and 25% died at 45 mg/kg
					Develop		30	45	LOAEL: decreased fetal, placental, and thymic weights in C57BL/6J mice Serious LOAEL: increased early resorptions in C57BL/6J mice
Hong and Boorman 1993									
37	Mouse (B6C3F1) 7 M	3 days (GO)	0, 10, 20, 40	CS, BW, HE, OW HP	Bd wt	40			
					Hemato		20		Transient reductions in marrow progenitor cell numbers
					Immuno	10	20	40	LOAEL: decreased thymus weights Serious LOAEL: atrophy of thymic cortex
Hong and Boorman 1993									
38	Mouse (B6C3F1) 7 M	10 days (GO)	0, 10, 20	CS, BW, HE, OW HP	Bd wt	20			
					Hemato		10		Transient decrease in marrow progenitor cell numbers
					Immuno		10		Decreased relative thymus and spleen weights
La Sala et al. 2009									
39	Mouse (CD-1) NS F	3 days (GO)	0, 15, 30	DX	Develop		15		Decreased numbers of primordial germ cells in male and female offspring
Liu and Morgan 1986									
40	Mouse (DBA/2) 6 F	10 days	20	LE, CS, BC	Death			20	6/6 died

Table 2-4. Levels of Significant Exposure to γ-Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Maranghi et al. 2007									
41	Mouse (CD) 12 F	GDs 9–16 (GO)	0, 15	BW, FI, BI, OW, HP, DX	Bd wt	15			
					Repro	15			
					Develop		15		Early vaginal patency; increased absolute (17%) and relative (13%) uterine weight at PND 22; decreased oocyte diameter (21%) in primary follicles at PND 60 in F1 females
Scascitelli and Pacchierotti 2003									
42	Mouse (CD-1) 16–29 F	3 days (GO)	0, 15, 25	RX	Repro	15	25		Increase in degenerating two-cell embryos following preovulatory exposure
Sinha and Shukla 2003									
43	Mouse Swiss 8 M	3 days (GO)	0, 5.9	BW, OW	Bd wt	5.9			
Traina et al. 2003									
44	Mouse (CD-1) 10–24 F	GDs 9–16 (GO)	0, 15, 25	BW, DX	Bd wt	25			
					Develop		15		14% decrease in sperm count in F1 offspring with more severe effects observed at higher dose
Palmer et al. 1978									
45	Rabbit (New Zealand) 13 F	GDs 6–18 (G)	0, 5, 10, 20	DX	Develop	20			

Table 2-4. Levels of Significant Exposure to γ-Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
INTERMEDIATE EXPOSURE									
Ahmed et al. 2008									
46	Rat (Wistar) 10 M	4 weeks, 7 days/week (GO)	0, 30	CS, BW, FI, BC	Bd wt	30			
Ali and Shakoori 1998									
47	Rat (Sprague-Dawley) 3–5 NS	15 days (F)	0, 18	HP	Hepatic		18		Reduced number of cells per field; increased cell, nucleus, and nucleolus size; vacuoles in the cytoplasm and granulation; apparent fatty degeneration
Amyes 1990									
48	Rat (Wistar) 15 M, 15 F	Up to 52 weeks (F)	Males: 0, 0.07, 0.7, 7, 28 Females: 0, 0.08, 0.8, 8, 32	LE, CS, BW, FI, WI, HE, BC, BI, UR, GN, OW, HP, NX	Death			32 F	Statistically significant decreased survival
					Bd wt	32F 28 M			
					Hemato	32F 28 M			
					Hepatic	0.8 F 0.7 M	8 F 7 M		Periacinar hepatocytic hypertrophy
					Renal	32 F	0.07 M		Hyaline droplets, interstitial chronic nephritis, and regeneration in proximal tubules
					Neuro			32 F	Convulsions in 11/55 females

Table 2-4. Levels of Significant Exposure to γ-Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Anand et al. 1995									
49	Rat (albino) NS M	6 weeks (G)	0, 3	BW, BC, OF	Cardio		3		Tachycardia (~30% increase in heart rate); increased blood pressure plasma calcium levels, and myocardial calcium influx; decreased Ca, K-ATPase activity; ECG changes
Andrews and Gray 1990									
50	Rat (Long-Evans) NS M	10 weeks 7 days/week (G)	0, 10, 20	BW, OW, BC	Bd wt	20			
					Renal		10		Increased kidney weight; hyaline droplet accumulation and tubular regeneration
					Musc/skel	10	20		Decreased femur medullary area
Arisi et al. 1994									
51	Rat (Wistar) 4–12 M	90 days (F)	0, 90	CS	Neuro			90	Tonic convulsions
Chadwick et al. 1988									
52	Rat (Fischer-344) 6–12 F	15 weeks (GO)	0, 5, 10, 20, 40	LE, BW, FI, BI, OW	Death			20	2/12 died at 20 mg/kg/day; 7/12 died at 40 mg/kg/day
					Repro	5	10		Delayed vaginal opening, disrupted ovarian cycling
Desi 1974									
53	Rat (Wistar) 8–10 NS	40 days (F)	0, 2.5, 5, 10, 50	NX, OW, OF, HP	Hepatic	50			
					Neuro		2.5		Significantly altered Skinner box behavior

Table 2-4. Levels of Significant Exposure to γ-Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Dewan et al. 1980									
54	Rat (Charles Foster) 5 M, 5 F	35 days	0, 6.25, 25	IX	Immuno		6.25		Immunosuppression (decreased antibody titers)
EPA 1991a									
55	Rat (CD) 30 M, 30 F	2 generations; 70 days prior to mating until sacrifice	0, 0.09, 1.7, 13.1	CS, BW, FI, HP, RX, DX	Bd Wt	1.7 F 13.1 M	13.1 F		Decreased body weight gain during gestation in F0 females
					Hepatic	0.09 M 13.1 F	1.7 M		In F1 males: hepatocellular hypertrophy
					Renal	0.09 M 13.1 F	1.7 M		In F0 and F1 males: Increased kidney weights; nephritis, tubular cell regeneration, hyaline droplets, tubular necrosis
					Repro	13.1			
					Develop		13.1		Reduced F1 and F2 pup weight and viability; delayed tooth eruption and hair growth in F2
EPA 1999b									
56	Rat (CD) 10 M, 10 F	13 weeks (F)	Males: 0, 1.4, 7.1, 28.1 Females: 0, 1.6, 7.9, 30.2	NX	Death			30.2 F	3/10 females died during the study
					Neuro	7.1 M 7.9 F	28.1 M 30.2 F		Increased rearing, walking on tiptoes, hypersensitivity to touch, and hunched posture

Table 2-4. Levels of Significant Exposure to γ-Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
EPA 1999c									
57	Rat (Wistar) 10 M, 10 F	GD 6 to LD 10 (F)	Gestation: 0.8–0.9, 4.2–4.6, 8.0–10.5, Lactation:1.2–1.7, 5.6–8.3, 13.7–19.1	DX	Develop	1.2		5.6	Up to 18% reduction in pup body weight and 24% lower body weight gain during lactation
Fatih Fidan et al. 2008									
58	Rat (Sprague-Dawley) 10 M	30 days (GO)	0, 10, 20, 40	BC, BI, HP	Hepatic	10		20	Megalocytosis; vacuolar degeneration; severe venous and sinusoidal congestion; and lymphocytic infiltration
					Renal	10		20	Severe kidney congestion, medullary and cortical hemorrhage, and degeneration and vacuolation of proximal convoluted tubules
Fitzhugh et al. 1950									
59	Rat (Wistar) 10 F, 10 M	10 months (F)	Males: 0, 30, 60, 120 Females: 0, 30, 70, 140	LE, BW	Death			60 M 70 F	Mean age at death was 39.7 weeks versus 58.3 weeks in controls
					Bd wt	60 M 70 F	120 M 140 F		13–17% decrease in body weight gain at 6 months
					Resp	120 M 140 F			
					Cardio	120 M 140 F			
					Gastro	120 M 140 F			

Table 2-4. Levels of Significant Exposure to γ-Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Hemato	120 M 140 F			
					Musc/skel	120 M 140 F			
					Hepatic		60 M 70 F		Slight microscopic damage
					Renal		60 M 70 F		Very slight microscopic damage
					Neuro			60 M 70 F	Convulsions
					Endo	120 M 140 F			
					Repro	120 M 140 F			
Gilbert 1995									
60	Rat (Long-Evans) 15–16 M	30 days (GO)	0, 10	CS	Neuro			10	Myoclonic jerks and clonic seizures
Hfaiedh et al. 2011									
61	Rat (Wistar) 6 M	30 days (W)	0, 50	BC, BI, OW, HP, RX	Endocr		50		85% increase in T4, 74% decrease in TSH
					Repro			50	Decreased testes (52%), epididymides (42%), prostate gland (50%), and seminal vesicles (5%) weights; 56% reduced sperm count; 37% reduced sperm motility; 74% decrease in FSH
Ito et al. 1975									
62	Rat (W strain) 18–24 M	48 weeks (F)	0, 35	BW, OW, HP	Hepatic		35		Hepatocellular hypertrophy

Table 2-4. Levels of Significant Exposure to γ-Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Johri et al. 2007									
63	Rat (Wistar) 13–14 F	GDs 5–21 (GO)	0, 0.0625, 0.125, 0.25	DX, BI	Develop	0.125	0.25		Persistent hyperactivity
Johri et al. 2008									
64	Rat (Wistar) 13 F	GDs 5–21 and PND 45 (GO)	0, 0.25 (prenatal) and 30 (postnatal)	CS, BI	Develop			30	Convulsions in 8/10 animals
Koner et al. 1998									
65	Rat (Wistar) 8–10 M	8 weeks (F)	0, 3.6, 7.0	IX	Immuno		3.6		Reduced serum antibody response to SRBC
Martinez and Martinez-Conde 1995									
66	Rat (Wistar) 8 M, 8 F	30 days, every 3 days (GO)	0, 6	CS, NX	Neuro		6		Decreased brain dopamine levels
Matsuura et al. 2005									
67	Rat (Crj:CD [SD] IGS) 24 M, 24 F	~10 weeks (2-generation ; premating to PND 21) (F)	Males, F0: 0, 0.56, 3.4, 17.2 Males, F1: 0.74, 4.5, 23.3 Females, F0: 0, 0.88, 5.2, 26.1 Females, F1: 0.95, 5.6, 28.0	LE, CS, BW, FI, BC, BI, GN, OW, HP, RX, DX, NX	Death			26.1 F	2 F0 females died
					Bd wt	26.1 F 17.2 M			
					Hepatic	0.88 F 0.56 M	5.2 F 3.4 M		Hepatocellular hypertrophy in F0 and F1 male and female parents
					Renal	26.1 F	0.56 M		Basophilic tubules and hyaline droplets in the proximal tubules
					Endocr	5.2 F 3.4 M	26.1 F 17.2 M		Decreased absolute and relative pituitary weights in F0 and F1 females; altered serum thyroid hormone levels; thyroid follicular cell hypertrophy in F0 females and F1 males

Table 2-4. Levels of Significant Exposure to γ-Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Neuro			28 F	Convulsions in two F1 females
					Repro	26.1 F 17.2 M			
					Develop	0.95	5.6	26.1	LOAEL: 10% decrease in F2 female offspring body weight at PND 4 Serious LOAEL: 49% decrease in F2 offspring viability (PNDs 0–4); 8–29% decreases in male and female F1 and F2 offspring weights on PNDs 0, 4, and 21; delayed sexual maturation (preputial separation in males and vaginal opening in females) in F1 generation
Mediratta et al. 2008									
68	Rat (Wistar) 8 M	21 days (NS)	0, 10	BC, IX	Immuno		10		Decreased anti-SRBC antibody titer (32%)
Mudawal et al. 2018									
69	Rat (Wistar) 6 M	3 weeks 7 days/week (NS)	0, 2.5	BI, NX, DX	Neuro		2.5		Decreased conditioned avoidance, alternations, and locomotor activity; ultrastructural changes in the hippocampus and substantia nigra in adult animals
Muller et al. 1981									
70	Rat (Wistar) 15 M	30 days (F)	0, 1.3, 12.3, 25.4	NX	Neuro	12.3	25.4		Reduced tail nerve conduction velocity

Table 2-4. Levels of Significant Exposure to γ-Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Parmar et al. 2003									
71	Rat (Wistar) 10 M	15 or 21 days (GO)	0, 2.5	CS, BW, BI, OW	Bd wt	2.5			
Prasad et al. 2016									
72	Rat (Wistar) 6 M	15, 30, or 45 days (GO)	0, 20	BC, BI, GN, HP	Renal			20	Severe corticomedullary and glomerular congestion, intertubular hemorrhage, severe tubular degeneration, desquamation of tubular epithelium, cystic dilatation, mononuclear cell infiltrate, necrosis, and atrophic glomeruli
Sahaya et al. 2007									
73	Rat (Wistar) 10 M	6 weeks, 7 days/week (NS)	0, 15	BI, NX	Neuro		15		Impaired neurocognition (decreased step-down latency in passive avoidance test and prolonged transfer latency in elevated plus maze)
Saradha and Mathur 2006									
74	Rat (Wistar) 4 M	45 days (GO)	0, 1, 5, 50	BW, OW, RX	Repro	1	5	50	LOAEL: decreased sperm count (~27%) and motility (~25%) Serious LOAEL: decreased sperm count (~40%), motility (~40%), and viability (~15%); decreased epididymal weight (~10%)

Table 2-4. Levels of Significant Exposure to γ-Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Sauviat et al. 2005									
75	Rat (Sprague-Dawley) NS F	~13 weeks (W)	0, 0.000076, 0.00015, 0.00030	GN, OW, HP	Develop	0.000076[c]	0.00015	0.0003	LOAEL: altered ventricular electrophysiology Serious LOAEL: 21% decrease in pup body weight; altered heart morphometry and electrophysiology; cardiac histopathology (hypertrophy in left ventricular area, unorganized collagen bundles and layers, fibroblast destruction)
Sharma and Singh 2010									
76	Rat (Wistar) 6 M	28 days (GO)	0, 30	RX	Repro			30	Decreased cauda epididymis (32%) and testes (70%) weights; ≥89% decreases in sperm head count, motility, and percent live sperm; 4-fold increase in percent abnormal sperm.
Srinivasan et al. 1991									
77	Rat (Wistar) 6 F	GDs 0–21 and LDs 1–28 or LDs 1–28 (F)	0, 25	DX	Develop		25		Increased pup relative liver weights
Srivastava et al. 2019									
78	Rat (Wistar) 25 F	GDs 5–21 (GO)	0, 0.25	DX	Develop			0.25	Ultrastructural changes in the brain (moderately distorted mitochondria and demyelinated neurons)

Table 2-4. Levels of Significant Exposure to γ-Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Srivastava et al. 2019									
79	Rat (Wistar) 6 M	21 days (GO)	0, 2.5	NX	Neuro			2.5	Reduced locomotor activity and spatial memory; ultrastructural changes in the hippocampus and substantia nigra (swollen mitochondria with disintegrated cristae, shortened fuzzy synapse, disintegrated myelin layer, and autophagosomes)
Sumida et al. 2007									
80	Rat (Fischer-344) 4 M	28 days (GO)	0, 1, 10	BW, BC, OW, HP	Bd wt Hepatic	10 10			
Suter 1983									
81	Rat (Wistar) 15 M, 15 F	12 weeks (F)	0, 0.02, 0.08, 0.4, 2.0, 10	LE, CS, BW, FI, HE, UR, OW, HP	Hemato Hepatic Renal	10 0.4 0.4 F	 2 0.4 M 2 F		 Centrilobular hypertrophy Basophilic proximal tubules; proximal tubular distention hyaline droplet formation; and minimal to moderate interstitial nephritis in males; slight epithelial cell necrosis in proximal convoluted tubules in both sexes

Table 2-4. Levels of Significant Exposure to γ-Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Vijaya Padma et al. 2011									
82	Rat (Wistar) 6 F	30 days (GO)	0, 100	BC, BI, HP	Hepatic			100	"Extensive" liver injuries consisting of vacuolar degeneration of hepatocytes and "massive" degradation of the central vein
					Renal		100		Glomerular degeneration and shrinkage; degeneration of proximal and distal tubules
Vijaya Padma et al. 2013									
83	Rat (Wistar) 6 M	30 days (GO)	0, 100	BC, BI, OW, HP	Cardio		100		Histopathology changes (inflammatory cells and separated muscle fibers)
Yang et al. 2014; Zhang et al. 2016									
84	Rat (Sprague-Dawley) 7–9 F	4 weeks, 7 days/week (GO)	0, 4, 8	BW, BC, OW, HP	Bd wt	8			
					Repro	4	8		Low columnar endometrial glandular epithelial cells in the uterus
Yuksel et al. 2009									
85	Rat (Sprague-Dawley) 10 M	30 days (GO)	0, 10, 20, 40	CS, BC, GN, OW, HP, RX	Death			20	1/10 rats died at 20 mg/kg/day and 1/10 died at 40 mg/kg/day
Banerjee et al. 1996									
86	Mouse (Hissar) NS M	3–12 weeks	0, 1.8, 5.4, 9	IX	Immuno	1.8	5.4		Immunosuppression (decreased splenic plaque-forming colonies) after 6 weeks; decreased antibody titers at 9 mg/kg/day

Table 2-4. Levels of Significant Exposure to γ-Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Hanada et al. 1973									
87	Mouse (dd) 10–11 M, 10–11 F	32 weeks	Males: 0, 18, 54, 108 Females: 0, 20, 60, 120	BC, GN, HP	Cancer			120	CEL: hepatoma
Ito et al. 1973									
88	Mouse (dd) 20–40 M	24 weeks (F)	0, 18, 45, 90	BW, OW, HP	Bd wt	90			
					Hepatic	45	90		Relative liver weight increase of 33% and centrilobular hypertrophy
Meera et al. 1992									
89	Mouse (Swiss albino) 6 F	24 weeks (F)	0, 0.012, 0.12, 1.2	CS, HP, IX	Immuno		0.012	1.2	LOAEL: changes in cell- and humoral-mediated immune system Serious LOAEL: histopathology changes in thymus consisting of marked decrease in cortical lymphocytes, many necrosed cells in medulla, congestion of blood vessels, and severe loss of cortex and medulla distinction
Nagda and Bhatt 2011									
90	Mouse (Swiss) 8–10 M	60 days (GO)	0, 40	BI, OW, HP	Repro			40	10% decrease testes weight; histopathology changes in testes (shrunken and distorted seminiferous tubules, sparse Leydig cells, and oligospermia)

Table 2-4. Levels of Significant Exposure to γ-Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Thorpe and Walker 1973									
91	Mouse (CF1) 30 M, 30 F	3 months (F)	0, 68	LE	Death			68	10% of males and 20% of females died in first 3 months of chronic study
Rivett et al. 1978									
92	Dog (Beagle) 1 M, 1 F	7 weeks	0.9, 2, 4, 7	CS, BW, HE, BC, UR, GN, OW, HP	Bd wt	4	7		Decreased body weight gain
Desi et al. 1978									
93	Rabbit (NS) 6 M	5–6 weeks 5 days/week (C)	0, 1.5, 3, 6, 12	LE, OF, IX	Death			12	“Numerous” deaths
Lindenau et al. 1994									
94	Rabbit (hybrid) 5 F	12 weeks 3 days/week (GO)	0, 0.8	CS, BC, BI	Repro		0.8		Reduced ovulation rate
Seiler et al. 1994									
95	Rabbit (New Zealand) 5 F	12–15 weeks 3 days/week (GO)	0, 0.8	DX, RX	Repro Develop	0.8 0.8			
Beard and Rawlings 1998									
96	Mink (NS) 8–10 F	3 generations (F)	0, 1	CS, BW, FI, GN, OW, HP, RX, DX	Repro			1	Reduced litter size in F2 females (~40% lower than controls); reduced testis size (11–13% shorter length and 34–36% lower mass) in F3 males

Table 2-4. Levels of Significant Exposure to γ-Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Beard et al. 1997									
97	Mink (NS) 10 F	12 weeks 3 weeks premating to 8 weeks postpartum (F)	0, 1	CS, BW, FI, BC, GN, OW, HP, RX, DX	Repro		1		Reduced mating receptivity and whelping rate
Beard et al. 1997									
98	Mink (NS) 15 F	17 weeks 6 weeks premating to 10 weeks postpartum (F)	0, 1	CS, BW, FI, BC, GN, OW, HP, RX, DX	Repro		1		Reduced whelping rate and increased post-implantation embryo loss
CHRONIC EXPOSURE									
Ali and Shakoori 1998									
99	Rat (Sprague-Dawley) 3–5, NS	18 months (F)	0, 9	HP	Hepatic		9		Increased cell, nucleus, and nucleolus size; extensive cytoplasmolysis; slight cytoplasmic degeneration; increasing nuclear distortion
Fitzhugh et al. 1950									
100	Rat (Wistar) 10 F, 10 M	107 weeks (F)	Males: 0, 0.4, 0.7, 4, 7, 30 Females: 0, 0.4, 0.9, 4, 9, 30	LE, BW, FI, GN, OW, HP	Resp	30			
					Cardio	30			
					Gastro	30			
					Hemato	30			
					Musc/skel	30			
					Hepatic	4	9 F 7 M		Increased relative liver weight (35%); very slight microscopic liver damage
					Renal	4	9 F 7 M		Very slight microscopic kidney damage

Table 2-4. Levels of Significant Exposure to γ-Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Endo	30			
					Repro	30			
EPA 2000a									
101	Mouse (CD-1) 50 M, 50 F	78 weeks (F)	Males: 0, 1.3, 5.2, 20.5 Females: 0, 1.8, 7.1, 26.8	LE, BW, FI, GN, OW, HP	Bd wt	20.5 M 26.8 F			
					Resp	20.5 M 26.8 F			
					Hemato	20.5 M			
					Hepatic	5.2 M 26.8 F	20.5 M		Centrilobular hepatocyte hypertrophy
					Renal	20.5 M 26.8 F			
					Endocr	20.5 M 26.8 F			
					Neuro	20.5 M 26.8 F			
					Cancer			26.8 F	CEL: bronchiolar-alveolar adenomas and carcinomas
Herbst et al. 1975; Weisse and Herbst 1977									
102	Mouse (NMRI) 50 M, 50 F	80 weeks (F)	Males: 0, 2.1, 4.1, 8.2 Females: 0, 2.0, 3.9, 7.8	BW, GN, HP	Bd wt	8.2 M 7.8 F			
					Hepatic	8.2 M 7.8 F			
NCI 1977									
103	Mouse (B6C3F1) 50 M, 50 F	80 weeks (F)	0, 13.6, 27.2	CS, BW, BI, HP	Cancer			13.6 M	CEL: hepatocellular carcinoma
Thorpe and Walker 1973									
104	Mouse (CF1) 30 M, 30 F	104 weeks (F)	0, 68	CS, GN, HP	Cancer			68	CEL: liver and other unspecified tumors in both sexes

Table 2-4. Levels of Significant Exposure to γ-Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Wolff et al. 1987									
105	Mouse (F-1 hybrid) 24–96 F	24 months (F)	0, 27.2	CS, BW, BI, HP	Cancer			27.2	CEL: hepatocellular carcinoma, lung tumors
Rivett et al. 1978									
106	Dog (Beagle) 4 M, 4 F	104 weeks (F)	0, 0.83, 1.60, 2.92	CS, BW, HE, BC, UR, GN, OW, HP, NX	Bd wt	2.92			
					Hepatic	2.92			Livers were dark but without histopathology changes
					Hemato	2.92			
					Ocular	2.92			

[a]The number corresponds to entries in Figure 2-7; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-7. Where such differences exist, only the levels of effect for the most sensitive sex are presented.
[b]Used to derive a provisional acute-duration oral minimal risk level (MRL). The LOAEL of 1 mg/kg/day was divided by an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for human variability, and 10 for animal to human extrapolation), resulting in a provisional MRL of 0.003 mg/kg/day ($3x10^{-3}$ mg/kg/day).
[c]Used to derive a provisional intermediate-duration oral MRL. The NOAEL of 0.000076 mg/kg/day was divided by an uncertainty factor of 100 (10 for human variability, and 10 for animal to human extrapolation), resulting in a provisional MRL of 0.0000008 mg/kg/day ($8x10^{-7}$ mg/kg/day).

BC = serum (blood) chemistry; Bd wt or BW = body weight; BI = biochemical changes; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; Develop = developmental; DX = developmental toxicity; ECG = electrocardiogram; Endocr = endocrine; (F) = feed; F = female(s); F0 = parental generation; F1 = first generation; F2 = second generation; F3 = third generation; FI = food intake; FSH = follicle stimulating hormone; (G) = gavage; GD = gestation day; GN = gross necropsy; (GO) = gavage in oil;; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; IX = immunotoxicity; LD = lactation day; LD_{50} = lethal dose, 50% kill; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; NX = neurotoxicity; OF = organ function; OW = organ weight; PND = postnatal day; Repro = reproductive; Resp = respiratory; RX = reproductive toxicity; SRBC = sheep red blood cell; T4 = thyroxine; TSH = thyroid stimulating hormone; UR = urinalysis; (W) = drinking water; WI = water intake

Figure 2-7. Levels of Significant Exposure to γ-Hexachlorocyclohexane – Oral
Acute (≤14 days)

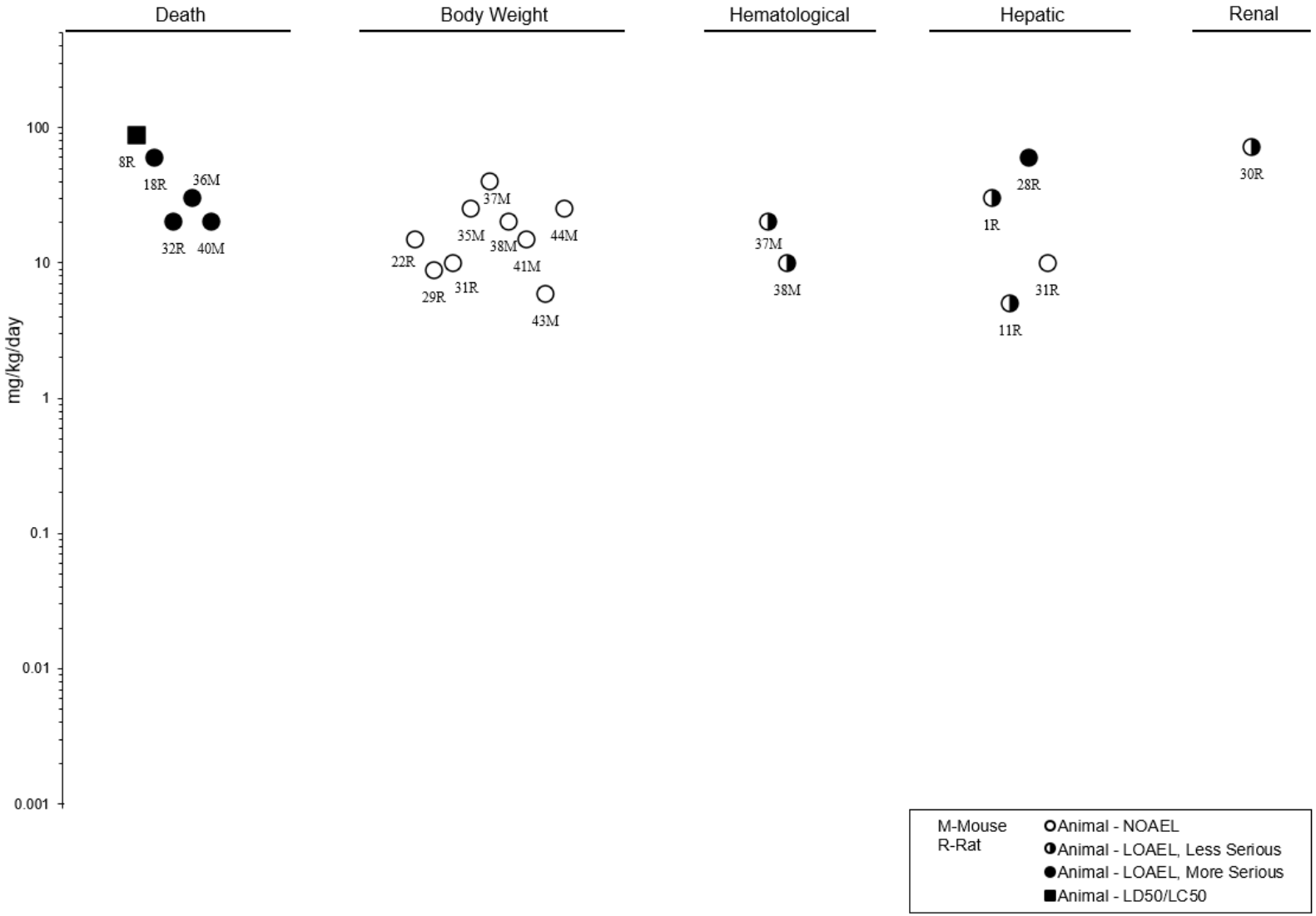


Figure 2-7. Levels of Significant Exposure to γ-Hexachlorocyclohexane – Oral
Acute (≤14 days)

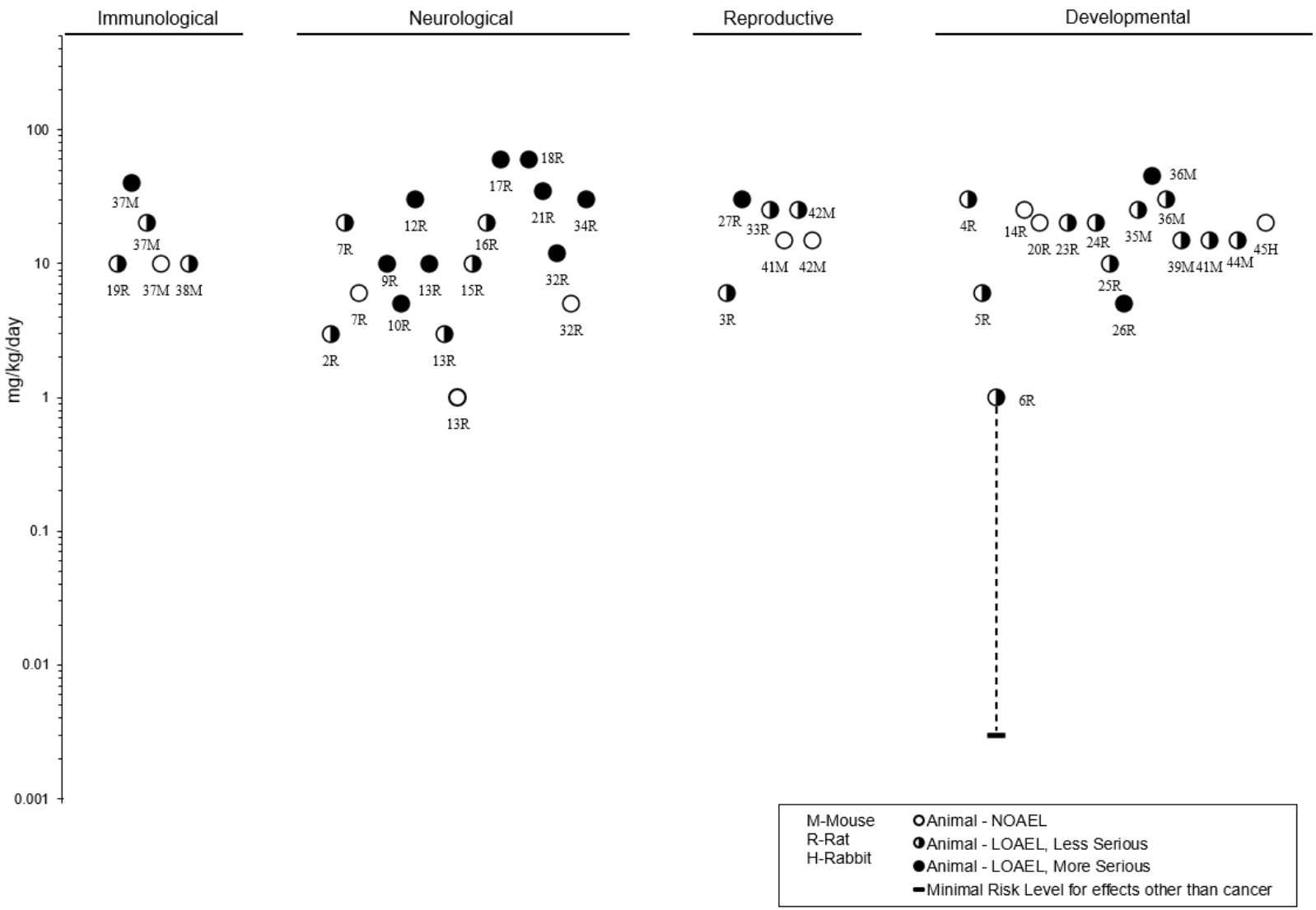


Figure 2-7. Levels of Significant Exposure to γ-Hexachlorocyclohexane – Oral

Intermediate (15-364 days)

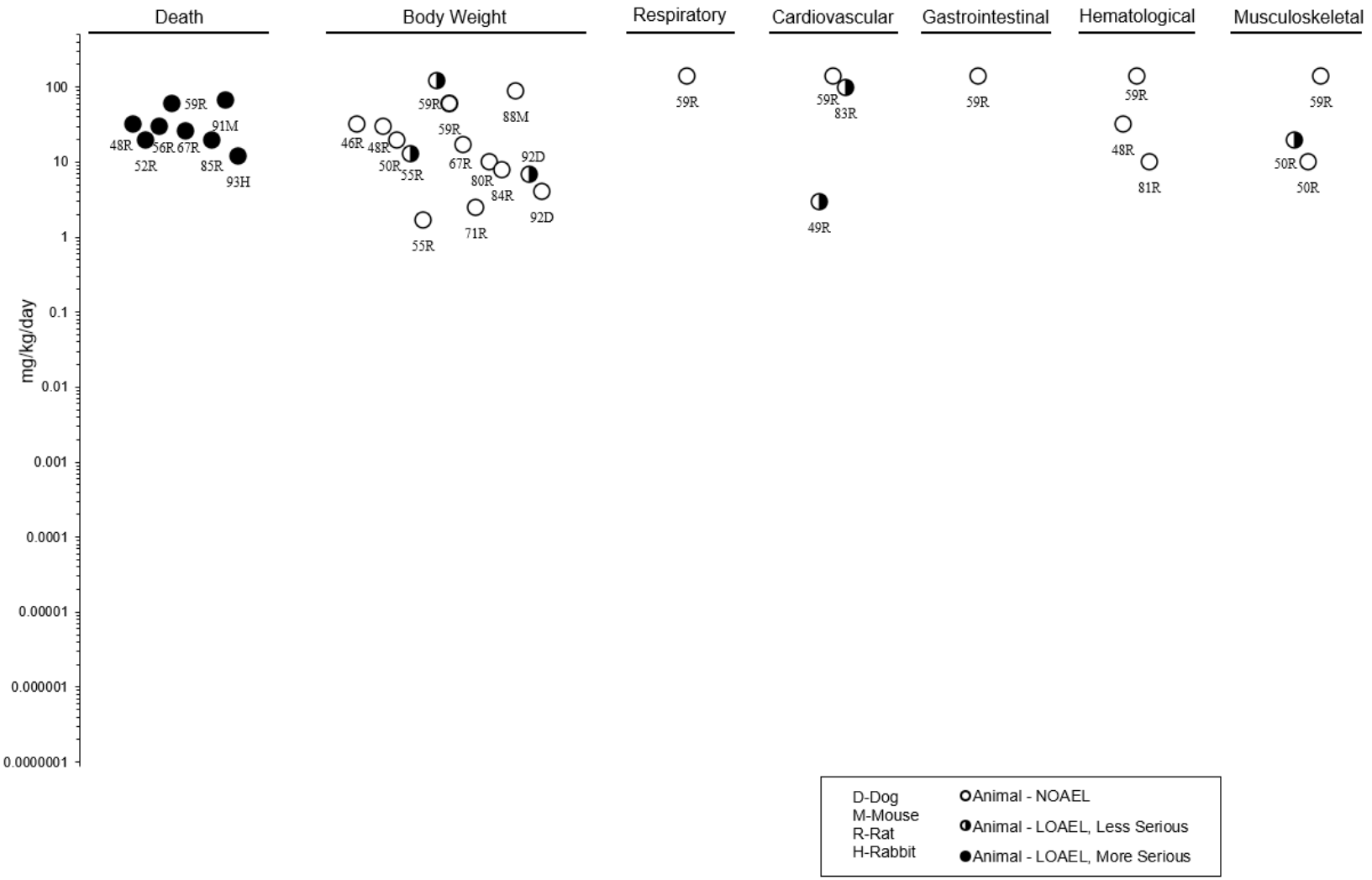


Figure 2-7. Levels of Significant Exposure to γ-Hexachlorocyclohexane – Oral

Intermediate (15-364 days)

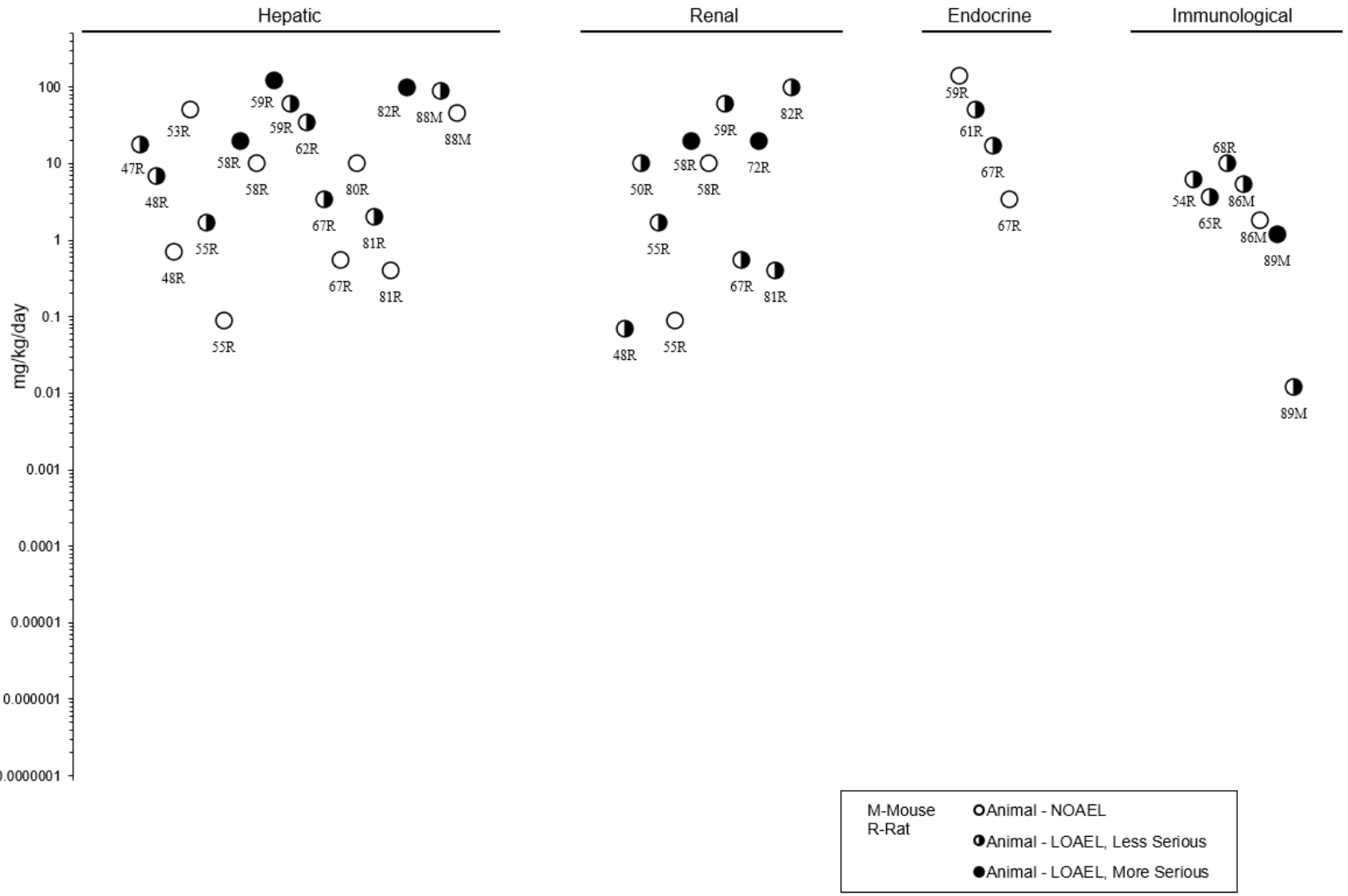


Figure 2-7. Levels of Significant Exposure to γ-Hexachlorocyclohexane – Oral
Intermediate (15-364 days)

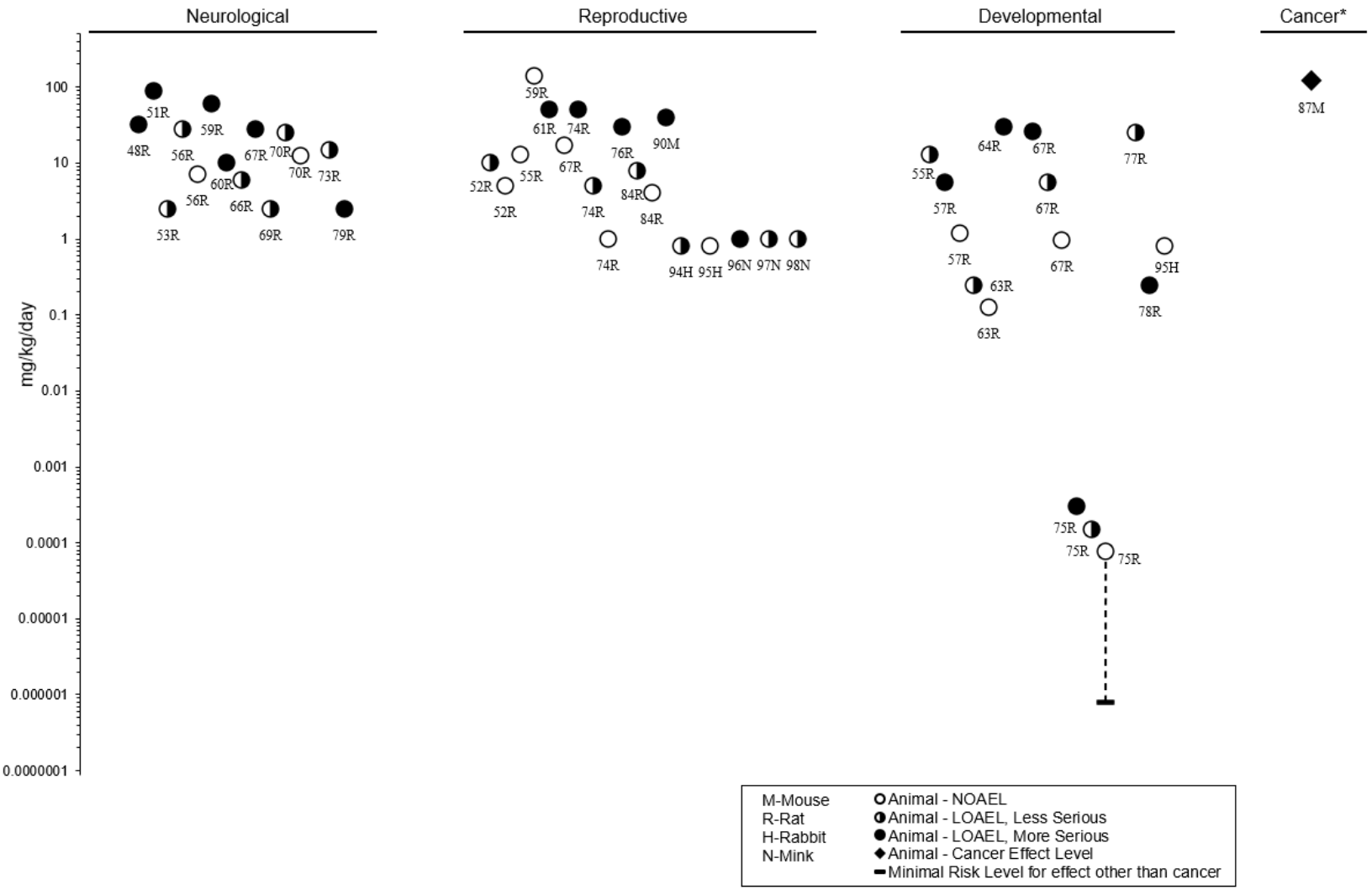


Figure 2-7. Levels of Significant Exposure to γ-Hexachlorocyclohexane – Oral

Chronic (≥365 days)

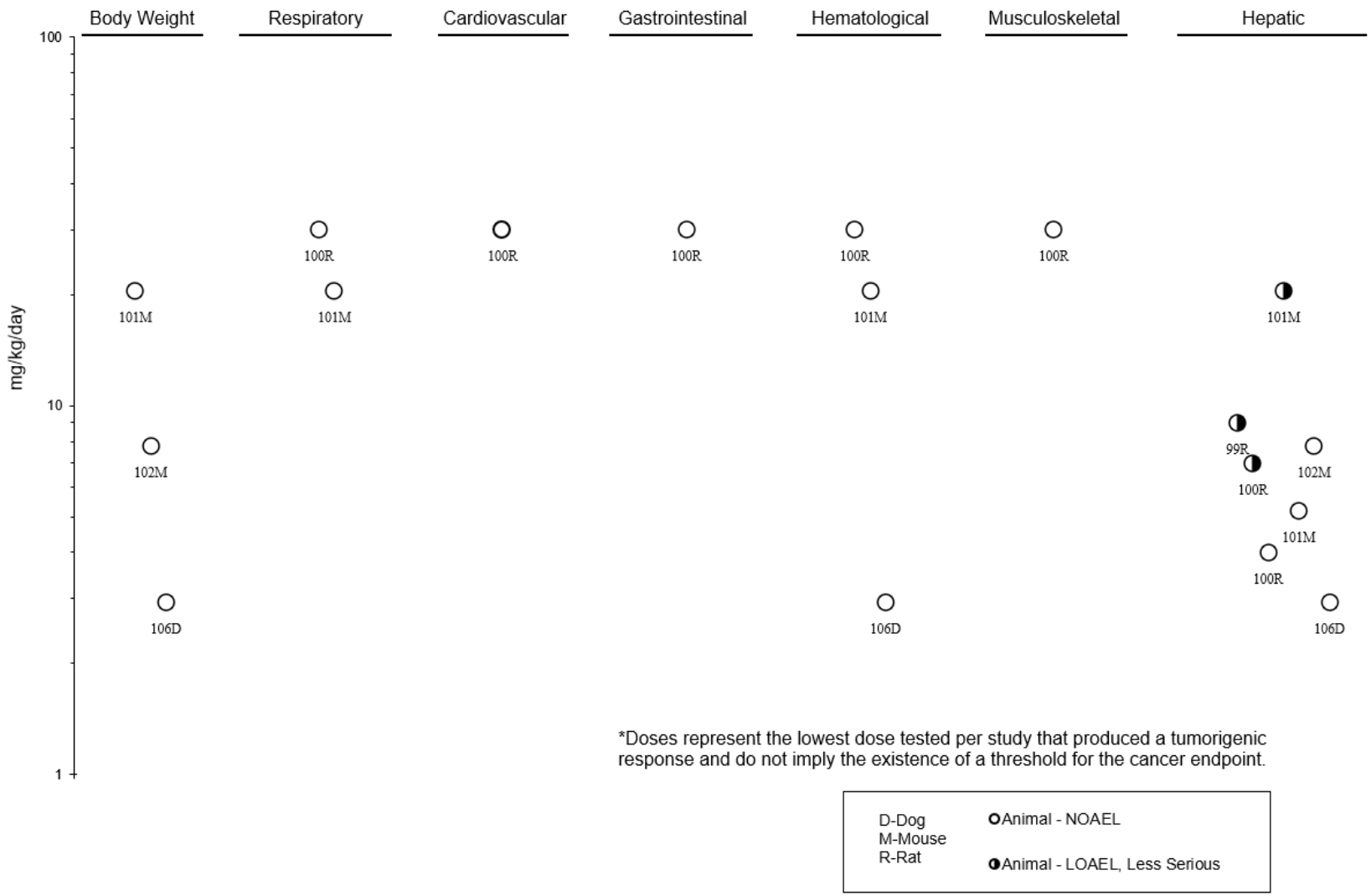


Figure 2-7. Levels of Significant Exposure to γ-Hexachlorocyclohexane – Oral

Chronic (≥365 days)

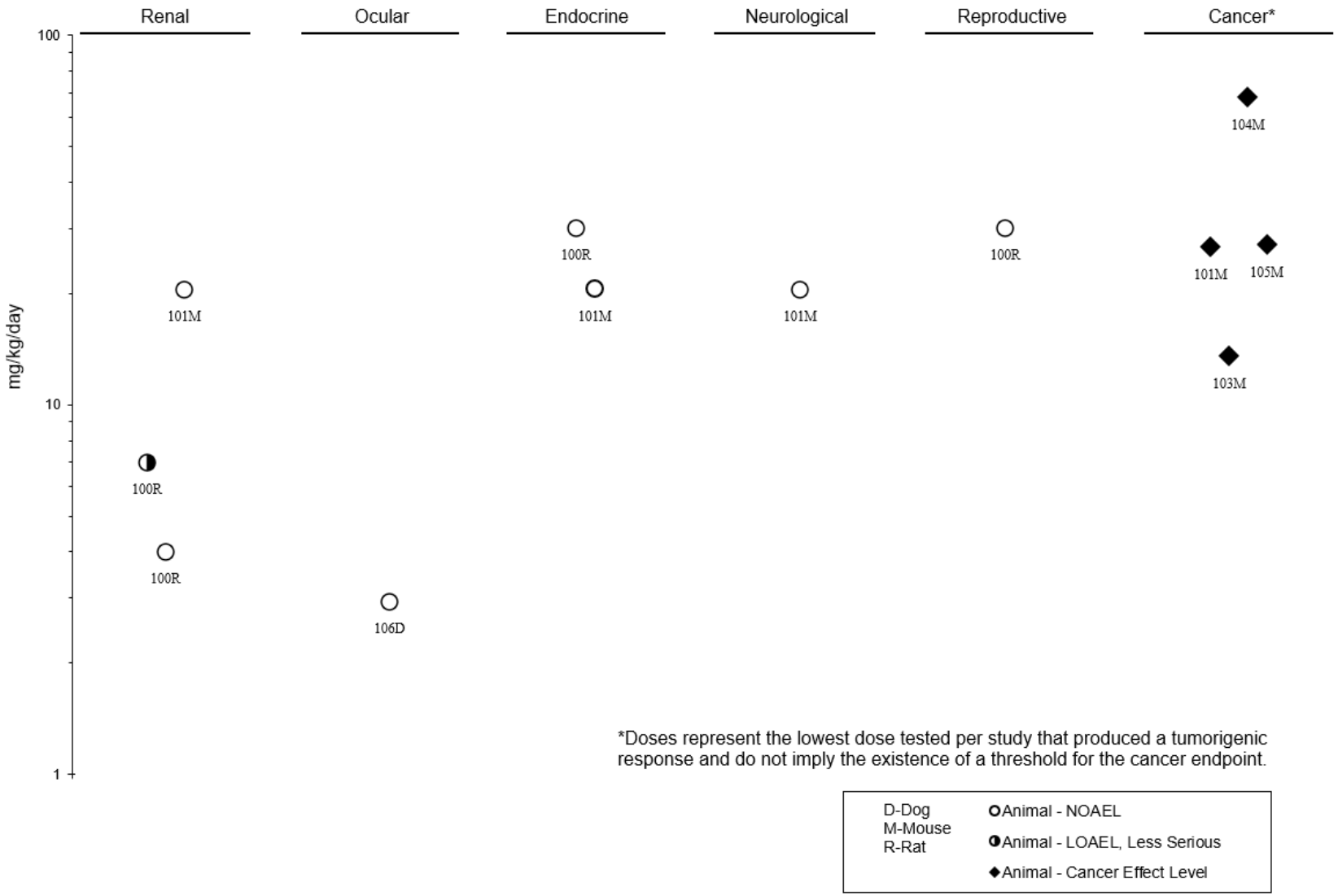


Table 2-5. Levels of Significant Exposure to δ- and Technical Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
ACUTE EXPOSURE									
Joseph et al. 1992a									**Technical HCH**
1	Rat (CFT-Wistar) 6 M	Once (GO)	0–4,000	LE	Death			2,428	LD_{50}
Sahoo et al. 1999									**Technical HCH**
2	Rat (Wistar) 10 M	7 days	0, 10, 20	BI, NX	Neuro		10		Reduced brain ATPase activities; 12% reduction in brain acetylcholinesterase activity; increased motor activity at 20 mg/kg/day
Samanta et al. 1999									**Technical HCH**
3	Rat (Wistar) 10 M	7 days (GO)	0, 10, 20	BW, BC, BI, OW, HP	Repro			10	54% reduction in total sperm count in adult rats; increased frequency of damaged sperm and sperm with anomalous heads
Dikshith et al. 1990									**Technical HCH**
4	Mouse (Swiss albino) 6 F	GD 9 once (GO)	0, 5, 25, 50, 100, 200	BW, DX	Repro			25	Increased fetal resorptions
Philip et al. 1989									**Technical HCH**
5	Mouse (NS) NS	1 or 5 days (GO)	0, 50	HP	Hepatic			50	Marked damage including severe congestion of portal vessels and central vein, severe fatty changes in periportal cells
					Renal		50		A few cases of interstitial hemorrhaging in medulla, cystic dilation of tubules, hyaline casts

Table 2-5. Levels of Significant Exposure to δ- and Technical Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Ravinder et al. 1989, 1990									**Technical HCH**
6	Mouse (Swiss albino) 10 M	2 weeks (F)	0, 72, 144	BI, OW, OF	Death			144	14% mortality
					Hepatic		72		>2-fold increase in relative liver weight, hepatocellular hypertrophy, mild centrilobular degeneration, focal necrosis in a few specimens
INTERMEDIATE EXPOSURE									
Anand et al. 1991									**Technical HCH**
7	Rat (NS) 45 M	90 days 6 days/week (GO)	0, 50	BI, NX	Neuro		50		Increased dopamine and decreased norepinephrine in brain; behavioral changes; increased brain wave frequency
Dikshith et al. 1989a									**Technical HCH**
8	Rat (NS) 10 M	30 days (GO)	0, 60	CS, HE, BC, BI, OW, HP	Hemato	60			
					Hepatic		60		65% increase in liver weight
					Renal	60			,
					Repro	60			
Dikshith et al. 1991a									**Technical HCH**
9	Rat (NS) 20 M	360 days (F)	0, 0.04, 0.4, 2, 20, 40	BW, FI, BC, BI, OW, OF, HP	Death			0.4	4/20 deaths
					Hepatic	2	20		Focal necrosis, enlargement of hepatocytes, nuclear pyknosis, vacuolation, margination
					Renal	2	20		Debris cells in lumen, glomerular degeneration
					Neuro	0.04		0.4	Tremors, convulsions, hind limb paralysis

Table 2-5. Levels of Significant Exposure to δ- and Technical Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Repro	2		20	Testicular necrosis and degeneration
Dikshith et al. 1991b									**Technical HCH**
10	Rat (NS) 12 M, 12 F	90 days (GO)	0, 5, 25	LE, BW, BI, BC, OW, HP, OF	Death			5	33% mortality in females and 50% mortality in males
Fitzhugh et al. 1950									**Technical HCH**
11	Rat (Wistar) 10 F, 10 M	6 months (F)	Males: 0, 7, 60 Females: 0, 9, 70	LE, BW	Death			60 M 70 F	Decreased mean age at death (32.9 versus 58.3 weeks in controls)
					Bd wt	7 M 9 F	70 F	60 M	LOAEL: 16% decrease in body weight of females Serious LOAEL: 26% decrease in body weight of males
					Resp	60 M 70 F			
					Cardio	60 M 70 F			
					Gastro	60 M 70 F			
					Hemato	60 M 70 F			
					Hepatic		60 M 70 F		Moderate liver damage
					Renal		60 M 70 F		Slight kidney damage
					Musc/skel	60 M 70 F			
					Endo	60 M 70 F			
					Repro	70 F		60 M	Moderate testicular atrophy

Table 2-5. Levels of Significant Exposure to δ- and Technical Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Gautam et al. 1989									**Technical HCH**
12	Rat (Charles Foster) 10 M	180 days (GO)	0, 3, 6	BW	Bd wt		3		17% decrease in body weight gain
					Repro		3		6% decrease in vas deferens weight, degeneration of inner muscle and cell layers of vas deferens
Gopal et al. 1992									**Technical HCH**
13	Rat (NS) 50 M	120 days (GO)	0, 50	CS, NX	Neuro		50		Increased motor activity, decreased resting stereotypic time
Joseph et al. 1992c									**Technical HCH**
14	Rat (CFT-Wistar) 4 M	7 weeks (F)	0, 90	HE, BC	Hemato		90		Decreased white blood cell counts
Ito et al. 1975									**Delta HCH**
15	Rat (W strain) 18–24 M	48 weeks	0, 35, 70	BW, OW, HP	Hepatic	35	70		Hepatocellular hypertrophy
Mudawal et al. 2018									**Technical HCH**
16	Rat (Wistar) 6 M	3 weeks 7 days/week (NS)	0, 2.5	BI, NX, DX	Neuro		2.5		Statistically significant decreases in conditioned avoidance, alternations, and locomotor activity; ultrastructural changes in the hippocampus and substantia nigra in adult animals

Table 2-5. Levels of Significant Exposure to δ- and Technical Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Nagaraja and Desiraju 1994									**Technical HCH**
17	Rat (Wistar) 6–8 F	PNDs 2–60 (GO)	0, 10, 20	CS, BW, BI	Develop		10		Alterations in levels of dopamine, serotonin, and noradrenaline in pup brains
Nagaraja and Desiraju 1994									**Technical HCH**
18	Rat (Wistar) 6–7 F	90 days (F)	0, 20	CS, BW, BI	Bd wt			20	Significantly decreased (23%) terminal body weight
					Neuro		20		Increased GABA levels, increased GAD activity, decreased glutamate levels
Roy Chowdhury and Gautam 1990									**Technical HCH**
19	Rat (Charles Foster) 5–10 M	180 days (G)	0, 3, 6	BW, OW, HP	Repro		3	6	LOAEL: detachment of germinal cells from peritubular membrane of seminiferous tubules, atrophy of Leydig cells, and intertubular edema Serious LOAEL: “complete degeneration” of testicular tissue
Sahoo et al. 1999									**Technical HCH**
20	Rat (Wistar) 10 M	15 or 30 days 7 days/week	0, 10, 20	BI, NX	Neuro		10		Reduced brain ATPase activity; 39% decrease in acetylcholinesterase activity after 15 days, with reduced grooming behavior at 20 mg/kg/day after 30 days
Samanta et al. 1999									**Technical HCH**
21	Rat (Wistar) 10 M	15 or 30 days (GO)	0, 10, 20	BW, BC, BI, OW, HP	Repro			10	58–65% reduction in total sperm count in adult rats; increased frequency of damaged sperm and sperm with anomalous heads

Table 2-5. Levels of Significant Exposure to δ- and Technical Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Bhatt and Bano 2009									**Technical HCH**
22	Mouse (Swiss) 6–18 M	2, 4, or 6 months (F)	0, 90	BI, HP	Cancer			90	CEL: Liver tumors
Bhatt and Nagda 2012									**HCH Not further specified**
23	Mouse (Swiss) 18–20 M	2, 4, or 6 months (F)	0, 90	BI, HP	Hepatic		90		Hepatocyte degeneration, vacuolation, fatty changes; hypertrophy, and hyperplasia after 4 months
					Cancer			90	CEL: liver tumors
Ito et al. 1973									**Delta HCH**
24	Mouse (dd) 20–40 M	24 weeks (F)	0, 18, 45, 90	BW, OW, HP	Bd wt	90			
					Hepatic	45	90		23% increase in relative liver weight and centrilobular hypertrophy
Karnik et al. 1981									**Technical HCH**
25	Mouse (Swiss) 6 NS	2–8 months (F)	0, 90	OW, OF	Hepatic		90		100% increase in liver weight; glycogen accumulation, smooth endoplasmic reticulum proliferation
					Cancer			90	CEL: hepatocellular carcinoma
Nigam et al. 1979									**Technical HCH**
26	Mouse (Swiss) 6 M	3 months (F)	0, 90	BW, OW, HP	Repro			90	Increased (27%) relative testis weight, degeneration of seminiferous tubules, shrunken and edematous tubules (some completely hyalinized); decreased (sparse) and damaged spermatocytes

Table 2-5. Levels of Significant Exposure to δ- and Technical Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Philip et al. 1989									
27	Mouse (NS) NS	15 d (GO)	0, 50	HP	Hepatic			50	Marked damage consisting of congestion of portal vessels and central vein, granular degeneration
					Renal			50	Marked damage consisting of congestion of blood vessels and glomeruli, vacuolation of epithelial cells in glomeruli, fatty changes, cystic dilation of the tubules, and interstitial hemorrhaging
Thakore et al. 1981									**Technical HCH**
28	Mouse (Swiss) 6 NS	2–8 months (F)	0, 90	BW, BI, OW	Cancer			90	CEL: hepatocellular carcinoma
Trivedi et al. 2007, 2009									**Technical HCH**
29	Mouse (Swiss) 6 M	1–8 months (F)	0, 90	BC, BI, GN, HP	Hepatic			90	"Severe" liver damage after 6 months
					Cancer			90	CEL: liver tumors
Wang et al. 2006									**Technical HCH**
30	Pig (Duroc X Landrace X Large white) 12 M, 12 F	90 days (F)	0, 0.4, 0.8	BW, FI, BC, BI, OW, IX	Bd wt	0.8			
					Hepatic	0.8			No effect on liver weight; <30% increases in serum ALT and ALP
					Renal	0.4	0.8		24% increase in relative kidney weight

Table 2-5. Levels of Significant Exposure to δ- and Technical Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
CHRONIC EXPOSURE									
Fitzhugh et al. 1950									**Technical HCH**
31	Rat (Wistar) 10 F, 10 M	107 weeks (F)	Males: 0, 0.7, 4, 7 Females: 0, 0.4, 0.9, 4, 9,	LE, BW, FI, GN, OW, HP	Resp	7 M 9 F			
					Cardio	7 M 9 F			
					Gastro	7 M 9 F			
					Hemato	7 M 9 F			
					Musc/skel	7 M 9 F			
					Hepatic	0.7 M 0.9 F	4		Very slight microscopic damage
					Renal	7 M 9 F			
					Endo	7 M 9 F			
					Repro	7 M 9 F			
Kashyap et al. 1979									**Technical HCH**
32	Mouse (Swiss) 30 M, 30 F	80 weeks (GO)	0, 10	CS, BW, FI, GN, HP	Neuro			10	Convulsions
					Cancer			10	CEL: hepatocellular carcinoma
Kashyap et al. 1979									**Technical HCH**
33	Mouse (Swiss) 30 M, 30 F	80 weeks (F)	0, 17	CS, BW, FI, GN, HP	Neuro			17	Convulsions
					Cancer			17	CEL: hepatocellular carcinoma

Table 2-5. Levels of Significant Exposure to δ- and Technical Hexachlorocyclohexane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Munir et al. 1983									**Technical HCH**
34	Mouse (Swiss) 10–37 M	20 months (F)	0, 21.3, 42.5, 85	BW, OW, HP	Cancer			21.3	CEL: hepatocellular carcinoma

[a]The number corresponds to entries in Figure 2-8; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-8. Where such differences exist, only the levels of effect for the most sensitive sex are presented.

ALP = alkaline phosphatase; ALT= alanine aminotransferase; BC = serum (blood) chemistry; Bd wt or BW = body weight; BI = biochemical changes; CEL = cancer effect level; CS = clinical signs; Develop = developmental; DX = developmental toxicity; (F) = feed; F = female(s); FI = food intake; (G) = gavage; GABA = gamma-aminobutyric acid; GAD =glutamate decarboxylase; GD = gestation day; GN = gross necropsy; (GO) = gavage in oil; HCH = hexachlorocyclohexane; HE = hematology; Hemato = hematological; HP = histopathology; IX = immunotoxicity; LD_{50} = lethal dose, 50% kill; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = muscular/skeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; NX = neurotoxicity; OF = organ function; OW = organ weight; PND = postnatal day; Repro = reproductive; (W) = drinking water

Figure 2-8. Levels of Significant Exposure to δ- and Technical Hexachlorocyclohexane (HCH) – Oral
Acute (≤14 days)

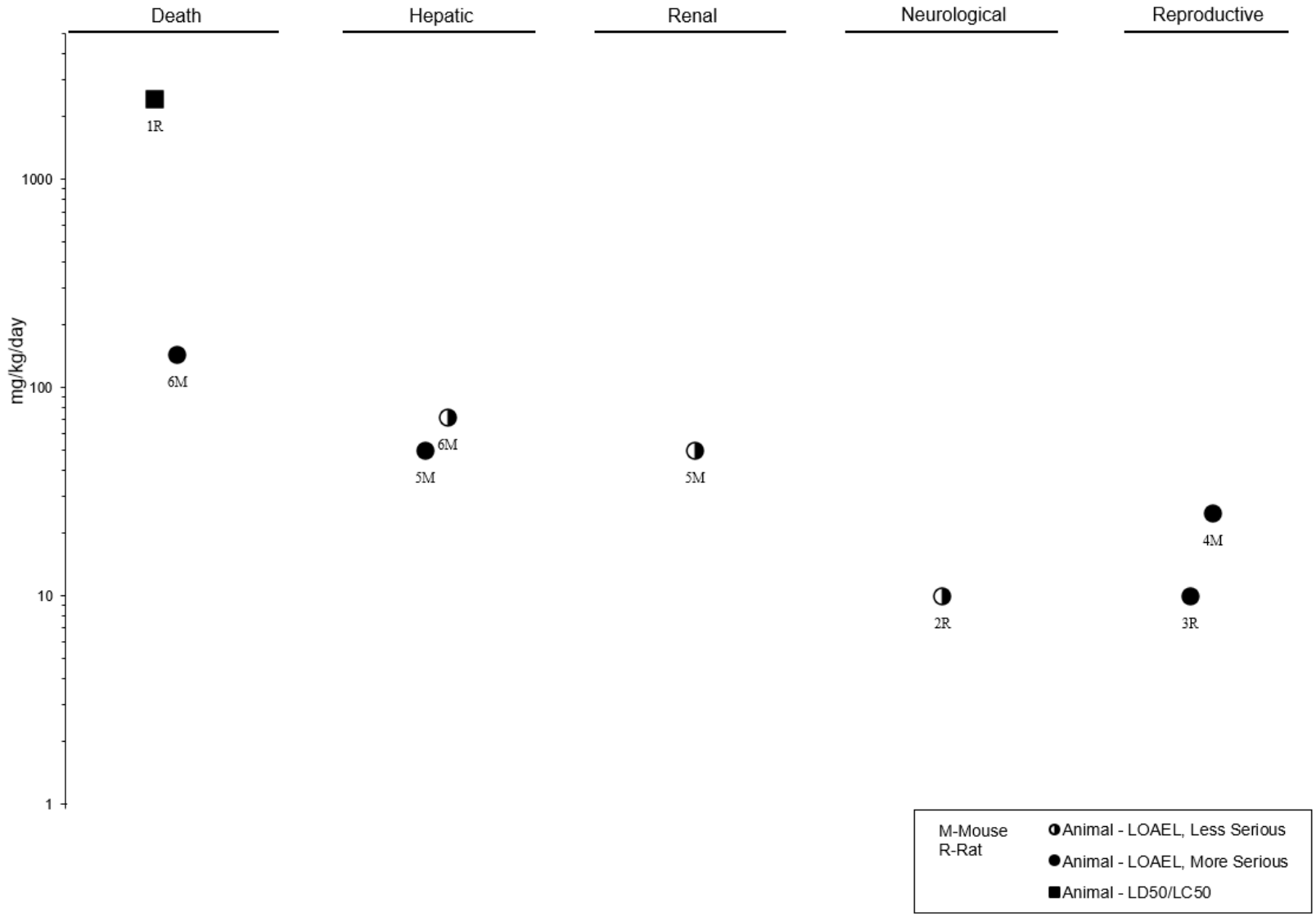


Figure 2-8. Levels of Significant Exposure to δ- and Technical Hexachlorocyclohexane (HCH) – Oral
Intermediate (15-364 days)

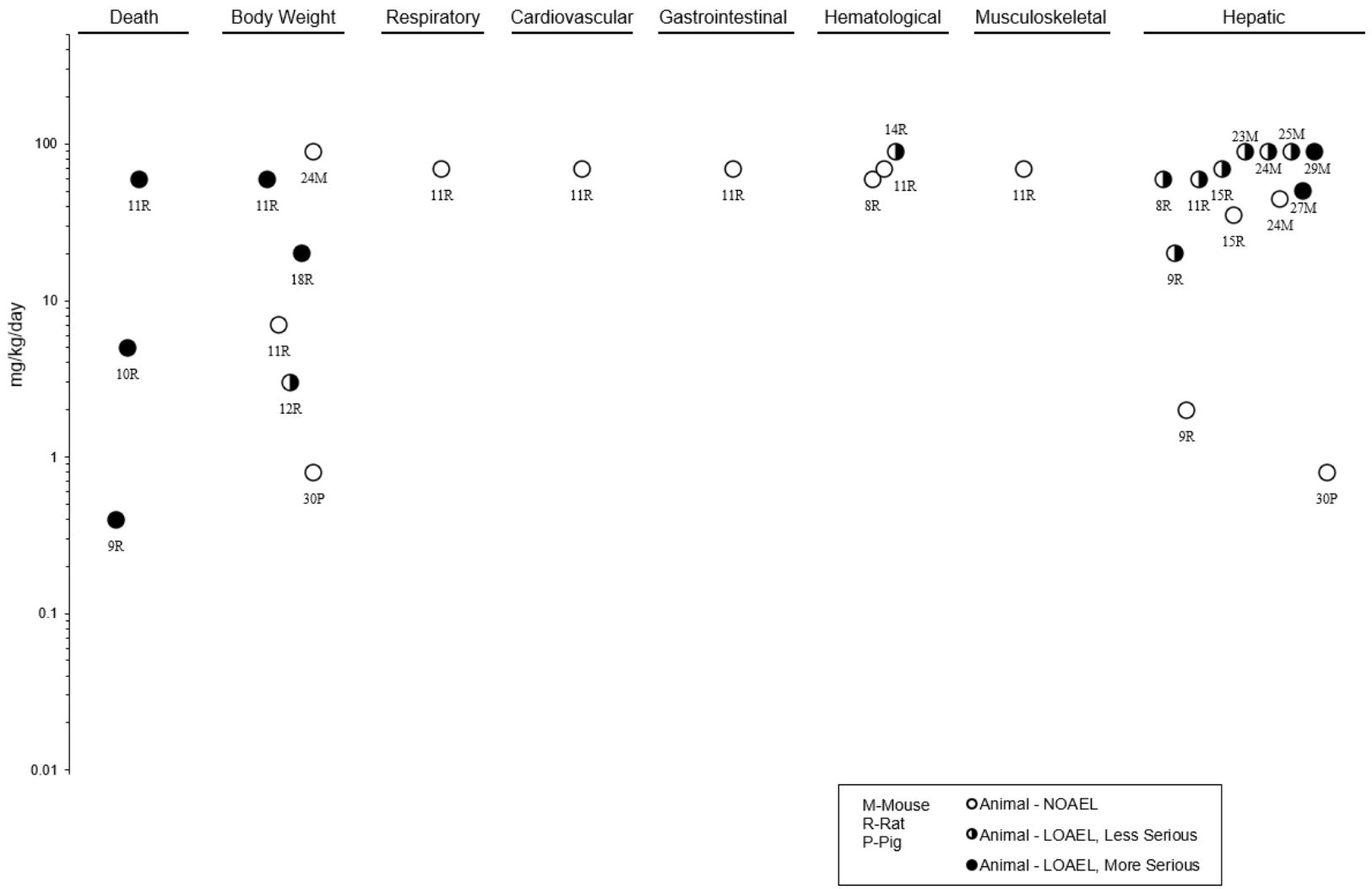
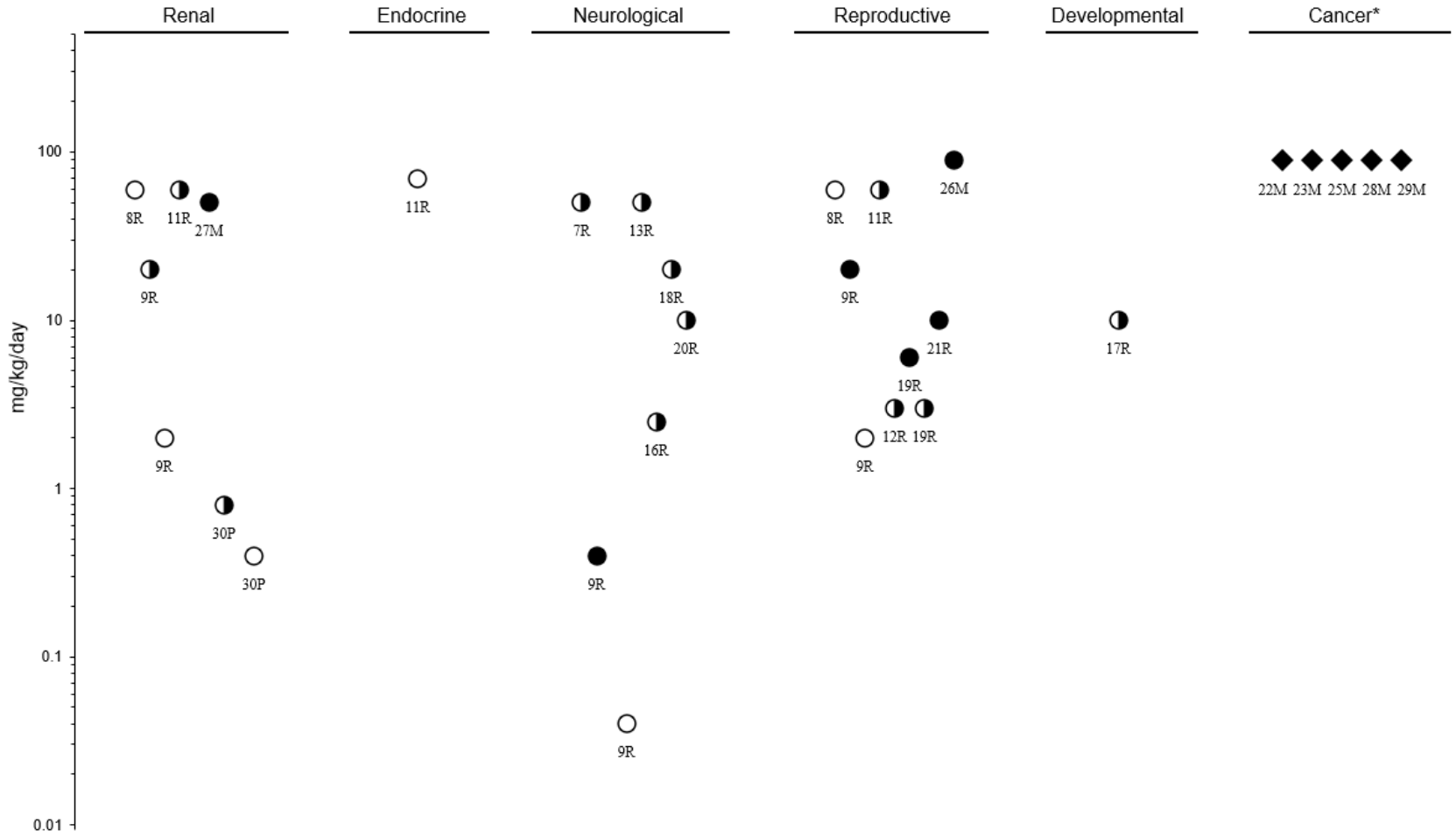


Figure 2-8. Levels of Significant Exposure to δ- and Technical Hexachlorocyclohexane (HCH) – Oral
Intermediate (15-364 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

M-Mouse
R-Rat

○ Animal - NOAEL
◑ Animal - LOAEL, Less Serious
● Animal - LOAEL, More Serious
◆ Animal - Cancer Effect Level

Figure 2-8. Levels of Significant Exposure to δ- and Technical Hexachlorocyclohexane (HCH) – Oral

Chronic (≥365 days)

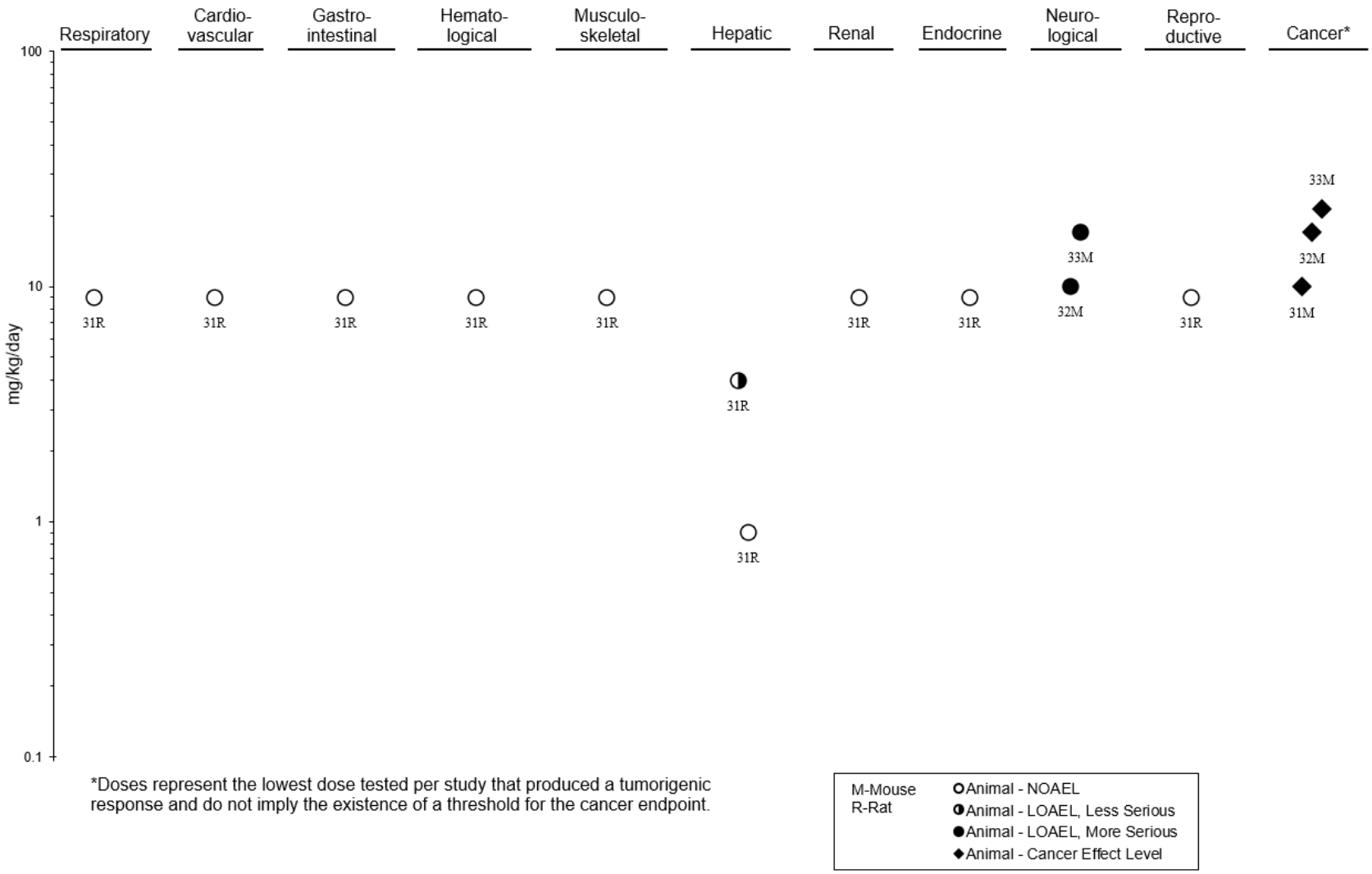


Table 2-6. Levels of Significant Exposure to γ-Hexachlorocyclohexane – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE								
Gaines 1960								
Rat (Sherman) 100 M, 70 F	Once (GO)	NS	LE, CS	Death			900 F	LD_{50}
							1,000 M	LD_{50}
Hanig et al. 1976								
Rabbit (New Zealand) 2–6 M	Once	0, 60 mg/kg	LE, CS	Death			60	Deaths among weanlings
				Neuro			60	Convulsions
Ullmann 1986a								
Rat (Wistar) 5 M, 5 F	24 hours once	0, 250, 600, 1,000, 2,000 mg/kg	LE, CS, BW, GN	Death			600	2/10 died at 600 mg/kg; LD_{50}=1,000 mg/kg
				Neuro	600	1,000	2,000 F	LOAEL: sedation, curved body position Serious LOAEL: severe sedation and spasms in one female
Ullmann 1986c								
Rabbit (New Zealand) 3 M, 3 F	Once	0, 40 mg/kg	LE, CS, BW	Ocular		40		Mild eye irritation
INTERMEDIATE EXPOSURE								
Dikshith et al. 1973								
Rat (I.T.R.C.) 30 F	25 days	0, 180 mg/kg/day	CS	Dermal		180		Mild dermatitis

Table 2-6. Levels of Significant Exposure to γ-Hexachlorocyclohexane – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
EPA 1988a								
Rat (Crl:(WI)BR) 13–23 M, 13–23 F	13 weeks 5 days/week 6 hours/day	0, 10, 60, 400 mg/kg/day	LE, CS, BW, FI, HE, BC, UR, GN, OF, HP, NX	Death			400 F	23 deaths out of 49
				Bd wt	400			
				Resp		10		Rapid respiration or wheezing
				Hemato	400			
				Hepatic	10	60		Centrilobular hypertrophy, increased absolute liver weight (8%) in females
				Renal	10 M 60 F	60 M		Basophilic tubules in males
				Neuro		10	60 F	LOAEL: hyperactivity Serious LOAEL: ataxia, tremors, convulsions

BC = serum (blood) chemistry; Bd wt or BW = body weight; CS = clinical signs; F = female(s); FI = food intake; GN = gross necropsy; HE = hematology; HP = histopathology; LE = lethality; LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level;; M = male(s); Neuro = neurological; NOAEL = no-observed-adverse-effect level; NR = not reported; NS = not specified; NX = neurotoxicity; OF = organ function; Resp = respiratory; UR = urinalysis

Table 2-7. Levels of Significant Exposure to Technical Hexachlorocyclohexane – Dermal

Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
ACUTE EXPOSURE								
Dikshith et al. 1978								
Guinea pig (NS) 24 M	5–12 days	0, 100, 200, 500	LE	Death			200	24/24 deaths
INTERMEDIATE EXPOSURE								
Dikshith et al. 1991c								
Rat (Wistar) 6 F	15–30 days	0, 100	LE, BW, BC, BI, OW, HP	Death			100	Two deaths by day 15 and 2 by day 30
				Hepatic			100	Severe liver injury including hypertrophy, fatty degeneration, nuclear pyknosis of hepatocytes, diffuse and focal liver necrosis, and bile duct proliferation
				Renal			100	Mild to severe tubular epithelial cell necrosis and glomerular atrophy
				Dermal		100		Hyperkeratosis, epidermal cell vacuolization, thickening of collagen fibers
				Neuro			100	Tremors, degenerative changes in the cerebellum
Dikshith et al. 1989b								
Rabbit (NS) 8 M	30 days	0, 25	LE, CS, BW, BC, BI, UR, OW, HP	Death			25	6/24 deaths
				Hepatic		25		Hepatocyte degeneration, pycnotic nuclei, enlarged liver, altered ALT, AST, LDH, and ALP activities

Table 2-7. Levels of Significant Exposure to Technical Hexachlorocyclohexane – Dermal

Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
				Renal		25		Altered epithelial lining of proximal convoluted tubules, loss of brush borders of tubules, atrophy of glomerular capsules
				Dermal		25		Thickened epidermis, hyperkeratinization, and infiltration of mononuclear cells
				Neuro			25	Convulsions, tremor, and paralysis; changes in Purkinje cells of cerebellum including loss of dendrites and presence of deciduomatous cell body
				Repro			25	Severe effects on germinal cells of testes, including vacuolation, cytoplasmic changes, cell sloughing, and multinucleated giant cells
Dikshith et al. 1978								
Guinea pig (NS) 24 M	30 days	0, 100, 200, 500	BW, BC, BI, OW, HP	Hepatic		100		38% increase in liver weight, hepatic hypertrophy, pycnotic nuclei in cytoplasm, focal fatty inclusions, increased ALT and ALP activity
				Renal	100			
				Repro			100	Degeneration of seminiferous tubules, necrosed spermatogenic cells, multinucleated giant cells and no active sperm in lumen

Table 2-7. Levels of Significant Exposure to Technical Hexachlorocyclohexane – Dermal

Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Mathur et al. 1992								
Guinea pig (NS) 6 NS	30 days	0, 100	BI, HP	Hepatic		100		Increased enzyme activity and fatty and degenerative changes
				Renal		100		increased enzyme activity and histopathological changes
Mathur et al. 1993								
Guinea pig (NS) 6 M	15, 30 days	0, 100	BI, HP	Dermal		100		Dermal histopathology: hyperkeratinization, mononuclear infiltration, sloughing
CHRONIC EXPOSURE								
Kashyap et al. 1979								
Mouse (Swiss) 30 M, 30 F	80 weeks 2 days/week	0, 2.4	BW, FI, GN, HP, CS	Cancer			2.4	CEL: liver tumors
Prasad et al. 1995								
Rat (Wistar) 10 M	120 days	0, 50, 100	CS, BI, OF, RX	Repro			50	Decreased sperm count (57% relative to vehicle control) and motility (38%), increased percent abnormal sperm (>5-fold), alterations in testicular enzyme activity

ALP = alkaline phosphatase; ALT= alanine aminotransferase; AST = aspartate aminotransferase; BC = serum (blood) chemistry; BW = body weight; BI = biochemical changes; CEL = cancer effect level; CS = clinical signs; F = female(s); FI = food intake; GN = gross necropsy; HP = histopathology; LDH = lactate dehydrogenase; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OF = organ function; OW = organ weight; Repro = reproductive; RX = reproductive toxicity; UR = urinalysis

2.2 DEATH

Human fatalities have been reported for γ-HCH but not for other isomers or for mixtures of isomers. Studies reporting deaths associated with γ-HCH are described below in the subsection on γ-HCH.

α-HCH. In a long-term study where Wistar rats were administered α-HCH in the diet, mean age of death was significantly decreased to 35.9 weeks in animals administered 60–70 mg/kg/day compared to 58.3 weeks in control animals (Fitzhugh et al. 1950). No inhalation or dermal studies of mortality in animals were identified for α-HCH.

β-HCH. Mortalities have occurred in rats and mice exposed to β-HCH in the diet for acute and intermediate exposure durations, often after showing signs of pronounced neurotoxicity. In the first week of a 30-day study, 80% of female mice receiving 200 mg/kg/day β-HCH in feed exhibited ataxia progressing to lateral recumbent position and were humanely sacrificed (Cornacoff et al. 1988). No deaths were observed in male rats exposed to 72 mg/kg/day β-HCH in food for 2 weeks (Srinivasan et al. 1984). However, maternal mortality occurred in a developmental study in rats (Srinivasan et al. 1991), in which all dams exposed to 80 mg/kg/day β-HCH in feed died within 3 weeks of treatment (during gestation). Similarly, in the first 2 weeks of a 13-week dietary study, two male and three female rats exposed to doses of 38 mg/kg/day exhibited ataxia and hypoactivity, progressing within 3 days to coma and leading to their humane sacrifice[1] (Van Velsen et al. 1986). Subsequently, five males and six females in this dose group became moribund and were euthanized later in the study (timing not reported) (Van Velsen et al. 1986). In a dietary study where Wistar rats were administered β-HCH, mean age of death for both males and females administered 60–70 mg/kg/day was 4.4 weeks compared to 58.3 weeks in control animals (Fitzhugh et al. 1950). All animals exposed to β-HCH at this dose died by 10 weeks of exposure (Fitzhugh et al. 1950). Finally, in a chronic study in which CF1 mice were administered 34 mg/kg/day β-HCH for up to 104 weeks, 12% of males and 25% of females died within the first 3 months (Thorpe and Walker 1973). Survival of the remaining animals did not differ from controls. No inhalation or dermal studies of mortality in animals were identified for β-HCH.

No information on the causes or mechanisms of death in animals exposed to β-HCH was located, although neurotoxicity preceded death in most instances. There appears to be substantial variability in susceptibility to the lethal effects of β-HCH, as demonstrated by the chronic study by Thorpe and Walker

[1]Because the deaths occurred after the end of 2 weeks, they were considered to occur as a result of intermediate-duration exposure.

(1973), in which animals that survived the first 3 months did not have any reductions in subsequent survival.

γ-HCH (Lindane). γ-HCH was once used in insecticide vaporizer and fumigator devices, resulting in human inhalation and dermal exposure to unspecified levels. Occasional deaths associated with the use of this product for several months or years have been reported, but it is not clear that γ-HCH was responsible for the deaths (Loge 1965). Two cases of pulmonary edema resulting in fatalities were reported in toddlers inhaling and ingesting unknown quantities of γ-HCH-containing pesticidal powder (McQueen et al. 1968).

Case reports of deaths in humans, often in children or suicidal adults, following ingestion of γ-HCH in tablets (doses unknown) intended for y-HCH vaporizers have been reported (Storen 1955; Sunder Ram Rao et al. 1988). A single acute, whole-body dermal application of 1% γ-HCH in lotion to a 2-month-old infant for scabies treatment resulted in death (Davies et al. 1983). Autopsy identified pulmonary and epicardial petechiae and a concentration in the brain of 110 ppb γ-HCH. The death of an elderly woman was reported following a 6-hour dermal application of γ-HCH-containing lotion (approximately 40 mg total γ-HCH) to the head for the treatment of scabies (Katsumata and Katsumata 2003). No data were reported for blood or tissue levels of γ-HCH. A 66-year-old man died after being treated for scabies in a hospital with a 1% γ-HCH lotion applied dermally from neck to toes (Sudakin 2007). Eight hours after application, the man exhibited worsening of mental status and hypoxemia. Over the next 2 hours, his neurological symptoms increased in severity to include seizure and myoclonic jerks, and were accompanied by severe hypoxemia, tachycardia, diaphoresis, hypotension, and respiratory acidosis. The man remained in intensive care and subsequently died after 50 days in the hospital. The autopsy attributed the cause of death to hypoxic ischemic encephalopathy from γ-HCH poisoning. The dose of γ-HCH was not estimated, and neither blood nor tissue levels of γ-HCH were measured during hospitalization or at autopsy (Sudakin 2007).

In an acute animal study of rats exposed nose-only to γ-HCH aerosol for 4 hours, the LC_{50} was determined to be 1,560 mg/m^3 (Ullmann 1986b); the lowest concentration associated with lethality was 378 mg/m^3. No rats exposed whole body to γ-HCH for 4 hours up to a concentration of 603 mg/m^3 died throughout the 14-day observation period (Oldiges et al. 1980). In the beginning of a 14-week study, 12/45 female and 2/45 male mice that were exposed to 10 mg/m^3 of γ-HCH dust aerosol via whole body (6 hours/day) died during the first week (Klonne and Kintigh 1988). In this study, the concentration was decreased from 10 to 5 mg/m^3 after the first week; additional deaths occurred at 5 mg/m^3 (two males and

three females) and 1 mg/m^3 (one male and one female), but there no deaths at 0.3 mg/m^3. One unexplained death in a control mouse was also reported (Klonne and Kintigh 1988).

Studies in laboratory animals have reported deaths after acute-duration oral administration of γ-HCH doses ≥20 mg/kg/day (Chadwick et al. 1988; Fitzhugh et al. 1950; Gaines 1960; Hassoun and Stohs 1996a; Liu and Morgan 1986; Martinez et al. 1991; Matsuura et al. 2005; Thorpe and Walker 1973; Tusell et al. 1988; Yuksel et al. 2009). In studies of rats administered a single dose of γ-HCH via gavage, LD_{50} values of 88 mg/kg in males and 91 mg/kg in females were obtained (Gaines 1960). One of seven male rats died following a single administration of γ-HCH at a dose of 60 mg/kg via gavage (Martinez et al. 1991), while 2/18 rats died within the third day of exposure to doses of 20 mg/kg/day (Tusell et al. 1988). Acute studies in mice showed similar lethal doses in some strains. Pregnant DBA/2J and C57BL/6J mice both exhibited mortality (14–25%) upon single gavage doses of 30 and 45 mg/kg, respectively, administered on gestation day (GD) 12 (Hassoun and Stohs 1996a). In another study, no mortality was reported in nonpregnant adult female C57BL/6 mice; however, six of six DBA/2 mice died after 20 mg γ-HCH/kg was administered by daily gavage for up to 10 days (Liu and Morgan 1986).

In intermediate- and chronic-duration studies, the doses inducing lethality were similar to those seen after acute exposure. Two F0 female rats exposed to doses of 26.1 mg/kg/day in a 2-generation reproductive toxicity study died, but the times of death were not reported (Matsuura et al. 2005). In F344 rats administered γ-HCH for up to 15 weeks, 2/12 animals died at 20 mg/kg/day and 7/12 died at 40 mg/kg/day (Chadwick et al. 1988). When groups of 10 Sprague-Dawley rats were administered 20 or 40 mg/kg/day γ-HCH by gavage for 30 days, one animal in each group died during week 3 (Yuksel et al. 2009). The age at death in Wistar rats was significantly decreased to 39.7 weeks in animals administered 60–70 mg/kg/day, compared to 58.3 weeks in control animals (Fitzhugh et al. 1950). In a 2-year study with interim sacrifices, dietary administration of technical-grade γ-HCH at a dose of 32 mg/kg/day resulted in significantly decreased survival when compared with controls (Amyes 1990).

Acute dermal exposure to γ-HCH resulted in death. Dermal LD_{50} values in rats exposed to γ-HCH once and observed for 10 days were 1,000 mg/kg in males and 900 mg/kg in females (Gaines 1960). In an acute dermal study in which male and female rats were exposed to γ-HCH for 24 hours, mortality rates across both sexes were 0, 20, 40, and 30% at 250, 600, 1,000, and 2,000 mg/kg, respectively (Ullmann 1986a). Weanling rabbits were more sensitive to γ-HCH treatment than young adults, as seen by increased mortality rates accompanied by excitement and convulsions after a single whole-body treatment with a 1% solution at a dose of 60 mg/kg γ-HCH (Hanig et al. 1976). Significant mortality (47%) was

seen in female rats, but not male rats, exposed dermally to γ-HCH at 400 mg/kg/day for 6 hours/day, 5 days/week, for 13 weeks (EPA 1988a). No studies regarding chronic dermal exposure to γ-HCH were located.

Technical HCH or Unspecified Isomers of HCH. Joseph et al. (1992a) reported an LD_{50} of 2,428 mg/kg in male rats administered a single gavage dose of technical-grade HCH (72.8% α-HCH, 12.6% γ-HCH, 7.95% δ-HCH, 5% β-HCH). Technical-grade HCH administered to rats for 90 days resulted in increased mortality: 6/12 males and 4/12 females exposed to 5 mg/kg/day died, and a 58% increase in mortality (incidence not reported) was observed at 25 mg/kg/day (Dikshith et al. 1991b). When Wistar rats were administered technical-HCH in the diet as part of a chronic study, age at death was significantly decreased to 32.9 weeks in animals administered 64 mg/kg/day compared to 58.3 weeks in control animals (Fitzhugh et al. 1950). Exposure to low levels (0.4 mg/kg/day) of technical-grade HCH in the diet for 360 days resulted in deaths of 4/20 rats (Dikshith et al. 1991a).

Dikshith et al. (1978) reported that guinea pigs dermally exposed to 200 mg technical-grade HCH/kg died within 5–12 days. Four of 20 rats died from dermal exposure to technical-grade HCH at 100 mg/kg/day for 15–30 days (Dikshith et al. 1991c). Rabbits treated with 25 mg/kg/day technical-grade HCH for 30 days by skin painting on shaved dorsal, ventral, or thigh areas exhibited no deaths in the group exposed by dorsal application, but two of eight rabbits died in the group exposed by ventral application, and four of eight died in the group exposed by thigh application (Dikshith et al. 1989b).

2.3 BODY WEIGHT

Epidemiological Studies. Studies of body weight effects in humans include only two studies of β-HCH; these are summarized in Table 2-8. In a cohort of women residing in an agricultural area of California, serum levels of β-HCH were associated with increased body mass index (BMI), waist circumference, body fat percent, and obesity when measured over the 3 years after serum collection (Warner et al. 2018). A cross-sectional study of surgical patients in Spain provided support for an association between β-HCH (measured in serum or adipose tissue) and increased BMI (Arrebola et al. 2014).

Table 2-8. Summary of Epidemiological Studies of β-Hexachlorocyclohexane (β-HCH) Exposure and Body weight Effects

Reference, study type, and population	Biomarker	Concentration	Outcome evaluated	Result
Arrebola et al. 2014 Cross-sectional, 298 noncancer surgical patients >16 years old, Spain	Serum or adipose	19.60±28.74 ng/g lipid (mean)	**BMI**	↑[a]
Warner et al. 2018 Cohort, 468 women >18 years old, residing in agricultural area of California, United States	Serum	>5.2 ng/g lipid (median)	**BMI**	↑
			Waist circumference	↑
			Body fat %	↑
			Obesity	↑

[a]BMI exhibited a quadratic association with β-HCH, increasing at low concentrations and then decreasing at higher concentrations.

↑ = association with increase; BMI = body mass index

Data on body weight changes in animals exposed by inhalation or dermal contact were limited to γ-HCH.

α-HCH. Sumida et al. (2007) reported no body weight changes in male rats administered α-HCH via gavage at 20 mg/kg/day for up to 28 days. In rats exposed for 24 weeks to 45 mg/kg/day in feed, terminal body weight was decreased by 15% (Nagasaki et al. 1975); food intake was not reported. Significantly decreased body weight gain in the absence of changes in food intake was also seen in rats treated with 60–70 mg/kg/day of α-HCH in the diet for 6 months (Fitzhugh et al. 1950). In studies of several mouse strains given 90 mg/kg/day α-HCH in feed for 24 weeks, a significant (17%) decrease in terminal body weight was observed in male C57BL/6 mice, but not in other strains (dd, DDY, ICR, DBA/2, or C3H/He) or in females of any strain (Ito et al. 1973; Nagasaki et al. 1975). These authors conducted a similar experiment in male hamsters given 45 mg/kg/day in feed for 24 weeks. Terminal body weight was 14% lower than controls in the hamsters (Nagasaki et al. 1975).

β-HCH. Intermediate-duration oral studies of body weight effects after exposure to β-HCH exposure show effects in rats, but not in mice. A body weight decrease of at least 10% was observed in Wistar rats administered dietary β-HCH at a dose of 22.5 mg/kg/day in males or 25 mg/kg/day in females for 13 weeks; however, at this dose, half of the animals were sacrificed moribund prior to study termination (Van Velsen et al. 1986). No body weight effects were observed at doses up to 5 mg/kg/day in males or females (Van Velsen et al. 1986). After 6 months of β-HCH administration in the diet, body weight gain was decreased by 11% in female Wistar rats exposed to 9 mg/kg/day (Fitzhugh et al. 1950); body weight

data for the lower dose group were not reported. No effect on body weight was observed in mice administered β-HCH at doses of 60 mg/kg/day for 30 days (Cornacoff et al. 1988) or 90 mg/kg/day for 24 weeks (Ito et al. 1973).

γ-HCH (Lindane). Limited information is available on body weight effects of γ-HCH in animals exposed by inhalation. In Wistar rats exposed for 4 hours to 603 mg/m^3 γ-HCH, females lost weight for the first post-exposure observation week. Neither mice nor rats exposed to γ-HCH aerosols at concentrations up to 5 mg/m^3 on 6 hours each day (5 or 7 days/week) for 13–14 weeks exhibited any change in body weight (Oldiges et al. 1983; Klonne and Kintigh 1988).

No effects on body weight were observed in rats administered acute oral doses ranging from 8.8 to 15 mg/kg/day (Parmar et al. 2003; Sinha and Shukla 2003; Sumida et al. 2007) or in mice at doses ranging from 5.9 to 40 mg/kg/day (Di Consiglio et al. 2009; Hong and Boorman 1993; Maranghi et al. 2007; Serrano et al. 1990; Sinha and Shukla 2003). One study of Wistar rat dams exposed to ≥8 mg/kg/day exhibited decreased body weight gain (25% less than controls) on GDs 6–20; decreased food consumption was seen at the same dose (EPA 1999c). Body weights of pregnant mice administered 15–25 mg/kg/day γ-HCH via gavage during gestation were not affected (Maranghi et al. 2007; Traina et al. 2003). In a 7-week study of beagle dogs given γ-HCH in the diet, Rivett et al. (1978) reported suppression of body weight gain at 7 mg/kg/day; however, only two dogs per group were used in this study.

In intermediate-duration studies, there were no effects on body weight in rats administered γ-HCH via gavage at doses between 2.5 and 30 mg/kg/day for 15–28 days (Ahmed et al. 2008; Andrews and Gray 1990; Parmar et al. 2003; Sumida et al. 2007; Yang et al. 2014; Zhang et al. 2016) or up to 26.1 mg/kg/day for about 10 weeks in a 2-generation reproductive toxicity study (Matsuura et al. 2005). In another 2-generation reproductive toxicity study (EPA 1991a), body weight gain decreased, without changes in food intake, in high-dose (13.1 mg/kg/day) F0 parental females during gestation. Mice exposed to γ-HCH in feed for 24 weeks exhibited no body weight changes at doses up to 90 mg/kg/day (Ito et al. 1973).

Significantly decreased body weight gain was seen after 6 months in rats treated with 120–140 mg/kg/day γ-HCH in feed as part of a chronic study, but this dose was also associated with significantly reduced survival (Fitzhugh et al. 1950). Beagle dogs given doses up to 2.92 mg/kg/day γ-HCH in feed displayed no changes in body weight over the 102-week exposure (Rivett et al. 1978).

Technical HCH or Unspecified Isomers of HCH. Wistar rats administered technical-grade HCH via gavage at doses up to 20 mg/kg/day for 7 days exhibited no effect on body weight (Samanta et al. 1999). Swiss albino mice had significantly decreased body weight after administration of a single dose of 100 mg/kg technical-grade HCH via gavage in oil (Dikshith et al. 1990). Significantly decreased body weight gain has been observed in rats treated orally with 3 or 20 mg/kg/day technical-grade HCH for up to 6 months (Gautam et al. 1989; Nagaraja and Desiraju 1994; Roy Chowdhury and Gautam 1990). Rats administered technical-grade HCH via gavage at a dose of 50 mg/kg/day for 30 days exhibited a 21% body weight loss (Khanna et al. 1990). In an 80-week study, Swiss mice administered technical-grade HCH at 17 mg/kg/day exhibited no changes in body weight or body weight gain, despite decreased food consumption (Kashyap et al. 1979). After 6 months of technical-grade HCH administration, no effect on body weight was observed at 7–9 mg/kg/day, but body weight was decreased by 16% in female rats exposed to 70 mg/kg/day and by 26% in males exposed to 60 mg/kg/day (Fitzhugh et al. 1950). No effect on body weight was observed in mice chronically administered technical-grade HCH at 10 mg/kg/day by gavage or 17 mg/kg/day in the diet (Kashyap et al. 1979).

2.4 RESPIRATORY

α-HCH. No studies were located regarding respiratory effects in humans after exposure to α-HCH. In rats exposed via diet to α-HCH doses up to 70 mg/kg/day for an average of 9 months or up to 9 mg/kg/day for 2 years, there were no histopathology findings in the lungs (Fitzhugh et al. 1950).

β-HCH. In a cross-sectional study in southern Ghana, vegetable farmers who reported pesticide use showed a significant, positive association between serum levels of β-HCH and respiratory symptoms of cough, phlegm production, and wheezing (Quansah et al. 2016). Rats given doses up to 70 mg/kg/day for up to 10 weeks or up to 9 mg/kg/day for 2 years exhibited no microscopic pathology in the lungs (Fitzhugh et al. 1950).

γ-HCH (Lindane). In a cross-sectional study of vegetable farmers in southern Ghana who used pesticides, no association was observed between serum levels of γ-HCH and respiratory symptoms (cough, phlegm production, and wheezing) (Quansah et al. 2016). In humans, mucous membrane irritation of the nose and throat was observed after acute exposure to the HCH products dispensed by an overheated γ-HCH vaporizer (Conley 1952). Exposure levels were not reported and dermal exposure may also have occurred, although the observed irritation was probably due to direct action upon the

mucous membranes. An acute dermal poisoning of a 2-month-old infant exposed to a whole-body application of 1% γ-HCH lotion resulted in death. The autopsy revealed pulmonary petechiae (Davies et al. 1983).

No respiratory effects and no histopathology changes in the nasal cavities or lungs were observed in rats exposed to γ-HCH aerosol (up to 5 mg/m^3) 6 hours/day for 90 days (Oldiges et al. 1983) or in mice similarly exposed for 14 weeks (Klonne and Kintigh 1988). Mononuclear cell infiltrates in peribronchial and perivascular regions of the lung were observed in male mice administered 0.25 mg/kg/day γ-HCH by gavage in groundnut oil for 61 days (Tewari et al. 2017). Bronchoalveolar lavage (BAL) from the treated mice contained increased total leukocyte counts and neutrophil percentages.

In rats, dietary exposure to γ-HCH at doses up to 140 mg/kg/day for ~10 months or 30 mg/kg/day for 2 years resulted in histopathology changes in the lungs (Fitzhugh et al. 1950). Slight dyspnea was reported in rats exposed dermally for 24 hours to 1,000 or 2,000 mg/kg γ-HCH on a shaved patch of dorsal skin (Ullmann 1986a). The dyspnea was severe in one female administered the high dose. Rapid respiration or wheezing was noted in rats exposed dermally to ≥10 mg /kg/day γ-HCH for 13 weeks (EPA 1988a).

δ-HCH. No association between serum concentrations of δ-HCH and respiratory symptoms was observed in a cross-sectional study of vegetable farmers using pesticides in southern Ghana (Quansah et al. 2016).

Technical HCH or Unspecified Isomers of HCH. Neither intermediate- nor chronic-duration dietary exposure to technical HCH resulted in lung histopathology changes in rats given doses up to 70 mg/kg/day for 6 months or 9 mg/kg/day for 2 years (Fitzhugh et al. 1950).

2.5 CARDIOVASCULAR

Epidemiological Studies. Epidemiological studies of associations between cardiovascular effects in humans and biomarkers of exposure to β-HCH have been conducted. Table 2-9 provides a summary of the epidemiological data pertaining to cardiovascular effects and exposure to β-HCH in humans. Arrebola et al. (2015a) observed an association between serum β-HCH concentrations and incident hypertension in a cohort of 297 surgical patients followed for 10 years. A positive association between serum β-HCH concentrations and hypertension was seen among surgical patients with a BMI >26.3,

whereas no association was observed in those with a BMI <26.3 (Arrebola et al. 2015a). In cross-sectional studies, no association was reported between blood β-HCH concentrations and hypertension in a study of 1,615 Inuit adults in Greenland (Valera et al. 2013b), while an inverse association with hypertension was reported in a smaller study of Inuit adults in Quebec (Valera et al. 2013a). No association with peripheral artery disease was observed in a cross-sectional study of U.S. adult participants in the National Health and Nutrition Examination Survey (NHANES) (1999–2004) (Min et al. 2011). Epidemiological studies of cardiovascular effects and exposure to other HCH isomers were not located, but there are case reports of these effects in humans accidentally or intentionally exposed to γ-HCH.

Table 2-9. Summary of Epidemiological Studies of β-Hexachlorocyclohexane Exposure and Cardiovascular Effects

Reference, study type, and population	Outcome evaluated	Biomarker	Mean concentration (unless otherwise noted)	Result
Arrebola et al. 2015a Cohort, 297 noncancer surgical patients >16 years old, Spain, follow-up 10 years	**Hyper-tension**	Serum	11.2 ng/g lipid (median) (BMI >26.3 kg/m^2)	↑
			6.6 (BMI <26.3kg/m^2)	↔
Valera et al. 2013a Cross-sectional, 315 Inuit ≥18 years, Quebec, Canada	**Hype-rtension**	Plasma	0.13 µg/L lipid (GM)	↓
Valera et al. 2013b Cross-sectional, 1,614 Inuit aged ≥18 years, Greenland	Hyper-tension	Plasma	27.0 µg/kg lipid (GM)	↔
Min et al. 2011 Cross-sectional, 2,032 adults >40 years old, NHANES (1999–2004)	PAD	Serum	15.37 ng/g lipid (obese with PAD) 10.05 (non-obese with PAD) 10.90 (obese without PAD) 7.92 (non-obese without PAD)	↔

↑ = association with increase; ↓ = association with decrease; ↔ = no association; GM = geometric mean; NHANES = National Health and Nutrition Examination Survey; PAD = peripheral artery disease

Data regarding cardiovascular effects in animals are limited to the γ-HCH isoform.

α-HCH. No histopathology changes were noted in the hearts of rats given α-HCH via the diet at doses up to 70 mg/kg/day for ~9 months or up to 9 mg/kg/day for 2 years (Fitzhugh et al. 1950).

β-HCH. There were no microscopic lesions in the heart when rats were exposed by dietary administration to β-HCH doses up to 70 mg/kg/day for up to 10 weeks or up to 9 mg/kg/day for 2 years (Fitzhugh et al. 1950).

γ-HCH (Lindane). Autopsy findings in a 2-month-old infant who expired after whole-body application of 1% γ-HCH lotion were minimal but revealed epicardial petechiae (Davies et al. 1983). In a suicide attempt, a 56-year-old man intentionally ingested approximately 12 ounces of an insecticide containing 20% γ-HCH (Wiles et al. 2015). Cardiac symptoms of premature atrial and ventricular contractions, and atrial fibrillation after 3–5 days were observed. The man died on day 12 by committing suicide by means unrelated to γ-HCH, and no cardiac abnormalities were noted at autopsy.

There were no treatment-related changes to cardiac histopathology findings in rats or mice exposed by inhalation to γ-HCH concentrations up to 5 mg/m^3 for 13–14 weeks (Klonne and Kintigh 1988; Oldiges et al. 1983). Evidence for cardiac effects comes from studies of animals exposed orally. Increased serum levels of lactate dehydrogenase (LDH) and creatine phosphokinase and cardiac histopathological changes including separated muscle fibers and inflammatory cells were observed in male rats administered 100 mg/kg/day γ-HCH by gavage in olive oil for 30 days (Vijaya Padma et al. 2013). Rats receiving gavage doses of 3 mg/kg/day γ-HCH for 6 weeks exhibited tachycardia, increased blood pressure and plasma calcium levels, an increase in myocardial calcium influx, and decreased calcium-potassium-ATPase activity. Electrocardiographic changes included increased ST segment and T-wave amplitude and reduced R-R interval and P-wave (Anand et al. 1995). Rats exposed to γ-HCH *in utero* exhibited alterations in cardiac electrophysiology and histopathology; see Section 2.17 for details. Fitzhugh et al. (1950) reported no histopathology findings in the hearts of rats given γ-HCH in feed at doses up to 140 mg/kg/day for 10 months or 30 mg/kg/day for 2 years.

Mechanisms. Oxidative stress may contribute to the cardiovascular effects of γ-HCH. Lipid peroxidation was increased and antioxidant enzyme activities (superoxide dismutase, catalase, glutathione peroxidase, and glutathione) were reduced in cardiac tissue from male rats treated with 8.8 mg/kg/day γ-HCH via gavage for 3 weeks (Kamal El-Dein et al. 2016). Serum lipid and creatine phosphokinase levels were also increased at this dose. Pre-treatment with the antioxidant α-lipoic acid attenuated the γ-HCH-induced effects on serum lipids, CPK, lipid peroxidation and antioxidant enzyme activities in the heart.

Technical HCH or Unspecified Isomers of HCH. Kashyap (1986) reported electrocardiogram (ECG) abnormalities in 15% of 45 factory workers involved in the production of technical-grade HCH; exposure concentrations were not reported and dermal exposure may have occurred. Technical HCH administered to rats in feed did not induce cardiac histopathology changes at doses up to 70 mg/kg/day for 6 months or 9 mg/kg/day for 2 years (Fitzhugh et al. 1950).

2.6 GASTROINTESTINAL

Data on gastrointestinal effects in humans were limited to γ-HCH. No studies were located regarding gastrointestinal effects in animals following dermal exposure to any of the HCH isomers.

α-HCH. There were no microscopic gastrointestinal lesions in rats given α-HCH via the diet at doses up to 70 mg/kg/day for ~9 months or up to 9 mg/kg/day for 2 years (Fitzhugh et al. 1950).

β-HCH. Dietary administration of β-HCH doses up to 70 mg/kg/day for up to 10 weeks or up to 9 mg/kg/day for 2 years did not result in histopathology changes in the gastrointestinal tracts of rats (Fitzhugh et al. 1950).

γ-HCH (Lindane) Lindane exposures reported to the Texas poison control network between 1998 and 2002 were reviewed by Forrester et al. (2004). Ingestion was the primary exposure route (79%), and reported symptoms included vomiting, nausea, and abdominal pain (doses were not specified). Vomiting and diarrhea occurred in a child (Ramchander et al. 1991) and a woman (Hall and Hall 1999) who were exposed to 1% γ-HCH applied to the skin to treat rash or scabies.

Rats exposed to 5 mg/m^3 γ-HCH aerosol for 6 hours/day, 7 days/week exhibited persistent diarrhea beginning after 2 weeks of exposure and continuing for nearly 3 weeks; exposure to 1 mg/m^3 did not induce diarrhea (Oldiges et al. 1983). No gross necropsy or histopathology changes were observed in the gastrointestinal tracts of these rats (Oldiges et al. 1983). In mice exposed to concentrations up to 5 mg/mg^3 for 14 weeks, no gastrointestinal effects were noted, and there were no gross or microscopic changes to the gastrointestinal tract at necropsy (Klonne and Kintigh 1988). Microscopic examination of the stomach, small intestine, and colon showed no treatment-related changes in rats given γ-HCH via feed for 10 months at up to 140 mg/kg/day or 2 years at up to 30 mg/kg/day (Fitzhugh et al. 1950).

Technical HCH or Unspecified Isomers of HCH. Fitzhugh et al. (1950) did not observe any effects of treatment on the gastrointestinal tract of rats given technical HCH via diet for 6 months (up to 70 mg/kg/day) or 2 years (up to 9 mg/kg/day).

2.7 HEMATOLOGICAL

Epidemiological Studies. In a cross-sectional study of adolescents and adults living near a former HCH production facility in Brazil, an increase in eosinophilia was associated with serum β-HCH levels (Freire et al. 2015). The results of a case-control study showed a positive association between serum levels of α-HCH and childhood aplastic anemia, but no association with serum β- or γ-HCH (Ahamed et al. 2006).

α-HCH. Dietary administration of α-HCH doses up to 70 mg/kg/day for up to 9 months or up to 9 mg/kg/day for 2 years did not result in histopathology changes in the spleen or bone marrow of rats (Fitzhugh et al. 1950).

β-HCH. Exposure to β-HCH at doses of 22.5–25 mg/kg/day in the diet for 13 weeks in rats resulted in statistically significant decreases in numbers of red blood cells and white blood cells, as well as reduced hemoglobin and packed cell volume values (Van Velsen et al. 1986). At this dose, 50% of the exposed animals were sacrificed moribund. Extramedullary hematopoiesis was observed in males and females surviving for 13 weeks at 23-26 mg/kg/day, but not in the early decedents. There were no histopathology findings in the spleen or bone marrow of rats given β-HCH in the diet for up to 10 weeks at 70 mg/kg/day or 2 years at 9 mg/kg/day (Fitzhugh et al. 1950). No other data on hematological effects in animals exposed to β-HCH were located.

γ-HCH (Lindane). Hematological effects have been reported in case reports of humans following exposure to γ-HCH. Hypochromic anemia was reported in a 2.5-year-old boy who was exposed to γ-HCH in a home in which a pesticide vaporizer was operated. Air γ-HCH concentrations measured in the basement and living room of the house were 2.4–5.5 μg/m^3; however, the actual concentration the child was exposed to and the duration of exposure were not determined (Morgan et al. 1980). Aplastic anemia was reported in a boy exposed to γ-HCH used as an insecticide in his home and in a man exposed at work (Rugman and Cosstick 1990). In both cases, the anemia was reversible and was not present in other family members. The levels and routes of exposure are not known, although they are presumed to be inhalation and dermal. Aplastic anemia was also documented in a man who applied γ-HCH to his skin for 3 weeks for treatment of scabies (Rauch et al. 1990).

A woman who committed suicide by drinking γ-HCH was found to have disseminated intravascular coagulation (a condition where abnormal blood clotting occurs in blood vessels throughout the body) during the period when serum γ-HCH levels were elevated (Sunder Ram Rao et al. 1988). Reduced

hemoglobin and hematocrit values and a nearly complete absence of red blood cell precursors in bone marrow were reported in a 2-year-old boy exposed to a family dog that was dipped regularly in mange treatment containing 12% γ-HCH (Vodopick 1975).

In an inhalation study of rats exposed to 5 mg/m^3 γ-HCH aerosol for 90 days, bone marrow myelogram changes were observed, including increased reticulocytes in males and females, increased stem cells and myeloblasts in males, and decreased lymphocytes in females (Oldiges et al. 1983). No changes to blood parameters were noted in this study (Oldiges et al. 1983). Mice exposed to concentrations of γ-HCH up to 5 mg/m^3 for 14 weeks exhibited no hematological changes or effects on bone marrow smears (Klonne and Kintigh 1988).

Hong and Boorman (1993) reported significant suppression in bone marrow cellularity, erythrocyte precursors, and granulocyte-macrophage progenitor cells, and residual progenitor cell damage in male B6C3F$_1$ mice given 20 or 40 mg γ-HCH/kg/day by gavage in corn oil for 3 days. In a similar experiment, dose-dependent decreases in bone marrow cellularity, granulocyte-macrophage progenitor cells, and pluripotent bone marrow stem cells were noted following 10 days of exposure to 10 or 20 mg γ-HCH/kg/day (Hong and Boorman 1993). No effects on blood leukocytes were reported in male mice administered 0.25 mg/kg/day γ-HCH by gavage in oil for 61 days (Tewari et al. 2017). No hematological effects were noted in rats exposed to 10 mg γ-HCH/kg/day in the diet for 12 weeks (Suter 1983) or in beagle dogs exposed to 2.92 mg/kg/day γ-HCH in the diet for 104 weeks (Rivett et al. 1978). No histopathology changes were observed in the spleen or bone marrow of rats exposed to γ-HCH in feed for up to 10 months at 140 mg/kg/day or up to 2 years at 30 mg/kg/day (Fitzhugh et al. 1950).

Technical HCH or Unspecified Isomers of HCH. The results of a case-control study of childhood aplastic anemia indicated no association between this disease and serum levels of total-HCH (including α-, β-, γ-, and δ-HCH) (Ahamed et al. 2006). Hematological abnormalities, including alterations in polymorphonuclear leukocyte count, lymphocyte count, reticulocyte count, and prothrombin time have been reported following chronic human occupational exposure to γ-HCH (Brassow et al. 1981). Exposure concentrations were not specified in these studies and concomitant dermal exposure probably occurred. Granulocytopenia, aplastic anemia, and pancytopenia have been reported in a number of case reports of individuals following exposure to γ-HCH and other pesticides such as DDT in the home, during the handling of the pesticide, or from a nearby formulating plant (Danopoulos et al. 1953; Friberg and Martensson 1953; Gewin 1939; Loge 1965; Mendeloff and Smith 1955). Exposure concentrations were not reported, dermal exposure was likely, and in many cases, there was concomitant exposure to other

pesticides. Excessive dermal exposure to HCH was reported to result in aplastic anemia and bone marrow hyperplasia in a woman who bathed her dog once a week for 2 years with a preparation that reportedly contained 2% HCH (Woodliff et al. 1966).

No hematological effects were seen in rats following oral exposure to 60 mg/kg/day technical-grade HCH for 30 days (Dikshith et al. 1989a). In a study evaluating the influence of vitamin A on the toxicity of technical-grade HCH, significant decreases in total white blood cell counts and clotting time were reported in rats fed vitamin A-deficient diets containing technical-grade HCH at a dose level of 90 mg/kg/day for 7 weeks (Joseph et al. 1992c). In a similar study, rats fed a vitamin A-supplemented diet containing the same dose level of technical-grade HCH for 7 weeks exhibited a significant reduction in total white blood cell count, but not red blood cell count (Joseph et al. 1992c). No treatment-related histopathology changes were seen in the spleen or bone marrow of rats after 6 months of dietary exposure to technical HCH at 70 mg/kg/day or 2 years of dietary exposure at 9 mg/kg/day (Fitzhugh et al. 1950).

2.8 MUSCULOSKELETAL

Data regarding musculoskeletal effects in humans were limited to oral exposure to γ-HCH (see γ-HCH subsection below).

α-HCH. There were no microscopic lesions in the leg muscles or bones of rats given α-HCH via the diet at doses up to 70 mg/kg/day for ~9 months or up to 9 mg/kg/day for 2 years (Fitzhugh et al. 1950).

β-HCH. Dietary administration of β-HCH at doses up to 70 mg/kg/day for up to 10 weeks or up to 9 mg/kg/day for 2 years did not induce histopathology changes in the leg muscles or bones of rats (Fitzhugh et al. 1950).

γ-HCH (Lindane) Ingestion of a single dose of approximately 15–30 mL γ-HCH powder (was associated with seizures and limb muscle weakness and necrosis in an adult man (Munk and Nantel 1977); a muscle biopsy conducted 15 days after ingestion showed no evidence of denervation or neuropathy. Widespread striatal muscle necrosis was seen in a woman who died 11 days after intentionally ingesting 8 ounces of a 20% γ-HCH solution (Sunder Ram Rao et al. 1988). A suicidal 21-year-old male developed rhabdomyolysis as indicated by muscle pain, muscle tenderness, proteinuria, myoglobinuria, elevated serum levels of aspartate aminotransferase (AST), potassium, creatinine, and creatinine protein kinase

(CPK) 1–3 days following ingestion of a single unknown dose of γ-HCH (Shah et al. 2013). The man recovered after 3 weeks of clinical care.

Microscopic examination of skeletal muscle in mice and rats (as well as femur in mice) exposed by inhalation to concentrations up to 5 mg/m^3 for 13–14 weeks did not show any treatment-related effects (Klonne and Kintigh 1988; Oldiges et al. 1983). Decreased medullary area in the femur bone was found in young rats treated with 20 mg/kg/day of γ-HCH by gavage for 10 weeks (Andrews and Gray 1990). Fitzhugh et al. (1950) reported no treatment-related histopathology changes in the leg muscles or bones of rats exposed via diet for 10 months at doses up to 140 mg/kg/day or for 2 years at 30 mg/kg/day.

Technical HCH or Unspecified Isomers of HCH. No microscopic lesions were observed in the leg muscles or bones of rats given dietary technical HCH doses up to 70 mg/kg/day for 6 months or 9 mg/kg/day for 2 years (Fitzhugh et al. 1950).

2.9 HEPATIC

Epidemiological Studies. Human epidemiological data pertaining to HCH exposure and hepatic effects (see Table 2-10) are limited to two cross-sectional studies of β-HCH (Arrebola et al. 2014; Freire et al. 2015). No association between serum lipids and serum or adipose concentrations of β-HCH was observed in a study of 298 non-surgical cancer patients in Spain (Arrebola et al. 2014). In a study of adolescents and adults residing near a former HCH production facility in Brazil, serum β-HCH was associated with increased risk of elevated total and indirect serum bilirubin in females, but not in males (Freire et al. 2015). There were no associations between serum β-HCH and risk of elevated direct serum bilirubin or serum enzymes (Freire et al. 2015).

Table 2-10. Summary of Epidemiological Studies of β-Hexachlorocyclohexane Exposure and Hepatic Effects

Reference, study type, and population	Outcome evaluated	Biomarker	Mean concentration	Result
Arrebola et al. 2014 Cross-sectional, 298 noncancer surgical patients >16 years old, Spain	Measures of serum lipids (total triglycerides, HDL, LDL, and total cholesterol)	Serum or adipose	19.60±28.74 ng/g lipid (biomarker not reported)	↔

Table 2-10. Summary of Epidemiological Studies of β-Hexachlorocyclohexane Exposure and Hepatic Effects

Reference, study type, and population	Outcome evaluated	Biomarker	Mean concentration	Result
Freire et al. 2015 Cross-sectional, 339 males and 375 females, age >14 years residing near former HCH production facility, Brazil	**Elevated total and indirect serum bilirubin**	Serum	Males: 3.72 µg/g lipid Females: 3.09 µg/g lipid	M: ↔ F: ↑
	Elevated direct serum bilirubin			M: ↔ F: ↔
	Elevated serum AST, ALT, GGT			M: ↔ F: ↔

↑ = association with increase; ↔ = no association; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = γ-glutamyl transferase; HCH = hexachlorocyclohexane; HDL = high-density lipoprotein; LDL = low density lipoprotein

α-HCH. Hepatic effects have been observed in rats, mice, and hamsters after intermediate- and chronic-duration oral exposures to α-HCH. Increases in absolute and relative liver weight, coupled with hepatocellular hypertrophy and/or hyperplasia, have been observed in F344 rats at doses of at least 20 mg/kg/day for 28 days (Sumida et al. 2007) and in Wistar rats at doses of 45 mg/kg/day for 24 weeks (Nagasaki et al. 1975) or 35 mg/kg/day for 48 weeks (Ito et al. 1975). Rats receiving 60–70 mg/kg/day α-HCH in the diet as part of a chronic study died early (mean survival 35.9 weeks compared with 58.3 weeks in controls); at necropsy, these animals exhibited 2-fold increases in liver weight and histopathology changes of moderate severity, including focal necrosis and fatty degeneration (Fitzhugh et al. 1950). Hypertrophied liver cells were reported in mice fed 18 mg/kg/day α-HCH for 24 weeks (Ito et al. 1973). More severe effects, including hepatomegaly, bile duct proliferation, oval cells, nodular hyperplasia, megalocytosis, and a doubling of liver weight, were observed in several strains of mice (DDY, ICR, DBA/2, C57BL/6, C3H/He, and HPBC57BL) given feed containing 90 mg/kg/day for at least 21 weeks (Nagasaki et al. 1975; Tryphonas and Iverson 1983). This dose (90 mg/kg/day) yielded a significant increase in hepatocellular carcinomas in all but the C57BL/6 strain of mouse (Nagasaki et al. 1975; Tryphonas and Iverson 1983). Nagasaki et al. (1975) also conducted an experiment using male Syrian hamsters exposed to α-HCH in diet for 24 weeks. In hamsters, a 38% increase in relative liver weight, with increased liver cell hypertrophy, was observed at 45 mg/kg/day.

Chronic (107 weeks) exposure to α-HCH in feed resulted in dose-related increases in the severity of liver histopathology changes in rats (Fitzhugh et al. 1950). Very slight to slight microscopic damage in the liver, along with ≥32% increase in relative liver weight, was seen at ≥4 mg/kg/day (Fitzhugh et al. 1950). The microscopic changes were described as "characteristic of certain chlorinated cyclic compounds" without further detail. Rats at the highest dose in this study (60–70 mg/kg/day) exhibited reduced

survival (mean <1 year); these animals exhibited more severe liver effects, as described above with the intermediate-duration studies.

Both rats and mice exposed to α-HCH have developed liver cancers. Hepatocellular carcinomas were reported in rats administered 70 mg/kg/day in the diet for 48 or 72 weeks (Ito et al. 1975), and liver cancers were observed in mice given 18–90 mg α-HCH/kg/day for 16–36 weeks (Hanada et al. 1973; Ito et al. 1973, 1976; Nagasaki et al. 1975; Tryphonas and Iverson 1983; Tsukada et al. 1979) (see Section 2.19). Hamsters exposed to 45 mg/kg/day for 24 weeks did not develop liver tumors (Nagasaki et al. 1975).

Mechanisms: Little information is available on potential mechanisms of α-HCH-induced hepatotoxicity but is possible that oxidative stress and/or mitotic disturbances may be involved. Administration of 1.8 mg/kg/day α-HCH in the diet to rats for 15 or 30 days resulted in increases in lipid peroxidation and microsomal superoxide production in the liver (Barros et al. 1991). In male Donryu rats, a 3-week dietary exposure to α-HCH resulted in mitotic disturbances including an increased mitotic rate and an increased frequency of polyploid hepatic cells (Hitachi et al. 1975).

β-HCH. Hepatic effects have been observed in intermediate-and chronic-duration studies of β-HCH in rats and mice exposed via the diet. Moderate to marked liver damage, including fatty degeneration and focal necrosis, was reported in rats that died prematurely (within 10 weeks of study initiation) after dietary exposure to doses of 60–70 mg/kg/day (Fitzhugh et al. 1950). In a comprehensive 13-week study of rats (Van Velsen et al. 1986), dose-related increases in hepatic effects were seen at all doses (≥0.18 mg/kg/day) in males. At 0.18 mg/kg/day, the effects consisted of hyalinization of centrilobular cells; at ≥4.5 mg/kg/day, increased mitoses in females, periportal fat accumulation in both sexes, and isolated instances of focal necrosis in males were observed. Relative liver weights were increased by 10% or more at 1.0 mg/kg/day in females and 4.5 mg/kg/day in males (Van Velsen et al. 1986). At the highest dose in this study (22.5–25 mg/kg/day), liver weights were doubled; at this dose, 50% of the animals were sacrificed moribund before the end of the study (Van Velsen et al. 1986). Liver cell hypertrophy was reported in rats fed 35 mg/kg/day in the diet for 48 weeks or 70 mg/kg/day for 24 weeks (Ito et al. 1975). In mice, exposure for 24 weeks to 18 mg/kg/day in the diet resulted in an 18% increase in liver weight, and liver cell hypertrophy at higher doses (≥45 mg/kg/day) (Ito et al. 1973). Mice exposed to 50–60 mg/kg/day in the diet for 32 weeks exhibited hepatic foci of degeneration (Hanada et al. 1973).

Chronic dietary exposure of rats to lower doses of β-HCH resulted in increased liver weight and dose-related histopathology changes in the liver (Fitzhugh et al. 1950). At 0.7–0.9 mg/kg/day, a 34% increase in liver weight and slight microscopic changes described as "characteristic of certain chlorinated cyclic compounds" were observed.

Liver tumors were not reported in mice exposed to β-HCH for 24–32 weeks (Hanada et al. 1973; Ito et al. 1973) or in rats exposed for 24–48 weeks (Ito et al. 1975); however, Thorpe and Walker (1973) reported liver cancer in mice fed 34 mg/kg/day for 26 months.

γ-HCH (Lindane). Two case reports of intentional ingestion of γ-HCH have documented increases in serum liver enzymes; neither report provided an estimate of the associated dose of γ-HCH. A 30-year-old male farmer from rural India ingested a single dose of approximately 50 mL of 2% γ-HCH solution in a suicide attempt (Paul et al. 2013). Six hours after the ingestion, the man went to the emergency department where initial examination and laboratory tests were normal. Nausea was noted on the second day, and abdominal tenderness and increased serum levels of bilirubin, AST, and alanine aminotransferase (ALT) were observed on day 5. Treatment with hemodialysis for acute kidney injury spontaneously reduced the hepatic enzymes and the man recovered after 3 weeks. A 56-year-old man ingested approximately 12 ounces of an insecticide containing 20% γ-HCH intentionally in a suicide attempt (Wiles et al. 2015). Hepatic enzymes (AST, ALT, alkaline phosphatase [ALP], and γ-glutamyl transferase [GGT]) were increased after 3 days. The man died on day 12 after committing suicide by other means; at autopsy, no gross or microscopic abnormalities were noted.

Rats exposed to γ-HCH aerosol (5 mg/m^3 for 6 hours/day) exhibited increased hepatic cytochrome P450 concentration after 90 consecutive days, but this level returned to control values after a 4-week recovery period (Oldiges et al. 1983). Statistically significant, but modest, increases in absolute and relative liver weights (up to 12%) were observed at this exposure concentration, but there were no concomitant effects of treatment on serum chemistry or liver histopathology in the rats (Oldiges et al. 1983). Mice exposed to the same concentration 5 days/week for 14 weeks exhibited no changes in clinical chemistry, liver weights, or liver histology (Klonne and Kintigh 1988).

Hepatic effects have been documented in rats and mice exposed to γ-HCH via oral administration for acute, intermediate, and chronic durations. At lower doses, effects include increased serum enzymes,

increased liver weight, and hepatocellular hypertrophy. Higher doses and/or longer exposure durations result in liver effects of increasing severity, including vacuolar degeneration, necrosis, and congestion.

Acute-duration oral studies in rats show increases in liver weight as well as histopathology changes in animals exposed to γ-HCH. In male Wistar rats, a single gavage dose of 60 mg/kg/day resulted in marked centrilobular hepatic necrosis (Singh and Sharma 2011), and fatty degeneration, vacuolation, and necrosis were observed after gavage doses of 5 mg/kg/day for 3 days (Hfaiedh et al. 2012). Ultrastructural changes observed in the liver of Sprague-Dawley rats (sex not specified) after 2 days of exposure to 30 mg/kg/day in feed were reduced number of cells per field; increased cell, nucleus, and nucleolus size; and slight cellular disorganization (Ali and Shakoori 1998). Although no histopathological examinations were performed, no significant increase in liver weight was noted in Sprague-Dawley rats exposed to 10 mg γ-HCH/kg/day for a minimum of 4 days (Joy et al. 1982). A significant increase (15% relative to controls) in absolute, but not relative, liver weight was observed in rats exposed to 15 mg γ-HCH/kg/day for 5 days (Parmar et al. 2003). A significant, but modest, increase (6% relative to controls) in relative liver weight was observed in a small group of male F344 rats given 10 mg/kg/day γ-HCH by gavage for 7 days, but not in a group similarly exposed for 14 days (Sumida et al. 2007). Histopathology evaluations of these animal were not reported.

Increases in serum enzymes indicative of hepatotoxicity have been reported in rats exposed once to 12 mg/kg/day (Attia et al. 2011) or for 3 days to 5 mg/kg/day (Hfaiedh et al. 2012). Male Wistar rats fed 13.5 mg γ-HCH/kg/day in their diet for 12 days exhibited decreased activities of liver enzymes (malic enzyme, glucose-6-phosphate dehydrogenase, phosphogluconate dehydrogenase, citrate cleavage enzyme, and fatty acid synthase) and increased levels of serum triglycerides (Boll et al. 1995). Significantly increased liver microsomal 7-ethoxycoumarin-O-dealkylase activity was found in Osborne-Mendel rats exposed to 11.2 mg/kg/day γ-HCH and in CF1 and B6C3F1 strain mice exposed to 23.6 and 50.5 mg/kg/day in the diet for 3 days (Oesch et al. 1982).

The most common histopathology finding in the livers of rats and mice exposed to oral doses of γ-HCH for intermediate durations is hepatocellular hypertrophy. A dose-dependent increased incidence of liver centrilobular hypertrophy was reported in Wistar rats dosed with ≥0.4 mg γ-HCH/kg/day in the diet for 12 weeks (Suter 1983). In multigeneration reproductive toxicity studies in rats, hepatocellular hypertrophy reportedly occurred at increased incidence in F0 and F1 male and female Sprague-Dawley rat parents exposed to 3–6 mg/kg/day (Matsuura et al. 2005) and in F1 male CD rat parents exposed to 1.7 mg/kg/day (EPA 1991a). In both studies, no hepatic effects were seen at a dose of about 1 mg/kg/day

γ-HCH (EPA 1991a; Matsuura et al. 2005). Rats exposed to 35 mg/kg/day γ-HCH for 48 weeks in the diet exhibited hepatocellular hypertrophy (Ito et al. 1975). Similar findings were reported in a study of Wistar rats given ≥7–8 mg γ-HCH/kg/day in the diet for up to 52 weeks, in which a dose-related increase in periacinar hepatocytic hypertrophy was seen (Amyes 1990). In mice, administration of 90 mg γ-HCH/kg/day in the diet for 24 weeks was reported to result in centrilobular hypertrophy and a significant increase (33%) in relative liver weight (Ito et al. 1973).

In other intermediate-duration studies, more severe lesions have been noted in the liver. An early study (Ortega et al. 1957) reported the development of liver cell "liposphere" in rats fed 2.5 mg γ-HCH/kg/day in the diet for 32 weeks; in older literature, these changes were described as spherical cytoplasmic inclusions of a fatty nature. Ali and Shakoori (1998) reported ultrastructural changes in the livers of Sprague-Dawley rats exposed for 15 days to a dose of 18 mg/kg/day in food. Findings observed in the treated animals included reduced number of cells per field; increased cell, nucleus, and nucleolus size; vacuoles in the cytoplasm; and apparent fatty degeneration. At a dose of 20 mg/kg/day γ-HCH administered by daily gavage for 30 days, liver histopathology changes in Sprague-Dawley rats included megalocytosis, vacuolar degeneration, venous and sinusoidal congestion, and lymphocytic infiltration (Fatih Fidan et al. 2008). At 100 mg/kg/day for the same duration, the livers of Wistar rats showed vacuolar degeneration of hepatocytes and marked degradation of the central vein (Vijaya Padma et al. 2011). Focal degeneration of hepatocytes was noted in rabbits given γ-HCH at a dose of 7 mg/kg/day by gavage for 4 weeks (Grabarczyk et al. 1990; Kopec-Szlezak et al. 1989).

Two intermediate-duration studies reported no liver effects in rats exposed to γ-HCH. Sumida et al. (2007) observed no treatment-related hepatic effects (clinical chemistry, liver weight, or histopathology) in F344 rats exposed for 28 days at 10 mg/kg/day via gavage. The lack of effect in this study may indicate a lower sensitivity of F344 rats to hepatic effects of this isomer, but also could be a reflection of the very small numbers of animals tested (four males per group). In an older study focused on neurotoxicity testing, groups of eight Wistar rats given 50 mg/kg/day for 40 days in feed exhibited increased liver weight, but normal liver function test results and histology (Desi 1974).

In addition to histopathology changes, intermediate-duration oral exposure to γ-HCH has resulted in increased liver weights. Rats exposed to 2.5 mg γ-HCH/kg/day for 21 days showed a significant increase (13% higher than controls) in absolute, but not relative, liver weight (Parmar et al. 2003). Treatment of female rats with ≥10.6 mg γ-HCH/kg/day or of male and female mice with ≥21.1 mg/kg/day in the diet for 3 months resulted in significant increases in absolute and relative liver weights; histopathological

examinations were not performed (Oesch et al. 1982). Increased absolute and relative liver weights occurred at doses (≥3–5 mg/kg/day) associated with increased incidences of hepatocellular hypertrophy in parental animals exposed to γ-HCH in the diet in a 2-generation reproduction toxicity study (Matsuura et al. 2005). Exposure of dd mice to dietary doses of 90 mg/kg/day for 24 weeks resulted in a 33% increase in relative liver weight (Ito et al. 1973).

Increased liver weights have also been reported in offspring of rats exposed to γ-HCH during gestation and/or lactation (Srinivasan et al. 1991). Additional details are provided in Section 2.17 (Developmental).

Increases in serum enzymes and lipids indicating hepatic effects have been observed in rats and rabbits exposed for intermediate durations to γ-HCH. Significant increases in serum AST, ALT, GGT, ALP, and/or LDH were observed in Wistar rats exposed to 100 mg/kg/day for 4 weeks (Etim et al. 2006; Vijaya Padma et al. 2011). Increased serum levels of AST, LDH, cholesterol, total triglycerides, free fatty acids, and total phospholipids were observed in male Sprague-Dawley rats administered 8.8 mg/kg/day γ-HCH by gavage in water for 3 weeks (Kamal El-Dein et al. 2016). Rabbits treated with 4.21 mg γ-HCH/kg/day by gavage for 28 days exhibited significant increases in plasma ALP and ALT activities immediately following initiation of dosing; these activities returned to control levels by day 14 (Cerón et al. 1995). The plasma level of AST activity also increased immediately following dosing and remained elevated up to 7 days postexposure (day 35) (Cerón et al. 1995).

Oral exposure to γ-HCH for intermediate durations has resulted in induction of hepatic cytochrome P450 levels in rats and mice. Significant increases in hepatic microsomal cytochrome P450 levels were found in Wistar rats fed diets containing 1.8 mg/kg/day γ-HCH for 15 or 30 days (Barros et al. 1991). A dose- and time-dependent increase of P450 and P450-dependent enzyme levels was observed in the liver of rats exposed to γ-HCH (Parmar et al. 2003). P450 content was significantly increased in rats exposed to 10 mg γ-HCH/kg/day for 5 days, and in rats exposed to 2.5 mg γ-HCH/kg/day for 15 and 21 days. There was no significant increase in P450 content in rats exposed to <10 mg γ-HCH/kg/day for 5 days. Several P450-dependent enzymes, 7-ethoxyresorufin-O-deethylase (EROD), 7-pentoxyresorufin-O-dealkylase (PROD), and N-nitrosodimethylamine demethylase (NDMA-d), were significantly increased in rats exposed to 5 mg γ-HCH/kg/day for 5 days or 2.5 mg γ-HCH/kg/day for 15 and 21 days (Parmar et al. 2003). Increases in liver microsomal mixed-function oxidase activity were observed in rats exposed to ≥10.6 mg γ-HCH/kg/day and mice exposed to ≥21.1 mg/kg/day in the diet for 3 months (Oesch et al. 1982).

Hepatotoxicity has been documented in animals exposed by oral administration to γ-HCH for chronic durations. After Sprague-Dawley rats were exposed for 18 months to γ-HCH at a dose of 9 mg/kg/day in feed, the following microscopic findings were observed in the liver: increased cell, nucleus, and nucleolus size; extensive cytoplasmolysis; slight cytoplasmic degeneration; and increasing nuclear distortion (Ali and Shakoori 1998). Chronic exposure of rats to 7–9 mg/kg/day γ-HCH in the diet for 107 weeks resulted in increased liver weight (35% higher than controls) and very slight microscopic liver damage described as "characteristic of certain chlorinated cyclic compounds" (Fitzhugh et al. 1950). At higher doses, liver necrosis and fatty degeneration were observed (Fitzhugh et al. 1950). Male CD-1 mice exposed to 20.5 mg/kg/day γ-HCH via feed for 78 weeks exhibited centrilobular hepatocyte hypertrophy (EPA 2000a). No liver lesions were observed by light or electron microscopy in NMRI mice given ~8 mg/kg/day for 80 weeks (Herbst et al. 1975; Weisse and Herbst 1977). At gross necropsy, the livers of dogs exposed to 2.9 mg/kg/day for 104 weeks were noted to be dark, but no histopathology changes were reported (Rivett et al. 1978).

Increased incidences of liver tumors (hepatomas, hepatocellular carcinomas) have been observed in mice exposed via diet to γ-HCH for intermediate and chronic durations at γ-HCH doses as low as 13.6 mg/kg/day (Hanada et al. 1973; NCI 1977; Thorpe and Walker 1973; Wolff et al. 1987). These studies are discussed further in Section 2.19 (Cancer).

One study of dermal exposure to γ-HCH reported also reported liver effects. Centrilobular hepatocellular hypertrophy was reported in male and female rats exposed to γ-HCH ≥60 mg /kg/day by dermal application for 6 hours/day, 5 days/week, for 13 weeks (EPA 1988a).

Mechanisms. There is some evidence that oxidative stress may contribute to the hepatic effects of γ-HCH. Significant increases in hepatic microsomal superoxide anion production and cytoplasmic superoxide dismutase activity and lipid peroxidation were found in the livers of Wistar rats fed diets containing 1.8 mg/kg/day γ-HCH for 15 or 30 days (Barros et al. 1991). Groups of 10 male rats (strain not reported) were administered a single dose of γ-HCH (98% purity) in corn oil at a dose of 0 or 12 mg/kg and then sacrificed 24 hours later in a study aimed at evaluating the ameliorating effects of co-treatment with the antioxidants nigella sativa oil and omega 3 fatty acids. Co-treatment with nigella sativa oil and omega 3 fatty acids attenuated the effects of γ-HCH on lipid parameters, clinical chemistry parameters, lipid peroxidation, and antioxidant enzyme activities (Attia et al. 2011). The mitigating effects of nigella sativa oil and omega 3 fatty acids could have resulted from their antioxidant activity or from effects on the absorption or metabolism of γ-HCH.

δ-HCH. Liver cell hypertrophy was observed in rats fed with 70 mg/kg/day of δ-HCH in the diet for 48 weeks (Ito et al. 1975). Similarly, mice exposed for 24 weeks to 90 mg/kg/day δ-HCH in feed exhibited a 23% increase in relative liver weight and centrilobular hypertrophy (Ito et al. 1973).

Unspecified HCH Isomers or Mixtures of HCH Isomers. In humans, statistically significant increases in the blood levels of the enzymes LDH (33%), leucine aminopeptidase (45%), and γ-glutamyl transpeptidase (174%) were reported in 19 individuals occupationally exposed to technical-grade HCH for over 10 years in an HCH-formulating plant (Kashyap 1986) compared to a control group of workers. The HCH isomer concentrations in serum were 10-fold higher in the exposed group than in the control group of workers. Both inhalation and dermal exposure probably occurred.

Increases in liver weight, serum enzymes and lipids, and liver histopathology changes have been observed in animals exposed to technical-grade HCH by oral administration for acute durations. Technical-grade HCH was reported to cause increases in liver weight and serum enzyme activities (e.g., ALP, aminotransferases) in male Swiss mice given 72 mg/kg in the diet for 2 weeks (Ravinder et al. 1989). Other effects seen in the mice included significantly increased serum triglycerides, phospholipids, and cholesterol, as well as hypertrophy of hepatocytes with enlargement of nuclei, centrilobular degeneration, and focal necrosis (Ravinder et al. 1990). Statistically significant decreases in the liver activities of AST and LDH were observed in pregnant mice administered a single dose of technical-grade HCH (5 mg/kg) on GD 9 (Dikshith et al. 1990). Pregnant animals dosed with 25 mg/kg also experienced decreases in liver ALT and ALP activity (Dikshith et al. 1990). Virgin mice administered a single dose of 5–200 mg/kg technical-grade HCH had statistically significant decreases in liver activity of ALT and AST, and increases in liver ALP activity were observed in the virgin mice at doses ≥25 mg/kg. However, with the exception of decreased AST activity in pregnant mice, the dose-response relationships were questionable (Dikshith et al. 1990). There were also no corresponding pathological changes in the livers of the treated mice. However, at a higher dose (50 mg/kg/day) of technical-grade HCH administered to mice for 1, 5, or 15 days by oil gavage, congestion of hepatic portal vessels and central vein, swollen hepatic cells with vacuolar or parenchymatous degeneration, and fatty changes in periportal and centrilobular cells were observed (Philip et al. 1989).

Liver enzyme level changes were seen in male, but not female, rats given 5 or 25 mg/kg/day by gavage for 90 days; at these doses, there were significant mortalities (Dikshith et al. 1991b). A 65% decrease in liver weight, decreased liver AST and LDH activities, and increased ALP activity were noted in male rats

given 60 mg/kg by gavage for 30 days, but animals had normal liver histology (Dikshith et al. 1989a). Technical-grade HCH was reported to deplete the hepatic vitamin A content in male rats fed a diet containing 90 mg/kg/day HCH for 7 weeks (Joseph et al. 1992b). No adverse hepatic effects were seen in rats treated with 50 mg/kg/day technical-grade HCH for 30 days (Khanna et al. 1990) or in pigs exposed to 0.8 mg/kg/day for 90 days (Wang et al. 2006). Mice fed diets containing 90 mg/kg/day of HCH for 8 months exhibited increased liver weight, glycogen accumulation, and decreased glucose-6-phosphatase and fructose-1,6-di- phosphatase activities (Karnik et al. 1981). Enlargement of hepatocytes, nuclear pyknosis, margination, and vacuolation were observed in rats fed 20 mg/kg/day technical-grade HCH in the diet for 360 days (Dikshith et al. 1991a). Chronic dietary administration of technical-grade HCH to rats at a dose of 4 mg/kg/day resulted in slight microscopic liver damage, which the study authors described as "characteristic of certain chlorinated cyclic compounds" (Fitzhugh et al. 1950).

Technical-grade HCH was also reported to cause liver cancer in mice following exposure to 90 mg/kg/day in the diet for time periods ranging from 2 to 8 months (Bhatt and Bano 2009; Bhatt and Nagda 2012; Karnik et al. 1981; Thakore et al. 1981; Trivedi et al. 2007, 2009) or exposure to 10–50 mg/kg/day for 80–88 weeks (Kashyap et al. 1979; Munir et al. 1983) (see Section 2.19).

Hepatic effects have been seen after dermal exposure to technical-grade HCH. Alterations in liver histopathology, including dilation of sinusoids, focal fatty inclusions, hypertrophy of hepatocytes, thickened blood vessels, swelling, and proliferation of epithelial cells of bile ducts, was observed in guinea pigs treated by dermal application of 100 mg/kg/day technical-grade HCH for 30 days (Dikshith et al. 1978). The area of the abdomen on which the HCH was applied was not covered to prevent licking, so oral exposure may also have occurred. In rabbits exposed to 25 mg technical-grade HCH/kg/day for 30 days, there were degenerative changes in hepatocytes along with increased liver and serum ALT and ALP (Dikshith et al. 1989b). Liver cell hypertrophy, fatty degeneration, nuclear pyknosis, and focal and diffuse necrosis were found in female rats treated with 100 mg/kg/day technical-grade HCH for 7–30 days, but the time that it took for these lesions to occur, the severity of changes, and the numbers of animals affected were not reported (Dikshith et al. 1991c).

2.10 RENAL

Epidemiological Studies. Very limited human epidemiological data on renal effects of HCH isomers are available, as shown in Table 2-11. A cohort study of 31,142 wives of pesticide applicators in Iowa and North Carolina followed for 15 years did not observe an association between self-reported pesticide

exposure and end-stage renal disease (Lebov et al. 2015). Case-control studies of chronic kidney disease (Ghosh et al. 2017; Siddarth et al. 2014) did not observe associations with β-HCH in blood or serum, and results were mixed for α- and γ-HCH. Ghosh et al. (2017) reported an association between blood levels of γ-HCH and chronic kidney disease and no association for α-HCH, while Siddarth et al. (2014) reported the converse (association for serum α-HCH and no association for γ-HCH). No association between serum β- or γ-HCH and hyperuricemia was noted in a cross-sectional study of 453 adults in Spain (Arrebola et al. 2019).

α-HCH. Fitzhugh et al. (1950) reported kidney damage (nephritis tubular dilatation, hyaline tubular casts, glomerular fibrosis or atrophy, pigment deposition) in rats fed 60–70 mg/kg/day α-HCH for an average of 35.9 weeks; no such effects were observed in rats fed up to 9 mg/kg/day for 107 weeks.

β-HCH. Renal effects have also been noted in rats exposed to β-HCH in the diet, often at doses associated with profound toxicity and/or death. Srinivasan et al. (1984) reported significantly increased excretion of glucose in urine and increased excretion of creatinine and urea, as well as hypertrophy and degeneration of the renal tubular epithelia in rats exposed to 72 mg/kg/day β-HCH for up to 2 weeks. Van Velsen et al. (1986) reported significantly increased kidney weights in female rats exposed to 0.2 mg β-HCH/kg/day for 13 weeks, but the change did not exhibit dose-dependence. In males, a significant increase in kidney weight was observed at 4.5 mg/kg/day. At the highest dose (22.5–25 mg/kg/day), a dose that was profoundly toxic and led to the humane sacrifice of half of the animals, males exhibited renal calcinosis in the outer medulla. The study authors noted that renal calcinosis is common in female rats but that this finding was unusual and therefore of significance in males (Van Velsen et al. 1986). Fitzhugh et al. (1950) examined the renal effects of exposure to β-HCH (60–70 mg/kg/day) in rats that died after an average of 4.4 weeks and found nephritis and basal vacuolation. At lower doses in this study, exposure to doses up to 9 mg/kg/day for up to 2 years did not induce renal histopathology changes (Fitzhugh et al. 1950).

γ-HCH (Lindane). Renal effects have been documented in case reports of accidental or intentional oral exposures to γ-HCH. In a suicide attempt, a 30-year-old male farmer from rural India ingested a single dose of approximately 50 mL of 2% γ-HCH solution (Paul et al. 2013). Six hours after the ingestion, the man went to the emergency department. On the second day symptoms of lethargy and reduced urinary output were noted, increasing in severity by day 5 to include additional symptoms of elevated pulse, increased serum levels of kidney enzymes (blood urea nitrogen [BUN] and creatinine), urinary white blood cells, red blood cells, and protein. An ultrasound of the kidneys indicated cortical echogenicity and

Table 2-11. Summary of Epidemiological Studies of Hexachlorocyclohexane (HCH) Exposure and Renal Effects

Reference, study type, and population	Outcome evaluated	Isomer	Biomarker	Mean concentration (unless otherwise noted)	Result
Arrebola et al. 2019 Cross-sectional, 453 working adults, median age 35 years, Spain	Hyperuricemia	α-HCH	Serum	<LOQ ng/g lipid (all)	NA[a]
		β-HCH		<LOQ (median) 0.12 (95th percentile)	↔[b]
		γ-HCH		<LOQ (median) 0.05 (95th percentile)	↔[b]
Ghosh et al. 2017 Case-control, 200 cases and 100 controls, ages 30–50 years, India	**CKD of known or unknown etiology**	α-HCH	Blood	1.26 ng/g (median) (CKD, known) 1.68 (CKD, unknown) 0.7 (controls)	↔
		β-HCH		2.49 (CKD, known) 2.15 (CKD, unknown) 1.7 (controls)	↔
		γ-HCH		2.15 (CKD, known) 2.03 (CKD, unknown) 2.6 (controls)	↑[c]
Siddarth et al. 2014 Case-control, 270 cases and 270 controls, mean ages 46 and 48 years (respectively), India	**CKD**	**α-HCH**	Serum	5.23 ng/mL (median, 3rd tertile) 0.87 (median, 1st tertile)	↑
		β-HCH		5.50 (3rd tertile) 0.20 (1st tertile)	↔
		γ-HCH		3.89 (3rd tertile) 1.86 (1st tertile)	↔
		Total HCH		12.51(3rd tertile) 3.63 (1st tertile)	↑

Table 2-11. Summary of Epidemiological Studies of Hexachlorocyclohexane (HCH) Exposure and Renal Effects

Reference, study type, and population	Outcome evaluated	Isomer	Biomarker	Mean concentration (unless otherwise noted)	Result
Lebov et al. 2015 Cohort, 31,142 wives of pesticide applicators, ≥18 years at enrollment, Iowa and North Carolina, United States, mean follow-up 15.4 years	End-stage renal disease	γ-HCH	NA (self-reported pesticide exposure)	Ever used versus never used	↔

[a]Analysis was not performed because all samples were below the LOQ.
[b]Odds ratios comparing serum levels ≥ LOQ to samples < LOQ.
[c]Positive association associated with CKD of unknown etiology; no association with CKD of known etiology.

↑ = association with increase; ↓ = association with decrease; ↔ = no association; CKD = chronic kidney disease; LOQ = limit of quantification; NA = not applicable

mild ascites. The man was treated for acute kidney injury by hemodialysis. Urine output started to increase on day 10 and serum kidney enzymes recovered in 3 weeks, after which he was discharged in stable condition that persisted though a 3-month follow up (Paul et al. 2013).

A suicidal 21-year-old male ingested γ-HCH (dose unknown) (Shah et al. 2013). One day after ingestion, the man experienced reduced urine output, dark urine, pedal edema, and muscular pain lasting 2 days before he went to a clinic. Clinical evaluation at 3 days post-ingestion showed proteinuria, myoglobinuria, muscle tenderness, elevated serum levels of AST, potassium, creatinine, and CPK, and metabolic acidosis indicating acute kidney injury from rhabdomyolysis. Treatment included hemodialysis and supportive care and the man recovered after 3 weeks (Shah et al. 2013). Progressive renal failure was seen in a woman who died 11 days after intentionally ingesting 8 ounces of a 20% γ-HCH solution (Sunder Ram Rao et al. 1988). Myoglobin release resulting from muscle lysis in this case led to kidney shutdown, which was the ultimate cause of death.

Small (<10%) increases in kidney weights, in the absence of clinical chemistry, urinalysis, and histopathology changes, were observed in female rats exposed to 5 mg/m^3 γ-HCH aerosol 6 hours/day for 90 consecutive days (Oldiges et al. 1983). Male rats at this concentration exhibited significantly increased kidney weights. Dose-related increases in the incidences of kidney lesions (dilated tubules with protein-containing contents; proliferated tubules) were observed in males, but not females, at concentrations of 0.5 and 5 mg/m^3 (Oldiges et al. 1983). No renal effects (including clinical chemistry, organ weight, and histopathology) were seen in mice exposed up to 5 mg/m^3 γ-HCH aerosol 6 hours/day, 5 days/week for 14 weeks (Klonne and Kintigh 1988).

In studies of animals exposed orally to γ-HCH, renal effects have largely been limited to male rats, although many studies did not test females, and two studies reported histopathology changes in females exposed to higher doses (Suter 1983; Vijaya Padma et al. 2011). In an acute study, male Fischer-344 rats receiving gavage doses of 10 mg/kg/day of γ-HCH for 4 days showed histopathological changes in the proximal tubule epithelial cells including accumulation of protein droplets, hypertrophy and necrosis, pyknotic nuclei, cellular exfoliation, and regenerative epithelium (Dietrich and Swenberg 1990, 1991). Significantly increased excretion of glucose in urine, and histological changes consisting of hypertrophy and degeneration of the renal tubular epithelia, were observed in male Wistar rats exposed to 72 mg/kg/day of γ-HCH for up to 2 weeks (Srinivasan and Radhakrishnamurty 1988; Srinivasan et al. 1984).

Male Sprague-Dawley rats exposed for 30 days to γ-HCH via gavage at doses ≥20 mg/kg/day exhibited medullary and cortical hemorrhage, and degeneration and vacuolation of proximal convoluted tubules (Fatih Fidan et al. 2008). Similarly, after 30 days of exposure to 20 mg/kg/day, male Wistar rats showed intertubular hemorrhage, tubular degeneration and desquamation of tubular epithelium, cystic dilatation, mononuclear cell infiltrate, and necrosis (Prasad et al. 2016). No renal effects other than significantly increased kidney weight were observed in rats exposed to γ-HCH doses up to 5–50 mg /kg/day in the diet for up to 40 days (Desi 1974); histological examination of the kidney did not reveal any changes. In female Wistar rats exposed for 30 days to daily gavage doses of 100 mg/kg/day, glomerular degeneration and shrinkage and degeneration of the proximal and distal tubules were observed (Vijaya Padma et al. 2011).

Increased kidney weight, hyaline droplet accumulation, and tubular regeneration were observed in male Long-Evans rats exposed for 10 weeks to 10 mg/kg/day γ-HCH via gavage (Andrews and Gray 1990). In male rats treated with 0.4–10 mg γ-HCH/kg/day in their diets for 12 weeks, dose-dependent renal effects of increasing severity were seen, including basophilic proximal tubules and proximal tubular distention with cell debris, as well as hyaline droplet formation, and minimal to moderate interstitial nephritis (Suter 1983). Both male and female rats exposed to doses ≥2 mg/kg/day exhibited minimal to slight epithelial cell necrosis in the proximal tubules (Suter 1983). In a 2-generation reproductive toxicity study, no renal effects were observed in female adult Crj:CD(SD)IGS rats exposed to doses up to 26.1 mg/kg/day (Matsuura et al. 2005). In contrast, doses ≥0.56 mg/kg/day resulted in increased incidences and severity of basophilic tubules and hyaline droplets in the proximal tubules of F0 and F1 parental males (Matsuura et al. 2005). EPA (1991a) also observed renal histopathological changes characteristic of alpha-2μ-globulin accumulation in F0 and F1 male CD rats at ≥1.7 mg/kg/day in a 2-generation reproduction study with γ-HCH. No gross or histopathological changes were observed in kidneys of females in either generation.

Male Wistar rats exposed for up to 52 weeks to γ-HCH in their diet exhibited hyaline droplets in the renal proximal tubules, interstitial chronic nephritis, and regeneration in proximal tubules at doses ≥0.07 mg/kg/day; and pale kidneys, increased kidney weights and urine volumes, and higher urinary protein excretions and tubular necrosis at 7 mg/kg/day (Amyes 1990). In contrast, no renal effects were seen in females at doses up to 32 mg/kg/day in this study (Amyes 1990). Very slight microscopic kidney damage (not further specified) was reported in Wistar rats exposed to 7–9 mg γ-HCH/kg/day for up to 104 weeks (Fitzhugh et al. 1950). The histopathology findings were not reported by sex, so it is not clear whether the effects were limited to males.

Male rats treated dermally with 10 mg/kg/day γ-HCH for 13 weeks exhibited hyaline droplet formation, and urinalysis showed increased cast formation and turbidity, proteinuria, and hematuria in treated males (EPA 1988a). Females in the same study exhibited a slight increase in the incidence of tubular basophilia at 60 mg/kg/day.

Mechanisms. Available data suggest that the renal effects of γ-HCH may result from at least two possible mechanisms: (1) alpha-2μ-globulin accumulation in male rats; and (2) increased oxidative stress in both male and female rats. Dietrich and Swenberg (1990, 1991) demonstrated α-2μ-globulin staining in the kidney cortex of male F-344 rats exposed for 4 days to 10 mg/kg/day of γ-HCH. No α-2μ-globulin staining was detected in the kidneys of F-344 male controls, F-344 control or exposed female rats, or exposed male NBR rats (a strain that does not synthesize α-2μ-globulin). Matsuura et al. (2005) used immunohistochemistry staining to examine kidneys of male parental rats in a 2-generation reproductive toxicity study, and observed that smaller hyaline droplets stained positive for α-2μ-globulin, while larger ones did not.

Renal effects seen only in male rats that are attributable to alpha-2μ-globulin accumulation are not relevant to human health (EPA 1991b). However, kidney effects have also been seen in female rats (Suter 1983; Vijaya Padma et al. 2011), and other mechanisms, such as induction of oxidative stress, may play a role in these effects. Increases in lipid peroxidation and nitric oxide, as well as depletion of antioxidant enzyme activities (superoxide dismutase, catalase, and glutathione peroxidase) and reduced glutathione, have been observed in the kidneys of male rats exposed by gavage to doses of ≥20 mg/kg/day γ-HCH in intermediate-duration studies (Fatih Fidan et al. 2008; Prasad et al. 2016; Vijaya Padma et al. 2011).

Technical HCH or Unspecified Isomers of HCH. Oral exposure to technical HCH has been shown to induce kidney effects in mice, rats, and pigs. Mice treated daily with 50 mg/kg/day technical-grade HCH for 1, 5, or 15 days by oil gavage exhibited renal changes including congestion of blood vessels and glomerular tufts, swollen tubules with hyaline casts, cystic dilation, fatty changes, some interstitial hemorrhaging in the medulla, and epithelial cell vacuolation (Philip et al. 1989). No adverse effects were seen in the kidneys of male rats treated with 50 or 60 mg/kg/day technical-grade HCH for 30 days (Dikshith et al. 1989a; Khanna et al. 1990). Wang et al. (2006) observed a 24% increase in kidney weights in pigs given technical-grade HCH at a dose of 0.8 mg/kg/day for 90 days; renal histopathology was not evaluated. Nephritis, pigmentation, and basal vacuolation were observed in kidneys of rats (sex

not specified) fed 60–70 mg/kg/day technical-grade HCH in the diet for an average of 32.9–64.6 weeks (Fitzhugh et al. 1950); poor survival (for which there was no explanation) was noted in both control and treated animals. Tubular necrosis and glomerular degeneration were seen in male rats exposed for 360 days to 20 mg/kg/day of technical-grade HCH (Dikshith et al. 1991a).

Renal changes have been reported in animals exposed to technical-grade HCH by dermal application. Female rats treated with 100 mg/kg/day of technical-grade HCH for 7, 15, or 30 days had necrosis and atrophy of the renal tubules and glomeruli, although the number of animals affected and the severity of the lesions were not reported (Dikshith et al. 1991c). Similar effects were noted in male rabbits treated with 25 mg/kg/day technical-grade HCH for 30 days (Dikshith et al. 1989b). In both of these studies, mortalities were seen at the doses associated with renal effects.

2.11 DERMAL

γ-HCH (Lindane). A 10-year-old boy who was being treated for scabies was exposed to a 1% γ-HCH solution by dermal application from the neck down for 8 hours/day on 3 consecutive days (Juan et al. 2004). Following the initial application, erythema developed on the neck, extending to the trunk and axillae after 2 days. On the third day, pustules were present on his neck, trunk, arms, and thighs. He was examined in a clinic, where symptoms of leukocytosis were noted. A biopsy of a skin lesion showed subcorneal and intraepidermal pustule formation with neutrophilic infiltrations and scattered eosinophils in the dermis, suggesting acute generalized exanthematous pustulosis. After discontinuation of the γ-HCH solution, the boy recovered within a week (Juan et al. 2004).

A 57-year-old man was admitted to the hospital and diagnosed with scabies for which he was treated with γ-HCH lotion (concentration not reported) by dermal application to the whole body for 8 hours/day for 3 consecutive days (Yu et al. 2015). Instructions included washing/removal of the lotion after 8 hours, but the man was only partially washed for unknown reasons. One week after exposure, multiple scattered and coalescent polymorphic ulcerations with hemorrhagic spots and black burn-like crusted edges developed. A skin biopsy revealed papillary edema, and acute and chronic inflammation indicating ulcerative irritant contact dermatitis. Patch testing was performed but the results were unavailable, as the patient died from sepsis. The time elapsed between exposure and death was not reported and it was not clear whether the ulceration caused the sepsis (Yu et al. 2015).

In a summary of γ-HCH poisoning cases reported to the Texas poison control network (Forrester et al. 2004), commonly-reported symptoms of exposure included erythema and dermal irritation or pain; the authors did not describe symptoms by routes of exposure, which included oral and dermal. An itchy red rash was observed in a 10-month-old boy after 7 days of twice-daily application of 1% γ-HCH for scabies treatment (Bhalla and Thami 2004). Rashes were observed in a boy following treatment with shampoo containing γ-HCH (Fagan 1981). No exposure level was reported, but the shampoo was rinsed over the boy's entire body.

Mild dermatitis was observed in rats after 15 skin paintings with 180 mg/kg/day γ-HCH/kg over a period up to 25 days (Dikshith et al. 1973). Rabbits exposed to 200 mg/kg moistened γ-HCH for 4 hours showed no primary skin irritation or other toxic symptoms (Ullmann 1986d).

Technical HCH or Unspecified Isomers of HCH. Rabbits exposed to technical-grade HCH (25 mg/kg/day for 30 days) had hyperkeratinization of the epidermal layer and swollen collagen fibers in the dermis, but no scoring level was provided (Dikshith et al. 1989b). Dermal treatment of rats with 100 mg/kg/day technical-grade HCH for 7–30 days resulted in hyperkeratosis, epidermal cell vacuolization, and thickening of collagen fibers (Dikshith et al. 1991c).

2.12 OCULAR

No studies were located regarding ocular effects in humans following exposure to HCH isomers.

γ-HCH (Lindane). In a survey of γ-HCH exposures reported to the Texas poison control network, Forrester et al. (2004) reported that ocular irritation and pain were common symptoms. The authors did not distinguish between effects seen after oral and dermal exposures, both of which were considered in the survey.

Mice exposed to γ-HCH aerosol (up to 5 mg/m^3) 6 hours/day for 14 weeks exhibited no ophthalmic effects (Klonne and Kintigh 1988), and histopathology of the eyes showed no changes in these mice or in rats exposed similarly (Oldiges et al. 1983). Mild eye irritation was seen in rabbits exposed to 40 mg/kg γ-HCH in the conjunctival sac for up to 72 hours. The irritation level was given a primary irritation score of 0.6 out of a maximum possible cumulative score of 16 (Ullmann 1986c).

2.13 ENDOCRINE

Epidemiological Studies. Several epidemiological studies have suggested that exposure to HCH may be associated with changes in thyroid function (see Table 2-12). In a cohort study of 21,788 male pesticide applicators, occupational exposure to γ-HCH was associated with increased odds of hypothyroid disease (Goldner et al. 2013). In other studies, there was suggestive evidence for associations between β-HCH in blood and alterations in serum thyroid hormone levels, but the direction of change and affected hormones were not consistent. A case-control study in Chinese subjects with thyroid disease found no association between serum levels of β-HCH and thyroid disease; however, serum β-HCH levels were associated with decreased total and free thyroxine (T4) in males and increased levels of free T4 in females (Han et al. 2019). Levels of total T4 in females was not related to serum β-HCH, nor were levels of total triiodothyronine (T3), free T3, and thyroid-stimulating hormone (TSH) in either sex (Han et al. 2019).

Several cross-sectional studies evaluated effects of β-HCH on thyroid hormone levels. Decreased total T3 and thyroxine binding globulin in serum were associated with higher plasma β-HCH levels in Canadian Inuit adults, while there were no associations with free T4 or TSH (Dallaire et al. 2009). In a study of pregnant women in Spain, there was an association between serum β-HCH and decreased total T3 levels in women in the city of Sabadell, but no association was seen in women from the city of Gipuzkoa (Alvarez-Pedrerol et al. 2009). In contrast, free T4 levels were not associated with serum β-HCH in Sabadell women, while there was an increased association in Gipuzkoa women (Alvarez-Pedrerol et al. 2009). No relationship between serum β-HCH levels and total T3, free T3, total T4, free T4, or TSH was observed in pregnant women in South Korea (Kim et al. 2013) or serum TSH and free T4 levels in pregnant women in Japan (Yamazaki et al. 2020).

A population-based survey of residents living near an HCH production factory (operating from late 1940s to 1955) in Brazil examined associations of serum levels of α-, β-, and γ-HCH and thyroid function in 193 children <15 years old (Freire et al. 2012) and in adolescent and adult (>14 years old) males (n=303) and females (n=305) (Freire et al. 2013). In children, serum levels of α-, β-, and γ-HCH were associated with increased serum total T3 levels, while no association was observed for serum free T4 or TSH levels (Freire et al. 2012). In adults, serum levels of β-HCH was associated with decreased free T4 and increased TSH levels in men, while no association was determined in women for either parameter. Further, there were no associations between serum β-HCH and total T3 or anti-thyroperoxidase levels nor were there associations between α-HCH and γ-HCH with total T3, free T4, TSH, and anti-thyroperoxidase (Freire et al. 2013). Increased total T3 levels corresponded to serum β-HCH levels in

Table 2-12. Summary of Epidemiological Studies of Hexachlorocyclohexane (HCH) Exposure and Endocrine Effects

Reference, study type, and population	Isomer	Concentration in serum (unless otherwise noted)	Outcome evaluated	Result
Han et al. 2019 Case-control, 186 cases of thyroid disease and 186 controls, mean ages 46 and 44 years, China	**β-HCH**	78.96 ng/g lipid (median) (cases) 65.58 (controls)	Thyroid disease	↔
			Serum total T4	M: ↓ F: ↔
			Serum free T4	M: ↓ F: ↑
			Serum total T3, free T3, and TSH	↔
Freire et al. 2013 Cross-sectional, 303 males and 305 females >14 years old, Brazil	**β-HCH**	6.00 ng/mL (median) (males) 6.98 (females)	Serum total T3	↔
			Serum Free T4	M: ↓ F: ↔
			Serum TSH	M: ↑ F: ↔
			Serum anti-thyroperoxidase	↔
	α-HCH	2.52 (males) 2.60 (females)	Serum total T3, free T4, TSH, and anti-thyroperoxidase	↔
	γ-HCH	0.95 (males) 0.97 (females)	Serum total T3, free T4, TSH, and anti-thyroperoxidase	↔
Alvarez-Pedrerol et al. 2009 Cross-sectional, 1,090 pregnant women, Spain	**β-HCH**	32.3 ng/mL (median) (Sabadell [S]) <LOD (median); 22.1 (75^{th} percentile) (Gipuzkoa [G])	**Serum total T3**	S: ↓ G: ↔
			Serum free T4	S: ↔ G: ↑
Dallaire et al. 2009 Cross-sectional, 623 Inuit adults ≥18 years old, Canada	**β-HCH**	8.33 µg/kg lipid (plasma) (mean)	**Serum total T3**	↓
			Serum thyroxine binding globulin	↓
			Serum free T4, TSH	↔

Table 2-12. Summary of Epidemiological Studies of Hexachlorocyclohexane (HCH) Exposure and Endocrine Effects

Reference, study type, and population	Isomer	Concentration in serum (unless otherwise noted)	Outcome evaluated	Result
Freire et al. 2012 Cross-sectional, 193 children <15 years old, Brazil	**β-HCH**	479 ng/mL (mean)	**Serum total T3**	↑
			Serum free T4, TSH	↔
	α-HCH	300	**Serum total T3**	↑
			Serum free T4, TSH	↔
	γ-HCH	77.5	**Serum total T3**	↑
			Serum free T4, TSH	↔
Kim et al. 2013 Cross-sectional, 105 pregnant women 22–46 years old, South Korea	β-HCH	7.58 ng/g lipid (median)	Serum total T3, free T3, total T4, free T4, TSH	↔
Piccoli et al. 2016 Cross-sectional, 275 farmers and farm residents, 18–69 years old, Brazil	**β-HCH**	<LOD ng/g (median) 77.87 (95^{th} percentile)	**Serum total T3**	↑
			Serum free T4, TSH	↔
	γ-HCH	3.71 (median) 24.35 (95^{th} percentile)	Serum total T3, free T4, TSH	↔
	α-HCH	<LOD (median) 21.8 (95^{th} percentile)	Serum total T3, free T4, TSH	↔
Yamazaki et al. 2020 Cross-sectional, 333 pregnant women 17–48 years old, Japan	β-HCH	235.6 pg/g (late gestation or post-partum) (75^{th} percentile)	Serum TSH (early gestation)	↔
			Serum free T4 (early gestation)	↔
Goldner et al. 2013 Cohort, 21,788 male private pesticide applicators, Iowa and North Carolina, United States	**Lindane**	NA (occupational, ever use)	**Hypothyroid disease**	↑

↑ = association with increase; ↓ = association with decrease; ↔ = no association; F= female; LOD = limit of detection; M = male; NA = not applicable; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone

275 adult Brazilian farmers and farm residents, while no relationship was found with α- or γ-HCH (Piccoli et al. 2016). In this study, there was also no association between serum α-, β-, or γ-HCH and free T4 or TSH levels (Piccoli et al. 2016).

α-HCH. No histopathology changes were noted in the adrenal glands or thyroids of rats given α-HCH via the diet at doses up to 70 mg/kg/day for ~9 months or up to 9 mg/kg/day for 2 years (Fitzhugh et al. 1950).

β-HCH. There were no microscopic lesions in the thyroid or adrenal glands when rats were exposed by dietary administration to β-HCH doses up to 70 mg/kg/day for up to 10 weeks or up to 9 mg/kg/day for 2 years (Fitzhugh et al. 1950).

γ-HCH (Lindane). In 13- and 14-week inhalation studies of rats and mice (respectively) exposed to concentrations up to 5 mg/m^3 for 6 hours/day, there were no effects of treatment on the histology of the pancreas, thyroid, or adrenal glands (Klonne and Kintigh 1988; Oldiges et al. 1983) or on the histology of the pituitary in the mice (Klonne and Kintigh 1988). Wistar rats administered 50 mg/kg/day γ-HCH in drinking water for 30 days had 84% higher serum levels of free T4 and 74% lower serum TSH compared to controls (Hfaiedh et al. 2011). In a 2-generation reproductive toxicity study, F0 and F1 male and/or female parental rats exposed via feed to doses of 17.2–26.1 mg/kg/day exhibited endocrine effects including decreased absolute and relative pituitary weights (F0 and F1 females), altered serum thyroid hormone levels, and increased incidences of thyroid follicular cell hypertrophy (F0 females and F1 males) (Matsuura et al. 2005). Fitzhugh et al. (1950) reported no histopathology findings in the thyroid or adrenal glands of rats given γ-HCH in feed at doses up to 140 mg/kg/day for 10 months or 30 mg/kg/day for 2 years. No effect on adrenal gland weights or adrenal, thyroid, or parathyroid histopathology findings in CD-1 mice given γ-HCH in the diet at doses up to 26.8 mg/kg/day for 78 weeks (EPA 2000a).

Technical HCH or Unspecified Isomers of HCH. Technical HCH administered to rats in feed did not induce thyroid or adrenal gland histopathology changes at doses up to 70 mg/kg/day for 6 months or 9 mg/kg/day for 2 years (Fitzhugh et al. 1950).

2.14 IMMUNOLOGICAL

Epidemiological Studies. Few studies of immune system effects in humans exposed to HCH isomers were located, and the available studies examined limited endpoints. Table 2-13 provides an overview of the epidemiological studies. Landgren et al. (2009) followed a cohort of 678 male pesticide applicators in the United States for 9 years and evaluated the risk of monoclonal gammopathy of undetermined significance (MGUS). MGUS is a condition in which an abnormal protein (monoclonal or M protein) accumulates in the blood; this condition sometimes progresses to lymphoma or multiple myeloma. There was no increase in risk for MGUS among applicators who reported use of γ-HCH compared with those who had never used γ-HCH (Landgren et al. 2009). Ryu et al. (2018) reported a positive association between serum levels of β-HCH and specific T-lymphocyte frequencies (CD8+ CD57+ and CD8+ CD28-) in a cross-sectional study of healthy adults over 30 years of age. In a case-control study of children 3–6 years old, associations between asthma and increased plasma α-, β-, and γ-HCH levels were reported (Meng et al. 2016); however, in this study, exposure (blood level) was measured after the outcome (asthma) occurred.

β-HCH. Decreased lympho-proliferative responses to mitogens were seen in mice exposed to 60 mg/kg/day β-HCH in the diet for 30 days (Cornacoff et al. 1988). There were no associated changes in immunoglobulins, red blood cell counts, or histology of the thymus, spleen, or lymph nodes (Cornacoff et al. 1988). Cortical atrophy of the thymus and depletion of splenic lymphoid tissue were observed in rats fed 22.5–25 mg/kg/day β-HCH in the diet (Van Velsen et al. 1986). In this 13-week study (Van Velsen et al. 1986), 50% of the rats exposed at this dose were sacrificed humanely before study termination (as early as the first 3 weeks) due to moribund condition.

γ-HCH (Lindane) Immune system parameters in blood were evaluated in a group of 20 patients seen in a hospital in India with γ-HCH poisoning, and compared with results in a group of age- and sex-matched controls without pesticide exposure (Seth et al. 2005). The dose, route, nature, and timing of γ-HCH exposures were not reported, and there was no effort to adjust for potential confounders. No differences in serum immunoglobulin levels (IgG, IgM, IgA, or IgE) were seen; however, several serum cytokine levels, including interleukin-2 (IL-2), interleukin-4 (IL-4), and tumor necrosis factor-alpha (TNF-α) were higher in the poisoning victims, and serum IFN-γ levels were lower (Seth et al. 2005).

Table 2-13. Summary of Epidemiological Studies of Hexachlorocyclohexane (HCH) Exposure and Immune Effects

Reference, study type, and population	Outcome evaluated	Isomer	Biomarker	Mean concentration (unless otherwise noted)	Result
Meng et al. 2016 Case-control, 124 cases of asthma, 109 controls, children ages 3–6 years, China	**Asthma**	**α-HCH**	Plasma	Cases: 40.73±36.01 ng/g lipid Controls: 12.52±16.03	↑
		β-HCH		Cases: 111.11±70.1 Controls: 31.49±74.02	↑
		γ-HCH		Cases: 27.5±12.13 Controls: 9.34±20.21	↑
	Severe asthma[a]	α-HCH		See above	↔
		β-HCH		See above	↔
		γ-HCH		See above	↔
Landgren et al. 2009 Cohort, 678 male pesticide applicators followed for at least 9 years, Iowa and North Carolina, United States	Monoclonal gammopathy of undetermined significance	γ-HCH	None (occupational)	Ever versus never used	↔
Ryu et al. 2018 Cross-sectional, 95 healthy adults, age 30–69 years, Korea	T-lymphocyte frequencies: **CD8+ CD57+**	**β-HCH**	Serum	10.7 ng/g lipid (median of 4th quartile)	↑
	CD8+ CD28-				↑
	CD4+ CD57+				↔
	CD4+ CD28-				↔

Table 2-13. Summary of Epidemiological Studies of Hexachlorocyclohexane (HCH) Exposure and Immune Effects

Reference, study type, and population	Outcome evaluated	Isomer	Biomarker	Mean concentration (unless otherwise noted)	Result
Seth et al. 2005 Case-control, 20 patients hospitalized with lindane poisoning and 20 unexposed age- and sex-matched healthy subjects, India	Serum immunoglobulins and cytokines:	γ-HCH	None (exposure assessed based on clinical symptoms, history, and AChE activity)	Exposed versus unexposed	
	IgG, IgM, IgA, and IgE				↔
	IL-2,IL-4, and TNF-α				↑
	IFN-γ				↓

[a]Severe asthma was defined as “asthma attacks more than 10 times over the year with repeated episodes (more than 3 times) during the last month, or if severe oxygen deficiency occurred in one attack.”

↑ = association with increase; ↔ = no association; AChE = acetylcholinesterase; Ig = immunoglobulin; IL = interleukin; TNF = tumor necrosis factor; IFN = interferon.

A 14-day exposure to 10 mg/kg/day γ-HCH in male rats previously sensitized to Keyhole Limpet Hemocyanin (KLH) resulted in a reduction in delayed-type hypersensitivity response (measured as a 43% decrease in foot pad thickness in response to KLH challenge) (Mediratta et al. 2008). Decreased relative thymus weight (28% less than controls) was observed in mice gavaged with 20 mg/kg/day γ-HCH for 3 days; at 40 mg/kg/day, atrophy of the thymic cortex was seen (Hong and Boorman 1993). Another experiment by these authors showed significant decreases in relative weights of thymus (≥7% decrements) and spleen (≥17% decrements) in mice exposed to 10–20 mg/kg/day γ-HCH for 10 days (Hong and Boorman 1993).

Immunosuppression, as measured by decreased antibody titers against typhoid vaccine and *Salmonella* vaccine, was reported in rats exposed by gavage to doses of ≥6.25 mg/kg/day γ-HCH for 5 weeks (Dewan et al. 1980) and in rabbits exposed by capsules 5 times each week to 1.5, 6, and 12 mg/kg/day for 5–6 weeks (Desi et al. 1978). Humoral immune response, as indicated by serum antibody response to sheep red blood cells (SRBC), was suppressed in rats that were exposed to γ-HCH in estimated dietary doses of 3.6 or 7 mg/kg/day for 8 weeks (Koner et al. 1998). The primary antibody response to SRBC was also suppressed in albino mice after exposure to 9 mg/kg/day γ-HCH in the diet for 12 weeks (Banerjee et al. 1996). Suppression of secondary antibody response (response after repeat exposure) was also observed after 3 weeks of exposure to 9 mg/kg/day γ-HCH and after 12 weeks of 5.4 mg/kg/day γ-HCH exposure (Banerjee et al. 1996). A biphasic, dose-dependent immunological effect of γ-HCH on components of cell- and humoral-mediated immunity, characterized by initial stimulation followed by immuno-suppression, was reported in mice fed 0.012, 0.12, or 1.2 mg γ-HCH/kg/day for 24 weeks (Meera et al. 1992). Histological examinations in these animals revealed decreased lymphocyte populations in the thymus and lymph nodes, a reduction in overall cellularity in the spleen, and necrosis of the thymus at 1.2 mg/kg/day. Cell-mediated immune response, as measured by delayed-type hypersensitivity reaction to dinitrofluorobenzene antigen, was suppressed in sheep that were exposed to 1.25 ppm γ-HCH in the diet for 6 months (Khurana et al. 1999).

Technical HCH or Unspecified Isomers of HCH. A statistically significant increase (approximately 18%) in the level of immunoglobulin M (IgM) was noted in 19 workers occupationally exposed to technical-grade HCH during pesticide formulation, as compared to 14 nonexposed workers (Kashyap 1986). The HCH isomer concentrations in serum showed a 10-fold increase when compared to the control group. Both inhalation and dermal exposure probably occurred, and the measurement of IgM alone is not a reliable measure of immune function in adults.

2.15 NEUROLOGICAL

Epidemiological Studies. Epidemiological studies of neurological effects in humans exposed to HCH isomers are summarized in Table 2-14. Most of the studies used serum or blood levels of β-HCH to assess exposure; only Singh et al. (2012, 2013, 2014) measured α- and γ-HCH levels as well. A cohort study of 669 Canadian adults at least 65 years old who were followed for 10 years showed no association between blood levels of β-HCH and dementia, Alzheimer's disease, or cognitive deficits (Medehouenou et al. 2019). In contrast, case-control studies reported increased risks of Parkinson's disease, Alzheimer's disease, and cognitive deficits with higher β-HCH levels in blood or serum (Kim et al. 2015; Petersen et al. 2008; Richardson et al. 2009, 2011; Singh et al. 2012, 2013, 2014). However, in the case-control studies, exposures were measured after the outcome occurred, so there is no clear temporal relationship between exposure and effect. A small cross-sectional study that suffered from the same limitation reported no association between β-HCH in serum and tremors at rest or cognitive deficits (Steenland et al. 2014).

α-HCH. Muller et al. (1981) reported no delay in tail nerve conduction velocity in rats fed 5.1, 54.2, or 106.2 mg α-HCH/kg/day for 30 days. No other data on neurological effects of α-HCH were located.

β-HCH. Clinical signs of neurotoxicity have often preceded death in rats and mice exposed to β-HCH via oral administration. Mice treated with 60 or 200 mg/kg/day β-HCH in the diet in a 30-day study developed ataxia within the first week of treatment (Cornacoff et al. 1988). The animals receiving 60 mg/kg/day recovered within a few days, while those receiving 200 mg/kg/day became markedly worse, leading to humane sacrifice of 80% of the animals in this group (Cornacoff et al. 1988). In the first 2 weeks of a 13-week study, male and female rats exposed to 38 mg/kg/day in the diet exhibited ataxia and hypoactivity, progressing to coma within 3 days (Van Velsen et al. 1986). The animals were humanely sacrificed, as were five additional males and six additional females that showed similar signs later in the study. A single study of electrophysiology was located; in this study, Muller et al. (1981) reported a significant delay in tail nerve conduction velocity in rats fed 66.3 mg β-HCH/kg/day for 30 days. No comprehensive tests of sensitive neurotoxicity endpoints other than electrophysiology in animals exposed to β-HCH were located.

γ-HCH (Lindane). Neurological effects have been seen in humans and animals exposed to γ-HCH by inhalation, oral, and dermal routes. The effects range in severity from subtle neurobehavioral changes and altered neurotransmitter levels to tremors, convulsions, and ultrastructural changes in the brain.

Table 2-14. Summary of Epidemiological Studies of Hexachlorocyclohexane (HCH) Exposure and Neurological Effects

Reference, study type, and population	Outcome evaluated	Isomer	Exposure Biomarker	Mean concentration (unless otherwise noted)	Result
Richardson et al. 2009, 2011 Case-control, 149 cases of Parkinson's disease, 134 controls, four sites in Texas and Georgia, United States	**Parkinson's disease**	**β-HCH**	Serum	10.77–79.43 ng/mg cholesterol (range of medians among cases across four sites)	↑
Petersen et al. 2008 Case-control, 79 cases of Parkinson's disease, 154 controls, mean ages 74 and 75 years, respectively, Faroe Islands	**Parkinson's disease**	**β-HCH**	Serum	0.06 µg/g lipid (GM) (cases) 0.04 (controls	↑
Singh et al. 2012, 2013, 2014 Case-control, 100 patients with Alzheimer's disease, 100 age-matched controls, Delhi, India	**Alzheimer's disease**	**β-HCH**	Serum	4.42±0.54 ng/mL (in cases)	↑
		α-HCH	Serum	0.37±0.11 ng/mL	↔
		γ-HCH	Serum	0.78±0.23 ng/mL	↔
Kim et al. 2015 Cross-sectional, 633 adults aged 60–85 years, NHANES 1999–2002, United States	**Cognitive deficit**	**β-HCH**	Blood	89.6 ng/g lipid (median of 4th quartile)	↑
Medehouenou et al. 2019 Cohort, 669 adults ≥65 years old, Canadian Study of Health and Aging (CSHA), Canada	Dementia, Alzheimer's disease, cognitive deficit	β-HCH	Blood	0.13 µg/L (median) (cases) 0.12 (controls)	↔
Steenland et al. 2014 Cross-sectional, 89 adults >65 years of age, Costa Rica	Movement disorder (tremor at rest)	β-HCH	Serum	≥0.88 ng/mL (4th quartile cutoff)	↔
	Cognitive deficit	β-HCH	Serum	≥0.88 ng/mL (4th quartile cutoff)	↔
Sullivan et al. 2018 Cohort, 159 Gulf War veterans who had worked in pest control, mean age 48 years, United States	**Depression, fatigue scores on mood test**	**γ-HCH**	NA (self-reported exposure)	(high exposure versus low exposure)	↑
	Anger, confusion, tension scores on mood test				↔

↑ = association with increase; ↔ = no association; GM = geometric mean; NHANES = National Health and Nutrition Examination Survey

Studies in animals exposed *in utero* and/or during lactation show that γ-HCH can also elicit these neurological effects in offspring of exposed parents; neurotoxic effects in animals exposed during development are discussed in Section 2.17.

Abnormal electroencephalographic (EEG) patterns (increased variation in the frequency and amplitude of wave pattern or more serious changes without specific EEG signs) were recorded in 16 of 37 workers following exposure to γ-HCH for 0.5–2 years in a fertilizer plant (Czeglédi-Jankó and Avar 1970). Exposure concentrations were not reported; however, these EEG changes were found to correlate with blood levels of γ-HCH. Effects on mood were examined in a cohort of 159 Gulf War veterans who had been engaged in pesticide application (Sullivan et al. 2018). In this group, higher self-reported exposure to γ-HCH was associated with higher scores for depression and fatigue in mood tests, while no association was seen with anger, confusion, or tension scores on the tests (Sullivan et al. 2018).

Seizures and convulsions have been observed in individuals who accidentally or intentionally ingested γ-HCH in insecticide pellets, liquid scabicide, or contaminated food (Davies et al. 1983; Forrester et al. 2004; Harris et al. 1969; Munk and Nantel 1977; Nordt and Chew 2000; Powell 1980; Ramabhatta et al. 2014; Starr and Clifford 1972; Storen 1955; Wiles et al. 2015). In most cases, the amount of γ-HCH ingested could not be determined. A 56-year-old man intentionally ingested approximately 12 ounces of an insecticide containing 20% γ-HCH in a suicide attempt (Wiles et al. 2015). Thirty minutes later, he developed a progressive decline in consciousness and multiple seizures ensued between 3 and 14 hours later. After 18 hours, the man was conscious and responsive, but neurological symptoms were noted 6 days later, including ataxia, slurred speech, paranoia, depression, and defects in higher mental functioning. The man committed suicide 12 days later by other means. At autopsy, γ-HCH levels in blood and adipose tissue were 0.248 μg/mL and 132.83 μg/g, respectively.

Several case studies of acute γ-HCH exposure to children ingesting liquid scabicide reported similar neurological effects, including tremors and tonic/clonic seizures (Aks et al. 1995; CDC 2005; Lifshitz and Gavrilov 2002; Wheeler 1977). One hour after a 3-year-old boy ingested approximately one teaspoon of a 1% γ-HCH shampoo, the boy had a tonic-clonic seizure for a duration of 4–5 minutes, despite the mother's efforts to induce vomiting (CDC 2005). Three hours later, the boy's condition was stable, and he was discharged from the hospital emergency room. Ramabhatta et al. (2014) reported two cases of neurological effects in children after accidental γ-HCH ingestion. In the first case, a 3-year-old boy was orally administered a single dose of 10 mL of a γ-HCH lotion (due to a mix-up of prescribed oral and dermal medications). The child had convulsions 1 hour after ingestion, and recovered in 24 hours with

supportive measures. In the second case, a 6-year-old girl ingested a γ-HCH lotion (amount and concentration not reported) and had a generalized seizure lasting 10–15 minutes. The child recovered 24 hours after clinic admission (Ramabhatta et al. 2014).

There have been many reports of human intoxication involving seizures or convulsions in adults and children after excessive topical application of γ-HCH (Boffa et al. 1995; Fischer 1994; Hall and Hall 1999; Lee and Groth 1977; Matsuoka 1981; Ramchander et al. 1991; Solomon et al. 1995; Sudakin 2007; Telch and Jarvis 1982; Tenenbein 1991); exposure levels were generally not quantified. Central nervous systems symptoms of severe γ-HCH poisoning, including uncontrollable shaking and myoclonic jerking and tonic-clonic movements of the extremities, developed in a woman following three dermal applications of a considerable amount (not quantified) of an anti-scabies product over a period of approximately 2 weeks (Hall and Hall 1999). Fever, tachycardia, grand mal seizure, and hallucinations were reported in a teenager treated with a 1% γ-HCH lotion for 3 consecutive nights (Boffa et al. 1995). Weakness of the left and right limbs, dysarthria, and dysphagia were seen in an agricultural worker exposed by inhalation and dermal contact to unspecified levels of several organochlorine pesticides, including γ-HCH (Fonseca et al. 1993).

A 10-month-old boy was exposed to 1% γ-HCH by repeated dermal application to the whole body 2 times/day for the treatment of scabies developed jerky movements, listlessness, and loss of consciousness after 7 days (Bhalla and Thami 2004). Upon examination by a medical professional after 10 days, the boy exhibited apathy, semi-consciousness, absence of superficial reflexes, reduced response to touch, pain, and pressure, and tremor in tongue and limbs. Use of γ-HCH was immediately discontinued and the infant regained normal consciousness and interaction with environmental stimuli over the subsequent 2 weeks (Bhalla and Thami 2004). The study authors reported that the boy showed evidence of anemia and malnutrition, which were described as risk factors for γ-HCH-induced neurotoxicity. A 7-year-old boy exposed to γ-HCH by dermal application 3 times in 4 days (dose not reported) exhibited ataxia, weakness, and burning paresthesia, and following the third application, the boy had myoclonic jerks and tonic-clonic seizures, whereupon he was brought to the hospital (Daud et al. 2010). No details of the extent of exposure were reported. After treatment to control the seizures, induction of diuresis, and frequent bathing and changing of clothing, the boy was discharged after 2 days (Daud et al. 2010).

Rats exposed to various concentrations of γ-HCH aerosol via nose-only inhalation for 4 hours exhibited concentration-related neurological effects (Oldiges et al. 1980; Ullmann 1986b). Slight-to-moderate

sedation was observed after exposure to 101 mg/m^3; slight-to-severe sedation was noted after exposure to 378 mg/m^3; restlessness, excitation, and ataxia were seen after exposure to ≥273 mg/m^3; and spasms were also noted at the highest concentration (2,104 mg/m^3). Concentrations ≥378 mg/m^3 were also associated with mortality in one study (Ullmann 1986b) but not in the other even at concentrations up to 603 mg/m^3 (Oldiges et al. 1980). Rats exposed to 0.02–5 mg/m^3 γ-HCH aerosol for 90 consecutive days exhibited a "slightly disturbed general condition" (not further characterized) within 2 weeks (Oldiges et al. 1983). At the end of the 90-day exposure, there were no treatment-related changes in brain weight or histology, or on histology of the sciatic or optic nerves. Mice were exposed to similar concentrations (0.3–5 mg/m^3) for 14 weeks (5 days/week) and exhibited no clinical signs of neurotoxicity (Klonne and Kintigh 1988).

Neurotoxic effects have been reported in several species of animals exposed to γ-HCH. The most serious effects were seizures and/or convulsions following intragastric administration of approximately 15–60 mg/kg for ≥1 day in rats (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).

Kindling, the induction of seizures with repeated application of subthreshold electrical or chemical stimuli to the brain, has been used as a method of investigating neurological response to γ-HCH poisoning. A single oral dose of 5–20 mg/kg γ-HCH to either naïve or rats previously kindled by electrical stimulus produced myoclonic jerks and clonic seizures, which increased in a dose-dependent manner and were increased in kindled animals (Gilbert and Mack 1995). Enhanced susceptibility to kindled seizures brought on by electrical stimulation was seen in rats exposed for 10 weeks to 10 mg/kg/day γ-HCH, 3 days/week (Gilbert 1995). Increased rates of acquisition of kindled seizures were observed following dosing of rats with 3–10 mg γ-HCH/kg/day for 4 days (Joy et al. 1982). Single daily doses of 20 mg/kg γ-HCH in mice significantly reduced the convulsive threshold, as measured by the dose of pentylenetetrazol required to induce seizures 1–4 hours after treatment, but increased the convulsive threshold 48 hours following treatment (Hulth et al. 1978). A dose of 50 mg/kg γ-HCH significantly increased the convulsive threshold 2, 4, and 10 days following dosing (Hulth et al. 1978).

Two studies of rats showed that oral administration of γ-HCH can alter neurotransmitter levels in the brain. Decreased levels of brain serotonin were reported in rats exposed for 6 days to a dose of 3 mg/kg/day γ-HCH (Attia et al. 1991), while 10 doses totaling 60 mg/kg γ-HCH over a period of 30 days resulted in decreased brain dopamine levels (Martinez and Martinez-Conde 1995).

Acute and subchronic neurotoxicity screening bioassays including functional observational battery, motor activity assessments, and neuropathology were reported in unpublished Confidential Business Information (CBI) submissions summarized by EPA (1999a, 1999b). In the acute neurotoxicity screening study, exposure to γ-HCH caused decreased motor activity 3 hours after gavage dosing of female rats with ≥20 mg/kg and males at 60 mg/kg (EPA 1999a). Females also had increased forelimb grip strength and decreased grooming behavior at 20 mg/kg, and an absence of grooming behavior at 60 mg/kg. Other effects at 60 mg/kg included clinical signs (e.g., piloerection, urine-stained fur, tremors, and/or convulsions) in both sexes and increased hindlimb foot splay in males (EPA 1999a). A 13-week neurotoxicity screening study in Crl:CDBR rats by the same author (EPA 1999b) showed neurological effects in both sexes at the highest dose (28.1–30.2 mg/mg/day), including clinical signs (e.g., piloerection, abnormal grooming behavior), increased rearing, walking on tiptoes, hypersensitivity to touch, hunched posture, and several deaths. There were no effects on forelimb or hindlimb grip strength, hindlimb splay, motor activity, or neuropathology (EPA 1999b).

Neurobehavioral testing in rats exposed for acute and intermediate durations have shown effects on activity, cognition, and memory. Increased anxiety (Llorens et al. 1990) and decreased motor activity (EPA 1999a) were reported in rats following a single gavage dose of 20 mg/kg, and increased spontaneous motor behavior was observed at 10 mg/kg (Llorens et al. 1989). Avoidance response latency was significantly increased in rats administered a single dose of 15 mg/kg by gavage (Tilson et al. 1987). Impaired neurocognition, measured as decreased step-down latency in passive avoidance test and prolonged transfer latency in the elevated plus maze test, occurred in rats exposed for 6 weeks to a γ-HCH dose of 15 mg/kg/day (Sahaya et al. 2007). Srivastava et al. (2019) observed behavioral changes (reduced locomotor activity and impaired spatial memory) in rats exposed to 2.5 mg/kg/day for 21 days. A longer exposure (40 days) at this dose (2.5 mg/kg/day) resulted in significantly altered Skinner box behavior (operant conditioning) in a small number of rats (Desi 1974).

At a γ-HCH dose (2.5 mg/kg/day for 21 days) that induced changes in locomotor activity and spatial memory, Srivastava et al. (2019) detected ultrastructural changes in the hippocampus and substantia nigra of rats. Changes in the brain included swollen mitochondria with disintegrated cristae, shortened fuzzy synapse, disintegrated myelin layer, and autophagosomes (Srivastava et al. 2019). Peripheral nerve effects were seen in one oral study of γ-HCH. Significantly decreased nerve conduction velocity was measured in rats exposed to 25.4 mg/kg/day for 30 days (Muller et al. 1981).

While data are more limited, neurotoxicity has been documented in rats and rabbits exposed to γ-HCH via dermal application. Clinical signs such as excitability, seizures, and convulsions were observed in rabbits following a single topical application of 60 mg/kg γ-HCH in a 1% solution (Hanig et al. 1976); young rabbits were more susceptible than older rabbits. Slight sedation was observed in rats exposed once for 24 hours to 1,000 mg/kg γ-HCH through shaved dorsal skin (Ullmann 1986a). One female exposed to 2,000 mg/kg in this study exhibited severe sedation and spasms (Ullmann 1986a). Aggressiveness or hyperactivity was noted in rats exposed dermally for 13 weeks to ≥10 mg γ-HCH/kg/day, while ataxia, tremors, and convulsions were seen in females at 60 mg/kg/day (EPA 1988a).

Mechanisms. Gavage administration of 2.5, 5, 10, or 15 mg γ-HCH/kg/day for 5 days produced a dose-dependent increase in the activities of EROD, PROD, and NDMA-d in the brain of Wistar rats (Parmar et al. 2003). In the same study, Parmar et al. (2003) examined the effect of metabolism on the convulsive effect of γ-HCH in rats. A single dose of 35 mg/kg of γ-HCH induced convulsions in 4 out of 10 animals. Pretreatment of the rats with 3-methylcholanthrene (MC), an inducer of CYP1A1/1A2, had no significant effect in the incidence of convulsions induced by γ-HCH. However, induction of CYP 2B1/2B2 (by pretreatment with phenobarbital) or CYP2E1 (by pretreatment with ethanol) significantly increased the incidence of convulsions caused by γ-HCH, as did blocking of cytochrome P450-mediated metabolism with cobalt chloride (Parmar et al. 2003). Taken together, the results suggest that the convulsive activity is due to γ-HCH *per se* and/or to metabolites formed by phenobarbital- or ethanol-inducible P450 isoenzymes.

Decreased myelin was observed in rats exposed to 5 mg/kg/day by gavage for 3 days (Serrano et al. 1990). These authors also detected a significant decrease in 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNP) activity was seen in treated animals, although no dose-response was seen. This enzyme is myelin-specific, but its exact function in normal myelin in unknown (Serrano et al. 1990).

Increased lipid peroxidation (thiobarbituric acid reactive substances [TBARS]) and decreases in antioxidant enzyme activities (superoxide dismutase, catalase, and glutathione peroxidase) were measured in the brains of Wistar rats after three daily doses of 5 mg/kg/day γ-HCH; neurological endpoints were not evaluated in these animals (Hfaiedh et al. 2012). Fatih Fidan et al. (2008) reported increased malondialdehyde and decreased levels of reduced glutathione in the brains of rats exposed to γ-HCH (≥10 mg/kg/day) by daily gavage for 30 days. Similarly, a 30-day exposure to doses of 50 mg/kg/day induced lipid peroxidation (measured as TBARS) and depletion of antioxidant enzymes (glutathione peroxidase and catalase) in the brains of rats exposed by drinking water (Hfaiedh et al. 2011). After

6 weeks of daily exposures to 15 mg/kg/day, rats exhibited increased malondialdehyde and non-protein thiols in the brain (Sahaya et al. 2007). In contrast, no significant changes were seen in lipid peroxidation in brain tissue from rats treated for 90 days with 90 mg γ-HCH/kg/day in food (Arisi et al. 1994).

Technical HCH or Unspecified Isomers of HCH. Paresthesia of the face and extremities, headache, and vertigo were reported in a group of 45 workers occupationally exposed during manufacture and formulation of technical-grade HCH for several years (Kashyap 1986); exposure concentrations were not reported. Both inhalation and dermal exposures were possible. Heiberg and Wright (1955) reported convulsions in a woman who had treated cattle with an insecticide containing 11% γ-HCH and 16% other HCH isomers.

In animals exposed to technical-grade HCH by oral administration, effects similar to those seen with β- and γ-HCH were seen. Behavioral and neurochemical changes were evaluated in rats that were administered technical-grade HCH in doses of 10 or 20 mg/kg/day in oil by gavage for 7–30 days (Sahoo et al. 1999). Assessment of open-field behavior (horizontal motor activity, vertical exploratory rearing, and grooming activities) and brain biochemistry (ATPases and acetylcholinesterase) showed effects that included reduced brain total ATPase and Na^+-, K^+-, and/or Mg^{2+}-ATPase activities after 7–30 days at ≥10 mg/kg/day, reduced brain acetylcholinesterase activity after 15 and 30 days at 20 mg/kg/day, increased motor activity after 7 days at 20 mg/kg/day, and reduced grooming behavior after 30 days at 20 mg/kg/day (Sahoo et al. 1999). Mudawal et al. (2018) observed impairments in learning (conditioned avoidance response and Y-maze continuous alternation test) and increased spontaneous locomotor activity in rats given technical-grade HCH for 21 days beginning at 3, 18, or 48 weeks of age. The most pronounced effects were observed in the aged rats. After exposure that began at 48 weeks of age, the animals also exhibited ultrastructural changes in the hippocampus and substantia nigra when examined by transmission electron microscopy; in contrast, similar exposure beginning at 3 or 18 weeks of age did not result in ultrastructural changes (Mudawal et al. 2018). Increased motor activity was also observed in rats exposed to technical-grade HCH at a level of 50 mg/kg/day for 120 days (Gopal et al. 1992).

Alterations in neurotransmitter levels, increased brain wave frequency, and behavioral changes were reported in male rats administered 50 mg/kg/day technical-grade HCH by gavage for 1 or 3 months (Anand et al. 1991). Exposure to 0.4 mg/kg/day technical-grade HCH for 360 days resulted in convulsions, tremors, and paralysis in male rats after 270 days, although the number of animals affected and the severity of the symptoms were not reported (Dikshith et al. 1991a). This study also found degeneration of the cerebellum and cerebellar cortex in animals sacrificed after a 1-year exposure to

20 mg/kg/day. Seizures were noted in mice exposed to technical-grade HCH through feed or gavage at levels of 10–17 mg/kg/day in the feed for 80 weeks (Kashyap et al. 1979). Damage to Purkinje cells in the cerebellum and tremors were found in female Wistar rats treated with 100 mg/kg/day technical-grade HCH for 7–30 days (Dikshith et al. 1991c).

Increased levels of brain catecholamines, particularly norepinephrine and dopamine, and associated signs of toxicity such as mild tremor, lacrimation, salivation, and dyspnea were observed in female rats given oral doses of 100 mg/kg/day of technical-grade HCH for 7 days (Raizada et al. 1993). The activity of monoamine oxidase (MAO, an enzyme that oxidizes monoamine neurotransmitters) in the cerebrum showed a marginal decrease, while significant increases and decreases were observed in the cerebellum and spinal cord, respectively (Raizada et al. 1993). Rats treated with 20 mg technical-grade HCH/kg/day in food for 90 days exhibited increased γ-aminobutyric acid (GABA) levels, increased glutamate decarboxylase (GAD) activity, and decreased glutamate levels in the brain (Nagaraja and Desiraju 1994).

Mechanisms. As with γ-HCH, there is some evidence that oxidative stress may contribute to the neurotoxic effects of technical-HCH. Mudawal et al. (2018) observed increased lipid peroxidation and decreases in both antioxidant enzyme activities (superoxide dismutase and catalase) and reduced glutathione in the hippocampus and substantia nigra of rats given 2.5 mg/kg/day technical HCH for 21 days. These changes correlated with neurobehavioral effects, as discussed above.

2.16 REPRODUCTIVE

Epidemiological Studies. Few epidemiological studies on the reproductive effects of HCH isomers were located; the available studies are summarized in Table 2-15. With one exception (Freire et al. 2014), the studies were conducted in populations without known sources of exposure to HCH; in these populations, consumption of contaminated food is expected to be the primary exposure route. All of these studies measured HCH isomers in serum, fat, or follicular fluid as biomarkers of exposure, and exposure was measured simultaneously with outcome assessment or after the outcome occurred.

Freire et al. (2014) conducted a cross-sectional study of reproductive hormone and HCH levels in the serum of 604 people residing near a former HCH manufacturing facility in Brazil. In this population, an inverse association between serum testosterone concentrations and serum α- and β-HCH concentrations was observed in men. In women, increases in serum β-HCH were associated with increased serum

Table 2-15. Summary of Epidemiological Studies of Hexachlorocyclohexane (HCH) Exposure and Reproductive Effects

Reference, study type, and population	Outcome evaluated	Isomer	Biomarker	Mean concentration (unless otherwise noted)	Result
Akkina et al. 2004 Cross-sectional, 219 menopausal women, Hispanic Health and Nutrition Examination survey (HHANES), United States	**Age at menopause**	**β-HCH**	Serum	>2.09 ng/g (> median)	↓
Buck Louis et al. 2012 Matched cohort, operative cohort: 473 women undergoing laparoscopy or laparotomy; population-based cohort: 127 women matched on age and residence, 18–44 years old, United States	**Endometriosis**	**β-HCH**	Serum	Operative cohort, medians: 0.0063 ng/g (cases) 0.0063 (non-cases)	↔
				Population cohort, medians: 0.0066 (cases) 0.0063 (non-cases)	↑
		γ-HCH	Omental fat	Operative cohort, medians: 0.1991 ng/g fat (cases) 0.1200 (non-cases)	↑
Ploteau et al. 2017 Case-control, 55 cases of deep infiltrating endometriosis and 44 controls, 18–45 years old, France	Deep infiltrating endometriosis	**β-HCH**	Adipose tissue	13.62 ng/g lipid (median) (cases) 14.33 (controls)	↔
	Deep infiltrating endometriosis with ovarian endometrioma			21.61(cases) 14.33 (controls)	↑
Upson et al. 2013 Case-control, 248 cases of endometriosis and 538 population-based controls, Washington, United States	**Endometriosis**	**β-HCH**	Serum	>43.06 pg/g (3rd quartile)	↑
		γ-HCH		>13.89 (4th quartile)	↔
		Sum HCH		>0.29 mol/g (4th quartile)	↔
	Ovarian endometriosis	**β-HCH**	Serum	>43.06 pg/g (3rd quartile)	↑
		γ-HCH		>13.89 (4th quartile)	↔
		Sum HCH		>0.29 mol/g (4th quartile)	↔
Al-Hussaini et al. 2018 Cross-sectional, 94 women in infertile couples undergoing intracytoplasmic sperm injection, 20–38 years old, Egypt	**Endometrial thickness**	**γ-HCH**	Follicular fluid	418.6±171.4 µg/L (mean±SD)	↑
	Implantation rate				↓

Table 2-15. Summary of Epidemiological Studies of Hexachlorocyclohexane (HCH) Exposure and Reproductive Effects

Reference, study type, and population	Outcome evaluated	Isomer	Biomarker	Mean concentration (unless otherwise noted)	Result
Freire et al. 2014 Cross-sectional, 604 persons 15–94 years old, residing near former HCH manufacturing facility, Brazil	In men:				
	Serum testosterone	**α-HCH**	Serum	2.52 ng/mL (median)	↓[a]
		β-HCH		6.00	↓
		γ-HCH		0.95	↔
	In premenopausal women:				
	Serum estradiol, progesterone, prolactin, LH, and FSH	α-HCH	Serum	2.77 ng/mL (median)	↔
		β-HCH		6.32	↔
		γ-HCH		0.89	↔
	In peri- or post-menopausal women:				
	Serum estradiol	α-HCH	Serum	2.43 ng/mL (median)	↔
		β-HCH		11.72	↑[a]
		γ-HCH		1.07	↔
	Serum LH	α-HCH	Serum	See above	↔
		β-HCH		See above	↓
		γ-HCH		See above	↔
	Serum progesterone, prolactin, and FSH	α-HCH	Serum	See above	↔
		β-HCH		See above	↔
		γ-HCH		See above	↔

[a]Borderline significant.

↑ = association with increase; ↓ = association with decrease; ↔ = no association; FSH = follicle-stimulating hormone; LH = luteinizing hormone; SD = standard deviation

estradiol and decreased serum luteinizing hormone (LH) levels among peri- and post-menopausal women, but not premenopausal women. No associations were seen between any HCH isomer and serum progesterone, prolactin, or follicle-stimulating hormone (FSH) in women. Serum α- and γ-HCH levels showed no association with reproductive hormone levels in women (Freire et al. 2014).

In a matched cohort study of 473 women undergoing laparoscopy or laparotomy (operative cohort) and 127 women matched on age and residence (population-based cohort), both β-HCH levels in serum and γ-HCH levels in omental fat were associated with increased risk of endometriosis (Buck Louis et al. 2012). Two case-control studies also reported associations between endometriosis and biomarkers of β-HCH exposure. An association between deep infiltrating endometriosis with ovarian endometrioma and β-HCH in adipose tissue was seen in a study of 99 adult women in France (55 cases and 44 controls) (Ploteau et al. 2017). Upson et al. (2013) observed associations between serum levels of β-HCH and both endometriosis and ovarian endometriosis in a larger study in the United States (248 cases and 538 controls). Serum concentrations of γ-HCH were not associated with endometriosis in this study (Upson et al. 2013). Measurements of γ-HCH in follicular fluid from 94 women undergoing intracytoplasmic sperm injection were associated with increased endometrial thickness and decreased implantation rate (Al-Hussaini et al. 2018).

A small cross-sectional study (Akkina et al. 2004) of Hispanic women in the United States reported a decrease in the age at menopause associated with higher serum levels of β-HCH; no other studies of this endpoint were located.

α-HCH. No treatment-related histopathology findings were noted in the testes or uterus and ovaries of rats given α-HCH in feed at doses up to 70 mg/kg/day for an average of 6 months or 9 mg/kg/day for 2 years (Fitzhugh et al. 1950).

β-HCH. Oral exposure to 60 mg β-HCH/kg for 30 days resulted in normal uteri and reproductive cycling in female mice (Cornacoff et al. 1988). Atrophy of the ovaries and testes, hyperplastic and vacuolized endometrial epithelium, degeneration of the seminiferous tubules, and disruption of spermatogenesis were seen in rats exposed to 22.5–25 mg/kg/day β-HCH in the diet (Van Velsen et al. 1986). Half of the animals in this group showed significant clinical signs of neurotoxicity and were humanely sacrificed before the end of the 13-week study; abnormal reproductive organ pathology was seen in both survivors and early decedents (Van Velsen et al. 1986). While no effects were seen upon microscopic examination of the testes, uteri, and ovaries of rats given β-HCH in the diet at doses up to 70 mg/kg/day for up to

10 weeks, slight testicular atrophy was seen after 2 years of exposure to 7 mg/kg/day (Fitzhugh et al. 1950).

γ-HCH (Lindane). Statistically significant increases in the levels of serum LH were reported in a group of 54 men occupationally exposed to unspecified concentrations of γ-HCH for approximately 8 years in a γ-HCH-producing factory (Tomczak et al. 1981). Although the mean serum concentration of FSH was increased and testosterone was decreased, these differences were not statistically significant compared to mean values determined in a control group.

Studies of reproductive effects in animals exposed by inhalation are limited to two intermediate-duration studies focused on systemic toxicity endpoints. Histopathology evaluation of the testes, prostate, ovaries, and uterus of rats and mice exposed by inhalation to 5 mg/m^3 γ-HCH for 13–14 weeks showed no effects of treatment (Klonne and Kintigh 1988; Oldiges et al. 1983).

In animals exposed orally for acute and intermediate durations, γ-HCH induced effects on the male reproductive system, female reproductive system, and on mating, fertility, and early gestation endpoints, as discussed below.

Effects on male reproductive system. The male reproductive system appears to be sensitive to the toxic effects of orally administered γ-HCH. Rats and mice exposed to this isomer have exhibited effects on spermatogenesis, reproductive organ weight changes, and histopathology changes in the testes, while altered sexual behavior was reported in sheep. The lowest dose associated with effects on the male reproductive tract in acute-duration studies is 6 mg/kg/day (Dalsenter et al. 1996); for intermediate-duration studies, it is 1 mg/kg/day in mink (Beard and Rawlings 1998).

In male rats, oral administration of 6 mg/kg for 5 days or a single dose of 30 mg/kg of γ-HCH resulted in a reduction in the number of testicular spermatids and epididymal sperms of both treated groups 2 weeks after treatment (Dalsenter et al. 1996). γ-HCH was detected in the testes of both groups 24 hours and 2 weeks after the last treatment. Histological examination by electron microscopy revealed ballooning of the Sertoli cells with fragmentation or loss of organelles (Dalsenter et al. 1996). Sharma and Singh (2010) administered γ-HCH (30 mg/kg/day) by gavage to Wistar rats for 14 and 28 days for evaluation of effects on the male reproductive tract. After 14 days, the rats had markedly decreased epididymis (27%) and testes (68%) weights. In addition, substantial and persistent reductions (≥85% less than controls) in sperm head count, motility, and percent live sperm, and marked and persistent increases (4-fold) in

percent abnormal sperm were observed (Sharma and Singh 2010). After 28 days at this dose, the effects on epididymis and testes weights were more pronounced, as were the changes in sperm parameters: decreases of ≥89% compared to controls were seen in sperm head count, motility, and percent live sperm, as well as a 4-fold increase in percent abnormal sperm (Sharma and Singh 2010). Similar results were seen in Wistar rats given 50 mg/kg/day γ-HCH in water for 30 days (Hfaiedh et al. 2011). The weights of the testes, epididymides, and prostate gland were decreased by 42–52% relative to controls, and the seminal vesicle weight was reduced by 5%. Compared to control values, sperm count was diminished by 56% and sperm motility by 37% at this dose (Hfaiedh et al. 2011). In a 45-day exposure study, Saradha and Mathur (2006) observed decreased sperm count (~7%) and motility (~15%) in male Wistar rats administered doses of 1 mg/kg/day by gavage. At the higher dose of 5 mg/kg/day in this study, the effects were more severe, with a 27% decrease in sperm count and ~25% decrease in sperm motility (Saradha and Mathur 2006). In a 2-generation reproductive toxicity study in Crj:CD(SD)IGS rats given dietary doses up to 23.3 mg/kg/day, no statistically significant treatment-related effects on sperm count, motility, or percent abnormal sperm were noted in F0 or F1 males (Matsuura et al. 2005). Histology of the parental male reproductive organs was also normal (Matsuura et al. 2005). Dietary exposure to up to 120 mg/day γ-HCH for 10 months or 30 mg/kg/day for 2 years or did not result in histopathology changes in the testes of rats (Fitzhugh et al. 1950).

Exposure to γ-HCH has also induced altered levels of reproductive hormones in male rats. When male Wistar rats were exposed to 50 mg/kg/day γ-HCH in water for 30 days, serum FSH levels were decreased by 74% relative to controls (Hfaiedh et al. 2011). Effects of γ-HCH on the levels of reproductive hormones in blood of male animals appear to be more significant in younger animals compared with older animals. Groups of 30 male Wistar rats were administered 5 mg/kg/day γ-HCH for 5 days beginning at 9, 18, or 27 weeks of age (Agrahari et al. 2019). Animals treated with γ-HCH beginning at 9 weeks of age exhibited significantly decreased serum testosterone (39%) and growth hormone (29%), and increased serum LH (42%) and FSH (31%), compared to controls. Similar results were observed in the group treated at 18 weeks of age, but treatment at 27 weeks of age resulted in smaller decreases in serum testosterone and growth hormone, and no significant effect on serum LH or FSH. No dose-related effects on serum hormone levels were observed in F0 or F1 male parents in a 2-generation study of Crl:CD(SD)IGS rats at doses of 17.2–26.1 mg/kg/day in diet for ~10 weeks (Matsuura et al. 2005).

One study reported male reproductive tract effects in mice exposed to γ-HCH. Nagda and Bhatt (2011) exposed Swiss mice by gavage (40 mg/kg/day) for 60 days. At sacrifice at the end of exposure, the mice exhibited a 10% decrease in testes weight as well as histopathology changes in the testes, including

shrunken and distorted seminiferous tubules, sparse Leydig cells, and oligospermia (Nagda and Bhatt 2011). The male reproductive effects of γ-HCH were also studied in young rams given 1 mg/kg/day in treated feed from conception to sexual maturity (Beard et al. 1999a). The subjectively-scored sexual behavior in the rams was significantly reduced in treated animals presented with estrous ewes (Beard et al. 1999a).

Effects on female reproductive system. Studies examining female reproductive effects in animals exposed to γ-HCH are more limited, but suggest effects on estrous cycling and other endpoints in a variety of species. Oral administration of γ-HCH for acute and intermediate durations has resulted in alterations in estrous cycling, sexual behavior, and uterine histopathology. In acute-duration studies, the lowest dose associated with these effects was 25 mg/kg/day (Uphouse and Williams 1989); in intermediate-duration studies, the lowest dose associated with these effects was 1 mg/kg/day (Beard and Rawlings 1999). Increased length of estrous cycle and decreased sexual receptivity were found in female rats treated with a single dose of γ-HCH (≥25 mg/kg) given by gavage (Uphouse and Williams 1989). Female rabbits exposed to 0.8 mg γ-HCH/kg/day, 3 days/week for 12 weeks had a reduced ovulation rate (Lindenau et al. 1994). Histopathological changes were observed in the uteri of female Sprague-Dawley rats given γ-HCH by gavage at a dose of 8 mg/kg/day for 4 weeks. The uterine changes were described as low columnar endometrial glandular epithelial cells (Yang et al. 2014; Zhang et al. 2016). Delayed vaginal opening and disrupted ovarian cycling in female F344 rats given ≥10 mg/kg/day by gavage for 15 weeks beginning at weaning (Chadwick et al. 1988). Finally, in estrus synchronized ewe lambs dosed with γ-HCH in feed at 1 mg/kg/day from conception to sexual maturity, significantly shorter estrous cycle length and reduced number and total volume of corpus lutea were observed (Beard and Rawlings 1999). No other detrimental fertility effects were observed. No effects on maternal female reproductive organ weights or histology were noted in CD mice exposed to 15 mg/kg/day via gavage on GDs 9–16 (Maranghi et al. 2007). In a 2-generation reproductive toxicity study in Crj:CD(SD)IGS rats, doses of 28.0 mg/kg/day in diet for ~10 weeks resulted in a significantly decreased estrus cycle length (4 days versus 4.45 days in controls) in F1, but not F0 female adults (Matsuura et al. 2005). No effects were observed on ovarian follicle counts at any dose in F1 females, and no changes in reproductive organ weights or histology were observed at sacrifice of F0 or F1 female parental animals (Matsuura et al. 2005). Fitzhugh et al. (1950) observed no effects on the histopathology of the uterus or ovaries of rats given γ-HCH via the diet for up to 140 mg/kg/day for 10 months or up to 30 mg/kg/day for 2 years.

In female Wistar rats dosed with γ-HCH by daily gavage for 4 weeks, significantly decreased serum levels of estradiol (20 and 26%) and testosterone (28 and 37%) were observed at 4 and 8 mg/kg/day

γ-HCH, respectively (Zhang et al. 2016; Yang et al. 2014). Significant, dose-related increases in serum LH were seen at all doses (23–44% relative to controls at doses from 0.95 to 28 mg/kg/day) in F1 females during proestrus in a 2-generation study of Crj:CD(SD)IGS rats (Matsuura et al. 2005). Serum hormone levels in F0 female parents were not impacted by exposure in this study. Female mink exposed to 1 mg/kg/day γ-HCH before mating and through mating, gestation, and lactation exhibited no effects on serum estradiol or progesterone when evaluated at weaning of their kits (Beard et al. 1997). Sheep exposed on a similar schedule to the same dose did not show changes in serum LH or FSH (Beard et al. 1999b)

Effects on mating, fertility, and early gestation. In a multigeneration reproduction study with γ-HCH, Charles River CD rats were exposed to estimated dietary doses of 0, 0.09, 1.7, or 13.1 mg/kg/day for 2 generations (EPA 1991a). No treatment-related effects on mating, fertility, gestation survival, liveborn indices, or mean litter sizes occurred in either generation, although developmental toxicity occurred at 13.1 mg/kg/day, as shown by reduced body weight and decreased viability in pups of both generations and delayed maturation of F2 pups (see Section 2.17). Similar findings were noted in the 2-generation study reported by Matsuura et al. (2005). No effects on mating, fertility, gestation length, birth index, or gestation index were seen in Crj:CD(SD)IGS rats of either generation at doses up to 28 mg/kg/day, but there were developmental effects on offspring body weight, viability, and sexual maturation (see Section 2.17). Female rabbits dosed with 0.8 mg γ-HCH/kg/day, 3 days/week for 12 weeks followed by artificial insemination exhibited no effects on the fertilization rate or on pre- or postimplantation losses (Seiler et al. 1994).

Mice and mink appear to be more sensitive than rats to the effects of γ-HCH on fertility and early gestation. When mouse dams were treated with γ-HCH (6.2 mg/kg) during GDs 6–12, all fetuses were resorbed (Sircar and Lahiri 1989). In another experiment by these authors, pregnant mice exposed to 10.8 mg/kg/day on GDs 1–4 exhibited no implantation sites. When pregnant mice were exposed to 3.6 mg/kg/day on GDs 14–19, all pups died (Sircar and Lahiri 1989). Acute preovulatory exposure to γ-HCH caused embryonic effects in mice (Scascitelli and Pacchierotti 2003). Three consecutive daily doses of γ-HCH in olive oil were administered to female mice either before mating (during the preovulatory period) or immediately after mating. Oocyte maturation, ovulation, and fertilization were evaluated by assessing percentage of vaginal plug positive females, number of embryos/female, percentage of one-cell embryos (corresponding to unfertilized oocytes or zygotes that did not undergo cleavage), and gross morphologic alterations of two-cell embryos. Preimplantation embryonic development was evaluated by morphological examinations of morulae for determinations of one-cell

embryos (unfertilized eggs or zygotes that did not undergo cleavage), embryos retarded in their cleavage, and abnormal embryos, as well as by cytological examinations of morulae for determinations of interphase nuclei, meta-anaphases, apoptotic nuclei, micronuclei, and mitotic index. Preovulatory exposure caused a significant increase of degenerating two-cell embryos (lysis or fragmentation of blastomeres), but there were no exposure-related effects of post-mating treatment.

Reproductive toxicity studies in mink showed effects on sexual receptivity, whelping rate, and embryo mortality. A 2-generation reproduction study of γ-HCH was conducted in mink that were exposed to dietary doses of 0 or 1 mg/kg/day (Beard and Rawlings 1998). The parental (P0) generation was exposed from 3 weeks before breeding until weaning of the offspring. Following weaning, the F1 females were exposed throughout growth and mating (to untreated males), and subsequently throughout pregnancy and lactation until 3 months post-lactation. The F2 females were exposed until they reached full adult body size at 30 weeks of age. The F1 and F2 males were exposed until the time their testis development was maximal (sexual maturity) at about 42 weeks of age. In addition to standard reproductive indices, serum hormone levels (estradiol, testosterone) and histology of male and female reproductive tissues were evaluated in offspring of both generations. There were no overt signs of toxicity or effects on mating percentage. Fertility was reduced in both generations, as shown by reductions in whelping rate and litter size, such that exposed mink produced approximately 60% fewer kits than controls. Other effects included reduced testis size in F2 males. In a single-generation study, female mink treated with 1 mg/kg/day γ-HCH in their diet from 3–6 weeks before mating until weaning at 8–10 weeks postpartum showed effects on reproductive efficiency that included reduced receptivity to a second mating and reduced whelping rate, although litter size was not affected (Beard et al. 1997). This decreased fertility effect was primarily a result of embryo mortality after implantation.

Mechanisms. Inhibition of the formation of estradiol-receptor complex in the rat uterus cytosol was reported in female rats administered 30 mg γ-HCH/kg/day by oral intubation for 7 days (Tezak et al. 1992). Statistically significant increases in the glycogen content of the uterus, cervix, and vagina (but no increase in organ weight) were reported in female rats exposed to 20 mg γ-HCH/kg/day in the diet for 30 days (Raizada et al. 1980). Antiestrogenic properties were found in female rats given gavage doses of 10 mg/kg/day γ-HCH for 15 weeks (Chadwick et al. 1988). These responses were not seen at 5 mg/kg/day. Ovariectomized rats exposed for 5 days and sexually immature female rats exposed for 7 days to 40 mg γ-HCH/kg/day showed no effects on the number of estrogen and estrogen-dependent progesterone receptors (Laws et al. 1994). Thus, γ-HCH's antiestrogenic effects in reproductive tissue do not appear to be due to direct action on estrogen receptors or its induction of progesterone receptors.

In vitro studies have not shown binding of γ-HCH to the estrogen receptor, but one study showed that this isomer could inhibit the activity of aromatase (the enzyme that forms estrogen in mammals) in human placental and embryonic kidney cells transfected with the associated gene (reviewed by IARC 2018).

Technical or Unspecified HCH. Studies of reproductive toxicity in animals exposed orally to technical-grade HCH have shown effects on the male reproductive tract of rats and mice. Dermal exposure of rats and guinea pigs induced similar changes.

Immature (15-day-old) and mature (90-day-old) rats were administered technical-grade HCH in doses of 10 or 20 mg/kg/day in oil by gavage for 7, 15, or 30 days (Samanta et al. 1999). Exposure to ≥10 mg/kg/day for 7 days caused effects that included reduced epididymis weight in immature rats and reduced seminal vesicle and ventral prostate weights in adult rats. Effects observed following exposure to ≥10 mg/kg/day for 7–30 days included reduced total sperm count and increased frequencies of damaged sperm and sperm with anomalous heads in adult rats. Shivanandappa and Krishnakumari (1983) reported testicular atrophy, degeneration of seminiferous tubules, and disruption of spermatogenesis in male rats fed technical-grade HCH at 75 mg/kg/day for 90 days. After 180 days of exposure to 3 mg/kg/day technical-grade HCH, male Charles Foster rats exhibited significant decreases in testes and vas deferens weights, as well as decreases in seminiferous tubule diameter and degeneration of muscle tissue in the vas deferens (Gautam et al. 1989; Roy Chowdhury and Gautam 1990). At a higher dose of 6 mg/kg/day, complete degeneration of testicular tissue, post-meiotic spermatogenic arrest, and degeneration of spermatogenic cells were seen (Roy Chowdhury and Gautam 1990). Testicular degeneration was reported in male rats exposed to 20 mg/kg/day technical-grade HCH in the diet for 360 days (Dikshith et al. 1991a). Fitzhugh et al. (1950) observed no effects on the histopathology of the testes, uterus, or ovaries of rats given technical HCH via the diet for up to 9 mg/kg/day for 2 years. Moderate testicular atrophy was observed in rats given technical HCH in the diet for 6 months at a dose of 60 mg/kg/day (Fitzhugh et al. 1950). In mice, exposure to 90 mg technical-grade HCH/kg/day (isomer composition unknown) for 3 months led to increased testicular weight and degeneration of seminiferous tubules (Nigam et al. 1979).

Male and female Druckrey rats were exposed via diet and drinking water to estimated total daily doses of 0, 16, or 32 mg/kg/day technical-HCH throughout 3 generations (Srivastava and Raizada 2000). There were no exposure-related effects on reproduction in any of the 3 parental generations, and no morphological or teratological changes in any of the offspring generations (F1b, F2b, or F3b).

In studies of dermal exposure, the backs of male rats were sprayed with 50 or 100 mg/kg/day technical-grade HCH for 120 days and the rats were housed in separate cages to prevent licking (Prasad et al. 1995). Depletion of germ cells and impaired function of Leydig and Sertoli cells was suggested by significant dose-related changes in activities of testicular enzymes such as sorbitol dehydrogenase, glucose-6-P-dehydrogenase, γ-glutamyl transpeptidase, and β-glucuronidase. Significant reductions in sperm count and motility and increased percentages of abnormal sperm were also observed in both groups. A significant reduction in testosterone level was observed in the high-dose group. Dikshith et al. (1978) reported testicular hypertrophy and atrophy and complete inhibition of spermatogenesis in guinea pigs dermally treated with technical-grade HCH for 7, 15, or 30 days at doses as low as 100 mg/kg/day. The patch of the abdomen on which the HCH was applied was not covered to prevent licking, so oral exposure more than likely occurred.

Mechanisms. There is evidence that oxidative stress may contribute to the effects of technical-grade HCH on the male reproductive system. Testicular oxidative stress was studied in immature (15-day-old) and mature (90-day-old) rats that were administered technical-grade HCH in doses of 10 or 20 mg/kg/day in oil by gavage for 7, 15, or 30 days (Samanta et al. 1999). Endpoints that were evaluated included testicular protein and lipid peroxidation, testicular levels of antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase) and non-enzymatic antioxidants (reduced glutathione, ascorbic acid, hydrogen peroxide). Testes from immature and adult rats exposed to ≥10 mg/kg/day for 7–30 days also showed increased lipid peroxidation and changes in glutathione peroxidase, ascorbic acid, and hydrogen peroxide levels.

2.17 DEVELOPMENTAL

Developmental effects of HCH isomers have been evaluated in human populations and in animals. These studies are discussed below in the individual isomer subsections. However, the epidemiological studies of all isomers share limitations that render the reported associations uncertain, especially when considered without any supporting animal data. Epidemiological studies of developmental effects were conducted in the general population (without occupational exposure), generally using measurements of HCH isomers in physiological fluids or tissues of mothers and infants. In the general population, the route(s) of exposure is unknown. In the studies discussed herein, other organochlorine compounds (such as hexachlorobenzene, aldrin, heptachlor and its epoxide, DDT and its metabolites, polychlorinated biphenyls, and/or polychlorinated dioxins and furans) were also present in the blood. Few of the studies

controlled for these coexposures; thus, the role of HCH isomers in the observed effects, if any, cannot be ascertained. In addition, the case-control studies examined levels of HCH isomers in blood and tissues after the outcome was established, rendering the temporal association between exposure and outcome uncertain.

α-HCH. Data on the developmental effects of α-HCH are limited to a small number of human epidemiological studies; there are no animal studies of developmental toxicity for this isomer. Table 2-16 provides a summary of human epidemiological data on developmental effects of α-HCH. As the table shows, the epidemiology data suggest possible associations between growth retardation and maternal or placental levels of α-HCH. Increased risks of fetal growth restriction (defined as $<10^{th}$ percentile of birth weight for gestational age and also referred to as intrauterine growth retardation) were associated with maternal blood levels of α-HCH in two small case-control studies in India (Sharma et al. 2012; Siddiqui et al. 2003). Reduced birth weight was associated with higher levels of α-HCH in placenta in a small cross-sectional study in India (Anand and Taneja 2020), but not with maternal serum levels of α-HCH in a cross-sectional study in an Arctic population in Russia (Bravo et al. 2019) or with cord serum levels in a large cross-sectional analysis of 1,028 mother-infant pairs in China (Fang et al. 2019a, 2019b). None of the available studies suggested associations between biomarkers of α-HCH exposure in maternal and infant tissues and birth length, head circumference, or ponderal index (Anand and Taneja 2020; Bravo et al. 2019; Fang et al. 2019a, 2019b).

In cross-sectional studies, a negative association between gestational age among term births and α-HCH in cord serum was observed in a study of 1,028 mother-infant pairs in China (Fang et al. 2019a, 2019b), but no association was seen in a smaller group of 247 mother-infant pairs in Russia (Bravo et al. 2019). Increased risk of preterm birth was associated with higher maternal blood levels of α-HCH in a case-control study in India (Mustafa et al. 2013).

β-HCH. Epidemiological studies of developmental endpoints in humans exposed to β-HCH are summarized in Table 2-17. As the table shows, most of the studies examined metrics pertaining to fetal growth and gestational age. The studies provide suggestive evidence for an association between β-HCH concentrations in maternal or umbilical cord blood and reduced birth weight.

Table 2-16. Summary of Epidemiological Studies of α-Hexachlorocyclohexane (HCH) Exposure and Developmental Effects

Reference, study type, and population	Outcome evaluated	Biomarker	Mean concentration (unless otherwise noted)	Result
Siddiqui et al. 2003 Case-control, 30 mothers of infants with intra-uterine growth retardation, 24 mothers of normal weight infants, India	**Intra-uterine growth retardation**	Maternal blood	5.82±3.22 ng/g (mean±SD) (cases) 3.79±3.14 (controls)	↑
		Placenta	9.91±3.89 (cases) 8.88±5.17 (controls)	NR
		Cord blood	9.84±5.12 (cases) 6.74±7.83 (controls)	NR
Fang et al. 2019a, 2019b Cross-sectional, 1,028 pregnant mother-infant pairs, China	Birth weight	Cord serum	≥0.718 ng/g lipid (3rd tertile)	↔
	Birth length			↔
	Ponderal index			↔
	Gestational age			↓ (among term births)
Anand and Taneja 2020 Cross-sectional, 90 mother-infant pairs, India	**Birth weight**	Placenta tissue	1.09–211.43 µg/L (range)	↓
	Birth length			↔
	Head circumference			↔
	Ponderal index			↔
Bravo et al. 2019 Cross-sectional, 247 mother-child pairs, Russia	Gestational age	Maternal serum (last week of pregnancy)	3.3 ng/g lipid (median)	↔
	Birth weight			↔
	Birth length			↔
	Head circumference			↔
Mustafa et al. 2013 Case-control, 156 mothers with preterm births and 150 mothers with term births, India	**Preterm birth**	Maternal blood	4.04±2.63 ng/g (mean±SD) (cases) 2.93±2.59 (controls)	↑
		Cord blood	1.91±2.03 (cases) 1.69±2.25 (controls)	↔

Table 2-16. Summary of Epidemiological Studies of α-Hexachlorocyclohexane (HCH) Exposure and Developmental Effects

Reference, study type, and population	Outcome evaluated	Biomarker	Mean concentration (unless otherwise noted)	Result
Sharma et al. 2012 Case-control, 50 cases delivering babies with fetal growth restriction and 50 women with healthy term infants, mean ages 23–24 years, India	**Fetal growth restriction**	Maternal blood	4.55±3.2 ng/g (mean±SD) (cases) 2.92±2.7 (controls)	↑
		Cord blood	2.01±1.6 (cases) 1.90±2.3 (controls)	↔

↑ = association with increase; ↓ = association with decrease; ↔ = no association; SD = standard deviation

Table 2-17. Summary of Epidemiological Studies of β-Hexachlorocyclohexane Exposure and Developmental Effects

Reference, study type, and population	Outcome evaluated	Biomarker	Concentration	Result
Birth outcomes				
Siddiqui et al. 2003 Case-control, 30 mothers of infants with intra-uterine growth retardation, 24 mothers of normal weight infants, India	Fetal growth restriction (intrauterine growth retardation)	Maternal blood	7.95±11.43 ng/g (mean±SD) (cases) 6.55±5.43 (controls)	↔
		Placenta	7.30±10.92 (cases) 7.00±7.14 (controls)	↔
		Cord blood	3.03±5.22 (cases) 2.96±3.62 (controls)	↔
Callan et al. 2016 Cross-sectional, 161 mother-infant pairs, Australia	**Birth weight, proportion of optimal birth weight**	Maternal plasma (2 weeks prior to birth)	0.18 µg/L (mean)	↓ (boys) ↔ (girls)
	Ponderal index			↔
Hjermitslev et al. 2020 Cross-sectional, 468 mother-infant pairs, Greenland	Birth weight	Maternal serum	3.6 µg/kg lipid (median)	↔
	Gestational age			↓
Fenster et al. 2006 Cohort, 385 mother-infant pairs, California, United States	Length of gestation	Maternal serum (2nd trimester or at delivery)	37.2 ng/g lipid (median)	↔
	Birth weight		See above	↔
	Crown-heel length		See above	↔
Khanjani and Sim 2006 Cross-sectional, 815 mother-infant pairs, Australia	Prematurity	Breast milk	0.0098±0.0286 mg/kg milk fat (mean±SD)	↔
	Previous miscarriage or still birth			↔
	Low birth weight			↔
	Small for gestation age			↔
	Head circumference			↔
	Sex ratio			↔
Gladen et al. 2003 Cross-sectional, 197 mother-infant pairs, Ukraine	Birth weight	Breast milk	860 ng/g milk fat (3rd tertile)	↔

Table 2-17. Summary of Epidemiological Studies of β-Hexachlorocyclohexane Exposure and Developmental Effects

Reference, study type, and population	Outcome evaluated	Biomarker	Concentration	Result
Lopez-Espinosa et al. 2011 Cross-sectional, 494 mothers-infant pairs, Spain	**Birth weight**	Cord serum	0.085 ng/mL (median)	↓ (marginal)
	Birth length			↔
	Head circumference			↔
Fang et al. 2019a, 2019b Cross-sectional, 1,028 pregnant mother-infant pairs, China	**Birth weight**	Cord serum	≥12.64 ng/g lipid (3rd tertile)	↓ (boys)
	Birth length			↔
	Ponderal index			↓ (boys)
	Gestational age			↔
Guo et al. 2014 Cross-sectional, 81 mother-infant pairs, China	**Birth weight**	Maternal serum at birth	73.96 (median)	↓
		Cord serum	35.29 (median)	↓
Anand and Taneja 2020 Cross-sectional, 90 mother-infant pairs, India	**Birth weight**	Placenta tissue	1.10–678.74 µg/L (range)	↓
	Birth length			↔
	Head circumference			↔
	Ponderal index			↔
Mustafa et al. 2013 Case-control, 156 mothers with preterm births and 150 mothers with term births, India	Preterm birth	Maternal blood	5.07±3.40 ng/g (mean±SD) (cases) 4.03±3.40 (controls)	↔
		Cord blood	2.10±1.83 (cases) 1.84±2.10 (controls)	↔
Tan et al. 2009 Cross-sectional, 41 mother-infant pairs, Singapore	Birth weight	Cord blood	85.4±173 ng/g lipid (mean±SD)	↔
	Birth length			↑
	Head circumference			↑
	Gender			↔
Tyagi et al. 2016 Cross-sectional, 30 mothers with preterm births and 30 mothers with term births, India	**Preterm birth**	Maternal blood	6.42±2.158 ng/mL (mean±SD) (cases) 3.06±2.05 (controls)	↑

Table 2-17. Summary of Epidemiological Studies of β-Hexachlorocyclohexane Exposure and Developmental Effects

Reference, study type, and population	Outcome evaluated	Biomarker	Concentration	Result
Bravo et al. 2019 Cross-sectional, 247 mother-child pairs, Russia	Gestational age	Maternal serum (last week of pregnancy)	38 ng/g lipid (median)	↔
				↔
	Birth weight			↔
	Birth length			↔
	Head circumference			↔
Yang et al. 2020 Cohort, 102 healthy pregnant women, mean age 28 years, China	**Birth weight**	Maternal serum	7.44 ng/mL (mean)	↓
Sharma et al. 2012 Case-control, 50 cases delivering babies with fetal growth restriction and 50 women with healthy term infants, mean ages 23–24 years, India	**Fetal growth restriction**	Maternal blood	3.97±3.9 ng/g (mean±SD) (cases)	↑
		Cord blood	2.67±2.4 (cases)	↔
Torres-Arreola et al. 2003 Case-cohort, 100 mothers with preterm births, 133 controls with full-term births, Mexico	Preterm birth (<37 weeks)	Maternal serum at birth	>76.53 ng/g (3rd tertile)	↔
Pierik et al. 2007 Case-control nested in birth cohort, 219 mothers of children with cryptorchidism, 564 controls, United States	Cryptorchidism within first year of life	Maternal serum (3rd trimester)	>3.41 µg/L (90th percentile)	↔
Warembourg et al. 2016 Cross-sectional, 282 newborns, France	Umbilical cord blood free testosterone, sex hormone binding globulin, anti-Müllerian hormone, estradiol, aromatase index	Cord blood	11.27 ng/g lipid (median)	↔
Debost-Legrand et al. 2016 Cross-sectional, 268 mother-infant pairs, France	Umbilical cord serum insulin, adiponectin	Cord serum	>0.061µg/L (4th quartile)	↔

Table 2-17. Summary of Epidemiological Studies of β-Hexachlorocyclohexane Exposure and Developmental Effects

Reference, study type, and population	Outcome evaluated	Biomarker	Concentration	Result
Postnatal development				
Namulanda et al. 2016 Case-control, 218 girls with early menarche (<11.5 years of age), 230 controls, England	Early menarche	Maternal serum	47.4 ng/g lipid (median)	↔
Lam et al. 2014, 2015 Cohort, 350 boys 8–9 years old, followed for 8 years, Russia	Age of pubertal onset	Serum at cohort entry	1.3–14 ng/g (4th quartile)	↔
	Age of sexual maturity			↑
Cupul-Uicab et al. 2013 Birth cohort, 1,915 children followed until age 7 years, United States	Childhood obesity or overweight and obese	Maternal serum (3rd trimester)	≥2.12 µg/L (4th quartile)	↔
Lauritzen et al. 2018 Cohort, 412 mother-child pairs followed to child age 5 years, Norway and Sweden	Childhood obesity at 5 years old (BMI, triceps skinfold, subscapular skinfold, overweight)	Maternal serum (2nd trimester)	Norway: 21.2 ng/g lipid (median) Sweden: 25 ng/g lipid (median)	↔
Mendez et al. 2011 Birth cohort, 518 mother-infant pairs followed for 14 months, Spain	Rapid infant growth during first 6 months; elevated BMI at 14 months	Maternal serum (1st trimester)	≥47.28 ng/g lipid (4th quartile)	↔
Salo et al. 2019 Case-control, 40 cases with autoantibodies and 11 control children up to 6 years old, Finland	Diabetes-associated autoantibodies	Cord plasma	>LOQ (not specified)	↔
Alvarez-Pedrerol et al. 2008a Cross-sectional, 21 newborn infants, Spain	**Neonatal plasma TSH (3 days postpartum)**	Cord serum	0.48 ng/mL (geometric mean) (group with TSH ≥10 mU/L) 0.24 (group with TSH <10 mU/L)	↑
Alvarez-Pedrerol et al. 2008b Cross-sectional, 259 children 4 years old, Spain	Serum free T4, TSH at age 4 years	Serum (child)	≥0.305 ng/mL (4th quartile)	↔
	Serum total T3 at age 4 years		≥0.191 ng/mL (3rd quartile)	↓
Ribas-Fito et al. 2003 Cross-sectional, 98 newborn infants, Spain	**Neonatal plasma TSH ≥10 mU/l**	Cord serum	0.54 ng/mL (median)	↑

Table 2-17. Summary of Epidemiological Studies of β-Hexachlorocyclohexane Exposure and Developmental Effects

Reference, study type, and population	Outcome evaluated	Biomarker	Concentration	Result
Lopez-Espinosa et al. 2010 Cross-sectional, 453 newborn infants, Spain	**Postpartum (≥2 days) neonatal serum TSH**	Cord serum	>104 ng/g lipid (90th percentile)	↑
Yamazaki et al. 2020 Cross-sectional, 333 mother-child pairs, Japan	Serum free T4 or TSH in infants 7–43 days old	Maternal serum	235.6 pg/g (75th percentile)	↔
Li et al. 2014 Cross-sectional, 247 pregnant women, Yanchen City, China	Umbilical cord serum free T3, free T4, TSH	Cord serum	13.336 ng/g (median)	↔
Sunyer et al. 2008 Cross-sectional, 52 children, 4 years old, Spain	Urinary porphyrins (child)	Serum (child)	>0.37 ng/mL	↔
Neurodevelopmental endpoints				
Lenters et al. 2019 Birth cohort, 1,199 mother-child pairs, Norway	ADHD by 13 years of age	Breast milk	4.367 ng/g lipid (median)	↑
Kokroko et al. 2020 Cohort, 256 mother child pairs, United States	IQ at 7 years old (Wechsler Intelligence Scale for Children)	Maternal serum during pregnancy	33.3 ng/g lipid (geometric mean)	↔[a]
Braun et al. 2014 Cohort, 175 mother-child pairs, Ohio, United States	Social responsiveness scale score, children age 4 and 5 years	Maternal serum	<LOD (median) 1.9 ng/g lipids (75th percentile)	↔[b]
Jeddy et al. 2018 Cohort, 400 mother-daughter pairs, England	Communication development: nonverbal communication, social development, verbal comprehension, vocabulary comprehension in daughters at 15 and 38 months	Maternal serum	>56.15 ng/g lipid (3rd tertile)	↔
Lee et al. 2007 Cross-sectional, 278 children aged 12–15 years, NHANES, United States	Learning disability	Serum (child)	17.9 ng/g lipid (median)	↔
	Attention deficit disorder			↔

Table 2-17. Summary of Epidemiological Studies of β-Hexachlorocyclohexane Exposure and Developmental Effects

Reference, study type, and population	Outcome evaluated	Biomarker	Concentration	Result
Fabisiková et al. 2012 Cross-sectional, 143 mother-infant pairs, Slovakia	Bayley mental development index at 10 months of age	Serum (child)	0.01–82.9 ng/g lipid (range)	↔
	Bayley psychomotor development index at 10 months of age			↔
Sisto et al. 2015 Cohort, 351 infants enrolled at birth, Slovakia	Cochlear deficits measured as altered distortion product otoacoustic emissions at 45 months of age	Cord blood	9.84±8.09 ng/g lipid	↑
		Serum at 6 months old	12.24±12.9	↓
		Serum at 16 months old	13.36±16.06	↓
		Serum at 45 months old	7.70±9.21	↓

[a]A significant increase in working memory IQ score was observed but is not shown here as it is not considered adverse.
[b]A significant decrease in SRS score, corresponding to lower autism-related behaviors, was observed but is shown here as it not considered adverse.

↑ = association with increase; ↓ = association with decrease; ↔ = no association; ADHD = attention deficit hyperactive disorder; BMI = body mass index; IQ = intelligence quotient; LOD = limit of detection; NHANES = National Health and Nutrition Examination Survey; SD = standard deviation; T3 = triiodothyronine, T4 = thyroxine; TSH = thyroid-stimulating hormone

In a birth cohort of 385 mother-infant pairs in California, birth weight showed no association with β-HCH in maternal serum sampled during the second trimester or at delivery (Fenster et al. 2006). Case-control studies of fetal growth restriction (<10th percentile weight for gestational age) reported conflicting findings. Siddiqui et al. (2003) reported no association of fetal growth restriction with maternal, cord blood, or placental concentrations of β-HCH in a small (30 cases and 24 controls) study conducted in India. However, a slightly larger study of 50 cases and 50 controls in India showed a positive association between increased risk of fetal growth restriction and β-HCH in maternal blood (but not cord blood) (Sharma et al. 2012).

Associations between reduced birth weight and increased maternal plasma, umbilical cord blood, or placental tissue concentrations of β-HCH were reported in cross-sectional studies in Australia (Callan et al. 2016), Spain (Lopez-Espinosa et al. 2011), China (Fang et al. 2019a, 2019b; Guo et al. 2014; Yang et al. 2020), and India (Anand and Taneja 2020), but not in cross-sectional studies in Greenland (Hjermitslev et al. 2020) or Russia (Bravo et al. 2019).

Studies evaluating whether β-HCH concentrations in maternal or infant blood were associated with preterm birth or gestational age have yielded mixed results. Tyagi et al. (2016) reported a positive association between risk of preterm birth and β-HCH in maternal blood in a small cross-sectional study in India, but no association was reported in a case-control study in India (Mustafa et al. 2013) or in a case-cohort study in Mexico (Torres-Arreola et al. 2003). In 468 mother-infant pairs in Greenland, decreased gestational age was associated with maternal serum levels of β-HCH (Hjermitslev et al. 2020), but no association was seen in cross-sectional studies in China (Fang et al. 2019a, 2019b) or Russia (Bravo et al. 2019) or between gestation length and β-HCH in maternal blood in a cohort study in the United States (Fenster et al. 2006).

A case-control study nested in a birth cohort in the United States observed no association between maternal serum concentrations of β-HCH and cryptorchidism or hypospadias (Pierik et al. 2007). Cross-sectional studies in France reported no association between β-HCH in umbilical cord blood and reproductive hormone levels (Warembourg et al. 2016), or insulin and adiponectin concentrations in umbilical cord (Debost-Legrand et al. 2016).

As shown in Table 2-17, serum and cord blood levels of β-HCH were associated with increased serum levels of TSH in cross-sectional studies conducted in Spain (Alvarez-Pedrerol et al. 2008a, 2008b; Lopez-Espinosa et al. 2010; Ribas-Fito et al. 2003) but not in a similar study in China (Li et al. 2014). No

association between maternal serum levels of β-HCH and concentrations of free T4 or TSH in infants from 1 to 6 weeks old (Yamazaki et al. 2020).

Studies examining neurodevelopmental effects in relationship to maternal serum, breast milk, or infant or child blood levels of β-HCH are shown in Table 2-17. In general, these studies showed no associations with IQ, social responsiveness, communication, or mental and psychomotor development (see Table 2-17). However, Lenters et al. (2019) showed an association between breast milk concentrations of β-HCH and diagnosis of attention deficit hyperactive disorder (ADHD) at approximately 13 years of age. Sisto et al. (2015) reported an association between serum concentrations of β-HCH in children and hearing deficits measured at 45 months of age. In this study, the investigators controlled for co-exposure confounding by evaluating the association between β-HCH and hearing deficits both with and without potentially ototoxic co-exposures. Sisto et al. (2015) also assessed tonotopicity (specificity of the effect on different regions of the basal membrane in the organ of Corti, which correspond to effects on different frequencies), observing that the strength of the association with each compound varied by noise frequency.

Limited data are available on developmental effects of β-HCH in animals. Dietary exposure of pregnant rats to 20 or 25 mg/kg/day of β-HCH during gestation caused increased perinatal mortality, with deaths of 48 or 100% of the pups within 5 days of birth; exposure to 5 mg/kg/day did not influence perinatal survival (Srinivasan et al. 1991). In another experiment by these authors, a dose 5 mg/kg/day of β-HCH during gestation and lactation or during lactation only resulted in increased liver weights of pups when measured at 28 days of age (Srinivasan et al. 1991).

γ-HCH (Lindane). Epidemiological studies of developmental endpoints in humans exposed to γ-HCH are summarized in Table 2-18. Two case-control studies in India reported associations between maternal and cord blood levels of γ-HCH and fetal growth restriction (Sharma et al. 2012; Siddiqui et al. 2003). In a birth cohort of 385 mother-infant pairs in California, birth weight and length were not associated with γ-HCH concentration in maternal serum collected during the second trimester and at delivery (Fenster et al. 2006). Birth weight, birth length, and ponderal index showed no association with γ-HCH in cord serum in a cross-sectional study of 1,028 infants in China (Fang et al. 2019a, 2019b).

Gestation length was not associated with γ-HCH concentration in maternal serum in a birth cohort of 385 mother-infant pairs in an agricultural area of California (Fenster et al. 2006). Gestational age

Table 2-18. Summary of Epidemiological Studies of γ-Hexachlorocyclohexane Exposure and Developmental Effects

Reference, study type, and population	Outcome evaluated	Biomarker	Concentration	Result
Siddiqui et al. 2003 Case-control, 30 mothers of infants with intrauterine growth retardation, 24 mothers of normal weight infants, India	**Intrauterine growth retardation**	Maternal blood	6.30±7.51 ng/g (mean±SD) (cases) 2.65±2.15 (controls)	↑
		Placenta	8.71±4.57 (cases) 6.86±4.46 (controls	↔
		Cord blood	9.23±10.31 (cases) 4.23±4.59 (controls)	↑
Fenster et al. 2006 Cohort, 385 mother-infant pairs, California, United States	Length of gestation	Maternal serum (2nd trimester and at delivery)	1.0 ng/g lipid (median)	↔
	Birth weight			↔
	Crown-heel length			↔
Fang et al. 2019a, 2019b Cross-sectional, 1,028 pregnant mother-infant pairs, China	Birth weight	Cord serum	≥1.125 ng/g lipid (3rd tertile)	↔
	Birth length			↔
	Ponderal index			↔
	Gestational age			↓
Mustafa et al. 2013 Case-control, 156 mothers with preterm births and 150 mothers with term births, India	**Preterm birth**	Maternal blood	2.63±2.46 ng/g (mean±SD) (cases) 1.52±1.83 (controls)	↑
		Cord blood	0.988±1.31 (cases) 0.887±1.24 (controls)	↔
Sharma et al. 2012 Case-control, 50 cases delivering babies with fetal growth restriction and 50 women with healthy term infants, mean ages 23–24 years, India	**Fetal growth restriction**	Maternal blood	7.06±6.7 ng/g (mean±SD) (cases) 2.58±3.9 (controls)	↑
		Cord blood	3.59±3.8 (cases) 1.44±2.1 (controls)	↑

Table 2-18. Summary of Epidemiological Studies of γ-Hexachlorocyclohexane Exposure and Developmental Effects

Reference, study type, and population	Outcome evaluated	Biomarker	Concentration	Result
Fernandez et al. 2007 Case-control (nested), 50 newborn boys with cryptorchidism or hypospadias, 114 boys without malformations, Spain	**Cryptorchidism or hypospadias**	Placenta	0.9±0.8 ng/g lipid (mean±SD) (cases) 0.7±1.0 (controls)	↑
Freire et al. 2011 Cross-sectional, 220 mother-infant son pairs, Spain	Umbilical cord serum TSH	Placenta	0.25 ng/g placenta (median)	↔

↑ = association with increase; ↓ = association with decrease; ↔ = no association; SD = standard deviation; TSH = thyroid-stimulating hormone

exhibited a negative association with γ-HCH in cord serum in a cross-sectional study of 1,028 infants in China (Fang et al. 2019a, 2019b). A case-control study in India observed an increased risk of preterm birth associated with maternal, but not cord blood levels of γ-HCH (Mustafa et al. 2013).

The concentration of γ-HCH in the placenta was associated with an increased risk of male reproductive tract abnormalities (cryptorchidism or hypospadias observed at birth and 1 month of age) in a case-control study nested within a birth cohort in Spain (Fernandez et al. 2007).

A cross-sectional study of 220 male newborns in Spain showed no association between placental γ-HCH and TSH levels in umbilical cord serum (Freire et al. 2011).

The effects of oral exposure to γ-HCH on development in animals have been extensively studied, primarily in rats and mice. Developmental effects of γ-HCH in these species include reduced viability and pup body weight; perturbation of male and female reproductive tract development; alterations in the developing liver, thymus, spleen, and heart; and developmental neurotoxicity.

Birth outcomes. Effects of γ-HCH administered orally to animals include stillbirths, reduced viability, and decreased body weight; in addition, some studies have suggested delays in developmental milestones. There is no evidence for teratogenic effects in animals exposed orally to γ-HCH.

In Wistar rats exposed from GD 6 through lactation to doses of 0, 0.8–0.9, 4.2–4.6, or 8.0–10.5 mg/kg/day during gestation and 0, 1.2–1.7, 5.6–8.3, or 13.7–19.1 mg/kg/day during lactation, effects observed at 8.0 to 19.1 mg/kg/day included increased stillbirths (live birth index of 77% compared to 99% in controls), and increased neonatal mortality (postnatal day [PND] 4 viability index of 71% compared to 89% in controls) (EPA 1999c). In a 2-generation reproductive toxicity study of rats, a dose of 13.1 mg/kg/day γ-HCH in food resulted in significant reductions in the pup survival on lactation day (LD) 4; for the F1 and F2 pups, survival was 81 and 85%, respectively, compared with ≥96% for the controls (EPA 1991a). In another 2-generation rat study, F0 dams exhibited normal lactation and maternal behavior, but six F1 dams exposed to 26–28 mg/kg/day γ-HCH showed abnormal lactation and retrieving behavior, leading to death of nearly all of their offspring by PND 4, and a significant (49%) reduction in the F2 PND 0–4 viability index for this group (Matsuura et al. 2005). In rats, dietary exposure to 25 mg/kg/day of γ-HCH during gestation (GDs 0–21) did not result in changes in numbers of litter or pup survivals (Srinivasan et al. 1991). When minks were treated with 1 mg/kg/day γ-HCH in their diet (Beard et al. 1997), the proportion of embryos lost after implantation was increased.

Reduced pup body weights have been reported in rats and mice exposed to γ-HCH during gestation and/or lactation. Sauviat et al. (2005) observed a 21% reduction in body weight on PND 42 in rats exposed to 0.0003 mg/kg/day γ-HCH in drinking water during gestation, lactation, and growth; body weight was not affected at 0.00015 mg/kg/day. Exposure of female Wistar rats from GD 6 through lactation to doses ≥4.2 mg/kg/day resulted in decreased pup body weights (up to 18% less than controls at the mid-dose and up to 20% less than controls at the high dose), and body weight gains (16–24% less than controls at the mid-dose, and up to 40% less than controls at the high dose) in both sexes during LDs 1–11 (EPA 1999c). Similarly, body weights of the pups of both generations were significantly lower than controls on in 2-generation studies of γ-HCH in rats exposed via feed at doses of 13.1 mg/kg/day (EPA 1991a) and 26.1 mg/kg/day (Matsuura et al. 2005). In the latter study, F2 female offspring also exhibited a 10% reduction in body weight at 5.6 mg/kg/day (Matsuura et al. 2005). Administration of 30 mg/kg to pregnant C57BL/6J mice and 45 mg/kg to pregnant DBA/2J mice on GD 12 resulted in significant decreases in fetal and placental weights (Hassoun and Stohs 1996a).

No malformations were observed in the fetuses of pregnant C57BL/6J or DBA/2J mice dosed with 30 and 45 mg/kg/day γ-HCH by gastric intubation on GD 12, even though both doses caused maternal deaths (Hassoun and Stohs 1996a). A dose-related increase in the incidence of fetuses with an extra 14th rib was reported in CFY rats exposed to 5, 10, or 20 mg/kg γ-HCH by gavage during GDs 6–15; statistical significance was attained only at 20 mg/kg (Palmer et al. 1978). The incidence of fetuses with an extra 13th rib was statistically increased in rabbits exposed to 20 mg/kg γ-HCH by gavage during GDs 6–18 (Palmer et al. 1978). In both rats and rabbits, the incidences of extra ribs were within or just greater than the ranges recorded for the control groups, and therefore, may not be sufficient evidence of teratogenicity of γ-HCH. Maternal toxicity (reduced body weight gain and food consumption) occurred at doses ≥10 mg/kg/day in the rats, but not in rabbits (highest tested dose 20 mg/kg/day) (Palmer et al. 1978). No effects on embryonic development were seen in rabbits treated by gavage with 0.8 mg/kg/day γ-HCH 3 times/week for 12–15 weeks before artificial insemination (at week 15) and throughout gestation (Seiler et al. 1994).

In a 2-generation study of γ-HCH in CD rats exposed via feed to a dose of 13.1 mg/kg/day, the onset and completion of tooth eruption and completion of hair growth were delayed by 10.5, 11.6, and 24% in the high-dose F2 pups, respectively, compared to controls (EPA 1991a). In contrast, doses up to 26–28 mg/kg/day in a 2-generation reproductive toxicity study of Crj:CD(SD)IGS rats did not influence

offspring developmental landmarks (pinna unfolding, incisor eruption or eye opening) (Matsuura et al. 2005).

Male reproductive system development. *S*tudies in rats and mice exposed to γ-HCH via oral administration during gestation and lactation show effects on the developing male reproductive system, including effects on serum hormone levels, spermatogenesis, reproductive organ weights, and testicular histopathology; effects on sexual behavior and fertility have not been seen in these studies. Serum testosterone was reduced in 7-month-old male rats exposed to 30 mg/kg/day γ-HCH on GD 15 (Dalsenter et al. 1997a) and in PND 65 male rats exposed to 6 mg/kg/day on LD 9 or 14 or 1 mg/kg/day on LDs 9–14 (Dalsenter et al. 1997b).

Lactational exposure of rats to 6 mg/kg/day on LD9 or 14 resulted in significantly reduced spermatid and sperm counts (~8–10%) at PND 140 (Dalsenter et al. 1997b). In rats exposed to 1 mg/kg/day on LDs 9–14, reduced spermatid numbers at PNDs 65 and 140 (29 and 12.8% less than controls, respectively) and reduced sperm number at PND 140 (13.2%) were observed (Dalsenter et al. 1997b). Similarly, CD-1 mice that were administered 15 or 25 mg/kg/day doses of γ-HCH in olive oil by gavage on GDs 9–16 showed reduced sperm count at ≥15 mg/kg/day on PND 60 and reduced sperm concentration at 25 mg/kg/day on PNDs 60–69 and 100 (Traina et al. 2003; Di Consiglio et al. 2009). La Sala et al. (2009) reported decreased numbers of primordial germ cells in male CD1 mouse embryos exposed to ≥15 mg/kg/day on days 8.5–11.5 post-coitum and collected on day 12.5.

Exposure of rats to 1 mg/kg/day on LDs 9–14 resulted in statistically significant reductions in relative testicular weight at PND 140 and relative epididymis weight at PND 65 (Dalsenter et al. 1997b). In another experiment by these authors, a single dose of 6 mg/kg/day on LD 9 or 14 resulted in 10% reductions in relative testicular weights on PNDs 66 and 140 (Dalsenter et al. 1997b). Traina et al. (2003) observed reduced absolute (8%) and relative (10%) testicular weights in male mouse offspring of dams exposed to 15 mg/kg/day during GDs 9–16, but not at 25 mg/kg/day; in addition, no change in testes weight was evident in 25 mg/kg/day F1 males sacrificed on PND 100. No change in testis weight was observed in PND 50 or 100 mouse offspring exposed *in utero* to 25 mg/kg/day γ-HCH on GDs 9–16 (Di Consiglio et al. 2009).

Gestational or lactational exposure to γ-HCH also resulted in histopathology changes in male reproductive organs. Dalsenter et al. (1997b) reported that microscopic examination of the testes in male rat pups exposed to 6 mg/kg/day on LD 9 or 14 showed large areas of normal tissue, but some areas had

distinct changes ranging from small alterations to a pronounced effect, including necrotic changes and reductions in Leydig cell numbers and spermatogenesis. However, there were no significant effects on sexual behavior or fertility in the group exposed to 1 mg/kg/day on LDs 9–14 or to 6 mg/kg on LD 9 or 14 (Dalsenter et al. 1997b). In CD-1 mice administered 15 or 25 mg/kg/day doses of γ-HCH by gavage on GDs 9–16, testicular histological alterations (increased number and size of Leydig cells) and increased number of epididymal sperm with chromatin abnormalities at ≥15 mg/kg/day on PND 60 and altered testicular germ cell distribution at 25 mg/kg/day on PNDs 60 and 100 (Traina et al. 2003). A multigeneration study in mink exposed to 1 mg/kg/day γ-HCH in the diet observed that testis size was reduced in F3 males, although there were no effects on testicular development in the second generation (Beard and Rawlings 1998).

Agrahari et al. (2019) showed that gestational exposure to γ-HCH could influence reproductive hormone levels in male offspring. Pregnant Wistar rats were administered γ-HCH by gavage in corn oil at doses of 0 or 0.25 mg/kg/day on GDs 5–21. Serum hormone levels were evaluated in male offspring at 9, 18, and 27 weeks of age. In offspring evaluated at 9 weeks of age, decreased serum levels of testosterone (16% compared to controls) and growth hormone (15%) were observed, while serum LH (22%) and FSH (18%) levels were significantly increased. Offspring evaluated at 18 and 27 weeks of age exhibited no statistically significant changes in serum hormone levels (Agrahari et al. 2019). In other groups of male offspring that were exposed similarly during gestation and then treated by gavage with 5 mg/kg/day for 5 days at 9, 18, or 27 weeks of age, significant hormone level changes were seen in all groups, including decreased testosterone and growth hormone, and increased LH and FSH (Agrahari et al. 2019).

The results of another study with γ-HCH, reported only as an abstract, indicate that the male reproductive system may be a particularly sensitive target of developmental toxicity in rats (Pages et al. 2000). Male Sprague-Dawley rats were exposed to γ-HCH in drinking water for 12 weeks from the beginning of gestation, lactation, or weaning at concentrations that provided estimated doses of 0.000075, 0.00015, or 0.0003 mg/kg/day. Body weight gain, plasma testosterone, sperm number, and sperm mobility values were approximately 18, 38, 40, and 52% reduced compared to controls, respectively, in groups exposed to 0.0003 mg/kg/day during gestation or lactation. The pup rate was normal when treated males were mated with untreated females, but newborn mortality was higher when treated males were exposed to treated females. Given the lack of a complete report, the results of this study cannot be regarded as conclusive.

A multigeneration reproduction toxicity study in Crj:CD(SD)IGS rats exposed to γ-HCH via diet showed a delay of 1.5 days in preputial separation in F1 animals exposed to 26.1 mg/kg/day (Matsuura et al.

2005). In contrast, the mean day of preputial separation was not affected by treatment in Wistar rat pups exposed to doses up to 10.5–19.1 mg/kg/day from GD 6 through lactation (EPA 1999c) or in mouse pups exposed to doses up to 25 mg/kg/day during GDs 9–16 (Traina et al. 2003).

Female reproductive system development. There are few data on the effects of γ-HCH on development of the female reproductive tract, but available studies show effects in mice exposed during gestation to oral doses of 15 mg/kg/day. La Sala et al. (2009) exposed CD-1 mice to 15 or 30 mg/kg/day γ-HCH by gavage for 3 days during gestation (days 8.5–11.5 post-coitum) and collected embryos 1 day after the last dose. The female embryos exhibited reduced numbers of primordial germ cells in the ovaries at both doses (La Sala et al. 2009). In female pups of CD mice exposed to 15 mg/kg/day γ-HCH on GDs 9–16 and sacrificed on PND 22, significant increases in uterine weight (13–17% higher than controls) were observed, while those pups sacrificed on PND 60 exhibited decreased oocyte diameter (21%) in primary follicles (Maranghi et al. 2007). Exposed female pups also developed vaginal patency earlier than controls; by PND 33, 93% of female pups exposed to 15 mg/kg/day and 36% of control females exhibited complete vaginal opening (Maranghi et al. 2007). No effect on vaginal opening was observed in Wistar rat pups exposed to doses as high as 10.5–19.1 mg/kg/day from GD 6 through lactation (EPA 1999c) or in CD-1 mouse pups exposed on GDs 9–16 to doses up to 25 mg/kg/day (Traina et al. 2003). In contrast, vaginal opening was delayed by 1.4 days in Crj:CD(SD)IGS rats exposed to 26.1 mg/kg/day γ-HCH via diet in a multigeneration reproductive toxicity study (Matsuura et al. 2005).

Systemic development. Oral exposure to γ-HCH during gestation and/or lactation has resulted in significant effects on liver, thymus, and spleen weights in the offspring, and on cardiac development. Srinivasan et al. (1991) observed significant increases in pup relative liver weight when rat dams were exposed to 25 mg/kg/day during gestation and lactation or during lactation only (LDs 0–28). When administered by gavage on GD 12 to pregnant C57BL/6J mice, a dose of 30 mg/kg γ-HCH resulted in significant decreases in fetal thymic weight; fetal body weight was also reduced (Hassoun et al. 1996). At doses of 26–28 mg/kg/day administered in feed to rats through 2 generations, treatment-related decreases in absolute and relative thymus (13–31%) and spleen (13–32%) weights were observed in both generations (Matsuura et al. 2005).

Development of the heart was examined in a study of female Sprague-Dawley rats exposed to very low doses (0.000076, 0.00015, or 0.0003 mg/kg/day) of γ-HCH in drinking water (0.5, 1, and 2 μg/L, respectively) prior to mating; during mating, gestation, and lactation; and for 3 weeks post-weaning (Sauviat et al. 2005). The pups were sacrificed at 6 weeks of age for evaluation of heart weight,

morphometry, and lipid content and electrophysiology of dissected left ventricular papillary muscles. Heart weights and lipid content of exposed rats did not differ from control. Morphometry analysis showed that hearts of pups in the 0.0003 mg/kg/day group had a 9% increase in heart width (relative to controls), but no significant change in length, with a corresponding 9% decrease in length-to-width ratio. At this dose, offspring heart morphology was described as rounder and "cherry like." The study authors reported that hearts of treated offspring showed hypertrophied area with thinning of the left ventricular wall and few developed papillary muscles. Histopathological examination in offspring exposed to 0.0003 mg/kg/day showed that the heart tissue muscle bundles and layers were unorganized and dissociated, with large hemorrhagic interspaces and dispersion of cell nuclei, destruction of fibroblasts, and dispersion and disorganization of collagen bundles, compared to control heart muscle. Histopathology was not assessed in the groups exposed to 0.000076 or 0.00015 mg/kg/day. Electrophysiology changes were also evident in the dissected left ventricular muscles of exposed pups. Action potential durations were unchanged at 0.000076 mg/kg/day, but the plateau was shortened moderately at 0.00015 mg/kg/day, and significantly shortened at 0.0003 mg/kg/day. At 0.0003 mg/kg/day, the slow repolarizing phase was also significantly shortened. The effects of γ-HCH on action potential durations were mitigated by addition of quinidine or E-4031 (blockers of the rapid delayed rectifier potassium current or I_{Kr}) to the test solution, indicating that γ-HCH may act directly on the I_{Kr}. Sauviat et al. (2005) noted that the I_{Kr} channel is involved in long QT syndrome (a disorder that increases the risk of cardiac arrhythmias).

These authors conducted a related study examining whether the cardiac effects could be induced by paternal exposure to γ-HCH in drinking water (Sauviat et al. 2007). In this study, male rats were exposed to a concentration of 2 μg/L for an unspecified "chronic" duration prior to mating with untreated females. The lack of information on exposure duration in the males precluded estimation of doses. In offspring sacrificed at 6 weeks of age, there were no effects on heart weight or shape or electrophysiology, but there were histopathology changes in the hearts similar to those reported by Sauviat et al. (2005) at the same water concentration.

Developmental neurotoxicity. Convulsions and seizures have been observed in offspring of rats exposed to γ-HCH during gestation and/or lactation. Johri et al. (2008) observed convulsions in 8/10 male rat pups that had been exposed during gestation (GDs 5–21) to 0.25 mg/kg/day γ-HCH and then received a single gavage dose of 30 mg/kg on PND 45. In pups exposed only during gestation, no convulsions were observed (Johri et al. 2008). Epileptiform seizures were reported in male rats fed milk from dams that were gavaged with 20 mg/kg/day γ-HCH on PNDs 3–15 (Albertson et al. 1985).

In a developmental neurotoxicity study, Han Wistar rats were exposed to 0, 10, 50 or 120 ppm γ-HCH in the diet from GD 6 through LD 10 (EPA 1999c). Reported daily maternal dose levels were 0, 0.8–0.9, 4.2–4.6, or 8.0–10.5 mg/kg/day during gestation, and 0, 1.2–1.7, 5.6–8.3, or 13.7–19.1 mg/kg/day during lactation. The F1 offspring were evaluated for functional observational battery, motor activity, auditory startle response, learning and memory, and brain endpoints (weight, histology, and morphometrics) on postpartum days 11 and 65. The offspring showed increased motor activity (both sexes) and decreased habituation of motor activity (females) at the two highest dose levels. Reduced auditory startle response habituation was observed at the high dose in both sexes on day 28 and day 60 postpartum (EPA 1999c). No significant changes in brain weight, morphometry, or histology were detected in the pups. This study was classified as an unacceptable developmental neurotoxicity study by EPA (2000a) because there was no laboratory validation of the neurobehavioral tests and the number of animals (six per dose level) was insufficient.

Increased motor activity was also reported in rat pups exposed during gestation only. Exposure on GDs 5–21 to doses ≥0.25 mg/kg/day resulted in increased locomotor activity (increases in distance traveled, ambulatory time, horizontal count, stereotypic time, and stereotypic movement burst) in 3-week-old rat pups, and some of the changes (increased distance traveled) persisted through 9 weeks of age (Johri et al. 2007). At a dose of 0.125 mg/kg/day, distance traveled was increased at 3 weeks of age, but not at subsequent evaluations (Johri et al. 2007). Srivastava et al. (2019) observed no significant changes in spontaneous locomotor activity or spatial memory (Y-maze activity) in 12-week-old male rat pups whose mothers were exposed by gavage from GD 5 through GD 21 to 0.25 mg/kg/day γ-HCH. However, other groups of pups similarly exposed *in utero* and then rechallenged at 12 weeks of age with 21 daily gavage doses of 2.5 mg/kg/day γ-HCH exhibited significantly reduced spontaneous locomotor activity (reductions in distance travelled, moving time, numbers of rearings, and stereotypic counts, along with significantly increased resting time) and spatial memory effects (significant reduction in percent alterations in Y-maze testing) (Srivastava et al. 2019). Acquisition of a passive avoidance task was improved in 15-day-old rat pups that were treated with γ-HCH by gavage as either a single 20 mg/kg dose or 7-day repeated 10 mg/kg/day doses (Rivera et al. 1998). Exposure to the single 20 mg/kg dose resulted in a decrease in motor activity, while repeated exposure to the lower dose increased motor activity in this study (Rivera et al. 1998).

Neurobehavioral testing of F1 offspring exposed to doses up to 26–28 mg/kg/day in a 2-generation reproductive toxicity study showed effects were noted in reflex, sensory function, surface righting reflex,

corneal reflex, startle response, pain response, or mid-air righting reflex at 4–6 weeks of age (Matsuura et al. 2005). In addition, no effects were observed in the open field test, rotarod test, or pole climbing test (Matsuura et al. 2005).

Studies of neurotransmitter levels in rats exposed to γ-HCH showed that the effects depended on the treatment schedule and brain region (Rivera et al. 1991, 1998). In suckling Wistar rats treated once with 20 mg/kg γ-HCH by gavage at PNDs 8, 15, 22, or 29, regional changes in brain noradrenaline, serotonin, and the dopamine metabolite, 3,4-dihydroxyphenyl- acetic acid (DOPAC) levels were seen, with differential effects depending on age at the time of exposure (Rivera et al. 1991). Similarly, Rivera et al. (1998) observed different patterns (e.g., ratios of 5-HIAA/serotonin and DOPAC/dopamine) in brain monoaminergic levels in rat pups after exposure on PND 15 to a single 20 mg/kg dose or 7 consecutive daily doses of 10 mg/kg/day γ-HCH. The patterns suggested that monoaminergic turnover was increased by the single dose but decreased by repeated exposure at lower doses (Rivera et al. 1998).

A study of rats exposed to γ-HCH in drinking water at very low doses (0.000055–0.00011 mg/kg/day) for 12 days prior to mating and through gestation and lactation examined effects of treatment on wake-sleep cycle in male offspring at 14 weeks of age (Breton et al. 2005). Sleep cycle was analyzed by EEG in three phases: wakefulness, slow wave sleep, and paradoxical sleep, and there were no treatment-related changes in the sleep cycle. Spectral electrocorticographic analysis showed slight changes in brain activity relative to controls (increased relative energy in the 11–15 Hz frequency during wakefulness and slow wave sleep, and increased activity in the 7–15 Hz range in all sleep phases) in both exposure groups, but the changes did not show dose-dependence. No histopathological effects were reported in the brain at any dose (Breton et al. 2005).

Srivastava et al. (2019) examined transmission electron ultrastructural microscopy of the brains in 15-week old male rat pups whose mothers were exposed by gavage from GD 5 through GD 21 to 0.25 mg/kg/day γ-HCH. Although neurobehavioral changes were not seen in these pups, ultrastructural changes were detected in the hippocampus and substantia nigra of exposed pups, including moderately distorted mitochondria, demyelinated neurons, and autophagic vesicles with damaged cytoplasmic contents (Srivastava et al. 2019). In another experiment by these authors, electron microscopy of the hippocampus and substantia nigra showed loss of mitochondrial integrity (loss of cristae and number), severe loss of synaptic structure, severe demyelination, and highly condensed nuclei with cytoplasmic content showing necrotic effects after similar prenatal exposure followed by a rechallenge exposure at 12 weeks of age (21 days at 2.5 mg/kg/day) (Srivastava et al. 2019).

Mechanisms. Superoxide production, lipid peroxidation, and deoxyribonucleic acid (DNA) single-strand breaks were increased in fetal and placental tissues, and lipid peroxidation markers were increased in maternal sera and the amniotic fluids 48 hours after administration of single dose of 30 mg/kg γ-HCH to pregnant mice on GD 12 (Hassoun and Stohs 1996b; Hassoun et al. 1996). Significant increases in lipid peroxidation also occurred in fetal livers collected on GD 18. Thus, it was suggested that fetotoxic effects of γ-HCH may be due to induced oxidative stress, enhanced lipid peroxidation, and DNA-single strand breaks in mice.

There is evidence that the developmental neurotoxicity effects of γ-HCH may be mediated by metabolites and involve alterations in the blood:brain barrier. Johri et al. (2007) detected dose-dependent increases in brain cytochrome P450 (CYP1A1, 1A2, 2B1, 2B2, and 2E1) protein expression and mRNA, and CYP-dependent enzyme (EROD, PROD, and NDMA-d) activities in F1 offspring exposed to 0.0625–0.25 mg/kg/day γ-HCH. The enzyme changes persisted longer at the high dose, correlating with the effects on locomotor activity and suggesting that metabolites of γ-HCH may be responsible for this effect (Johri et al. 2008). γ-HCH exposure causes functional impairment of the developing blood brain barrier in young rats (Gupta et al. 1999). The integrity (impermeability) of the blood brain barrier was studied by assessing uptake of sodium fluorescein (a micromolecular tracer dye) into the brain of neonatal rats following single or repeated acute gavage doses of γ-HCH. The brain uptake index of fluorescein was significantly increased in 10-day-old pups treated with a single 2 mg/kg dose (72 and 23% higher than controls after 2 hours and 3 days, respectively), as well as in those treated with 2 mg/kg/day for 8 days (50% higher than controls 7 days after the first exposure, with recovery 20 days after the first exposure). The effect appeared to be age-related because the brain uptake index was lower when rats were administered a single 2 mg/kg dose at 15 days of age (20% higher than controls after 2 hours) or a higher dose of 4 mg/kg/day for 3 days as adults (no effect on brain permeability).

δ-HCH. Epidemiological studies that have examined relationships between δ-HCH in maternal or fetal blood or tissues and developmental outcomes are shown in Table 2-19. A small case-control study in India reported positive associations between fetal growth restriction and higher δ-HCH concentrations in maternal and umbilical cord blood, but not with concentrations in placenta (Siddiqui et al. 2003). No association between infant birth size and δ-HCH in placental tissue was observed in a cross-sectional study in India (Anand and Taneja 2020). No studies of developmental outcomes in animals exposed to δ-HCH by any exposure route were located.

Table 2-19. Summary of Epidemiological Studies of δ-HCH and Total HCH Exposure and Developmental Effects

Reference, study type, and population	Outcome evaluated	Isomer	Biomarker	Mean concentration (unless otherwise noted)	Result
Siddiqui et al. 2003 Case-control, 30 mothers of infants with fetal growth restriction (intrauterine growth retardation), 24 mothers of normal weight infants, India	**Fetal growth restriction**	**δ-HCH**	Maternal blood	2.14±1.94	↑
			Placenta	2.92±3.99	↔
			Cord blood	4.51±4.63	↑
Anand and Taneja 2020 Cross-sectional, 90 mother-infant pairs, India	Birth weight	δ-HCH	Placenta tissue	1.18–24.4µg/L (range)	↔
	Birth length				↔
	Head circumference				↔
	Ponderal index				↔

↑ = association with increase; ↔ = no association; HCH = hexachlorocyclohexane

Technical HCH or Unspecified Isomers of HCH. A dose-related increase in fetal resorptions was seen in pregnant female mice treated once with 25–200 mg/kg technical-grade HCH by gavage on GD 9, but fetal development was normal (Dikshith et al. 1990). Srivastava and Raizada (2000) further studied the prenatal effect of orally administered technical-grade HCH. While mice exposed to HCH during the preimplantation period (GDs 2–6) did not show fetolethality, exposure during the postimplantation period (GDs 6–12) to 25 and 50 mg/kg/day HCH produced significant increases in resorption of fetuses, inhibition of maternal serum progesterone levels, and higher levels of HCH in fetal tissues. Oral exposure to Benesan (a pesticidal formulation containing 50% γ-HCH) given at doses of 6.25, 12.5, or 25 mg/kg/day by gavage on GDs 6–15 failed to produce teratogenic effects in rats (Khera et al. 1979). Alterations in levels of brain dopamine, serotonin, GABA, glutamate, glutamate decarboxylase, and noradrenaline were seen in various areas of the brains of female rat pups treated with 10 mg technical-grade HCH/kg/day for 60 days beginning at birth (Nagaraja and Desiraju 1994).

2.18 OTHER NONCANCER

Epidemiology Studies. Several case-control studies (Daniels et al. 2018; Li et al. 2016; Rylander et al. 2015; Zong et al. 2018) and cross-sectional studies (Arrebola et al. 2013; Everett and Matheson 2010; Gasull et al. 2012; Ukropec et al. 2010) evaluated associations between diabetes and exposure to HCH isomers (see Table 2-20). There were no associations with serum levels of α-, γ-, or δ-HCH isomers and type 2 diabetes reported in a case-control study of 723 cases of Chinese type 2 diabetes patients compared to control subjects, while higher mean serum levels of β-HCH and with total HCH levels were associated with type 2 diabetes (Li et al. 2016); significant interactions with several ADIPOQ (gene encoding adiponectin) genotypes were reported for the β-HCH isomer. Nested case-control studies also reported an association between serum and plasma β-HCH levels and increased incidences of type 2 diabetes in American nurses (Zong et al. 2018) and in Norwegian women (Rylander et al. 2015). One nested case-control study comparing South Asians and European whites living in London determined a significant association between plasma concentrations of β-HCH and increased prevalence of diabetes in a Tamil-descent population, while an elevated, but not significant, association was reported in a Telugu-descent population at plasma concentrations (Daniels et al. 2018).

In cross-sectional studies evaluating β-HCH, there was no association between the prevalence of diabetes and levels in adipose (Arrebola et al. 2013), and no association between diabetes and pre-diabetes and serum levels (Everett and Matheson 2010; Gasull et al. 2012). Another cross-sectional study similarly found no association with diabetes; however, an association was seen between serum β-HCH and

Table 2-20. Summary of Epidemiological Studies of Hexachlorocyclohexane (HCH) Exposure and Other Noncancer Effects

Reference, study type, and population	Outcome evaluated	Isomer	Biomarker	Concentration	Result
Arrebola et al. 2013 Cross-sectional, 386 patients undergoing noncancer-related surgery, Spain	Type 2 diabetes	β-HCH	Adipose	>16.81 ng/g lipid	↔
Li et al. 2016 Case-control, 723 cases and 723 controls, mean age 62 years, China	**Type 2 diabetes**	α-HCH	Serum	0.012 ng/mL (cases) (GM) 0.011 (controls)	↔
		β-HCH		0.575 (cases) 0.266 (controls)	↑[a]
		γ-HCH		0.020 (cases) 0.018 (controls)	↔
		δ-HCH		0.068 (cases) 0.060 (controls)	↔
		Total HCH		NR	↑
Zong et al. 2018 Nested case-control, 793 cases and 793 controls participating in Nurse Health Study II, age 32–52 years, United States	**Type 2 diabetes**	**β-HCH**	Serum	14.3 ng/g lipid (median) (cases) 9.84 (controls)	↑ (trend)
Rylander et al. 2015 Nested case-control, 106 cases and 106 control women, age 30–70 years, Norway	**Type 2 diabetes**	**β-HCH**	Plasma	20.3 ng/g lipid (mean) (cases) 10.0 (controls)	↑
Daniels et al. 2018 Nested case-control, 73 adults of Tamil descent and 47 adults of Telugu descent, >21 years old, United Kingdom	**Diabetes in Tamil population**	**β-HCH**	Plasma	≥50.58 ng/g lipid	↑
	Diabetes in Telugu population			≥369.30 ng/g lipid	↔
Everett and Matheson 2010 Cross-sectional, 3,414 adults ≥20 years old, NHANES, United States	Diabetes	β-HCH	Serum	>9.36 ng/g lipid	↔
	Pre-diabetes				↔

Table 2-20. Summary of Epidemiological Studies of Hexachlorocyclohexane (HCH) Exposure and Other Noncancer Effects

Reference, study type, and population	Outcome evaluated	Isomer	Biomarker	Concentration	Result
Gasull et al. 2012 Cross-sectional, 886 adults age 18–74 years, Spain	Diabetes	β-HCH	Serum	>1.547 ng/mL (4th quartile cutoff)	↔
	Pre-diabetes				↔
Ukropec et al. 2010 Cross-sectional, 2,047 adults 21–75 years old, Slovakia	Diabetes	**β-HCH**	Serum	83–781 ng/g lipid (5th quintile)	↔
	Pre-diabetes				↑
Everett and Thompson 2015 Cross-sectional, 2992 adults ≥20 years old, NHANES (1999-2004), United States	**Diabetes without nephropathy**	**β-HCH**	Serum	≥0.1018 ng/g	↑
	Diabetes with nephropathy	β-HCH	Serum	≥0.1018 ng/g	↔
Lee et al. 2017 Cross-sectional, 200 adults >30 years old, Korea	Insulin sensitivity and secretion indicators	β-HCH	Serum	157.97 pg/mL (4th quartile cutoff)	↔
Burns et al. 2014 Cohort, 318 boys, age 8–9 years, Russia	Leptin	β-HCH	Serum	165 ng/g lipid (median)	↔
	Insulin				↔
	Insulin resistance				↔
Gasull et al. 2018 Cross-sectional, 860 adults 18–74 years old, Spain	**Unhealthy metabolic phenotype[b]**	**β-HCH**	Serum	≥0.671 ng/mL (4th quartile)	↑
Lee et al. 2016 Cohort, 214 children 7–9 years old, Korea	Measures of metabolic syndrome	β-HCH	Serum	6.13 ng/g lipid (median)	↔

Table 2-20. Summary of Epidemiological Studies of Hexachlorocyclohexane (HCH) Exposure and Other Noncancer Effects

Reference, study type, and population	Outcome evaluated	Isomer	Biomarker	Concentration	Result
Mustieles et al. 2017 Cross-sectional and 10-year longitudinal, 387 noncancer surgical patients (at baseline), median age 52 years; 154 without metabolic disease at baseline followed for 10 years, median age 42 years, Spain	**Metabolically compromised[c] at baseline**	**β-HCH**	Adipose tissue	10.6 ng/g lipid (median)	↑
	Metabolically compromised[c] at follow up			6.9	↑

[a]Significant interactions with several ADIPOQ genotypes.
[b]Unhealthy metabolic phenotype was defined as exhibiting two or more of the following: hypertension, hypertriglyceridemia, low HDL cholesterol, hyperglycemia, insulin resistance, or systemic inflammation.
[c]Metabolically compromised was defined as exhibiting one or more of the following: type 2 diabetes, hypertension, hypertriglyceridemia, or low HDL cholesterol.

↑ = association with increase; ↔ = no association; GM = geometric mean; HDL = high-density lipoprotein; NHANES = National Health and Nutrition Examination Survey

increased incidence of pre-diabetes (Ukropec et al. 2010). Additionally, a cross-sectional study using NHANES data reported an association with serum β-HCH and increased incidence of diabetes without nephropathy, but no association in adults with both diabetes and nephropathy (Everett and Thompson 2015). There was no relationship between serum β-HCH and insulin sensitivity and secretion indicators (Lee et al. 2017), nor were there associations with leptin and insulin levels and insulin resistance (Burns et al. 2014).

Gasull et al. (2018) reported a positive association between unhealthy metabolic phenotypes (defined as exhibiting at least two of the following: hypertension, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, hyperglycemia, insulin resistance, or systemic inflammation) and serum β-HCH levels. A study of adult noncancer surgical patients also showed an association between β-HCH levels in adipose tissue and increased likelihood of being metabolically compromised (exhibiting type 2 diabetes, hypertension, hypertriglyceridemia, or low HDL cholesterol) at baseline and at a 10-year follow-up (Mustieles et al. 2017). There was no association between serum β-HCH levels and measures of metabolic syndrome in a cohort of 214 Korean children between 7 and 9 years of age (Lee et al. 2016).

2.19 CANCER

Epidemiological Studies. Epidemiological studies of HCH isomers and cancer are shown in Table 2-21. Studies shown in the table include only those that accounted for at least one potential confounding variable (i.e., studies reporting only univariate analyses were excluded). In addition, only the most recent analysis of a given cohort or case-control population is shown in the table.

Table 2-21. Summary of Epidemiological Studies Evaluating Possible Associations between Hexachlorocyclohexane Exposure and Risk of Selected Cancer Types

Cancer type	Isomer	Association[a]	No association[b]
Non-Hodgkin's lymphoma	Beta (β)	Bassig et al. 2020; Viel et al. 2011	Brauner et al. 2012; Cantor et al. 2003; Cocco et al. 2008
	Gamma (γ)	Alavanja et al. 2014[c]; Kachuri et al. 2020	Cocco et al. 2008; Viel et al. 2011
Multiple myeloma	Beta (β)	Weber et al. 2018	
	Gamma (γ)		Presutti et al. 2016
Leukemia	Beta (β)		Cocco et al. 2008
	Gamma (γ)	Purdue et al. 2007	

Table 2-21. Summary of Epidemiological Studies Evaluating Possible Associations between Hexachlorocyclohexane Exposure and Risk of Selected Cancer Types

Cancer type	Isomer	Association[a]	No association[b]
Colon/colorectal	Alpha (α)		Howsam et al. 2004
	Beta (β)	Lee et al. 2018a	Howsam et al. 2004
	Gamma (γ)		Howsam et al. 2004; Purdue et al. 2007
Female breast cancer	Beta (β)	Arrebola et al. 2015b Waliszewski et al. 2005	Hoyer et al. 1998; Lopez-Carrillo et al. 2002; McCready et al. 2004; Raaschou-Nielsen et al. 2005[d]; Ward et al. 2000; Wielsoe et al. 2017; Xu et al. 2010
	Gamma (γ)	Ibarluzea et al. 2004[e]	Hoyer et al. 1998
Prostate cancer	Alpha (α)		Pi et al. 2016[d]
	Beta (β)	Kumar et al. 2010; Xu et al. 2010	Aronson et al. 2010; Lim et al. 2017; Pi et al. 2016; Sawada et al. 2010
	Gamma (γ)	Band et al. 2011	Barry et al. 2011; Koutros et al. 2011; Pi et al. 2016
Lung	Gamma (γ)	Purdue et al. 2007	
Hepatocellular carcinoma	Beta (β)	Zhao et al. 2012	
Bladder cancer	Gamma (γ)		Purdue et al. 2007
Endometrial cancer	Beta (β)		Sturgeon et al. 1998
Melanoma	Gamma (γ)		Purdue et al. 2007
Soft tissue sarcoma	Gamma (γ)		Pahwa et al. 2011
Testicular germ cell tumors	Beta (β)		McGlynn et al. 2008
Thyroid	Beta (β)		Lerro et al. 2018

[a]Statistically significant positive association.
[b]No statistically significant positive association.
[c]Follicular B-cell subtype.
[d]Statistically significant inverse association.
[e]Among post-menopausal women only.

The available studies provide evidence for an association between exposure to HCH and NHL, and suggestive evidence for associations with some other cancer types (see Table 2-21). The strongest evidence for an association between HCH exposure and NHL comes from a prospective cohort study of 54,306 pesticide applicators (the Agricultural Health Study) in Iowa and North Carolina (Alavanja et al. 2014). Cohort members were enrolled between 1993 and 1997 and followed through 2011. At enrollment and 5 years later, the subjects filled out questionnaires about use of specific pesticides, including frequency and duration of γ-HCH use. A total of 523 incident cases of NHL were observed over 803,140 person-years of follow up. The risk of incident NHL was increased with total days of

γ-HCH exposure and with intensity-weighted total days of exposure after adjustment for confounders identified in the NHL literature and for herbicide use. Analysis by subtype of NHL showed the increased risk with HCH exposure to be limited to the follicular B-cell subtype (Alavanja et al. 2014).

Three case-control studies nested within prospective cohort studies of populations without known sources of HCH exposure examined associations between NHL and prediagnostic blood or adipose tissue levels. In an analysis of 167 cases and 167 controls from three prospective cohort studies (>150,000 subjects) in Shanghai and Singapore, Bassig et al. (2020) observed a positive association between NHL and blood levels of β-HCH measured approximately 7 years prior to diagnosis. In contrast, Cantor et al. (2003) observed no association between NHL and exposure among 74 cases and 157 controls from a large cohort (25,802 participants) in Maryland. In this study, serum concentrations of β-HCH were measured in 1974, and cases were identified through 1994. Importantly, the blood concentrations of β-HCH were markedly higher in the study by Bassig et al. (2020) (median among cases was 5,670 ng/g lipid) than in the study by Cantor et al. (2003) (mean among cases was 139.9 ng/g lipid). Finally, Brauner et al. (2012) did not observe a significant association between NHL and β-HCH in adipose tissue among 256 cases and 256 referents in a cohort of 57,053 participants in Denmark. Adipose samples were collected at enrollment between 1993 and 1997 and cases were identified through 2008; the median adipose concentration of β-HCH among cases was 59 ng/g. A large pooled case-control study provides support for the association between NHL and HCH exposure. 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).

Other epidemiological studies have 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, and hepatocellular carcinoma (see Table 2-21). However, the evidence for these cancer types is relatively weak. In an earlier analysis of cancer incidence in the Agricultural Health Study (cohort of 57,311 pesticide applicators), increased risks of incident leukemia and lung cancer were observed among subjects with any self-reported use of γ-HCH compared with those who never used it (Purdue et al. 2007). Band et al. (2011) reported an association between γ-HCH exposure assessed through a job-exposure matrix and increased risk of prostate cancer in a study of 1,153 cases and 3,999 controls. Many of the studies reporting positive associations between multiple myeloma, colorectal cancer, hepatocellular carcinoma, breast cancer, or prostate cancer and HCH exposures (Arrebola et al. 2015b; Ibarluzea et al. 2004; Kumar et al. 2010; Lee et al. 2018a; Waliszewski et al. 2005; Weber et al.

2018; Xu et al. 2010; Zhao et al. 2012) are case-control studies in which exposure was assessed using concentrations of HCH in blood or adipose samples collected after disease onset. The lack of temporal relationship between exposure and outcome render these studies of uncertain utility for hazard identification.

Epidemiological studies published to date have not shown any associations between exposure to HCH and cancers of the bladder, endometrium, thyroid, and testicular germ cells, or melanoma and soft tissue sarcoma (see Table 2-21).

α-HCH. Increased incidences of neoplastic nodules in the liver, hepatomas, and/or hepatocellular carcinomas were reported in a number of strains of mice exposed to doses between 13 and 95 mg/kg/day for 16–36 weeks (Hanada et al. 1973; Ito et al. 1973, 1976; Nagasaki et al. 1975; Tryphonas and Iverson 1983; Tsukada et al. 1979). No evidence of liver carcinogenicity was reported in Wistar rats exposed to 45 mg/kg/day α-HCH in the diet for 24 weeks (Nagasaki et al. 1975), but a dose of 70 mg/kg/day for 48 weeks resulted in liver tumors (Ito et al. 1975). Ito et al. (1975) also reported an increased incidence of hepatocellular carcinomas in male rats exposed to α-HCH in the diet at ≥70 mg/kg/day for 72 weeks.

In studies of α-HCH tumor promotion, mixed results were observed. In rats, administration of 35 mg/kg/day of α-HCH in the diet for 65 weeks inhibited the induction of liver tumors by 0.07 mg/kg/day of aflatoxin B_1 (Angsubhakorn et al. 1981). A study of γ-glutamyltranspeptidase-positive liver foci in rats pretreated with the tumor initiator *N*-nitrosomorpholine showed that administration of α-HCH at 20 mg/kg/day in food for 49 weeks increased the volume fraction of positive foci, largely by reducing apoptosis (Luebeck et al. 1995). Schröter et al. (1987) reported significant increases in the number and area of preneoplastic hepatic foci in female Wistar rats treated with doses ≥2 mg/kg/day in the diet.

β-HCH. Animal studies of β-HCH carcinogenicity are limited by short duration of exposure, concurrent mortality, and/or reporting limitations. β-HCH did not increase liver tumor incidences in Wistar rats exposed to 35 or 70 mg/kg/day in the diet for 24 or 48 weeks (Ito et al. 1975), but this study was hampered by significant mortality. No increase in liver tumor incidence was noted in dd mice exposed to 18–120 mg/kg/day in the diet for 24 or 32 weeks (Hanada et al. 1973; Ito et al. 1973). However, in a longer study, Thorpe and Walker (1973) reported an increased incidence of hepatocellular carcinomas in male CF1 mice and a significant increase in other (unspecified) tumors in female CF1 mice exposed to

34 mg/kg/day in the diet for 104 weeks. In this study, significant mortality occurred early in the study (12% of males and 25% of females died within 3 months).

β-HCH, at a single oral dose of 100 mg/kg/day, did not induce an increase in the number or size of preneoplastic hepatic foci in a two-stage study using female Wistar rats dosed with phenobarbital as a promoting agent (Schröter et al. 1987). However, a significant increase in preneoplastic hepatic foci was noted in rats exposed for 20 weeks to doses ≥3 mg/kg/day β-HCH in the diet after initiation with N-nitrosomorpholine (Schröter et al. 1987).

γ-HCH (Lindane). In Wistar rats, exposure to 25 mg γ-HCH/kg/day in the diet for 24 or 48 weeks did not result in any liver tumors (Ito et al. 1975); however, the abbreviated exposure duration and high mortality in the control and treatment groups preclude conclusions as to carcinogenicity under this experimental protocol. Mice (dd strain) exposed to as much as 90 mg γ-HCH/kg/day in the diet for 24 weeks did not exhibit any increased tumor incidences when compared to controls (Ito et al. 1973). An increased incidence of malignant hepatomas was reported in male dd mice exposed to 108–120 mg/kg/day in the diet for 32 weeks (Hanada et al. 1973). In that study, survival to study end at the carcinogenic dose was very low, so the magnitude of the effect may be underestimated.

Chronic studies have shown increased incidences of tumors in mice, but not rats, exposed to γ-HCH. No statistically significant increases in endocrine, thyroid, pituitary, adrenal gland, liver, or ovary tumors were observed in male and female Osborne-Mendel rats fed 10.8–33 mg/kg/day in the diet for 80 weeks (NCI 1977) or in Wistar rats fed 0.07–32 mg γ-HCH/kg/day in the diet for 104 weeks (Amyes 1990); however, poor survival rates limit the significance of these results. Liver tumors have been reported in CF1 and B6C3F1 mice exposed to 13.6–68 mg/kg/day in the diet for 80 to 104 weeks (NCI 1977; Thorpe and Walker 1973). In contrast, EPA (2000a) did not observe an increase in liver tumor incidence in CD-1 mice exposed to doses up to 26.8 mg/kg/day for 78 weeks. Female mice, but not male mice, in this study exhibited increased incidences of lung adenomas at the high dose (26.8 mg/kg/day) (EPA 2000a). Increased incidences of hepatocellular adenomas and carcinomas were also observed in obese mottled yellow A^{vy}/a and lean pseudoagouti A^{vy}/a (YSxVY) F1 mice exposed to 27.2 mg/kg/day in the diet for 96 weeks, but not in lean black *a/a* (YSxVY) F1 mice (Wolff et al. 1987). The obese mottled yellow and lean pseudoagouti strains have a dominant mutation at the agouti locus (Avy) that increases their susceptibility to strain-specific neoplasms. Incidences of benign lung adenomas were also increased in female obese mottled yellow A^{vy}/a and lean pseudoagouti A^{vy}/a (YSxVY)F1 mice exposed to 27.2 mg/kg/day for 24 months (Wolff et al. 1987).

In mice, dermal exposure to a 0.5% solution of γ-HCH in acetone applied twice a day for 60 days was reported to result in no treatment-related tumors (Orr 1948). Limitations of this study include less-than-lifetime exposure and study duration, testing of only one dose, and potential for ingestion of some of the compound from the skin.

δ-HCH. δ-HCH did not induce a significant increase in liver tumors in male Wistar rats exposed to doses up to 70 mg/kg/day in the diet for 48 weeks (Ito et al. 1975) or in male dd mice exposed to doses up to 90 mg/kg/day in the diet for 24 weeks (Ito et al. 1973). However, these studies were of relatively short exposure durations, and organs other than the liver were not evaluated for histopathology.

Technical HCH or Unspecified Isomers of HCH. Ito et al. (1973) examined the carcinogenicity of pairs of HCH isomers in dd mice exposed to 45 mg/kg/day of each isomer in the diet (total HCH dosage of 90 mg/kg/day) for 24 weeks. Exposure to β-HCH with γ- or δ-HCH, or to γ-HCH together with δ-HCH did not result in hepatocellular carcinomas. However, when any of these isomers was administered with α-HCH, an increased incidence of hepatocellular carcinomas was observed.

Thakore et al. (1981) reported the appearance of neoplastic nodules in the livers of Swiss mice following dietary exposure to technical-grade HCH at 90 mg/kg/day for 6 months. Increased incidences of hepatocellular carcinoma were reported in Swiss mice exposed to 90 mg/kg/day in the diet for 6–8 months (Bhatt and Bano 2009; Bhatt and Nagda 2012; Trivedi et al. 2007, 2009); to 21.3–85 mg/kg/day in the diet for 20 months (Munir et al. 1983); and to 10 or 17 mg/kg/day through gavage or the diet, respectively, for 80 weeks (Kashyap et al. 1979). Dermal application of 2.4 mg technical-grade HCH/kg/day by skin painting on Swiss mice for 80 weeks resulted in nonsignificant increases in the incidences of hyperplastic and preneoplastic areas in the liver and hepatic tumors (Kashyap et al. 1979).

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. IRIS (1987b) lists 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- and ε-HCH were considered inadequate to classify the potential human carcinogenicity (IRIS 1987d, 1987e). 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 HHS NTP determined that γ-HCH and other HCH isomers may reasonably be anticipated to cause cancer in humans (NTP 2016). In 2018, 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.

Mechanisms. IARC (2018) conducted an extensive review of the available data on mechanisms of HCH carcinogenicity using the 10 key characteristics of carcinogens (Smith et al. 2016) as a framework. Their analysis noted that the metabolism of γ-HCH yields a number of intermediates and metabolites, but that to date, those involved in carcinogenesis have not yet been identified. *In vitro* data in rat liver microsomes have shown the formation of a stable epoxide, indicating that γ-HCH can form electrophilic metabolites (reviewed by IARC 2018). Based on the available *in vivo* and *in vitro* data, IARC (2018) concluded that there was strong evidence that γ-HCH induces immunosuppression and oxidative stress, and moderate evidence for genotoxicity and modulation of receptor-mediated effects. Section 2.14 provides details on the *in vivo* evidence for immunosuppression in animals exposed orally to γ-HCH; little to no data are available for immune system effects of other isomers. A number of *in vivo* studies reported increased measures of oxidative stress in the heart, liver, kidney, central nervous system, testes, and maternal or fetal tissues after oral exposure to γ-HCH; these studies are described in the *Mechanisms* subsections of Sections 2.5, 2.9, 2.10, 2.15, 2.16, and 2.17. *In vivo* studies of estrogen-mediated effects are described under *Mechanisms* in Section 2.16. Genotoxicity studies of HCH isomers are summarized in Section 2.20.

2.20 GENOTOXICITY

Numerous *in vivo* and *in vitro* studies have assessed the genotoxic potential of HCH and its isomers (α-, β-, and γ-HCH). Genotoxicity testing results for HCH isomers are summarized below. Results of *in vivo* and *in vitro* genotoxicity studies are presented in Tables 2-22 and 2-23, respectively.

Table 2-22. Genotoxicity of Hexachlorocyclohexane Isomers *In Vivo*

Species (test system)	Endpoint	Results	Isomer	Reference
Mammalian cells				
Human (peripheral blood)	DNA damage	–	Alpha, beta	Varona-Uribe et al. 2016
Human (peripheral blood)	Comet assay	–	Alpha, beta	Varona-Uribe et al. 2016
Human (peripheral lymphocytes)	Micronucleus test	–	Alpha, beta, and gamma	Jonnalagadda et al. 2012
Mouse (bone marrow)	Micronucleus test	+	Gamma	Yaduvanshi et al. 2012

Table 2-22. Genotoxicity of Hexachlorocyclohexane Isomers *In Vivo*

Species (test system)	Endpoint	Results	Isomer	Reference
Human (peripheral lymphocytes)	Chromosomal aberrations	+	Alpha, beta, and gamma	Jonnalagadda et al. 2012
Rat (bone marrow)	Chromosomal aberrations	+	Beta	Shimazu et al. 1972
Human (peripheral lymphocytes)	Chromosomal aberrations	–	Gamma	Kiraly et al. 1979
Syrian hamster (bone marrow)	Chromosomal aberrations	–	Gamma	Dzwonkowska and Hubner 1986
Mouse	Micronuclei	–	Gamma	Jenssen and Ramel 1980
Mouse (bone marrow)	Chromosomal aberrations	+	Gamma	Kumar et al. 1995
Rat (liver)	Mitotic disturbances	+	Alpha	Hitachi et al. 1975
Mouse (liver)	DNA binding	(+)	Alpha/ gamma	Iverson et al. 1984
Mouse (germ cells)	Dominant lethal	+	Technical	Lakkad et al. 1982
Human (MGMT tumor suppressor gene in colorectal cancer cells)	Hypermethylation	–	Alpha, beta, and gamma	Abolhassani et al. 2019
Human (P16 tumor suppressor gene in colorectal cancer cells)	Hypermethylation	–	Alpha and beta	Abolhassani et al. 2019
Human (P16 tumor suppressor gene in colorectal cancer cells)	Hypermethylation	+	Gamma	Abolhassani et al. 2019
Human (Leukocyte DNA)	DNA hypomethylation	+	Beta	Itoh et al. 2014
Human (tumor suppressor gene E-cadherin [CDH1] in peripheral blood mononuclear cells)	Methylation	(+)	Beta	Lee et al. 2018b

– = negative result; + = positive result; (+) = weakly positive result; DNA = deoxyribonucleic acid

Table 2-23. Genotoxicity of Hexachlorocyclohexane Isomers *In Vitro*

Species (test system)	Endpoint	Results		Isomer	Reference
		With activation	Without activation		
Prokaryotic organisms					
Salmonella typhimurium TA100, TA98, TA1535, TA1537, TA1538 (reversion assay)	Gene mutation	–	–	Gamma	Moriya et al. 1983

Table 2-23. Genotoxicity of Hexachlorocyclohexane Isomers *In Vitro*

Species (test system)	Endpoint	Results		Isomer	Reference
		With activation	Without activation		
S. typhimurium TA98, TA100, TA102 (*Salmonella*/microsome mutagenicity assay)	Gene mutation	–	–	Gamma	Yaduvanshi et al. 2012
Escherichia coli (WP2/spot test)	Gene mutation	NT	–	Gamma	Nagy et al. 1975
E. coli (WP2 *hcr*) (reversion assay)	Gene mutation	–	–	Gamma	Moriya et al. 1983
Bacillus subtilis (rec assay)	DNA damage	NT	–	Gamma	Shirasu et al. 1976
Eukaryotic organisms					
Fungi and plant cells:					
Saccharomyces cerevisiae	Gene mutation	–	–	Gamma	Shahin and von Borstel 1977
S. cerevisiae (transformed reporter strain HLYRGI)	DNA damage	NT	+	Gamma	Schmitt et al. 2005
Nostoc muscorum	Gene mutation	NT	–	Gamma	Kar and Singh 1979a
Allium cepa	Mitotic disturbances	NT	+	Gamma	Nybom and Knutsson 1947
Mammalian cells					
Human (peripheral lymphocytes)	Micronuclei	NT	–	Alpha	Ennaceur 2017
Human (peripheral lymphocytes)	Micronuclei	NT	+	Beta	Ennaceur 2017
Human (peripheral lymphocytes)	Micronuclei	NT	+	Gamma	Ennaceur 2017
Human (mammary carcinoma MCF-7)	Micronuclei	NT	+	Gamma	Kalantzi et al. 2004
Human (prostate carcinoma PC-3)	Micronuclei	NT	+	Gamma	Kalantzi et al. 2004
Human (SV-40 fibroblasts)	Unscheduled DNA synthesis	–	–	Gamma	Ahmed et al. 1977
Human (peripheral lymphocytes)	Unscheduled DNA synthesis	NT	+	Gamma	Rocchi et al. 1980
Rat (primary hepatocytes)	Unscheduled DNA synthesis	NT	–	Gamma	Cifone 1990
Human (mammary carcinoma MCF-7)	DNA damage	NT	–	Gamma	Kalantzi et al. 2004
Human (prostate carcinoma PC-3)	DNA damage	NT	–	Gamma	Kalantzi et al. 2004
Human (ovary surface epithelial cells)	DNA damage	NT	+	Beta	Shah et al. 2020
Human hepatocytes	DNA fragmentation	NT	+	Alpha	Mattioli et al. 1996

Table 2-23. Genotoxicity of Hexachlorocyclohexane Isomers *In Vitro*

Species (test system)	Endpoint	Results		Isomer	Reference
		With activation	Without activation		
Rat (primary cultures)	DNA fragmentation	NT	+	Alpha	Mattioli et al. 1996
Mouse (hepatocytes)	DNA fragmentation	NT	–	Alpha	Mattioli et al. 1996
Chinese hamster lung (CHL) cells	Chromosomal aberrations	NT	(+)	Gamma	Ishidate and Odashima 1977
Chinese hamster ovary (CHO) cells	Chromosomal aberrations	NT	–	Gamma	NTP 1984
CHO cells	Sister chromatid exchange	NT	–	Gamma	NTP 1984
CHO cells	Chromosomal aberrations	–	–	Gamma	Murli 1990
Human (peripheral lymphocytes)	Sister chromatid exchange	NT	+	Technical	Rupa et al. 1989d
Human (peripheral lymphocytes)	Chromosomal aberrations	NT	+	Technical	Rupa et al. 1989d
Calf (thymus DNA)	DNA binding	(+)	NT	Alpha/ gamma	Iverson et al. 1984

– = negative result; + = positive result; (+) = weakly positive result; DNA = deoxyribonucleic acid; NT = not tested

A number of studies in humans evaluated the genotoxicity of HCH. Several studies examined the genotoxicity of hexachlorocyclohexane in agricultural workers exposed to mixtures of pesticides. In rice field workers exposed to pesticide mixtures, there was no association between peripheral blood levels of α-HCH or β-HCH and DNA damage measured by comet assay (Varona-Uribe et al. 2016). The frequency of micronuclei in peripheral lymphocytes in agricultural workers exposed to a complex mixture of pesticides including HCH was not significantly different compared to unexposed workers, while the frequency of chromosomal aberrations was significantly increased in exposed workers (Jonnalagadda et al. 2012). In addition, a correlation between chromosomal aberrations per cell and HCH level was reported (Jonnalagadda et al. 2012).

In workers occupationally exposed primarily to γ-HCH by inhalation in a pesticide production factory, no appreciable increase in the frequency of chromosome aberrations was observed compared to the factory employee control group (Kiraly et al. 1979). In colorectal cancer patients, serum levels of the α-HCH isomer were not associated with changes in the methylation status of CpG island of MGMT and P16 tumor suppressor genes in colorectal cancer cells (Abolhassani et al. 2019). γ-HCH was not associated

with methylation status of the MGMT tumor suppression gene; however, hypermethylation was found in the P16 tumor suppressor gene (Abolhassani et al. 2019). There was no significant association between serum levels of β-HCH and methylation status of MGMT and P16 tumor suppressor genes (Abolhassani et al. 2019); however, serum β-HCH was associated with a slight increase in methylation of the tumor suppressor gene E-cadherin [CDH1] in peripheral blood mononuclear cells of healthy Korean subjects (Lee et al. 2018b). There was a decreased level of global methylation associated with β-HCH serum levels in human leukocyte DNA of Japanese women (Itoh et al. 2014).

Other studies are available regarding genotoxic effects (chromosomal aberrations, sister chromatid exchanges) in humans exposed to a wide variety of pesticides, including HCH, when they were used on farms (Rupa et al. 1988, 1989a, 1989b, 1989c). The specific effects of HCH, apart from the effects due to other exposures, are not evident from these studies.

α-HCH. Both *in vivo* and *in vitro* assays for genotoxicity of α-HCH are available. α-HCH was observed to bind to liver DNA in HPB mice following intraperitoneal administration (Iverson et al. 1984).

In human peripheral lymphocytes, *in vitro* exposure to α-HCH did not increase the frequency of micronuclei in a cytokinesis-block micronucleus assay (Ennaceur 2017). Exposure to α-HCH produced DNA fragmentation in primary cultures of rat and human hepatocytes, but not in mouse hepatocytes; DNA repair was not induced in hepatocytes from all three species tested (Mattioli et al. 1996). α-HCH was observed to bind to calf thymus DNA with metabolic activation (Iverson et al. 1984).

β-HCH. Limited *in vivo* and *in vitro* assays for the genotoxicity of β-HCH are available. In animals, chromosomal aberrations were induced in bone marrow cells of Long-Evans rats following intraperitoneal exposure to β-HCH in a study reported only as an abstract (Shimazu et al. 1972). *In vitro* exposure to β-HCH increased the frequency of micronuclei at cytotoxic concentrations in human peripheral lymphocytes in a cytokinesis-block micronucleus assay (Ennaceur 2017). β-HCH also induced DNA damage in ovary surface epithelial cells (Shah et al. 2020).

γ-HCH (Lindane). γ-HCH has been tested in several *in vivo* and *in vitro* genotoxicity assays. The incidence of chromosomal abnormalities (breaks and gaps with or without acentric fragments) in bone marrow cells was increased in mice exposed to 1.6 mg γ-HCH/kg body weight/day by gavage for 7 days (Kumar et al. 1995). In a mouse bone marrow micronucleus test, the frequency of micronucleated-polychromatic erythrocytes was increased, and the frequency of polychromatic erythrocytes was

decreased in bone marrow cells (Yaduvanshi et al. 2012). γ-HCH was negative in a micronucleus assay in CBA mice (Jenssen and Ramel 1980). Intraperitoneal exposure of Syrian hamsters did not induce chromosome aberrations in bone marrow cells (Dzwonkowska and Hubner 1986). γ-HCH was observed to bind to liver DNA in mice following intraperitoneal administration (Iverson et al. 1984).

γ-HCH did not induce gene mutations in *Salmonella typhimurium* (TA100, TA98, TA1535, TA1537, and TA1538) or *Escherichia coli* (WP2) with or without a metabolic activation system (Moriya et al. 1983) or in *E. coli* without metabolic activation in a WP2 spot test (Nagy et al. 1975). γ-HCH was also negative in an Ames *Salmonella*/microsome mutagenicity assay in *S. typhimurium* (TA98, TA100, TA102) with and without metabolic activation (Yaduvanshi et al. 2012). Exposure to γ-HCH did not produce DNA damage in *Bacillus subtilis* in a rec assay, although a mammalian metabolic activation system was not present (Shirasu et al. 1976). γ-HCH was not mutagenic in *Nostoc muscorum* algae (Kar and Singh 1979a). Mitotic disturbances (c-mitosis, which is characterized by spindle breakdown as that produced by colchicine) and chromosome aberrations were observed in onion root tip cells exposed to commercial γ-HCH (Nybom and Knutsson 1947). In yeast, exposure to γ-HCH did not induce mutations in *Saccharomyces cerevisiae* (XV185-14C) in a reversion study (Shahin and von Borstel 1977) but did induce DNA damage in transformed reporter strain HLYRGI (Schmitt et al. 2005).

In mammalian cells, γ-HCH induced a marginal increase in the frequency of chromosome aberrations (including chromosomal gaps) in Chinese hamster ovary (CHO) cells (without metabolic activation), which was interpreted by the authors of the study as providing suggestive, but not conclusive, evidence of an effect (Ishidate and Odashima 1977). Another study reported negative results in cytogenetic tests (chromosomal aberrations and sister chromatid exchange) in CHO cells exposed to γ-HCH without metabolic activation (NTP 1984). In addition, γ-HCH was reported to be negative for chromosomal aberrations in CHO cells with and without metabolic activation (Murli 1990).

In a cytokinesis-block micronucleus assay exposure to γ-HCH in human peripheral lymphocytes induced micronuclei and binucleated cells with micronucleus (BNMN) at a concentration of 100 µg/L, with significant cytotoxicity at that concentration (Ennaceur 2017). γ-HCH exposure in human mammary carcinoma MCF-7 and human prostate carcinoma PC-3 cell lines increased the frequency of micronuclei in both cell lines in the absence of DNA damage or cytotoxicity, suggesting a clastogenic effect (Kalantzi et al. 2004). In a microgel single cell assay, DNA damage was observed in cultures of rat nasal and gastric mucosa cells and human nasal mucosa cells following exposure to γ-HCH (Pool-Zobel et al. 1994). γ-HCH was found to induce unscheduled DNA synthesis in human peripheral lymphocytes without

metabolic activation (Rocchi et al. 1980), while it was inactive for inducing unscheduled DNA synthesis in human SV-40 fibroblasts, both with and without activation (Ahmed et al. 1977). In rat primary hepatocytes tested without metabolic activation mammalian cells, γ-HCH did not induce unscheduled DNA synthesis (Cifone 1990). γ-HCH was observed to bind to calf thymus DNA when tested with exogenous metabolic activation (Iverson et al. 1984).

Technical HCH or Unspecified HCH Isomers. Technical-grade HCH has been tested for genotoxic effects in one *in vivo* and one *in vitro* study. When male Swiss mice were exposed to technical-grade HCH prior to mating, dominant-lethal mutations were induced, as evidenced by the number of dead implantations per pregnant female (Lakkad et al. 1982). Cultured human lymphocytes showed a dose-dependent increase in chromosomal aberrations (gaps, breaks, and fragments) with significant increases at 0.1 μg/mL technical-grade HCH for 48-hour treatment and at 0.05 and 0.1 μg/mL for 72-hour treatment (Rupa et al. 1989d). In addition, sister chromatid exchanges increased in a dose-dependent manner with the high dose (0.1 μg/mL) producing the only significant result. These results suggest mild mutagenic activity at high doses in humans (Rupa et al. 1989d).

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

Human studies of HCH isomers provide limited quantitative information on absorption, metabolism, distribution, and excretion. Toxicokinetics have been studied in rodents, with most quantitative information derived from studies conducted in mice and rats. An overview of these data is provided below.

- Absorption of HCH isomers has been demonstrated in humans by increased serum levels of the isomers following inhalation, oral, or dermal exposure.
- No animal data are available from the inhalation route to quantify the extent or rate of absorption. Technical-grade HCH has been shown to be well absorbed from the gastrointestinal tract of animals (>90% recovery).
- The distribution of HCH isomers in humans and animals is primarily to the adipose tissue but also to the brain, kidney, muscle, blood, and other tissues. β-HCH accumulates to a much greater extent than other HCH isomers.
- HCH isomers have been measured in the placenta and umbilical cord blood of humans, indicating that transplacental exposure to fetuses is likely to occur. HCH isomers have also been detected in breast milk.
- The primary urinary metabolites are chlorophenols and 1,2,4-trichlorocyclohexane-4,5-epoxide. The conversion occurs mainly by the action of hepatic CYP enzymes.
- HCH isomer metabolites are primarily excreted through the urine as conjugates of mercapturic acid, glucuronide, and sulfate.
- A rat physiologically based pharmacokinetic (PBPK) model simulated the toxicokinetics of γ-HCH. Concentrations in blood, brain, muscle, and fat after a single intraperitoneal injection and chronic oral dosage compared adequately well with experimental results; however, the model is not validated via biological evaluation of kinetic parameters.
- A human PBPK model was developed to simulate toxicokinetics of β-HCH in pregnant mothers and infants exposed during gestation and lactation. The model was validated by comparing predicted concentrations in breast milk, cord blood, and infant blood to concentrations measured in mothers and infants from a Canadian Inuit population. Correlations between model-predicted

and measured values for β-HCH were relatively weak because measured concentrations were near the limit of detection.

- A human dermal PBPK model for γ-HCH was developed by modifying a flow-limited PBPK model to include a skin patch compartment for the exposure location. A comparison of model simulations in which the optimized diffusion constants were varied illustrated the importance of considering protein binding of γ-HCH, when predicting the steady-state dermal permeability constant (K_p).

3.1.1 Absorption

α-, β-, γ-, and δ-HCH have been detected in the blood serum, adipose tissue, and semen of occupationally and environmentally exposed individuals, indicating that absorption takes place following inhalation exposure (Baumann et al. 1980; Czeglédi-Jankó and Avar 1970; Kashyap 1986; Nigam et al. 1986; Quintana et al. 2004; Saxena et al. 1980, 1981a, 1981b). Human case reports of accidental poisoning indicate that HCH is also absorbed following oral exposure. High blood concentrations of γ-HCH have been demonstrated following oral exposure in these cases (Berry et al. 1987; Harris et al. 1969; Khare et al. 1977; Munk and Nantel 1977; Nantel et al. 1977; Powell 1980; Starr and Clifford 1972).

Dermal absorption of γ-HCH has been demonstrated in several studies that examined absorption from anti-scabies lotion or head lice shampoo (EPA 2002; Feldmann and Maibach 1974; Franz et al. 1996; Ginsburg et al. 1977; Lange et al. 1981). Maximum serum levels in healthy volunteers and scabies patients were reported within 4–6 hours following whole-body application (Lange et al. 1981). However, the maximum serum levels of γ-HCH in scabies patients were greater than those reported for normal volunteers. Studies involving a single topical application of γ-HCH to the forearm, which was left for 24 hours before washing, indicate that at least 9% of the applied dose was absorbed; maximum absorption occurred during the first 12 hours after application of γ-HCH to the skin, but absorption continued for at least 5 days (Feldmann and Maibach 1974). In infants and children dermally treated with 1% γ-HCH lotion, maximum blood concentrations of γ-HCH were observed in 6 hours, and averaged 0.028 µg/mL for the group infested with scabies and 0.024 µg/mL for the noninfested group (Ginsburg et al, 1977). The maximum blood level measured in children aged 33–64 months treated with 1% topical γ-HCH lotion was 64 µg/L (EPA 2002). Children aged 3.5–18 years treated for head lice with 1% γ-HCH shampoo had a maximum γ-HCH blood level of 6.13 µg/L (EPA 2002). HCH isomers are bioavailable from soil and can be absorbed dermally (Duff and Kissel 1996). In an *in vitro* study using abdominal skin

obtained from human cadavers, γ-HCH exhibited mean 24-hour dermal absorption values from 0.45 to 2.35% varying with different soil types and soil loadings of 1, 5, and 10 mg/cm^3.

The absorption of γ-HCH through the skin was studied following application of two different preparations to the forearm of volunteers (Dick et al. 1997a). The mean peak plasma concentrations of γ-HCH following exposure to 120 mg γ-HCH/mL acetone and a 3 mg γ-HCH/mL formulation containing white spirit (a petroleum-based solvent) were 0.91 and 0.47 ng/mL, respectively, although the preparation in acetone contained a 40-fold higher concentration of γ-HCH. The proportion of the applied dose absorbed into the systemic circulation in 6 hours was 5% for the dose applied in acetone and 60% of the applied dose in white spirit-based formulation. Thus, the white spirit enhanced the absorption of γ-HCH relative to acetone as the vehicle. About 30% of the applied dose for the white-spirit based formulation was observed in the stratum corneum at 6 hours of exposure and decreased by 90% at 24 hours. Fifteen percent of the applied dose for the acetone-based application was located in the stratum corneum. The absorption of γ-HCH through human skin was also assessed in an *in vitro* study (Dick et al. 1997b). γ-HCH absorption was reported to be 15–25% in 24 hours for the two formulations that contained white spirit as the predominant solvent, 3% in 24 hours from an aqueous spray dilution, and <1% in 24 hours for the acetone preparation.

No information is available on the absorption of α-, β-, γ-, and δ-HCH following inhalation exposure in experimental animals. γ-HCH is readily absorbed from the gastrointestinal tract of mice and rats (Ahdaya et al. 1981; Turner and Shanks 1980). Ahdaya et al. (1981) demonstrated that half of the administered dose was absorbed from the gastrointestinal tract of fasting mice approximately 14 minutes after administration of radiolabeled γ-HCH by stomach tube. Although this study demonstrates the rapid absorption of γ-HCH from the gastrointestinal tract, the use of fasted animals prevents an assessment of the effect of stomach contents on the rate of absorption. Turner and Shanks (1980) studied the rate of absorption of γ-HCH from the gastrointestinal tract and intestinal lymphatic system using rat intestinal loop preparations. Prepared loops were injected with γ-HCH, and the blood and lymph were sampled for 30 minutes. γ-HCH was readily absorbed from the intestine into the blood; however, only a small amount of γ-HCH entered the lymphatic system from the intestine. The extent of oral absorption of technical-grade HCH has been estimated to be 95.8% in rats within 4 days following the administration of single doses of the substance (Albro and Thomas 1974). Variation of the dosages from 30 to 125 mg/kg had no effect on the percent absorption. The overall degree of absorption of technical-grade HCH administered in the feed for 14 days was similar (94.9%), but the average absorption values of α-, β-, γ-, and δ-HCH

were 97.4, 90.7, 99.4, and 91.9%, respectively (Albro and Thomas 1974). HCH isomers in contaminated soil were shown to be bioaccessible in an *in vitro* gastrointestinal model (Tao et al. 2009).

Dermal absorption of γ-HCH was demonstrated in rats and rabbits (Bosch 1987a, 1987b). Male rats treated dermally with radiolabeled γ-HCH (20% emulsifiable concentrate) on a 4.9 cm^2 shaved dorsal area exhibited absorption of radiolabel, which increased with time of exposure (Bosch 1987a). After 4 hours, 10.1, 5.3, and 2.0% were absorbed from doses of 0.06, 0.6, and 6 $mg/cm^2/kg$, respectively. After 24 hours, 27.7, 20.9, and 5.1% were absorbed from doses of 0.06, 0.6, and 6 $mg/cm^2/kg$, respectively. Male rabbits treated dermally with radiolabeled γ-HCH (20% emulsifiable concentrate) in a 28.3-cm^2 shaved dorsal area absorbed, after 4 hours, 29.6, 18.3, and 7.3% radiolabel from doses of 0.005, 0.05, and 0.5 $mg/cm^2/kg$, respectively, and, after 24 hours, 55.7, 40.0, and 16.6% from the same respective doses (Bosch 1987b). In weanling rabbits, levels of γ-HCH in the blood after a single application of a 1% solution (60 mg γ-HCH/kg) were 1.67 and 2.48 μg/mL in two rabbits that had been shaved and depilated, then stripped to remove the keratin layer (Hanig et al. 1976). In contrast, a blood level of only 0.67 μg/mL was seen in a rabbit that had only been shaved and depilated, indicating that absorption increases with loss of skin integrity.

Dermal absorption of γ-HCH was evaluated in human skin grafted onto a nude mouse model and the results were compared to an *in vivo* rat model and *in vitro* rat and human models (Capt et al. 2007). The maximum percent absorbed, which included the amount directly absorbed and present in the skin and stratum corneum, was comparable for the human skin grafted onto a nude mouse (20.7% of applied dose) and the *in vitro* human skin model (24.5%). Data for the rat *in vivo* and *in vitro* models appeared to overestimate the potential human absorption. The maximum percent absorbed was 39.8% in the rat *in vivo* model and 62.5% in the rat *in vitro* model.

3.1.2 Distribution

Occupational studies provide information on the distribution of HCH isomers following inhalation exposure in humans. Air concentrations of α-HCH (0.002–1.99 mg/m^3), β-HCH (0.001–0.38 mg/m^3), and γ-HCH (0.004–0.15 mg/m^3) were associated with concurrent mean blood serum levels in workers of 69.6, 190.3, and 36.9 μg/L, respectively (Baumann et al. 1980). Serum total HCH concentrations of 0.14–0.60 ppm were found in workers with unknown levels of exposure to technical-grade HCH (Nigam et al. 1986). HCH isomers have also been detected in adipose tissues of occupational workers and the general population (Arrebola et al. 2013, 2014; Baumann et al. 1980; Kim et al. 2014; Mustieles et al. 2017;

Pestana et al. 2011; Ploteau et al. 2017; Quintana et al. 2004; Siddiqui et al. 1981). Accumulation of β-HCH has been shown to increase approximately linearly with time of exposure (Baumann et al. 1980). In a national EPA survey, adipose tissue samples collected from surgical procedures or autopsies between 1969 and 1983 showed β-HCH concentrations >0.37 ppm lipid in the highest quartile (Quintana et al. 2004).

Case reports of poisoning confirm that γ-HCH is distributed to the central nervous system. γ-HCH was detected in the cerebrospinal fluid of a young boy following ingestion of an unknown quantity of γ-HCH (Davies et al. 1983). γ-HCH was also detected in brain tissue (110 ppb) and heart blood (33.3 ppb) collected during the autopsy of an infant who was treated with a whole-body application of a 1% γ-HCH lotion after a hot bath (Davies et al. 1983).

HCH isomers have been measured in the placenta and/or umbilical cord blood of humans, indicating that transplacental exposure to fetuses is likely to occur (Alvarado-Hernandez et al. 2013; Anand and Taneja 2020; Anand and Taneja 2020; Anand et al. 2019; Dewan et al. 2013; Fukata et al. 2005; Hernik et al. 2016; Herrero-Mercado et al. 2010, 2011; Junque et al. 2020; Lopez-Espinosa et al. 2007; Morello-Frosch et al. 2016; Saxena et al. 1981a; Shen et al. 2007; Siddiqui et al. 2003; Vizcaino et al. 2011; Yin et al. 2019; Yu et al. 2013). Placental transfer of HCH isomers was analyzed using matched maternal serum, cord serum, and placenta samples in mother-infant pairs (Yin et al. 2019; Zhang et al. 2018). β-HCH was the predominant isomer measured in each sample type. An analysis of concentration ratios for all HCH isomers suggests that the rate of transfer from the placenta to cord blood is slower than for maternal serum to the placenta (Yin et al. 2019). Transfer data for the two enantiomers of α-HCH suggests that placental transfer may involve both simple diffusion and active transport (Yin et al. 2019). Experiments using an *in vitro* placenta model (human choriocarcinoma derived BeWo cells in a confluent, polarized monolayer) confirm that multiple mechanisms are likely involved in transplacental transfer of HCH isomers (Yin et al. 2020). Maternal serum concentrations of β-HCH were shown to increase between the first trimester of pregnancy and delivery, possibly due to mobilization of fat stores or changes in blood volume at different stages of pregnancy (Junque et al. 2020). Concentrations in cord blood serum were correlated with maternal serum concentrations at delivery in this study.

HCH isomers have also been detected in human breast milk (Bedi et al. 2013; Chen et al. 2018; Dewan et al. 2013; Dimitriadou et al. 2016; Elserougy et al. 2013; Fytianos et al. 1985; Hernik et al. 2016; Kao et al. 2019; Minh et al. 2004; Shen et al. 2007; Yalcin et al. 2015). α-, β-, and γ-HCH have been found to be bioconcentrated and excreted in breast milk of women who have been exposed to technical-grade HCH in

pesticide residues (Nair et al. 1996). All four of the HCH isomers (α, β, γ, and δ) discussed in this profile have been detected in human semen following environmental exposure (Szymczynski and Waliszewski 1981).

In a study of Wistar rats exposed to air concentrations of 0.02–5 mg/m^3 γ-HCH for 90 days, male rats exhibited higher serum γ-HCH levels than females, but females had higher liver, brain, and fat levels (Oldiges et al. 1983). The organ levels of γ-HCH were dose-dependent, but had returned to baseline levels after a 4-week recovery period. Oral animal studies provide more detailed information on the distribution of HCH or its isomers (Chand and Ramachandran 1980; Eichler et al. 1983; Srinivasan and Radhakrishnamurty 1983). γ- and β-HCH are primarily stored in the fat of rats acutely exposed for 5, 10, or 15 days (Srinivasan and Radhakrishnamurty 1983). The overall distribution of γ-HCH was greatest in fat, followed by brain, kidney, muscle, lungs, heart, spleen, liver, and blood. γ-HCH has also been found in the adrenal glands of rats (Lahiri et al. 1990; Sulik et al. 1988). In an experiment lasting 12 days, the accumulation of γ-HCH in the brain of rats dosed with 5 or 12 mg/kg/day by gavage began to decline after 8 days. This reduction was not observed in rats given 20 mg/kg/day (Tusell et al. 1988).

In the brain of rats, α-HCH has been found to accumulate preferentially in the white matter, an area containing lipid-rich myelin, as opposed to gray matter (Portig et al. 1989). However, the same brain distribution pattern was not noted for γ-HCH in mice, despite the fact that α- and γ-HCH are equally lipophilic. Differences in distribution of γ- and α-HCH are most likely due to stereospecificity, because only the +-enantiomer of α-HCH was shown to accumulate in white matter (Portig et al. 1989). A comparison of the enantiomeric fractions in the blood, liver, and brain of mice following administration of a single gavage dose of α-HCH, demonstrated enrichment of the +-enantiomer in the brain, but not in the liver or blood (Yang et al. 2010). Enantioselective transport across the blood-brain barrier was also demonstrated in rabbits exposed orally or dermally to α-HCH (Xue et al. 2010). Toxicokinetic modeling from this study suggested that enrichment of the +-enantiomer in blood was due to a faster elimination rate for the –-enantiomer in rabbits (Xue et al. 2010). In mice, gavage exposure to 5.9 mg/kg/day γ-HCH for 3 days was shown to increase the permeability of the blood-brain barrier, as measured by increased fluorescein dye uptake (Sinha and Shukla 2003). Similar effects were not observed in rats given 8.8 mg/kg/day for 3 days (Sinha and Shukla 2003).

The distribution pattern for β-HCH was found to be in the following order: fat > kidney > lungs > liver > muscle > heart > spleen > brain > blood. β-HCH accumulates in tissues to a greater degree than γ-HCH except in the brain, where the γ-HCH accumulates at a higher concentration (Srinivasan and

Radhakrishnamurty 1983). This accumulation increases with increasing dose and treatment period for β-HCH more so than for γ-HCH. The greater accumulation of β-HCH in tissues is expected since this isomer is known to be metabolized more slowly. In addition, γ-HCH is known to induce the liver cytochrome P-450 mixed-function oxygenase system (CYP), and thus, self-induced metabolism is an important factor that minimizes the accumulation of γ-HCH residues in animal tissues.

The preferential accumulation of HCH in fatty tissues is also observed following intermediate- and chronic-duration exposure of rats to HCH isomers in the diet (overall distribution: fat > liver > serum) (Amyes 1990; Chand and Ramachandran 1980; Dikshith et al. 1991c; Fitzhugh et al. 1950) or exposure to α- or γ-HCH by gavage (overall distribution: fat > kidney > liver > brain > blood) (Eichler et al. 1983). HCH has been shown to accumulate in amniotic fluid, placenta, and fetal tissues after oral treatment of pregnant mice (Srivastava and Raizada 2000). In rats gavaged with γ-HCH on LDs 9 or 14, γ-HCH levels were higher in their milk than plasma (Dalsenter et al. 1997b). Levels of γ-HCH in the offspring of those rats were approximately twice as high in kidneys and liver than in brain and testes.

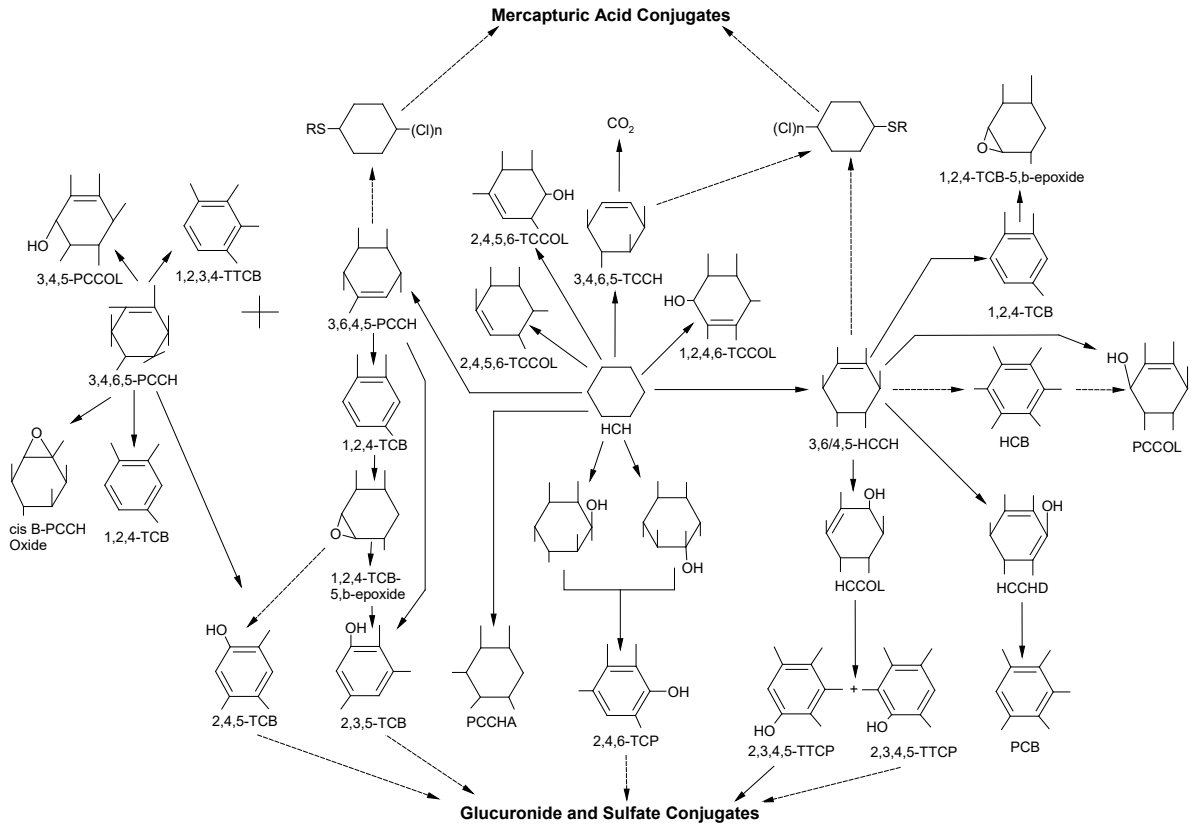
Some information on the distribution of γ-HCH is available from studies in which laboratory animals were exposed by dermal application (Bosch 1987a, 1987b; Hanig et al. 1976; Solomon et al. 1977a, 1977b). A study on the distribution of γ-HCH in guinea pigs following acute dermal exposure indicates that accumulation of γ-HCH in the brain is greater than in the blood after single and multiple topical applications (Solomon et al. 1977a, 1977b); the levels in both tissues increased with the number of applications. Following dermal treatment of rats with 50 or 100 mg/kg/day technical-grade HCH for 120 days, α-, β-, γ-, and δ-HCH were accumulated in testicular tissue and sperm in a dose-related manner (Prasad et al. 1995). β-HCH was present at the highest concentration in testicular tissue and sperm.

3.1.3 Metabolism

The metabolism of γ-HCH is illustrated in Figure 3-1. Angerer et al. (1983) determined that chlorophenols were the primary urinary metabolites of γ-HCH excreted by workers involved in γ-HCH production. In the study, glucuronides and sulfates of chlorophenols were cleaved by acidic hydrolysis of urine samples. The metabolites 2,3,5-, 2,4,6-, and 2,4,5-trichlorophenol accounted for almost 57.7% of the γ-HCH metabolites identified in the urine collected during the last 2 hours of the workers' shifts. Other urinary metabolites identified included other trichlorophenols, dichlorophenols, tetrachlorophenols, and dihydroxychlorobenzenes. Pentachlorophenol has also been identified as a urinary metabolite in humans following occupational exposure (Engst et al. 1979). *In vitro* investigations indicate that human

liver microsomes convert γ-HCH by dechlorination, dehydrogenation, dehydrochlorination, and hydroxylation to five primary metabolites: 3,6/4,5-hexachlorocyclohexene, pentachlorocyclohexene, 2,4,6-trichlorophenol, 2,3,4,6-tetrachlorophenol, and pentachlorobenzene (Fitzloff et al. 1982). Similar *in vitro* studies have demonstrated that an epoxide forms during the metabolism of pentachlorocyclohexene. This stable halogenated hydrocarbon epoxide metabolite may be responsible for the mutagenic and carcinogenic effects of γ-HCH (Fitzloff and Pan 1984).

Figure 3-1. The Proposed Metabolism of Hexachlorocyclohexane



3,6/4,5-HCCH = 3,6/4,5-hexachlorocyclohexene; HCB = hexachlorobenzene; HCCHD = hexachlorocyclohexadiene; HCCOL = hexachlorocyclohexenol; HCH = hexachlorocyclohexane; PCB = pentachlorobenzene; PCCH = pentachlorocyclohexene; PCCHA = pentachlorocyclohexane; PCCOL = pentachlorocyclohexenol; TCB = trichlorobenzene; TCCH = tetrachlorobenzene; TCCOL = tetrachlorocyclohexenol; TCP = trichlorophenol; TTCP = tetrachlorophenol

Sources: Chadwick et al. 1985; Fitzloff and Pan 1984; Fitzloff et al. 1982

In animals, γ-HCH appears to be transformed by hepatic enzymes to form chlorophenols, chlorobenzene, chlorocyclohexanes, chlorocyclohexanols, and conjugates of mercapturic acid, glucuronide, and sulfate (Chadwick and Freal 1972a; Chadwick et al. 1978a; Engst et al. 1979; Kujawa et al. 1977). These

metabolites have been identified in various tissues and in the urine of laboratory animals. Metabolites found in the liver of rats following intermediate exposure to γ-HCH via gavage or diet include di-, tri-, tetra-, and pentachlorobenzenes; pentachlorocyclohexenes; and pentachloro-2-cyclohexen-1-ol (Chadwick and Freal 1972a; Kujawa et al. 1977). Metabolites identified in the blood of these rats include di-, tri-, tetra-, and pentachlorophenols and pentachloro-2-cyclohexen-1-ol (Kujawa et al. 1977). Di-, tri-, and tetrachlorophenols; pentachlorocyclohexenes; and pentachloro-2-cyclohexen-1-ol have been identified in samples of kidney, spleen, heart, and brain tissue from rats fed γ-HCH (Kujawa et al. 1977). Metabolites found in the urine include tri-, tetra-, and pentachlorophenol; pentachloro-2-cyclohexen-1-ol; and isomers of tetrachloro-2-cyclohexen-1-ol (Chadwick and Freal 1972a; Chadwick et al. 1978c; Kujawa et al. 1977). The metabolism of γ-HCH in the intestine was reported to be very minor, or the metabolites were completely absorbed. No metabolites were detected in the feces or in the adrenal gland (Kujawa et al. 1977). *In vitro* preparations using rat liver slices have also found that γ-HCH is converted to hexachlorobenzene (Gopalaswamy and Aiyar 1984). However, these findings have not been confirmed in *in vivo* experiments.

The major urinary metabolites formed in rats, following intermediate oral exposure to α- or β-HCH, were identified as tri- and tetrachlorophenols; pentachlorocyclohexene was also identified as a metabolite of γ-HCH in kidney tissue (Macholz et al. 1982a, 1982b).

The toxicity of γ-HCH appears to be dependent on CYP enzymes. Intermediate exposure to γ-HCH resulted in greater toxicity in DBA/2 (D2) mice than in C57BL/6 (B6) mice; the former are considered unresponsive to microsomal enzyme induction by aromatic hydrocarbons (Liu and Morgan 1986). Increased toxicity was associated with higher blood and brain concentrations in D2 mice than in B6 mice at the time of sacrifice. In addition, D2 mice were found to have more 2,4,6-trichlorophenol in the liver, kidney, and spleen than the less-susceptible B6 mice. The inability of D2 mice to undergo enzyme induction to increase the rate of detoxification led to γ-HCH's enhanced toxicity in this strain. Other investigators have demonstrated the importance of the hepatic microsomal enzymes in the toxicity of γ-HCH (Baker et al. 1985; Chadwick and Freal 1972a; Chadwick et al. 1981; Chand and Ramachandran 1980; Tanaka et al. 1979). Chadwick et al. (1981) demonstrated that pretreatment of rats with inducers of hepatic enzymes significantly influenced the metabolism and excretion of γ-HCH and its metabolites by altering specific metabolic pathways; excretion of γ-HCH metabolites in the urine increased nearly 4-fold following pretreatment with Aroclor 1254 or phenobarbital. Following pretreatment with Aroclor 1254, a 7-fold increase in expired metabolites was observed. Naphthoflavone had no effect on the excretion rate.

3.1.4 Excretion

Humans excrete HCH isomers and their metabolites in urine, breast milk, sweat, and semen (Angerer et al. 1981; Genuis et al. 2016). Analysis of urine from humans occupationally exposed to HCH showed the presence of chlorinated phenols and all isomers of di-, tri-, and tetrachlorophenol (Angerer et al. 1981). In another study, the elimination of β-HCH (a byproduct of γ-HCH production studied due to its long half-life in humans) was investigated in a group of 40 former workers of a γ-HCH-producing plant by analyzing at least two blood specimens from different time points between 1952 and 1980. The median half-life of β-HCH was 7.2 years, calculated by concentrations in whole blood, and 7.6 years, calculated by concentrations in extractable lipids (Jung et al. 1997), assuming first-order kinetics for excretion.

Nonmetabolized γ-HCH was excreted in the urine and feces of healthy volunteers and scabies patients acutely exposed to a 0.3% γ-HCH emulsion by whole-body application. The cumulative excretion of nonmetabolized γ-HCH was almost the same in the healthy volunteers and the scabies patients (Zesch et al. 1982). The elimination of γ-HCH was studied following application of two different preparations to the forearm of volunteers (Dick et al. 1997a). The elimination half-life was between 50 and 111 hours for the acetone-based application, and 25–58 hours for the white-spirit based formulation. Absorbed γ-HCH was excreted in the urine as conjugates of 2,4,6-, 2,3,5-, and 2,4,5-trichlorophenol. Only 0.01–0.15% of the dose was excreted in the urine in 72 hours following dermal exposure for 6 hours. In a study in which children infested with scabies and their noninfested siblings were treated dermally with 1% γ-HCH lotion, the blood level was found to diminish rapidly after application, with a half-life of 17.9 hours in infested children and 21.4 hours in noninfested children (Ginsburg et al. 1977).

The excretion kinetics of β-HCH into breast milk were studied by monitoring breast milk concentrations in lactating mothers after birth (Song et al. 2018; Waliszewski et al. 2009). In 40 lactating women, breast milk concentrations of β-HCH decreased by approximately 30%, from 95 µg/kg fat on the 4th day after birth to 66 µg/kg fat on PND 30 (Waliszewski et al. 2009). Song et al. (2018) monitored monthly breast milk concentrations in 40 lactating women during the first 6 months after birth. The average breast milk concentrations of β-HCH decreased from 127 µg/kg lipid 1 month after birth to 84.8 µg/kg lipid 6 months after birth, representing a 32% reduction over this time period. The excretion profile for β-HCH in milk lipids followed zero-order kinetics and the mean excretion rate was approximately 7% per month.

Excretion of γ-HCH and its metabolites in laboratory animals has been well documented. Data indicate that the major route of elimination is via the urine following intermediate and chronic oral feeding in mice

(Chadwick et al. 1985). Very little is eliminated in exhaled air (Ahdaya et al. 1981; Chadwick et al. 1985) or in feces (Chadwick et al. 1985) following acute, intermediate, and chronic oral administration in rodents. Because of its high lipid solubility, γ-HCH is excreted through the dam's milk (Dalsenter et al. 1997b).

Very little γ-HCH is excreted unaltered. Various phenylmercapturic acid derivatives have been detected in the urine of rats, formed by the conjugation of γ-HCH metabolites with glutathione subsequent to dechlorinations and dehydrochlorinations (Allsup and Walsh 1982; Kurihara et al. 1979). *In vitro* investigations using rat liver cells indicate that glutathione conjungation is lower for β-HCH compared to γ- and α-HCH, which are readily conjugated (Fitzloff and Pan 1984; Fitzloff et al. 1982). γ-HCH metabolites are excreted in the form of phenylmercapturic acids and glucuronide and sulfate conjugates (Chadwick et al. 1978a).

In male rats treated dermally with radiolabeled γ-HCH, 0.28, 0.08, and 0.02% radiolabel was excreted in urine within 4 hours after doses of 0.06, 0.6, and 6 mg/cm^2/kg, respectively (Bosch 1987a). After 24 hours, 4.4, 3.2, and 0.6% radiolabel had been excreted in urine from the same respective doses. In a similar study with male rabbits, 3.8, 2.6, and 1.3% radiolabel was excreted in urine within 4 hours after doses of 0.005, 0.05, and 0.5 mg/cm^2/kg, respectively (Bosch 1987b). After 24 hours, 25.5, 11.6, and 6.8% radiolabel had been excreted in urine from the same respective doses.

3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

PBPK models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints.

DeJongh and Blaauboer (1997) simulated the toxicokinetics of γ-HCH in rats with a PBPK model. A five-compartment model was constructed: (1) the liver, serving as the metabolizing organ; (2) blood; (3) fat; (4) brain; and (5) a lumped compartment representing all other tissues, consisting mainly of

muscle tissue. Values for the physiological parameters and tissue-blood partition coefficients were obtained from the literature. The model was calibrated on a dataset from the literature on the disposition of γ-HCH from blood *in vivo* after single oral dosage and first-order biotransformation and gastrointestinal absorption constants for γ-HCH were obtained.

The model was validated by simulating the disposition of γ-HCH *in vivo* after single intraperitoneal and chronic oral dosing and comparing simulated with experimental results. Simulated γ-HCH concentrations in fat, brain, and muscle compared well with measured values obtained after single intraperitoneal exposure in rats. Simulated levels in blood were slightly higher than measured levels after oral and intraperitoneal exposure.

A human PBPK model was developed to assess pre- and postnatal exposure to β-HCH and other neutral persistent organic pollutants (Verner et al. 2009). The infant portion of the model was added to a previously published maternal model (Verner et al. 2008) that consisted of nine compartments (liver, brain, adipose tissue, richly perfused tissues, poorly perfused tissues, mammary tissue, uterus, placenta, and fetus). β-HCH was assumed to be completely absorbed from contaminated food and absorption was entered as a direct input to the maternal liver. Excretion into breast milk was modeled as an output from mammary tissue. The infant portion of the model consisted of five compartments, including liver, brain, adipose tissue, richly perfused tissues, and poorly perfused tissues. The infant liver was modeled as receiving β-HCH directly from breast milk for the first year of life (100% absorption was assumed) with subsequent first-pass metabolism. The brain was included as a potential target organ of toxicity and adipose tissue was considered the primary site for β-HCH storage. The initial body burden in the infant was equivalent to lipid-adjusted levels of β-HCH in maternal blood at delivery. Distribution between compartments in both the maternal and infant models was derived using blood flow and tissue:blood partition coefficients. Metabolism was parameterized by transforming a published physiological half-life of 7.6 years into a liver volume-adjusted intrinsic clearance value. Intrinsic clearance values based on hepatic metabolism were assumed to be the same in mothers and infants. Model parameters described by Verner et al. (2008) for the maternal model were adjusted for blood lipids during pregnancy, breast milk lipid content, and excreted volume in breast milk. Parameters for the infant model described infant physiology as a function of sex, age, body weight, and body height, and included sex-specific organ volumes and blood flows and tissue:blood and milk:blood partition coefficients.

The model was validated by comparing predicted concentrations in breast milk, cord blood, and infant blood to concentrations measured in mothers and infants from a Canadian Inuit population. Correlations

between model predictions and measured values for β-HCH were relatively weak (r=0.35 for cord blood; r=0.7 for breast milk; r=0.62 for infant blood) because measured concentrations were near the limit of detection. A sensitivity analysis was performed using Monte Carlo simulations based on variability in breast milk consumption, fraction of lipids in breast milk and fraction of lipids in infant adipose tissue for PCB-153 and *p,p'*-DDT. Variability was estimated to be approximately 2.5-fold between the 5th and 95th percentiles. Predicted blood concentrations were highly variable for β-HCH, with only 66% of individual values falling within the 2.5-fold range of variation.

A human dermal PBPK model for γ-HCH was developed by modifying a flow-limited PBPK model to include a skin patch compartment for the exposure location (Sawyer et al. 2016). Optimized dermal absorption parameters were calculated for γ-HCH by adjusting diffusion equations for binding to protein and lipids and these parameters were included in the PBPK model to describe *in vivo* toxicokinetics. Model simulations were run using the time course data from Dick et al. (1997a) where volunteers were exposed to a 3 mg γ-HCH/mL formulation containing white-spirit for 6 hours and blood samples were analyzed for γ-HCH for up to 80 hours after exposure. A comparison of model simulations in which the optimized diffusion constants were varied illustrated the importance of considering protein binding of γ-HCH, when predicting the steady-state dermal permeability constant (K_p).

3.1.6 Animal-to-Human Extrapolations

Extrapolating animal toxicity data to predict human risk from HCH exposure appears to be reasonable since similar effects are seen in both species.

CYP metabolism of HCH isomers occurs in both humans and rodents. The presence of chlorophenols and chlorobenzenes in urine of workers occupationally exposed to γ-HCH (Angerer et al. 1983; Engst et al. 1979) was similar to observations of rats experimentally exposed to γ-HCH (Chadwick and Freal 1972a; Chadwick et al. 1978a; Engst et al. 1976; Kujawa et al. 1977). *In vitro* investigations indicate that human liver microsomes convert γ-HCH to chlorocyclohexenes, chlorophenols, and chlorobenzenes (Fitzloff et al. 1982). Both human and rat microsomes have been shown to form an identical epoxide *in vitro* following γ-HCH exposure (Fitzloff and Pan 1984). An important difference in interspecies metabolism of γ-HCH is the production of α-2μ-globulin in the male rat (Dietrich and Swenberg 1990, 1991), a protein not present in humans, which is well known for its role in renal toxicity.

Similar clinical toxic effects resulting from HCH exposure have been observed in laboratory animals dosed experimentally and humans experiencing occupational, therapeutic, and accidental domestic exposures to HCH. These include neurological, hepatic, hematological, and dermatological effects. Though reproductive, immunological, and carcinogenic effects have been reported in occupationally exposed humans and in animals, the human studies lack both quantitative exposure data and strong causal associations and also involve concurrent exposures to other chemicals. While rodents appear to be adequate models for a variety of human effects of HCH exposure, care must be taken in interpreting data from reproductive toxicity feeding studies in sheep (Beard and Rawlings 1999; Beard et al. 1999a) since significant differences exist in the gastrointestinal physiology of ruminants and humans.

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels of HCH are discussed in Section 5.7, Populations with Potentially High Exposures.

Several human studies suggest that the developing fetus may be susceptible to health effects of prenatal exposure to HCH isomers, with reports of decreased birth weight or increased risk of fetal growth restriction associated with higher maternal or fetal concentrations of HCH isomers (see Section 2.17). Individuals with genetic polymorphisms that alter the metabolism and excretion of HCH isomers, may be at increased risk of these effects. For example, polymorphism of glutathione S-transferase mu 1 (GSTM1) was shown to contribute to the risk of preterm birth or fetal growth restriction following exposure to β-HCH (Mustafa et al. 2013; Sharma et al. 2012). A significant interaction was also observed

between polymorphism of the CYP17 gene (A1A2) and γ-HCH in maternal blood and the risk of preterm birth (Sharma et al. 2013).

In human studies, serum cord blood levels of β-HCH were associated with increased serum levels of TSH (see Section 2.17 and Table 2-16); altered thyroid hormone status may affect neurodevelopment of infants. In addition, adverse neurodevelopmental outcomes have been associated with elevated concentrations of total HCH or specific HCH isomers in maternal breast milk or children's blood (Lenters et al. 2019; Sisto et al. 2015).

Serious neurological effects and occasional deaths have been reported in children following exposure to γ-HCH by accidental ingestion or by topical application (see Sections 2.2 and 2.15).

Studies of animals exposed to γ-HCH by oral administration demonstrate that the developing organism is exquisitely sensitive to the toxic effects of this isomer. Developmental effects of γ-HCH observed in studies of rats, mice, and mink include reduced viability and pup body weight; perturbation of male and female reproductive tract development; alterations in the developing liver, thymus, spleen, and heart; and developmental neurotoxicity (see Section 2.17). Little to no data are available for the other isomers of HCH.

Few studies have compared effects in young and aged animals exposed by the same regimen to HCH isomers. Weanling rabbits were more sensitive to γ-HCH treatment than young adults, as seen by higher mortality rates accompanied by excitement and convulsions after a single whole-body treatment with a 1% solution at a dose of 60 mg/kg γ-HCH (Hanig et al. 1976). As discussed in Section 2.17, there is evidence that γ-HCH causes functional impairment of the developing blood brain barrier in young rats (Gupta et al. 1999). The brain uptake of fluorescein was significantly increased in 10-day-old pups treated with a single 2 mg/kg dose, as well as in those treated with 2 mg/kg/day for 8 days. The effect appeared to be age-related because the brain uptake index was lower when rats were administered a single 2 mg/kg dose at 15 days of age, and there was no effect on brain permeability at a higher dose of 4 mg/kg/day when administered for 3 days to adults (Gupta et al. 1999).

Following intraperitoneal dosing of dams with γ-HCH on GDs 12–17, GABAA receptors in rat fetuses were studied with radiolabeled t-butylbicyclophosphorothionate (TBPS), a ligand that binds to the GABAA receptor (Brannen et al. 1998). Treatment with γ-HCH significantly reduced the TBPS binding affinity in fetal brainstems and it was concluded that the effect could potentially lead to abnormal brain

activity, increased susceptibility to seizures, and behavioral effects. TBPS binding in brains of fetuses was reduced when compared to adults (Brannen et al. 1998).

Effects of γ-HCH on the levels of reproductive hormones in blood of male animals appear to be more significant in younger animals compared with older animals. Male Wistar rats treated with γ-HCH beginning at 9 weeks of age exhibited significantly decreased serum testosterone and growth hormone and increased serum LH and FSH (Agrahari et al. 2019). Similar results were observed in another group exposed at 18 weeks of age, but treatment at 27 weeks of age resulted in smaller decreases in serum testosterone and growth hormone, and no significant effect on serum LH or FSH (Agrahari et al. 2019).

Differences in oxidative effects have been observed in the testes of young (15-day-old) versus mature (90-day-old) rats following intraperitoneal injection with 10 or 20 mg/kg technical-grade HCH (Samanta and Chainy 1997). Lipid peroxidation occurred to a greater extent in mature rats. However, the percent decrease in cytosolic superoxide dismutase activity was greater in young rats, which have increased baseline activity of the enzyme. Based on the findings of this study, it does not appear that young rats are at increased risk of oxidative testicular damage.

Although it is unknown whether the ability to metabolize HCH specifically differs between children and adults, some enzymes, which belong to the enzyme superfamilies involved in phase II HCH metabolism, are developmentally regulated in humans. The development of uridine 5'-diphospho-glucuronosyl-transferase (UDP-glucuronosyltransferase; responsible for glucuronide conjugation) depends on the enzyme isoform, but, in general, adult activity is attained by 6–18 months of age (Leeder and Kearns 1997). Development of sulfotransferase (responsible for sulfate conjugates) activity is also substrate-specific and is usually earlier than UDP-glucuronosyltransferase. In fact, levels of some sulfotransferases may be greater during infancy and early childhood than during adulthood (Leeder and Kearns 1997). A series of enzymes are involved in the production of mercapturic acid conjugates: γ-glutamyltrans-peptidase, glutathione S-transferase, cysteinyl glycinase, and N-acetyl transferase (Sipes and Gandolfi 1991). There are two superfamilies of N-acetyltransferase, and the N-acetyltransferase 2 superfamily has members that are developmentally regulated in humans. There is some N-acetyltransferase 2 activity in fetuses by 16 weeks of gestation. Infants up to 2 months of age have the slow metabolizer phenotype of this gene; the adult distribution of slow and fast metabolizer phenotypes is reached by 4–6 months of age and full adult activity is achieved at 1–3 years of age (Leeder and Kearns 1997).

Case-control studies have evaluated the interactive effect of exposure to HCH isomers and genetic polymorphisms on the increased risk of cancer or diabetes (Li et al. 2013, 2016; McCready et al. 2004; Sharma et al. 2013, 2019). The risk of breast cancer associated with higher serum levels of HCH isomers was increased by the presence of a polymorphism in the GSTM1 gene (GSTM1 null) (Li et al. 2013; McCready et al. 2004). Genetic polymorphisms of CYP1A1 did not influence the breast cancer risk associated with β-HCH exposure (McCready et al. 2004). A significant interaction was demonstrated between the GSTM1 null polymorphism and β-HCH blood levels on risk of urinary bladder cancer (Sharma et al. 2013). Mortazavi et al. (2019) did not show a similar correlation between GSTM1 or GSTT1 polymorphisms and bladder cancer risk associated with HCH isomers. Sharma et al. (2019) evaluated the influence of CYP1A1, GSTM1, and GSTT1 polymorphisms on the increased risk of epithelial ovarian cancer risk associated with HCH isomers. Significant interactions between β-HCH blood levels and CYP1A1m1 and GSTM1 and GSTT1 null genotypes were observed for increased risk of ovarian cancer (measured as increased cancer antigen-125 or CA-125 levels). The risk of type 2 diabetes associated with exposure to β-HCH was elevated in individuals carrying a single-nucleotide polymorphism in the gene encoding adiponectin (*ADIPOQ*) (Li et al. 2016). Serum adiponectin levels were reduced in individuals with this polymorphism.

People with lowered convulsion thresholds due to epilepsy (treated or untreated), cerebrovascular accidents, or head injuries may be at greater risk of the central nervous system effects of γ-HCH toxicity and may suffer increased risk of or severity of seizures (Kramer et al. 1980; Matsuoka 1981). Exposure to β-HCH may increase the risk of hypertension in individuals with an elevated BMI (Arrebola et al. 2015a).

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to HCH are discussed in Section 3.3.1. The National Report on Human Exposure to

Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for HCH from this report are discussed in Section 5.6, General Population Exposure.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by HCH are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

HCH isomers measured in human serum are generally normalized by total lipid content, based on total cholesterol and triglycerides (e.g., ng/g lipid) (Bradman et al. 2007; Curren et al. 2014; Everett and Matheson 2010; Kaur et al. 2020; Mørck et al. 2014). Porta et al. (2009) suggested that adjustment of serum concentrations by total cholesterol may be more appropriate than total lipid in studies of patients with severe disease (e.g., pancreatic cancer). Concentrations of HCH isomers have also been measured using whole blood (Sexton and Ryan 2012; Sexton et al. 2011).

Urinary concentrations of 2,4,5- and 2,4,6-trichlorophenol (in units of µg/g creatinine) were measured as indicators of γ-HCH exposure in the NHANES III survey (1998–2004) (Allen et al. 2006). Pentachlorophenol was also included as a γ-HCH metabolite in some studies (Naeher et al. 2009). The use of these phenolic urinary metabolites as exposure biomarkers is limited because these are not specific

to γ-HCH and may result from exposure to other chlorinated benzenes or phenols (Angerer et al. 1981; Naeher et al. 2009).

Measurement of HCH isomers in hair has also been used as an exposure biomarker and was suggested to be a better measure of chronic exposure than blood or serum concentrations (Michalakis et al. 2012; Tsatsakis et al. 2008). A linear relationship between exposure level and hair concentration was observed in a 90-day gavage study in rats exposed to a mixture of pesticide including γ- and β-HCH (Appenzeller et al. 2017).

HCH isomers have been detected in adipose tissue samples taken by biopsy or following surgical procedures (Aulakh et al. 2007; Ociepa-Zawal et al. 2010).

There are few quantitative data to correlate levels of any of the HCH isomers in human tissue or fluids with past exposure. A study in which children infested with scabies and their noninfested siblings were treated dermally with 1% γ-HCH lotion found no correlation between the dose applied and the subsequent level of γ-HCH in blood (Ginsburg et al. 1977). The blood level was also seen to diminish rapidly after application, with a half-life of 17.9 hours in infested children and 21.4 hours in noninfested children.

In contrast, β-HCH persists in the blood for a longer period of time than the other isomers. A study of workers in a γ-HCH -producing factory found that levels of β-HCH in blood serum were higher than those of other isomers, and there was a significant correlation between serum levels of β-HCH and length of employment (Baumann et al. 1980). Studies of populations with general HCH exposure have consistently found the level of the β-isomer to be higher than those of the other isomers (Kashyap 1986; Nigam et al. 1986; Ramachandran et al. 1984). This is probably due to the greater tendency of β-HCH to persist and accumulate in the body, while the other isomers are more rapidly metabolized or excreted. A survey of epidemiological studies involving workers occupationally exposed to "crude benzene hexachloride" as much as 10–15 years prior to sampling reported serum levels of 20–348 μg/L β-HCH (Morgan and Lin 1978). Unfortunately, none of the above studies specified exposure levels, so it is still questionable whether blood HCH levels can be used as biomarkers to quantify exposure.

There is also a direct correlation between HCH levels in the blood and human adipose tissue and semen (Baumann et al. 1980; Radomski et al. 1971a, 1971b; Szymczynski and Waliszewski 1981); concentrations of β-HCH in subcutaneous adipose tissues were found to be 300 times higher than blood levels (Baumann et al. 1980). Levels of β-HCH detected in skin lipids correlated with those found in

human adipose tissue (Sasaki et al. 1991). Although exposure levels were not known, the results of this study indicate that measuring β-HCH in skin lipids can be an easy means of determining relative levels or times of individual exposure. The method of collecting the skin lipid samples was noninvasive, involving washing the face with soap and wiping 3–4 hours later with fat-free cotton soaked in 70% ethanol. β- and γ-HCH have also been found in samples of human maternal adipose tissue, maternal blood, cord blood, and breast milk in women who were exposed to unknown levels of various organochlorine pesticides in Kenya (Kanja et al. 1992).

3.3.2 Biomarkers of Effect

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, kidney, 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.

3.4 INTERACTIONS WITH OTHER CHEMICALS

Toxicokinetics. The metabolism of γ-HCH can be altered by exposure to other chlorinated hydrocarbon insecticides such as DDT. Exposure to various chlorinated hydrocarbon insecticides, including γ-HCH, is thought to produce generalized nonspecific induction of microsomal enzymes, including cytochrome P450s. Induction of these enzymes could affect the toxicokinetics of a variety of xenobiotics that are metabolized through microsomal oxidation. Induction of mixed-function oxidase activity by other chlorinated hydrocarbon insecticides stimulates the oxidative degradation of γ-HCH to the tetrachlorophenols and enhances its elimination in the urine (Chadwick and Freal 1972b). Guinea pigs maintained on diets deficient in vitamin C and protein showed altered γ-HCH metabolism and excretion. Vitamin C deficiency decreased the amount of γ-HCH and its metabolites excreted in the urine and increased the amount stored in the kidney (Chadwick et al. 1972). Cadmium, which is known to inhibit hepatic drug-metabolizing enzymes in mammals, also inhibited the metabolism of γ-HCH in adult male Wistar rats exposed to the compound after short- and long-term pretreatment with cadmium (Chadwick et al. 1978b). Cadmium may inhibit γ-HCH metabolism indirectly by increasing levels of zinc and reducing levels of copper in the liver (Chadwick et al. 1978b). The addition of cadmium to the diet also increased the concentration of γ-HCH measured in the plasma and liver (Khanna et al. 1988).

Liver Effects. Pretreatment with γ-HCH reduced the clearance and exacerbated the liver toxicity (i.e., increased ALT and AST levels) of a single oral dose of 500 mg/kg acetaminophen in rats (Akhlaq et al. 2006). Acute exposure to ethanol was shown to increase the hepatotoxicity of γ-HCH in an intraperitoneal injection study as measured by increased ALT and AST activity (Radosavljević et al. 2008). The increase in liver weight produced by oral subchronic exposure to commercial HCH was exacerbated by concurrent exposure to phenobarbital or carbon tetrachloride (Khanna et al. 2002).

A low-protein diet potentiated the effects of γ-HCH on reducing the weights of various organs in male rats (Khanna et al. 1990). Serum and liver lipid content and cholesterol levels were increased in animals fed low-protein diets. The low-protein diet increased the levels of γ-HCH found in the various organ tissues. Histopathological changes in the liver, kidneys, and muscles following dietary exposure to a pesticide mixture containing monocrotophos, endosulfan, and HCH were exacerbated in protein-malnourished and diabetic rats (Benjamin et al. 2006).

Natural plant extracts (i.e., ajwain extract, *Hyrtios aff. Erectus* sponge extract) have been shown to reduce rodent liver toxicity of HCH isomers administered individually (Anilakumar et al. 2009) or as a mixture with other organochlorine compounds (Abd El-Moneam et al. 2017). The mechanisms by which these plant extracts mitigate HCH toxicity may include antioxidant activity and/or alterations in HCH absorption, distribution, metabolism, or elimination. Oral administration of aloe vera extract prevented the liver toxicity of γ-HCH in rats (measured by serum enzymes), when administered concurrently for 4 weeks (Etim et al. 2006). Intravenous administration of gadolinium chloride to hyperthyroid rats resulted in Kupffer cell depletion and a reduction in oxidative stress and liver injury following intraperitoneal injection of γ-HCH (Simon-Giavarotti et al. 2002). Administration of the antioxidant plant extract andrographolide (from *Andrographis paniculate)* was shown to exert a hepatoprotective effect in mice chronically exposed to technical-grade HCH (Trivedi et al. 2007, 2009). Liver toxicity measured by serum enzymes and histopathology and liver tumor formation occurring in mice exposed to HCH in the diet were not seen in mice given the combined exposure to andrographolide and HCH. Measures of oxidative stress in the mouse liver associated with HCH were also ameliorated by the combined treatment (Trivedi et al. 2007).

γ-HCH was shown to be an aryl hydrocarbon receptor (AhR) antagonist in rat and human hepatoma cells (DR-H4IIE and DR-Hep-G2, respectively) and mammary gland carcinoma DR-T47-D cells. When administered as a mixture with other organochlorine compounds, an additive response on AhR antagonism was observed (Doan et al. 2019).

Gupta et al. (2011) showed that γ-HCH promoted the formation of preneoplastic lesions (glutathione-S-transferase placental [GST-P] positive foci) in the rat liver following initiation by diethylnitrosamine. Simultaneous treatment with the dietary flavonoid quercetin appeared to reverse this promotion resulting in decreased apoptosis, reduced incidence of GST-P positive foci and lower expression of p53.

Immunological Effects. γ-HCH produced apoptosis and necrotic cell death in isolated mouse thymocytes *in vitro* and a greater-than-additive effect was observed when γ-HCH was administered in combination with malathion or permethrin (Olgun et al. 2004). Each of these pesticides produced oxidative stress in mouse thymocytes (increased superoxide anion and hydrogen peroxide) with a greater-than-additive effect on superoxide anion production observed when γ-HCH and malathion were administered together (Olgun and Misra 2006). Hydrogen peroxide production was not significantly higher if pesticides were given in combination. γ-HCH given in combination with malathion or permethrin increased superoxide dismutase activity and decreased the activity of glutathione-peroxidase and glutathione-reductase in mouse thymocytes, suggesting a role for oxidative stress in cytotoxicity (Olgun and Misra 2006).

Ocimum sanctum seed oil (OSSO) antagonized the immunotoxic effects of γ-HCH on humoral immunity (i.e., anti-SRBC response) and delayed-type hypersensitivity (i.e., footpad thickness) (Mediratta et al. 2008).

Neurological Effects. γ-HCH is a central nervous system stimulant, whereas the α-, β-, and δ-isomers of HCH are mainly depressants (McNamara and Krop 1948; Smith 1991). Isomeric interactions can occur, such that α-, β-, and δ-HCH counteract the effects of γ-HCH; neurotoxicity is reduced when a dose of δ-HCH is accompanied by an equal or higher dose of the other isomers. These interactions likely account for differences in the neurotoxicity of γ-HCH and technical-grade HCH, the majority of which is comprised of isomers other than γ-HCH (60–70% α-HCH, 5–12% β-HCH, 10–15% γ-HCH, 6–10% δ-HCH, and 3–4% ε-HCH [Baumann et al. 1980; Kutz et al. 1991]).

γ-HCH and dieldrin, given in combination, produced a greater-than-additive effect on reactive oxygen species generation, caspase activation, reduced mitochondrial membrane potential, and enhanced cytotoxicity in immortalized rat dopaminergic neuronal cells *in vitro* (Sharma et al. 2010). Pretreatment with an antioxidant plant extract (*Decalepis hamiltonii*) for 7 days was shown to prevent lipid peroxidation, glutathione depletion, and altered activity of antioxidant enzymes in major rat brain regions induced by a single dose of technical-grade HCH (Srivastava and Shivanandappa 2014). The natural

product Chaetoglobosin K (ChK) was shown to prevent or reverse the γ-HCH-induced inhibition of gap junction-mediated communication in rat RG-2 astroglial cells *in vitro* (Sidorova and Matesic 2008). Ethanol acted as an antagonist to γ-HCH in the central nervous system by decreasing the seizure incidence and intensity of convulsions and prolonging the duration of the latency period in rats (Mladenović et al. 2007). Anticonvulsant medications (e.g., diazepam, clonazepam, phenobarbital) were also effective in reducing seizures and lethality induced by γ-HCH in mice (Tochman et al. 2000).

Reproductive Effects. Vitamin A supplements decreased HCH-induced toxicity in the rat testes, while deficiencies in vitamin A potentiated the toxicity (Pius et al. 1990). Combined antioxidant treatment with vitamin C, vitamin E, and α-lipoic acid was shown to reduce γ-HCH -induced testicular toxicity in mice (i.e., testes weight and histopathology) (Nagda and Bhatt 2011). Daily injection of garlic extracts following oral exposure to γ-HCH reversed the observed male reproductive toxicity of γ-HCH alone in rats (decreased weights of testes, epididymis, seminal vesicles and prostate, sperm effects, and altered serum hormone levels). Injection of garlic extracts also reduced measures of oxidative stress in the rat testes and brain (Hfaiedh et al. 2011). Oral administration of the antioxidant, curcumin, either before, concurrently, or after oral γ-HCH dosing for 14 or 28 days, protected against male reproductive toxicity including decreased testes and epididymis weight and effects on sperm count, morphology, and motility (Sharma and Singh 2010). Curcumin also reduced the testicular levels of superoxide dismutase, catalase, and glutathione-transferase; however, testicular glutathione content was not affected.

Soy isoflavones in the diet have been shown to alter uterine morphology (i.e., increased hyperplasia) and expression of ERα in the rat (Yang et al. 2014; Zhang et al. 2016). These effects were reduced by simultaneous gavage administration of γ-HCH.

Developmental Effects. Cadmium interacts with γ-HCH to cause significant embryotoxic and teratogenic effects in the developing rat fetus when administered together at a dosage that, for either toxin alone, is insufficient to cause any deleterious effects on development (Saxena et al. 1986).

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

HCH consists of eight isomers (Safe 1993). Only γ-HCH, α-HCH, β-HCH, and δ-HCH are of commercial significance and considered in this profile. The pesticide lindane refers to products that contain >99% γ-HCH. The α-, β-, and δ-isomers, as well as technical-grade HCH are not synonymous with γ-HCH (Farm Chemicals Handbook 1993). 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). Information regarding the chemical identities of α-, β-, γ-, and δ-HCH is located in Table 4-1.

Table 4-1. Chemical Identity of Hexachlorocyclohexane Isomers[a]

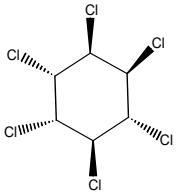
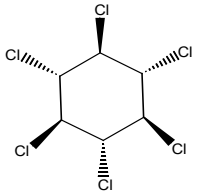
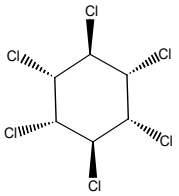
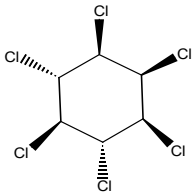
Characteristic	α-Hexachlorocyclohexane	β-Hexachlorocyclohexane
Synonym(s) and registered trade name(s)	1-alpha, 2-alpha, 3-beta, 4-alpha, 5-beta, 6-beta-benzene-trans-hexachloride; alpha-1,2,3,4,5,6-hexachlorocyclohexane; alpha-benzene hexachloride; alpha-BHC; alpha-HCH; alpha-hexachloran; alpha-hexachlorane; alpha-hexachlorocyclohexane; alpha-lindane; benzenehexachloride-alpha-isomer; cyclohexane 1,2,3,4,5,6-(alpha, DL); cyclohexane 1,2,3,4,5,6-hexachloro, alpha-; cyclohexane 1,2,3,4,5,6-hexachloro-, alpha-isomer; cyclohexane, alpha-1,2,3,4,5,6-hexachloro; ENT 9232	1-alpha, 2-beta, 3-alpha, 4-beta, 5-aplha, 6-beta-hexachlorocyclohexane; beta 1,2,3,4,5,6-hexachlorocyclohexane; beta-benzenehexachloride; beta-BHC; beta HCH; beta-hexachloran; beta-hexachlorobenzene; beta-lindane; cyclohexane, 1,2,3,4,5,6-hexachloro-, beta-; cyclohexane, 1,2,3,4,5,6-hexachloro-, beta-isomer; cyclohexane, 1,2,3,4,5,6-hexachloro-, trans-; cyclohexane, beta-1,2,3,4,5,6-hexachloro-; ENT 9233; trans-alpha-benzenehexachloride
Chemical formula	$C_6H_6Cl_6$	$C_6H_6Cl_6$
Chemical structure		
CAS Registry Number	319-84-6	319-85-7

Table 4-1. Chemical Identity of Hexachlorocyclohexane Isomers[a]

Characteristic	γ-Hexachlorocyclohexane	δ-Hexachlorocyclohexane
Synonym(s) and registered trade name(s)	Lindane; 1-alpha, 2-alpha, 3-beta, 4-alpha, 5-alpha, 6-beta-hexachlorocyclohexane; benzene hexachloride-gamma-isomer; BHC; cyclohexane 1,2,3,4,5,6-hexachloro-gamma-isomer; ENT 7796; gamma-benzene hexachloride; gamma-BHC; gamma-hexachlorocyclohexane; gamma-1,2,3,4,5,6-hexachlorocyclohexane; gamma-HCH; gamma-lindane; HCH; HCCH; hexachlorocyclohexane, gamma-isomer; 1,2,3,4,5,6-hexachlorocyclohexane, gamma-isomer, Etan 3G (Diachem S.P.A.); Forlin; Gamaphex; Isotox (Chevron Chemical Co.); Germate Plus (Gustafson Inc.); Gamma-Mean 400 and Gamma Mean L. (Oregon-California Chemicals, Inc.); Hammer (Exsin Industries); Lindagam; Novigam; Silvanol; Kwell	1-alpha,2-alpha,3-alpha, 4-beta, 5-alpha, 6-beta-hexachlorocyclohexane; cyclohexane, 1,2,3,4,5,6-hexachloro-, delta-isomer; cyclohexane, delta-1,2,3,4,5,6-hexachloro-; delta-(AEEEEE)- 1,2,3,4,5,6-hexachlorocyclohexane; delta-benzenehexachloride; delta-BHC; delta-HCH; delta-1,2,3,4,5,6-hexachlorocyclohexane; delta-lindane; ENT 9234
Chemical formula	$C_6H_6Cl_6$	$C_6H_6Cl_6$
Chemical structure		
CAS Registry Number	58-89-9	319-86-8

[a]All information obtained from NLM 2021.

CAS = Chemical Abstracts Service

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of α-, β-, γ-, and δ-HCH is located in Table 4-2.

Table 4-2. Physical and Chemical Properties of Hexachlorocyclohexane Isomers

Property	α-Hexachloro-cyclohexane (CAS 319-84-6)	β-Hexachloro-cyclohexane (CAS 319-85-7)	γ-Hexachlorocyclo-hexane (CAS 58-89-9)	δ-Hexachloro-cyclohexane (CAS 319-86-8)
Molecular weight	290.83[a]	290.83[a]	290.83[a]	290.83[a]
Color	Brownish to white[b]	No data	White[c]	No data
Physical state	Crystalline solid[b]; monclinic prisms[a]	Crystalline solid[a,d]	Crystalline solid[d]; monoclinic prisms[b]	Fine plates[a,c]
Melting point	159–160°C[a]	314–315°C[a]	112.5°C[a,e]	141–142°C[a]
Boiling point	288°C at 760 mmHg[b]	60°C at 0.5 mmHg[a]	323.4°C at 760 mmHg[b]	60°C at 0.36 mmHg[a]
Density (g/cm^3)	1.87 at 20°C[a]	1.89 at 19°C[a]	1.89 at 19°C[f]	No data
Odor	Phosgene-like odor[b]	No data	Slightly musty odor[b]	No data
Odor threshold:				
Water	0.88 ppm for unspecified purity[g]	0.00032 mg/kg[h]	12 mg/kg[h]	No data
Air	No data	No data	No data	No data
Solubility:				
Water	10 ppm[i]; 69.5 mg/L at 28°C[j]	5 ppm[k]	17 ppm[k]; 7.3 mg/L at 25°C[b]	10 ppm[j]
Organic solvents	Soluble in alcohol[j]; 1.8 g/100 g in ethanol[i]; 6.2 g/100 g in ether[j]	1.1 g/100 g in ethanol; 1.8 g/100 g in ether; 1.9 g/100 g in benzene[i]	6.4 g/100 g in ethanol; 20.8 g/100 g in ether; 28.9 g/100 g in benzene[i]	24.4 g/100 g in ethanol; 35.4 g/100 g in ether; 41.4 g/100 g in benzene[i]
Partition coefficients:				
Log K_{ow}	3.8[l]	3.78[l]	3.72[l]	4.14[l]
Log K_{oc}	3.57[f]	3.57[m]	3.0[m]; 3.57[f]	3.8[f]
Vapor pressure	4.5x10^{-5} mmHg at 25°C[b]	3.6x10^{-7} mmHg at 20°C[b]	4.2x10^{-5} mmHg at 20°C[b]; 9.4x10^{-6} mmHg at 20°C[b]	3.5x10^{-5} mmHg at 25°C[b]
Henry's law constant	6.86x10^{-6}[b]	4.5x10^{-7}[m,n]	3.5x10^{-6}[b]	2.1x10^{-7}[o,p]
Autoignition temperature	No data	No data	Not flammable[b]	No data
Flashpoint	No data	No data	Approximately 150°F (closed cup)[b]	No data

Table 4-2. Physical and Chemical Properties of Hexachlorocyclohexane Isomers

Property	α-Hexachloro-cyclohexane (CAS 319-84-6)	β-Hexachloro-cyclohexane (CAS 319-85-7)	γ-Hexachlorocyclo-hexane (CAS 58-89-9)	δ-Hexachloro-cyclohexane (CAS 319-86-8)
Flammability limits	No data	No data	Not flammable[b]	No data
Conversion factors[q]	ppm to mg/m^3 in air (20°C): ppm x 4.96 = mg/m^3; mg/m^3 to ppm in air (20°C): mg/m^3 x 0.20 = ppm			
Explosive limits	No data	No data	No data	No data

CAS = Chemical Abstracts Service

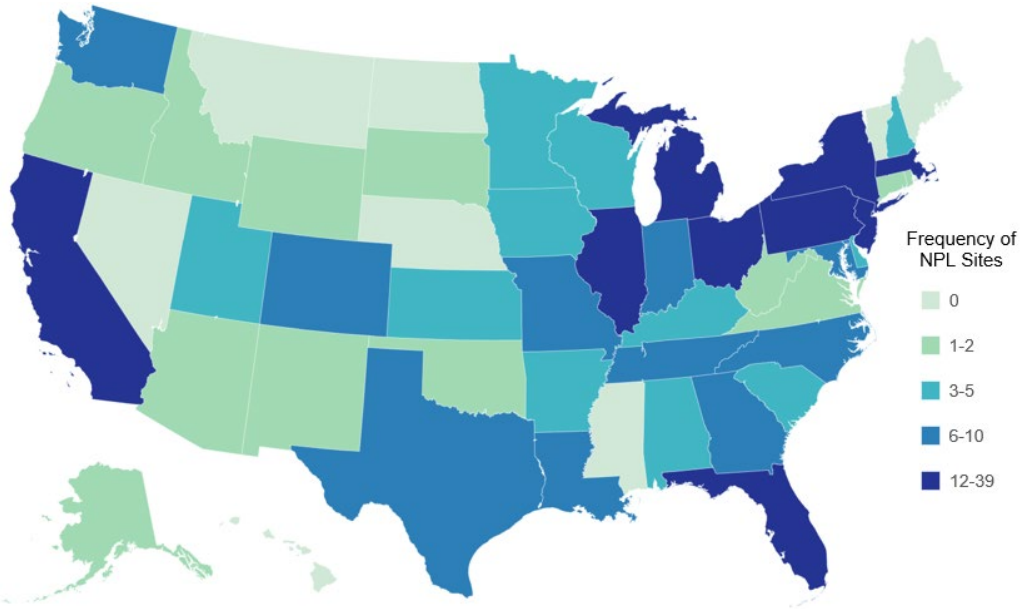
[a]Lide 1991.
[b]NLM 2021.
[c]Kirk and Othmer 1985.
[d]IARC 1979.
[e]Budavari et al. 1989.
[f]Weiss 1986.
[g]Fazzalari 1978.
[h]Verschueren 1983.
[i]Clayton and Clayton 1981.
[j]Kurihara et al. 1973.
[k]Hollifield 1979.
[l]Hansch and Leo 1995.
[m]Rippen et al. 1982.
[n]Veith et al. 1979.
[o]Pankow et al. 1984.
[p]EPA 1982a.
[q]Same for all isomers.

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

HCH isomers have been identified in at least 312 of the 1,867 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2019). However, the number of sites in which HCH isomers have been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 308 are located within the United States, 1 is located in the Virgin Islands, 1 is in Guam, and 2 are in Puerto Rico (not shown).

Figure 5-1. Number of NPL Sites with Hexachlorocyclohexane Contamination



Source: ATSDR 2019

- Registrations of γ-HCH agricultural products have been cancelled since 2006, significantly reducing most consumer exposure routes. The primary route of exposure is through medicinal use. One percent γ-HCH shampoos or lotions are registered with the FDA and are used for prescription treatment of lice and scabies.

- Individuals who live near contaminated sites may also experience higher exposures. Accidental ingestion or improper use of γ-HCH prescription treatments is likely the highest route of exposure.

- Historically, HCH has been released to the environment during its formulation process and through its use. HCH isomers are persistent and have been recently detected in air, water, and soil. The general public may be exposed to low levels of HCH through inhalation of contaminated ambient air, consumption of contaminated drinking water, or incidental ingestion of

or dermal contact with contaminated soils. HCH has not been found to be a major contaminant of drinking water supplies.

- Once released to the environment, HCH can partition to all environmental media. HCH can exist in the vapor and particulate phase in the atmosphere. HCH can volatilize from soils but is not expected to volatilize significantly from water. HCH has low to moderate mobility in soils and may leach to groundwater. HCH has low to moderate potential to bioaccumulate and has been detected in aquatic organisms in the United States.

- HCH has a long atmospheric lifetime but can be removed by photodegradation with hydroxyl radicals or wet and dry deposition. Biodegradation is believed to be the dominant decomposition process for HCH in soil and water, although hydrolysis and photolysis may occur to a lesser extent. The rates of degradation depend on the ambient environmental conditions.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

Table 5-1 lists the facilities in each state that process γ-HCH, the intended use, and the range of maximum amounts of γ-HCH that are stored on site (TRI21 2022). Most of the uses by these facilities are considered to be ancillary, indicating purposes other than chemical processing or manufacturing. Examples of ancillary uses as defined under TRI include cleaners, degreasers, lubricants, fuels, and waste treatment uses.

Table 5-1. Facilities that Produce, Process, or Use γ-Hexachlorocyclohexane

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AR	1	1,000	9,999	9, 12
NE	1	10,000	99,999	9, 12
OH	2	1,000	99,999	12
TX	2	1,000	99,999	9, 12
UT	1	10,000	99,999	9, 12

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/Uses:

1. Produce
2. Import
3. Used Processing
4. Sale/Distribution
5. Byproduct
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacture Aid
12. Ancillary
13. Manufacture Impurity
14. Process Impurity

Source: TRI21 2022 (Data are from 2021)

HCH does not occur as a natural substance. The manufacturing of technical-grade HCH involves the photochlorination of benzene, which yields an isomeric mixture consisting of α-HCH, β-HCH, γ-HCH, δ-HCH, ε-HCH, and inerts (IARC 1979); this reaction can be started by free-radical initiators such as visual or ultraviolet light, X-rays, or γ-rays (Kirk and Othmer 1985). Treatment with methanol or acetic acid, followed by fractional crystallization, concentrates γ-HCH to the 99.9% required in the technical-grade of γ-HCH (IARC 1979); nitric acid is used to remove odor (NLM 2021). None of the isomers or technical-grade HCH are currently produced in the United States. The production of γ-HCH exceeded $2.27x10^6$ g in 1976 (NLM 2021); commercial γ-HCH production in the United States reportedly ended in that year (EPA 1989a).

γ-HCH was available in emulsifiable and flowable concentrates, soluble concentrates/liquids, wettable powders, dusts, ready-to-use liquids, pressurized liquids and impregnated materials, oil base and aerosol sprays, and granules, as well as a smoke generator (Berg 1988; EPA 1985a). γ-HCH was sold separately or in combination with fungicides, fertilizers, other insecticides, or wood preservatives (Hayes 1982).

5.2.2 Import/Export

Current data on the importation of γ-HCH were not located. γ-HCH was not included in import/export information submitted by manufacturers under EPA's Chemical Data Reporting (CDR) database in the 2016 (covering 2012–2015) or 2012 (covering 2011) reporting cycles (EPA 2012, 2016). Reporting thresholds were 2,500 and 25,000 pounds for the 2016 and 2012 cycles, respectively.

γ-HCH historically was imported from France, Germany, Spain, Japan, and China (EPA 1985a). Currently, India is the only country where γ-HCH is reportedly produced; thus, India may be the current supplier to the United States (Vijgen et al. 2011). The U.S. imports of γ-HCH declined from $1.52x10^5$ kg in 1977 to $8.53x10^4$ kg in 1982 (NLM 2021). In 2002, it was estimated that 90 metric tons ($9.0x10^4$ kg) of γ-HCH were imported into the United States (Hauzenberger et al. 2002). Up until 2001, it was estimated that 500 metric tons of γ-HCH-containing pesticide products were exported annually by the United States (primarily to Canada) (Hauzenberger et al. 2002). That export volume dropped to 25 metric tons in 2001 and continued to decline significantly as other countries and the United States ceased the usage of γ-HCH containing pesticides.

5.2.3 Use

γ-HCH was initially registered by the U.S. Department of Agriculture (USDA) in the 1940s and over the years, was approved for use on a wide variety of fruit and vegetable crops (including seed treatment), tobacco, greenhouse vegetables and ornamentals, forestry (including Christmas tree plantations), farm animal premises, and other uses. In February 1977, EPA issued a notice of Rebuttal Presumption Against Registration (RPAR), now called a Special Review, and continued registration of pesticide products containing γ-HCH. EPA took this action in response to indications of γ-HCH's potential carcinogenic effect, possible developmental and reproductive effects, possible blood dyscrasias, and delayed toxic effects, as well as its acute toxic effects seen in aquatic wildlife (IARC 1979). In October of 1983, EPA issued a "Notice of Intent to Cancel Pesticide Products Containing γ-HCH." The contentions concerning developmental and reproductive effects were successfully challenged by industry. EPA no longer permits the use of γ-HCH for purposes involving direct aerial application (EPA 1985b). The notice restricted certain applications of γ-HCH on livestock, structures, and domestic pets to certified applicators or persons under their direct supervision (EPA 1985b). In November 1993, EPA issued a "Notice of Receipt of a Request for Amendments to Delete Uses" for several formulations of γ-HCH powder, 99.5% technical-grade HCH, and dust concentrate, which would delete from the pesticide label most uses of γ-HCH for agricultural crops and use on animals and humans (EPA 1993). According to the EPA's last Registration Eligibility Decision (RED), the last approved food/feed use of γ-HCH that was supported for re-registration was seed treatment on barley, corn, oats, rye, sorghum, and wheat (EPA 2002). Since the 1998 and 1999 use deletions, the registrants were no longer interested in supporting the seed treatment use on broccoli, Brussel sprouts, celery, cabbage, cauliflower, collards, kale, kohlrabi, mustard greens, lettuce, radishes, spinach, or Swiss Chard (EPA 2002). Based on EPA estimates from 1996 to 2001, about 233,000 pounds of γ-HCH were used annually as a seed treatment (EPA 2002). In August 2006, EPA issued "Notice of Receipt of Requests to Voluntarily Cancel Lindane Pesticide Registrations," which would end the use of γ-HCH as seed treatments, and notice of final orders of cancellation was issued in December of 2006 (EPA 2006a, 2006b).

γ-HCH is available and regulated by the FDA, for the pharmaceutical treatment of scabies and head lice (EPA 2002). A 1% γ-HCH lotion is available for the treatment of scabies, and a 1% shampoo is available for the treatment of head lice; both are prescription use only. Both uses have been on the market since 1947, but they were labeled as a second line therapy in 1995 after a review by the FDA. The FDA has issued revised labels for 1% γ-HCH lotion and 1% γ-HCH shampoo to be used with caution for infants, children, and the elderly or anyone who weighs <110 pounds (50 kg), and people with other skin

conditions (FDA 2015). The products are contraindicated in premature infants and people with disorders that cause seizures (FDA 2015). In the past, γ-HCH was used in veterinary products to control mites and other pests, but recent data suggest that no products are currently registered in the United States for this use (Hauzenberger et al. 2002).

5.2.4 Disposal

HCH is listed as a toxic substance under Section 313 of the Emergency Planning and Community Right to Know Act (EPCRA) under Title III of the Superfund Amendments and Reauthorization Act (SARA) (EPA 2020c). Disposal of wastes containing HCH is controlled by a number of federal regulations.

The recommended disposal technique for γ-HCH is incineration, at 400–500 °C in the presence of a catalytic mixture of 5–10% metal chloride (copper, iron, zinc, or aluminum) on activated carbon (EPA 1975). Residence times based on this method were not reported. Other effective waste disposal methods include treatment with strongly alkaline solution or oxidation. In a laboratory-scale study, 98.5% γ-HCH was removed after a 6.5-hour treatment at pH 11.5 (EPA 1975). γ-HCH can be effectively oxidized by ozone and somewhat effectively oxidized by potassium permanganate; oxidation with chlorine or hydrogen peroxide was ineffective (EPA 1975). EPA standard treatment for hazardous wastes containing α-, β-, δ-, and γ-HCH is through either incineration or removal from liquid wastes by adsorption, prior to land disposal (EPA 2014).

While current disposal techniques may be adequate, new methods provide increased efficiency and quality of disposal at a greatly reduced cost. The use of demulsification, sorption, and filtration in combination with chemical and biological degradation of pesticide wastewaters is being examined. This process is divided into two phases. First, demulsification agents (lignocellulosic materials, peat moss, wood products, etc.) are utilized in the removal of solubilized pesticides. In the second phase, the solid matter (pesticide-saturated sorbents and suspended particulates) is physically separated from the aqueous material through a variety of filtration techniques. The aqueous phase is either recycled or discarded, and the solid phase, in which the concentration of the pesticide is most significant, is further treated through composting (Mullins et al. 1992).

In order to facilitate the composting process, it is important to use sorption agents that provide a beneficial environment for the pesticide-degrading microorganisms. Peat moss, ground pine bark mulch, and steam-exploded wood fibers are excellent demulsifiers because they are highly sorbent, readily

available, and inexpensive. They also provide the nutrients required by the degrading microorganisms, although the peat moss media require some carbohydrate enrichment. The solid waste can be either directly metabolized or co-metabolized by multiple species of microbes. The number of compost cycles, and therefore the amount of energy input required, depends on the pesticide concentration and on how easily the pesticide can be biodegraded. In preliminary studies by Mullins and coworkers, this process has reduced the concentration of γ-HCH in waste materials significantly, with <1% of the original pesticide remaining after 24-hour incubation (Mullins et al. 1992).

Additional work is required, but the benefits of this disposal technique are clear. It is cost-effective, reliable, and can be adapted to the variety of disposal challenges presented by the multitude of pesticides that are currently used. The use of microbial consortia ensures that each pesticide will be degraded rapidly. This method can also be used on pesticide mixtures (Mullins et al. 1992).

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

5.3.1 Air

Estimated releases of 189 pounds (~0.086 metric tons) of γ-HCH to the atmosphere from 7 domestic manufacturing and processing facilities in 2021 accounted for about 69% of the estimated total

environmental releases from facilities required to report to the TRI (TRI21 2022). These releases are summarized in Table 5-2.

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use Hexachlorobenzenes[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
γ-HCH									
AR	1	0	0	0	35	0	0	35	35
NE	1	180	0	0	20	0	180	20	200
OH	2	0	0	0	1	0	0	1	1
TX	2	8	0	0	0	0	8	0	8
UT	1	0	0	0	0	28	0	28	28
Total	7	189	0	0	56	28	189	84	273

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, wastewater treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown.
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI21 2022 (Data are from 2021)

All isomers of HCH are considered hazardous air pollutants (HAPs) known to cause or suspected of causing cancer or other serious human health effects or harmful environmental effects (EPA 2020a), as regulated under the Clean Air Act. EPA's National Emission Inventory (NEI) database contains comprehensive and detailed estimates regarding sectors part of the emissions inventory system (EIS) which emit criteria air pollutants and HAPs for the 50 United States, Washington D.C., Puerto Rico, and the U.S. Virgin Islands. The NEI database includes point and non-point source emissions, onroad sources, non-road sources, and event sources such as emissions from wildfires or prescribed burning. According to data from the 2017 NEI, 62.40 pounds of γ-HCH were released from waste disposal,

industrial solvent use, industrial processes, and fuel combustion (EPA 2020b). These data are summarized in Table 5-3.

Table 5-3. HCH Emissions as Reported by the 2017 National Emission Inventory

Release sector	Emissions (pounds)
Waste disposal	54.607700078
Solvent; industrial surface coating and solvent use	5.91946
Industrial processes; ferrous metals	1.819
Industrial processes; NEC[a]	0.04
Fuel combustion; commercial/institutional oil	0.01

NEC = not elsewhere classified

Source: EPA 2020b

Historically, the largest source of γ-HCH releases to the air resulted from agricultural use of the pesticide γ-HCH, from aerial pesticide application or wind erosion of contaminated soils. γ-HCH may have also been released to the atmosphere via volatilization from treated agricultural soils and plant foliage (Lewis and Lee 1976). Evaporative loss of γ-HCH from water is not considered a significant potential source of atmospheric γ-HCH because of its relatively high water solubility (Mackay and Leinonen 1975). Quantitative historical estimates of the amount of γ-HCH released from these sources were not located in the literature. Aerial applications of γ-HCH were prohibited in the United States as its use as a pesticide was continuously restricted and eventually prohibited (EPA 1985b, 2006a, 2006b), and atmospheric releases from agricultural sources today are not expected.

5.3.2 Water

No releases of γ-HCH to water from 7 domestic manufacturing and processing facilities required to report to the TRI were reported in 2021 (TRI21 2022). This estimate includes releases to wastewater treatment and publicly owned treatment works (POTWs) (TRI21 2022). These releases are summarized in Table 5-2.

γ-HCH can be released to surface water via “down-the-drain” releases from consumer wash-off of treatments for lice and scabies (EPA 2002). These releases would be treated by wastewater treatment and POTWs, which did not report releases of γ-HCH to the TRI in 2019. Average γ-HCH concentrations in wastewater treated in Los Angeles County, California, have been reported to range from $3.6x10^{-5}$ to

0.03 µg/L (EPA 2002; Humphreys et al. 2008). α-HCH was not detected in 165 wastewater and wastewater treatment effluent samples collected between 2001 and 2010 (WQP 2021). One wastewater sample collected in 2003 contained a concentration of 0.014 µg/L α-HCH (WQP 2021). β-HCH was not detected in 24 wastewater samples collected between 2003 and 2009 (WQP 2021). Wastewater may be a negligible source of HCH to surface water and groundwater.

After soil or aerial application for agricultural use, γ-HCH could be released to surface water via surface runoff (as the dissolved chemical or adsorbed to particulates) or via wet deposition of rain and snow (Tanabe et al. 1982; Wheatley and Hardman 1965). Lake Ontario received 7 kg/year of α-HCH and <2 kg/year of γ-HCH due to suspended sediment loading from the Niagara River between 1979 and 1981 (Kuntz and Warry 1983). Historically, the Great Lakes in general received 0.77–3.3 metric tons/year of α-HCH and 3.7–15.9 metric tons/year of γ-HCH from atmospheric deposition of these contaminants (Eisenreich et al. 1981). Because γ-HCH is no longer allowed to be used for agricultural purposes, these are not expected to be significant sources of releases today.

Further from agricultural areas, urban stormwater runoff has historically resulted in releases of HCH to water in the range of parts per billion to parts per trillion. In 1982, α- and γ-HCH were detected in samples of urban stormwater runoff from Denver, Colorado, and Washington, D.C., at 0.0027–0.1 and 0.052–0.1 µg/L in 20 and 11%, respectively, of the 86 samples collected; β-HCH was detected only in runoff from Washington, D.C., in 5% of the samples at a concentration of 0.1 µg/L (Cole et al. 1984). In urban runoff samples collected in the Canadian Great Lakes Basin, γ-HCH was detected at mean concentrations of 0.0065 µg/L and 0.0035 mg/kg in the aqueous and sediment portions, respectively; the mean annual loading of the compound in runoff in the basin was reported to be 4.1 kg/year (Marsalek and Schroeter 1988). Stormwater samples collected in 2007, just after the ban on γ-HCH for agricultural use, showed concentrations between 6.0×10^{-5} and 0.14 µg/L α-HCH and 3.8×10^{-4} and 0.0976 µg/L β-HCH (WQP 2021).

γ-HCH could be released to groundwater via soil leachate after agricultural application or from improper disposal at contaminated sites. Available adsorption data indicate that γ-HCH has a low to moderate mobility in soils, and the results of monitoring studies suggest that γ-HCH does migrate to groundwater (Page 1981; Sandhu et al. 1978). Groundwater samples were collected from a packaging and reformulating pesticide facility in Florida, which had disposed of γ-HCH wastes in unlined trenches until 1996. Ground water concentrations for the site ranged from 30 to 420 µg/L for α-, γ-, and δ-HCH (Chartrand et al. 2015).

5.3.3 Soil

Estimated releases of 56 pounds (~0.025 metric tons) of γ-HCH to soil from 7 domestic manufacturing and processing facilities in 2021 accounted for about 20% of the estimated total environmental releases from facilities required to report to the TRI (TRI21 2022). No additional quantities were released via underground injection (TRI21 2022). These releases are summarized in Table 5-2.

γ-HCH has historically been released to the soil by direct application of the pesticide to soil, and can be released by direct or indirect releases during formulation, storage, and/or disposal. Hazardous waste sites where γ-HCH has been disposed of in the past are sources of γ-HCH in soils. However, the application of γ-HCH to laboratory refuse columns simulating municipal landfills indicated that γ-HCH did not volatilize or leach from the refuse surface, and movement through the column was slight, suggesting that codisposal of γ-HCH with municipal refuse will result in minimal releases (Reinhart and Pohland 1991; Reinhart et al. 1991).

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

Air. HCH isomers are volatile, relatively persistent substances in the atmosphere and are expected to be capable of long-range transportation. HCH can exist in the vapor and particulate phases based on the reported vapor pressures of the isomers (NLM 2021). Volatilization of γ-HCH used as a seed treatment was confirmed, with 12–30% of the applied pesticide volatilizing within 6 weeks of planting the seed (Waite et al. 2001, 2007). Correspondingly, atmospheric concentrations of γ-HCH were variable and increased when pesticide usage occurred; α-HCH concentrations were less variable throughout the year (Hoff et al. 1992a). During the winter, higher ratios of α-HCH to γ-HCH reflected the movement of air containing the more persistent α-HCH isomer from the colder Arctic regions to the south, while the lower ratios in the summer reflected both increased γ-HCH usage in the region and the lack of movement of Arctic air (Hoff et al. 1992a). γ-HCH was also seen to move with warm air during the summer months from the lower United States (or areas even further to the south) to the Great Lakes region, although a similar trajectory could not be identified for the more ubiquitous α-HCH. Levels of α-HCH in air are not dominated by volatilization or partitioning to surfaces, but are dependent on local temperature changes (Hoff et al. 1992b). α-HCH appears to have a long residence time in the atmosphere and is controlled

primarily by transport. Long-range transport potentials were estimated for α- and γ-HCH based on North American monitoring data, and were reported to be 11,151 miles (17,946 km) and 6,047 miles (9,732 km), respectively (Shen et al. 2004). The potential for widespread global distribution has been reported in several studies (Hargrave et al. 1988; Knap and Binkley 1991; Tanabe et al. 1982; Wittlinger and Ballschmiter 1990).

HCH isomers in the atmosphere are likely to be subject to rain-out and dry deposition, which may result in the contamination of surface soil and water. γ-HCH removal rates were 2.5%/week by rainfall and 3.3%/week by dry deposition, and the estimated residence time of γ-HCH in the atmosphere was 17 weeks (Atkins and Eggleton 1971). The dry deposition flux rate of α-HCH ranged from 0.1 to 5.1 ng/m^2/day in deposition samples collected in June–August 1997 near the southern Baltic Sea (Wiberg et al. 2001). The flux rate of γ-HCH was 0.9–32.6 ng/m^2/day over the same time frame. Seasonal variation resulted in lower dry deposition rates during the winter months. In samples collected between February and March 1998, the flux rate for α-HCH ranged from 0.25 to 0.54 ng/m^2/day, and the dry deposition flux rate for γ-HCH was 3.4–14.1 ng/m^2/day (Wiberg et al. 2001). The dry deposition flux rate of γ-HCH in south central Saskatchewan in 1998 where it had been used as a seed treatment in a canola field ranged from <29 to 2,203 ng/m^2/day, and the amount in rainfall over the same period ranged from <10 to 200 ng/L (Waite et al. 2001). Uptake by plants may be another removal pathway, as observed for α- and γ-HCH under experimental conditions with lettuce, romaine, and garlic leaf (Yang et al. 2007). Removal was controlled by plant-air equilibration and correlated strongly with the reported log octanol-air partition coefficients (K_{OA}), 7.44 and 7.72 α- and γ-HCH, respectively (Yang et al. 2007).

Water. In surface waters, HCH has a slight tendency to dissolve and remain in the water column based on the water solubilities and octanol-water partition coefficients (K_{ow}) of the isomers (Clayton and Clayton 1981; Hansch and Leo 1995; Hollifield 1979; Kurihara et al. 1973). Although γ-HCH has a relatively high vapor pressure and Henry's law constant compared with many other organochlorine insecticides, evaporative loss of γ-HCH from water is not considered to be significant. Mackay and Leinonen (1975) calculated theoretical losses of several pesticides from saturated water solutions and predicted a volatilization half-life of 191 days for γ-HCH.

γ-HCH released to water may undergo adsorption/desorption with sediments and other materials in the water. Adsorption and desorption studies of γ-HCH in natural water-sediment systems performed by Saleh et al. (1982) indicate that a diversity of the natural water-sediment characteristics may affect the sorption-desorption behavior of γ-HCH in addition to the organic carbon content of the sediments.

γ-HCH is sorbed to silt solutions with a slow desorption rate, indicating that transport through the environment is most likely to be particle mediated (Noegrohati and Hammers 1992). Biosorption of γ-HCH was seen for the fungus *Rhizopus arrhizus* and activated sludge, with equilibrium being reached within 1 and 4 hours, respectively. Death of the sludge biomass resulted in rapid desorption with zero-order kinetics, suggesting that adsorbed γ-HCH can be released back into the environment (Tsezos and Wang 1991a). The sorption of γ-HCH from water using wood charcoal has been described (Keerthinarayana and Bandyopadhyay 1998); it was found to be a good sorbent for γ-HCH from water.

Sediment and Soil. HCH present in soil can leach to groundwater, sorb to soil particulates, or volatilize to the atmosphere. In general, the leaching of organic chemicals through soil is governed by the water solubility of the chemicals and their propensity to bind to soil. Based on the results of a number of laboratory soil column leaching studies that used soils of both high and low organic carbon content as well as municipal refuse, γ-HCH generally has low to moderate mobility in soils, with K_{oc} values ranging from 641 to 3,362; log K_{oc} range of 2.810–3.5266 (EPA 1982b; Melancon et al. 1986; Reinhart et al. 1991). Adsorption of γ-HCH to soil particulates is generally a more important partitioning process than leaching to groundwater. However, groundwater sediments, which have low organic carbon content (<0.1%), are not sufficient to adsorb γ-HCH to the extent that groundwater contamination is prevented (Nordmeyer et al. 1992). The presence of black carbon in soils from incomplete combustion may impact sorption affinity. HCH isomers showed varying preference for partitioning to black carbon (α-HCH > β-HCH > δ-HCH) in soils with 0.82–2.26% organic carbon and 0.04–0.5% black carbon (Ali et al. 2016). Sorption was observed to be a limiting factor in bioavailability of γ-HCH in soil to earthworms (Smídová et al. 2012).

Using sediment (0.44% organic carbon) obtained from a sugar-cane growing region of Australia, the K_{oc} of γ-HCH was measured as 2,164 (Just et al. 1990). The K_{oc} of γ-HCH in a mineral soil containing 1.26% organic carbon content was measured as 832 (Chiou et al. 1998). In a sandy soil (0.105% organic carbon) γ-HCH had a measured K_{oc} of 3,362, and a desorption K_d of 3.53 (Melancon et al. 1986). The partition coefficient (K_p) of γ-HCH in a laboratory column experiment with municipal solid waste was 853 (Reinhart et al. 1991). In a study involving a laboratory sediment/water system (pH 7.42; 2.18% organic carbon), α- and γ-HCH isomers were adsorbed on sediments under both aerobic and anaerobic conditions and few differences were noted in the adsorption behavior of each isomer. Under aerobic and anaerobic conditions, the K_{oc} values of α-HCH were 681 and 617, respectively, while the K_{oc} values for γ-HCH were 641 and 694, respectively (Wu et al. 1997). A mixture of HCH isomers (α-, β-, γ-, and δ-HCH) sorbed very strongly to a soil from Nagpur, India (pH 7.6, 0.387% organic carbon), with a K_{oc}

value of 54,000. Some desorption was observed, believed to be due to the water solubility of HCH (Wadaskar et al. 2006). Desorption experiments with a sandy loam soil slurry showed isomeric differences in desorption capacity, α- ≥ γ- > δ- > β-HCH (Quintero et al. 2005).

γ-HCH sorbed to the soil can partition to the atmosphere by wind erosion of surface soil particulates (Stanley et al. 1971) and via volatilization from treated agricultural soils and plant foliage (Lewis and Lee 1976). In tests conducted in a model laboratory system at 10 and 20°C, volatilization half-lives of γ-HCH from soil and oat plant surfaces of 2.3–24.8 and 0.29–0.73 days, respectively, were reported (Dorfler et al. 1991a); half-lives were greater on dry, sandy soils versus peat soils; however, when moisture was added to the soils, the half-life was greater for the peat soil, while warmer temperatures decreased the half-life under all soil and moisture conditions (Dorfler et al. 1991b). In tests performed with a wind tunnel, a volatilization rate of >20% for γ-HCH from soil surfaces within a 24-hour period was determined (Rüdel 1997). A 6-fold increase in γ-HCH volatilization from soil was seen in laboratory experiments when the temperature increased from 15 to 45°C; flooding the soil also increased the volatilization (Samuel and Pillai 1990). A field study conducted in south central Saskatchewan, Canada in 1997–1998 in which γ-HCH was applied as a seed treatment to canola, determined that between 12 and 30% of the initial amount applied volatilized to the atmosphere (Waite et al. 2001); a follow-up study determined volatilization rates of 190 mg/hectare/week at 1 week after application and 420 mg/hectare/week 2 weeks after application (Waite et al. 2007). The volatilization rate from plant surfaces was 55% for γ-HCH. Application of γ-HCH to fields of sunflowers and sugarbeets resulted in a 54% evaporative loss of the pesticide within 24 hours (Neururer and Womastek 1991).

Other Media. γ-HCH has a low to moderate potential to bioaccumulate. A summary of some of the bioconcentration factors (BCFs) from experimental studies with γ-HCH are provided in Table 5-4. γ-HCH shows limited uptake from soils and bioconcentration by plants and terrestrial organisms and does not appear to biomagnify to a great extent.

Table 5-4. Results of Experimental Bioaccumulation Studies with γ-Hexachlorocyclohexane

Species	Exposure route	Bioconcentration factor	Reference
Brine shrimp	Water	183	Matsumura and Benezet 1973
Rainbow trout (fry)	Water	319	Ramamoorthy 1985
Pink shrimp	Water	84	Schimmel et al. 1977
Pinfish	Water	218	
Grass shrimp	Water	63	
Sheepshead minnow	Water	490	
Brine shrimp	Sand	95	Matsumura and Benezet 1973
Northern brook silverside fish	Sand	1,613	

A BCF of 1,273 (lipid basis) in prawns (crustacean) was seen to be 0.58 times the γ-HCH concentration in the underlying sediment, indicating that aquatic organisms may accumulate γ-HCH from the water column, and uptake from contaminated sediment alone may not be extensive (Just et al. 1990). BCFs for the isomers of HCH, using zebra fish under steady-state conditions, were 1,100 for α-HCH, 1,460 for β-HCH, 850 for γ-HCH, and 1,770 for δ-HCH; BCFs determined by uptake and clearance rate constants were slightly lower (Butte et al. 1991). Elimination of γ-HCH occurred rapidly in zebra mussels (BCF of 10) and metabolism of γ-HCH was not observed (Berny et al. 2002). BCFs on a wet weight basis for γ-HCH in different fish species were positively correlated with their lipid content (Geyer et al. 1997). The bioaccumulation of γ-HCH by tubificide oligochaetes from a static system consisting of sediment and water has been reported (Egeler et al. 1997). Microalgae *Scenedesmus quadricauda* and *Coccomyxa subellipsoidea* were exposed for 24 hours to mine dump effluent containing α-, β-, γ-, and δ-HCH, resulting in bioaccumulation factors (BAFs) of 74.6, 60.5, 29.4, and 107.2 for α-, β-, γ-, and δ-HCH, respectively, in *S. quadricauda,* and BAFs of 50.8, 47.6, 21.5, and 56.3 for α-, β-, γ-, and δ-HCH, respectively, in *C. subellipsoidea* (Kováčik et al. 2018).

γ-HCH applied to an aquatic mesocosm (i.e., a small, artificial ecosystem) at 61.3 µg/L was reduced by 50% at 24 hours post-application, while at 19 weeks post-application, the concentration in the water was only 0.2%; no γ-HCH was detected at 21 weeks. The biological half-life was estimated to be 16.7 days. Movement through the water column was shown by increasing sediment concentrations up to a maximum of 75.4 µg/kg at 96 hours post-application; however, sediment concentrations decreased to below the detection limit at 23 weeks to give a half-life in sediment of 48.1 days. Rooted aquatic macrophytes have a BCF of 56 at a maximum concentration of 1.7 mg/kg at 24 hours post-application; however, at 14 weeks, all residues were below the detection limit for a half-disappearance time of 18 days.

Gastropods in the system had a maximum γ-HCH concentration of 7.2 mg/kg at 24 hours post-treatment, yielding a BCF of 232.4 and a half-disappearance time of 13.7 days with all residues eliminated by 13 weeks (Caquet et al. 1992).

Trophic transfer of γ-HCH may occur in the foodweb. A study assessed the potential of transfer between zebra mussels and their predators, tufted ducks (*Aythia fugigula*) at the birds' wintering grounds in Lake Geneva, bordering Switzerland and France. γ-HCH concentrations in the mussels ranged from approximately 5 to 500 ng/g wet weight, while γ-HCH in the liver of the tufted ducks ranged from 8.9 to 175.6 ng/g wet weight (Bemy et al. 2003).

In tests with radiolabeled γ-HCH, grain, maize, and rice plants accumulated 0.95, 0.11, and 0.04%, respectively, of the amount of bound residues following 14–20 days growth in a sandy loam soil. Bioconcentration increased by 4–10 times when the plants were grown in test soils containing both bound and extractable residues of γ-HCH (Verma and Pillai 1991). Plants and grains grown on soil treated with γ-HCH showed α-HCH as the predominant isomer, although all isomers were found to some extent; amounts decreased with increasing time after application (Singh et al. 1991). A different trend in isomer uptake was observed in garlic. Garlic (*Allium sativum* L.) was planted in pots containing soil treated with α-, β-, γ-, and δ-HCH isomers. The BCFs of the underground parts were in the range of 0.48–0.90, 1.60–1.84, 1.40–2.34, and 2.60–3.64 for α-, β-, γ-, and δ-HCH, respectively, and above-ground parts were 1.50–2.26, 4.50–6.79, 5.16–6.81, and 9.30–12.18, respectively (Chen et al. 2013). The phytoavailability of the isomers was observed to be δ- > γ- ≥ β- > α-HCH, which generally agreed with the isomer's water solubility and vapor pressure (Chen et al. 2013). Evidence of plant uptake from air has been reported. Lettuce, romaine, and garlic leaf were maintained in air chambers that exposed them to air polluted with α- and γ-HCH for 5 days. Measured accumulation factors of α-HCH in the crops were 77.25, 190.8, and 95.23 for lettuce, romaine, and garlic leaf, respectively, and accumulation factors of γ-HCH were 187.6, 321.9, and 124.5, respectively (Yang et al. 2007).

Uptake of γ-HCH by earthworms from a treated soil has also been reported. *Eisenia andrei* exposed to grassland soil spiked with γ-HCH for 24 hours had measured BAFs ranging from 5 to 35 (Šmídová et al. 2015). Following exposure to 5 ppm of the compound for up to 8 weeks, earthworms bioconcentrated γ-HCH by a factor of 2.5. The earthworms biotransformed more than 50% of the accumulated γ-HCH; the main degradation product was γ-2,3,4,5,6-pentachlorocyclohex-1-ene (Viswanathan et al. 1988).

γ-HCH and the other isomers of HCH do not appear to undergo biomagnification in terrestrial food chains to a great extent, although there is a moderate potential for transfer of γ-HCH to animal tissue as a result of soil ingestion or ingestion of contaminated foliage (Wild and Jones 1992). Clark et al. (1974) found that γ-HCH levels in the adipose tissue of cattle were 10 times higher than in the feed (0.002 mg/kg). Szokolay et al. (1977) examined relative accumulation of HCH isomers including γ-HCH and various components in the food chain in Czechoslovakia. Lower γ-HCH residues were found in tissues of animals (chickens, sheep, pigeons) feeding entirely on plant material, whereas carnivores had higher concentrations.

γ-HCH that is adsorbed to sediments may be recycled to the atmosphere as gas bubbles are formed in the sediment by the methanogenesis and denitrification processes of bacteria. In one case studied, it was estimated that 85% of the γ-HCH associated with the sediment gas bubbles would be released to the atmosphere, with the remaining 15% being dissolved in the water column as the bubble rises toward the surface (Fendinger et al. 1992).

5.4.2 Transformation and Degradation

Air. HCH is degraded in the atmosphere by reacting with photochemically produced hydroxyl radicals. The rate of this reaction is not very rapid however, and all of the HCH isomers have rather long atmospheric lifetimes. The rate constants for the reaction of α- and γ-HCH with hydroxyl radicals were measured as 1.4×10^{-13} and 1.9×10^{-13} cm^3/molecule-second, respectively (Brubaker and Hites 1998). Using an average hydroxyl radical concentration of 5×10^5 molecule/cm^3, the corresponding half-lives are about 115 and 84 days for α- and γ-HCH, respectively. In locations where the atmospheric hydroxyl radical concentration is very low, the persistence times of these compounds are much longer. Cortes and Hites (2000) estimated that the average half-life of α- and γ-HCH around the Great Lakes region ranged from about 3 to 4 years. Since HCH does not absorb light >290 nm, direct photolysis in the atmosphere is not expected to be an important environmental fate process. However, Chen et al. (1984) reported photodegradation half-lives of 91, 152, 104, and 154 hours for thin films of α-HCH, β-HCH, γ-HCH, and δ-HCH, respectively, when irradiated with light of wavelength 295–305 nm. No absorption bands were observed in this spectral region, however, for any of the HCH isomers, and the mechanism of photodegradation and its environmental significance are uncertain. A direct photolysis study of α-HCH showed maximum absorption in the middle ultraviolet (UV) range at 252 nm, with a half-life around 2 hours (pseudo-first-order rate constant of 0.34/hour) (Zhang et al. 2014). The environmental relevance of this is unclear, since the middle UV range wavelengths are filtered out by the stratosphere. Similar

indirect photolysis studies were conducted at ≥280 nm with α-HCH in the presence of H_2O_2 at a molar ratio of 100:1 (H_2O_2:α-HCH). The indirect photolysis half-life was around 4.3 hours (pseudo-first-order rate constant 0.16/hour). A proposed final photolysis product is 2,4,6-trichlorophenol (Zhang et al. 2014).

Water. Biodegradation is believed to be the dominant degradative process for γ-HCH in aquatic systems, although hydrolysis and indirect photolysis may also occur. Sharom et al. (1980) found that <30% of the applied γ-HCH remained in unsterilized natural waters in capped bottles after 16 weeks. Biodegradation was concluded to be responsible for these results, although it was unclear to what extent hydrolysis or adsorption to the glass bottles may have contributed. Zoeteman et al. (1980) estimated river, lake, and groundwater half-lives for γ-HCH from degradation data in these environments to be 3–30, 30–300, and >300 days, respectively. In natural lake water with a pH of 9.0 and a hardness of >600 mg calcium carbonate/L, the half-life of γ-HCH was estimated to be 65 hours (Ferrando et al. 1992). γ-HCH, applied at concentrations of 50 or 500 μg/L to aerobic batch cultures of microorganisms with sodium acetate as a carbon source, was initially removed by adsorption and followed by desorption onto the biomass with subsequent decomposition (McTernan and Pereira 1991). Approximately 56–62% of the γ-HCH was removed from the water column in 23 days, with 26% removal by adsorption onto the biological solids produced in these batch reactors. Microbial growth, using γ-HCH in the absence of sodium acetate, increased as the microorganisms became acclimated; the pesticide still showed toxic properties, as evidenced by a concurrent increase in microbial death rates. Evidence of biodegradation of HCH isomers in groundwater has also been reported. In an *in situ* study of a former pesticide formulating plant, the biodegradation half-lives of α-, β-, and δ-HCH isomers were determined in groundwater below the site by compound-specific stable carbon isotope analysis respectively. Half-lives were determined based on isotopic depletion from samples collected over 3 years at various wells spreading out from the contaminant source. Half-lives were 223, 62–287, and 120–632 days for α-, β-, and δ-HCH isomers, respectively (Bashir et al. 2015).

It has been shown that γ-HCH is degraded by nitrogen-fixing blue-green algae. These algae reduce the toxic effects of γ-HCH following repeated inoculations (Kar and Singh 1979b). The degradation of γ-HCH became more efficient with time, thus reducing the pesticide's toxicity in cultures of nitrogen-fixing blue-green algae. Dechlorination of γ-HCH to γ-pentachlorocyclohexene was also shown to occur with fungi in aqueous suspensions (Macholz and Kujawa 1985) and in algal cultures (Sweeney 1969).

Hydrolysis is not considered an important degradation process for HCH in aquatic environments under neutral pH conditions. However, under alkaline conditions, γ-HCH is hydrolyzed fairly rapidly. Saleh et

al. (1982) tested rates of hydrolysis of γ-HCH in sterilized natural waters at 25°C and found that hydrolysis of γ-HCH followed first-order kinetics with half-lives of 92 hours at pH 9.3, 648 hours at pH 7.8, and 771 hours at pH 7.3. EPA (1989b) reported a hydrolysis half-life of 207 days at pH 7 and 25°C using distilled water. Alkaline hydrolysis (pH 9.78) of α-HCH was observed with a calculated half-life of 1,083 hours (based on pseudo-first-order rate constant of 0.0064/hour), giving 1,3,4,5,6-pentachlorocyclohexane, 1,2,4-trichlorobenzene, and 1,2,3-trichlorobenzene as the major products (Zhang et al. 2014).

Somewhat conflicting information is available on the rate of photolysis of γ-HCH in water. Since HCH does not contain chromophores that absorb light >290 nm, direct photolysis is not expected to occur. However indirect photolysis, whereby a photosensitizing agent may absorb light and then transfer its excitation energy to HCH, may occur. Humic and fulvic acids are well-known photosensitizing agents and are practically ubiquitous in natural waters. In the study by Saleh et al. (1982), the authors reported γ-HCH first-order photolysis half-lives of 169, 1,791, and 1,540 hours in pond water, lake water, and water from a quarry at pH 9.3, 7.3, and 7.8, respectively, when solutions were exposed to direct sunlight. However, the rapid rate of degradation at pH 9.3 may have been enhanced by hydrolysis reactions rather than by photolysis. In another study, α- and γ-HCH were shown to undergo enhanced photolysis when aqueous solutions were spiked with 5 and 25 ppm of soil fulvic acid, and irradiated with natural sunlight (Malaiyandi et al. 1982). Hamada et al. (1981) found that γ-HCH underwent photodegradation to form two isomers of tetrachlorohexene and pentachlorohexene in propanol solution when irradiated with UV light produced by a low-pressure mercury lamp. Oxidants commonly found in natural waters, such as peroxy radicals, hydroxyl radicals, and singlet oxygen species, can degrade HCH in water. Mill (1999) estimated that the indirect photolysis half-life of HCH in natural waters is about 270 days, and the dominant oxidant for HCH was the hydroxyl radical. Photolysis of γ-HCH in aqueous solution in the presence of polyoxomethallate, a strong oxidizing agent, has also been demonstrated (Hiskia et al. 1997).

Sediment and Soil. γ-HCH in soil or sediment is degraded primarily by biodegradation, although hydrolysis may occur in moist soils under alkaline conditions. Tu (1976) reported that 71 of 147 microorganisms isolated from a loamy sand soil were able to utilize a γ-HCH solution as the sole carbon source. White rot fungus degraded radiolabeled γ-HCH in aerobic pure culture laboratory tests. In a silt loam soil/corncob test matrix, 34.7% of the compound was degraded over a 60-day test period, whereas 53.5% degradation was observed in liquid cultures over a 30-day test period (Kennedy et al. 1990). The results of this study have been confirmed by more recent studies (Mougin et al. 1996, 1997). The isolation of γ-HCH-degrading bacteria, classified as *Sphingomonas paucimobilis*, from contaminated

soils has been reported (Thomas et al. 1996). A *Pseudomonas* species has also been isolated from pretreated soil that is able to degrade γ- and α-HCH, but not β-HCH, within 10–20 days under both flooded (anaerobic) and unflooded (aerobic) conditions; greater degradation rates were observed under aerobic conditions (Sahu et al. 1993). Under aerobic conditions, actinobacteria strains of *Streptomyces* sp. isolated from a polluted site were able to utilize α-HCH as its only carbon source, and some were able to utilize β-HCH when supplemented to the α-HCH system; no growth was observed in the presence of δ-HCH. At pH 7 and 30°C, the actinobacteria were able to degrade up to 100% α-HCH and 55% β-HCH after 7 days (Sineli et al. 2014). The concentrations and persistence of γ-HCH in soil may be dependent on soil types. An analysis of two soil types, loamy sand (approximately 1–2% organic matter) and muck (approximately 27–56% organic matter), for γ-HCH residues showed that mean residues in the loamy sand soil had decreased from 95 ppb dry weight in 1971 to below the detection limit of 10 ppb in 1989; however, in muck, residues had decreased from 426 ppb in 1971 to 168 ppb in 1989 (Szeto and Price 1991). The presence of crops on the soils also affects the persistence of HCH residues, with half-lives of 58.8 and 83.8 days for cropped and uncropped plots, respectively. β-HCH was the most persistent isomer, with half-lives of 184 and 100 days, respectively, on cropped and uncropped plots; γ-HCH was next at 107 and 62.1 days, followed by α-HCH at 54.4 and 56.1 days, and finally, δ-HCH at 33.9 and 23.4 days. Only trace amounts of the isomers were found to leach below 20 cm soil depth (Singh et al. 1991). The β-HCH isomer comprised 80–100% of the total HCH residues found in soil or vegetation on land surrounding an industrial landfill in Germany 10 years after the final HCH input (Heinisch et al. 1993). Biodegradation was observed to be a limiting factor in uptake of γ-HCH by earthworms (Smídová et al. 2012).

Most available information suggests that γ-HCH transformation is favored in biologically rich, anaerobic environments (EPA 1979; Haider 1979; Kalsch et al. 1998). In bench-scale anaerobic digestion tests designed to assess the fate of semivolatile organic pollutants in primary and secondary sludges, γ-HCH was found to undergo 98% degradation at 120 days. Sorption of the compound to the digester solids accounted for 2% of the initial feed; none of the compound was lost by volatilization. The digesters were operated at 35°C with a 30-day solids retention time (Govind et al. 1991). Similar results were seen with live activated sludge where initially reversible biosorption dominates the removal process followed by an increased aerobic biodegradation after approximately 10 hours of acclimation. The biodegradation process includes hydrolytic dechlorination with subsequent ring cleavage and finally, partial or total mineralization (Tsezos and Wang 1991b). Adaptation of sewage sludge is slow and may take 1–2 months; however, once acclimation occurs, 70–80% biodegradation of γ-HCH may occur, with the percentage of degradation decreasing with increasing sludge age (Nyholm et al. 1992). Co-oxidation and

reductive dechlorination are the probable degradation mechanisms (Jacobsen et al. 1991; Nyholm et al. 1992).

Numerous diverse studies on biological degradation have shown that γ-HCH was transformed to tetrachlorohexene; tri-, tetra-, and pentachlorinated benzenes; penta- and tetracyclohexanes; other isomers of HCH; and other related chemicals. The products varied depending on the organisms present, analytical methods applied, and when the sample was analyzed relative to its collection date (EPA 1979). Laboratory studies have demonstrated the bioisomerization of γ-HCH to α-, β-, and δ-HCH but bioisomerization in the environment was considered to be nonsignificant by an investigator who conducted a field study (Waliszewski 1993). Levels of individual isomers were approximately 0.1–1.4 and 0.8–4.0% of the γ-HCH concentrations at 3–31 and 34–46 weeks, respectively, following γ-HCH treatment of soil. The study authors suggested that their inability to simulate all environmental conditions in the laboratory could explain differences between laboratory and field results.

Abiotic transformation and degradation processes of γ-HCH in soil/sediment are not thought to be significant pathways. As discussed earlier for water, photolysis or hydrolysis are not considered important degradation pathways of γ-HCH and other isomers; the exception being hydrolysis under alkaline conditions.

Other Media. Several Organisation for Economic Cooperation and Development (OECD) and European Union standardized tests exist to quantify potential for biodegradation in a wastewater treatment facility. A closed bottle test, conducted according to EC directive 92/69/EEC, was initiated with 2 mg/L of γ-HCH in a 25 mg/L slurry of activated sludge in mineral nutrient medium, under aerobic conditions. γ-HCH achieved 100% degradation based on theoretical oxygen uptake after 9 days (Lapertot and Pulgarin 2006).

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to HCH depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of HCH in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on HCH levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

Table 5-5 shows the lowest limit of detections that are achieved by analytical analysis in environmental media. An overview summary of the range of concentrations detected in environmental media, including historical data prior to the cancellation of γ-HCH as a pesticide, is presented in Table 5-6.

Table 5-5. Lowest Limit of Detection Based on Standards[a]

Media	Detection limit	Reference
Air	0.2 pg/m^3 – 200 ng/m^3 (α-, β-, γ-HCH)	EPA 1999d
Drinking water	0.0053 µg/L (α-HCH) 0.0036 µg/L (β-HCH) 0.0060 µg/L (γ-HCH) 0.0020 µg/L (δ-HCH)	EPA 1995
Surface water and groundwater	7 pg/L – 0.0053 µg/L (α-HCH) 6 pg/L – 0.0036 µg/L (β-HCH) 9 pg/L – 0.0060 µg/L (γ-HCH) 5 pg/L – 0.0020 µg/L (δ-HCH)	EPA 1995, 2007
Soil	6 ng/L; 1.3 ng/kg (α-HCH) 7 ng/L; 0.6 ng/kg (β-HCH) 11 ng/L; 0.7 ng/kg (γ-HCH) 5 ng/L; 2.0 ng/kg (δ-HCH)	EPA 2000b, 2007
Sediment	0.500 µg/kg; 6 ng/L (α-HCH) 0.221; 7 ng/L (β-HCH) 0.200 µg/kg; 11 ng/L (γ-HCH) 5 ng/L (δ-HCH)	EPA 2000b; USGS 2003
Whole blood	1 ppb (α-, β-, γ-HCH) 1.3 ng/g lipid (β-HCH) 0.92 ng/g lipid (γ-HCH)	CDC 2019; EPA 1980

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.

Table 5-6. Summary of Ambient Environmental Levels of HCH

Media	Low	High	Reference
α-HCH			
Outdoor air (ng/m^3)	0.00016	0.142	Goel et al. 2010; WQP 2021
Indoor air	No data		
Surface water (ng/L)	1.4x10^{-5}	55,000	WQP 2021
Groundwater (ng/L)	0.96	2.5x10^6	WQP 2021
Drinking water	No data		
Food (ppm)		0.0010	Rogers et al. 1995
Soil and sediment (µg/kg)	4.0x10^{-5}	3800	WQP 2021

Table 5-6. Summary of Ambient Environmental Levels of HCH

Media	Low	High	Reference
β-HCH			
Outdoor air (ng/m^3)	0.00034	0.033	WQP 2021
Indoor air	No data		
Surface water (ng/L)	2.4x10^{-5}	80000	WQP 2021
Groundwater (ng/L)	0.94	2.5x10^6	WQP 2021
Drinking water	No data		
Food (ppm)		0.0027	Rogers et al. 1995
Soil and sediment (µg/kg)	4.0x10^{-5}	9390	WQP 2021
γ-HCH			
Outdoor air (ng/m^3)	<1.7	6.15	EPA 2021; Morgan et al. 2014
Indoor air (ng/m^3)	<0.09	18.5	Morgan et al. 2014
Surface water (ng/L)	0.04	100	Cole et al. 1984; Padma and Dickhut 2002
Groundwater (ng/L)	28	900	Adamski and Pugh 1996; Page 1981
Drinking water (ng/L)	0.01	319	Keith et al. 1976; Sandhu et al. 1978
Food (ppm)		0.0012	Rogers et al. 1995
Soil and sediment (µg/kg)	<0.02	150	Crockett et al. 1974; Sericano et al. 1990
δ-HCH			
Outdoor air	No data		
Indoor air	No data		
Surface water	No data		
Groundwater	No data		
Drinking water	No data		
Food (ppm)		0.0030	Rogers et al. 1995
Soil and sediment	No data		
HCH, technical grade			
Outdoor air	No data		
Indoor air	No data		
Surface water	No data		
Groundwater	No data		
Drinking water	No data		
Food (ppb)	No data		
Soil and sediment	No data		

Detections of HCH in air, water, and soil at NPL sites are summarized in Table 5-7.

Table 5-7. Hexachlorocyclohexanes Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
α-HCH					
Water (ppb)	0.987	1.08	45.2	43	29
Soil (ppb)	3,390	2,970	156	52	28
Air (ppbv)	0.0016	0.0010	11	6	5
β-HCH					
Water (ppb)	0.68	1.09	18.7	34	22
Soil (ppb)	950	911	61.7	44	33
Air (ppbv)	0.0017	0.00080	7.1	2	2
γ-HCH					
Water (ppb)	0.63	0.963	40.6	63	37
Soil (ppb)	2,800	2,090	127	66	42
Air (ppbv)	0.0044	0.0038	29	7	7
δ-HCH					
Water (ppb)	0.57	1.18	34.5	29	19
Soil (ppb)	1,100	392	71.9	31	22
Air (ppbv)	0.0002	0.00016	1.5	3	2
HCH, technical grade					
Water (ppb)	0.86	3.0	24	6	5
Soil (ppb)	8,700	2,300	81	10	6
Air (ppbv)	0.000017	0.000017	1	2	1

[a]Concentrations found in ATSDR site documents from 1981 to 2019 for 1,867 NPL sites (ATSDR 2019). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

HCH isomers have been detected in ambient air. The highest concentrations were found prior to γ-HCH agricultural use restrictions; available monitoring data after the restriction and ban of γ-HCH pesticides showed a gradual decrease and the results of the most recent monitoring studies are below the parts per billion range. The results of outdoor air monitoring studies are presented in Table 5-8. Precipitation samples, if available, are included in Table 5-8 because they reflect removal of atmospheric HCH.

One reference to indoor air monitoring was located in the literature search. In a study of preschool children's potential exposure to pesticides in North Carolina, indoor air samples from 13 daycare centers and 129 homes of the preschool children (ages 20–66 months) were collected between 2000 and 2001 (Morgan et al. 2014). γ-HCH was detected in ranges of below the limit of detection (<0.09 ng/m^3) to 18.5 ng/m^3 in the children's homes and <0.09–8.97 ng/m^3 in the preschools. Detection frequencies were 13 and 20%, respectively. Seventy-four percent of the homeowners reported applying insecticides at their homes, and 90% of these had applied an insecticide in the past year before sampling. Among the daycare centers, 62% reported using insecticides, and 88% of those reported usage within a year of sample collection (Morgan et al. 2014).

5.5.2 Water

Water monitoring data are presented in Table 5-9. HCH isomers have been detected in surface water, groundwater, and drinking water. The highest concentrations were found in groundwater below a facility that processed pesticides and stored wastes in unlined trenches until 1996 (Law et al. 2004). A study of the same site some years later still detected HCH isomers (Chartrand et al. 2015). Generally, surface water concentrations are lower than those detected in groundwater. Data from the EPA's Water Quality Portal (WQP), a system that maintains water monitoring data from stations across the United States, have been divided into two categories: prior to γ-HCH pesticide cancellation (years up to and including 2006) and post-cancellation (years after and including 2007) (WQP 2021). A decrease in surface and groundwater concentrations of α- and β-HCH can be seen in this dataset. A decrease of γ-HCH in surface water can be observed, possibly due to use limitations; trends for drinking water and groundwater are not as clear. Most recent monitoring data report concentrations below the parts per billion range for surface water and groundwater.

Table 5-8. Outdoor Air Monitoring Data for Hexachlorocyclohexanes (HCHs)

Locations	Geographic type	Date(s)	Range[a]	Mean[a]	Notes	Reference
α-HCH						
Alabama	Not reported	January–October 1996 and May 1997		0.092 ng/m^3		Jantunen et al. 2000
Eagle Harbor, Michigan; Sleeping Bear Dunes State Park, Michigan; Sturgeon Point, New York	Rural	1990–1997		0.110–0.140 ng/m^3		Cortes and Hites 2000
Chesapeake Bay	Rural and agricultural	April 2000–September 2003; excluding winter months	0.002–0.142 ng/m^3	0.026 ng/m^3	Gas phase; average of averages at three sites; detection frequency 99–100%	Goel et al. 2010
Chesapeake Bay	Rural and agricultural	April 2000 –September 2003; excluding winter months		0.0012 ng/m^3	Particulate phase; detection frequency 1%	Goel et al. 2010
Chesapeake Bay	Rural and agricultural	April 2000–September 2003; excluding winter months	0.2–11 ng/L	1.7 ng/L	Rainwater; average of averages at three sites; detection frequency 3–18%	Goel et al. 2010
Youngstown, Ohio	Urban/suburban	2000–2001		0.051 ng/m^3		Shen et al. 2004
Solomons, Maryland	Rural	2000–2001		0.091 ng/m^3		Shen et al. 2004
Wilmington, North Carolina	Urban/suburban	2000–2001		0.015 ng/m^3		Shen et al. 2004
Turkey Point, Florida	Rural	2000–2001		0.029 ng/m^3		Shen et al. 2004
Muscle Shoals	Suburban/rural	2000–2001		0.056 ng/m^3		Shen et al. 2004

Table 5-8. Outdoor Air Monitoring Data for Hexachlorocyclohexanes (HCHs)

Locations	Geographic type	Date(s)	Range[a]	Mean[a]	Notes	Reference
United States	Ambient air	2015–2018	0.00016–0.017 ng/m^3	0.0047 ng/m^3	Data collected by USGS monitoring stations across the United States; mean and ranges do not reflect samples reported as not detected/below detection limit	WQP 2021
β-HCH						
United States	Ambient air	2015–2018	0.00034–0.033 ng/m^3	0.004 ng/m^3	Data collected by USGS monitoring stations across the United States; mean and ranges do not reflect samples reported as not detected/below detection limit	WQP 2021
γ-HCH						
College Station, Texas	Rural	1979–1980	0.01–1.60 ng/m^3	0.23 ng/m^3	Ground level, ambient air	Atlas and Giam 1988
College Station, Texas	Rural	1979–1980	0.30–7.8 ng/L	2.81 ng/L	Rainwater samples	Atlas and Giam 1988
Adirondack Mountains, New York	Not reported	1985		0.509 ng/m^3	Troposphere samples	Knap and Binkley 1991
Newport News, Virginia	Not reported	1988		0.021 ng/m^3	Troposphere samples	Knap and Binkley 1991
Alabama	Not reported	January–October 1996 and May 1997		0.050 ng/m^3		Jantunen et al. 2000
Eagle Harbor, Michigan; Sleeping Bear Dunes State Park, Michigan; Sturgeon Point, New York	Rural	1990–1997		0.024–0.062 ng/m^3		Cortes and Hites 2000

Table 5-8. Outdoor Air Monitoring Data for Hexachlorocyclohexanes (HCHs)

Locations	Geographic type	Date(s)	Range[a]	Mean[a]	Notes	Reference
Lake Superior	Not reported	1984; wetfall season		3.0 ng/L	Rainwater samples, annual loading rate of 2.0 µg/m^2/year	Strachan 1988
Portland, Oregon	Urban	1982		0.45–1 ng/L	Rain and snow water	Pankow et al. 1984
Hawaii	Not reported	1970–1971	1–19 ng/L	5 ng/L	Rainwater	Bevenue et al. 1972
Youngstown, Ohio	Urban/suburban	2000–2001		0.049 ng/m^3		Shen et al. 2004
Solomons, Maryland	Rural	2000–2001		0.072 ng/m^3		Shen et al. 2004
Wilmington, North Carolina	Urban/suburban	2000–2001		0.026 ng/m^3		Shen et al. 2004
Turkey Point, Florida	Rural	2000–2001		0.031 ng/m^3		Shen et al. 2004
Muscle Shoals	Suburban/ agricultural	2000–2001		0.055 ng/m^3		Shen et al. 2004
North Carolina	Not reported	2000–2001	<0.09–0.11 ng/m^3		Air samples collected outside daycare centers; detection frequency 8%	Morgan et al. 2014
North Carolina	Not reported	2000–2001	<0.09–6.15 ng/m^3		Air samples collected outside students; homes; detection frequency 12%	Morgan et al. 2014
Chesapeake Bay	Rural and agricultural	April 2000–September 2003; excluding winter months	0.0012–0.382 ng/m^3	0.049 ng/m^3	Gas phase; average of averages at three sites; detection frequency 81–100%	Goel et al. 2010
Chesapeake Bay	Rural and agricultural	April 2000–September 2003; excluding winter months	0.0013–0.027 ng/m^3	0.024 ng/m^3	Particulate phase; average of averages at two sites; detection frequency 2–7%	Goel et al. 2010
Chesapeake Bay	Rural and agricultural	April 2000–September 2003; excluding winter months	0–35 ng/L	4.0 ng/L	Rainwater; average of averages at two sites; detection frequency 1–61%	Goel et al. 2010

Table 5-8. Outdoor Air Monitoring Data for Hexachlorocyclohexanes (HCHs)

Locations	Geographic type	Date(s)	Range[a]	Mean[a]	Notes	Reference
Texas	Various ambient air monitoring sites	January–December 2007		0.005 ng/m^3	Detected in 20 samples; below the limit of detection in 345 samples	EPA 2021
Texas	Various ambient air monitoring sites	January–December 2008		<1.7 ng/m^3	Below the limit of detection in 488 samples	EPA 2021
Texas	Various ambient air monitoring sites	January–June 2009		<1.7 ng/m^3	Below the limit of detection in 120 samples	EPA 2021

[a]Liquid unit conversion: 1 ng/L = 1 ppt = 0.001 ppb; gaseous unit conversion: ppbv = ([concentration ng/m^3] x 0.001) / 11.89, assuming standard temperature and pressure.

USGS = U.S. Geological Survey

Table 5-9. Water Monitoring Data for Hexachlorocyclohexanes (HCHs)

Locations	Geographic type	Date(s)	Range[a]	Mean[a]	Notes	Reference
α-HCH						
Lake Superior	Surface water	Spring 1997		2.8 ng/L		Marvin et al. 2004
Lake Erie	Surface water	Spring 1998		0.41 ng/L		Marvin et al. 2004
Lake Ontario	Surface water	Spring 1998		0.40 ng/L		Marvin et al. 2004
York River estuary	Surface water	June 1998–April 1999	~0.025–0.175 ng/L		Concentrations were lower in freshwater areas than areas with higher salinity	Padma and Dickhut 2002
United States	Surface water	1978–2006	$1.4x10^{-5}$–55,000 ng/L	150 ng/L	Data collected by USGS monitoring stations across the United States; mean and ranges do not reflect samples reported as not detected/below detection limit	WQP 2021
United States	Surface water	2007–2021	$1.3x10^{-4}$–310 ng/L	5.4 ng/L	Data collected by USGS monitoring stations across the United States; mean and ranges do not reflect samples reported as not detected/below detection limit	WQP 2021
United States	Groundwater	1981–2006	0.96–$2.5x10^{6}$ ng/L	7,000 ng/L	Data collected by USGS monitoring stations across the United States; mean and ranges do not reflect samples reported as not detected/below detection limit	WQP 2021
United States	Groundwater	2007–2020	1.2–500 ng/L	270 ng/L	Data collected by USGS monitoring stations across the United States; mean and ranges do not reflect samples reported as not detected/below detection limit	WQP 2021
Northeastern Florida	Groundwater below active pesticide reformulating and packaging facility	2000	58–$5.0x10^{5}$ ng/L	51,000 ng/L	Samples collected from 19 shallow wells; not detected (<20 ng/L) in 6 wells; mean and ranges do not reflect samples reported as not detected/below detection limit	Law et al. 2004
Northeastern Florida	Groundwater below active pesticide reformulating and packaging facility	2000	30–$4.2x10^{5}$ ng/L	44,000 ng/L	Samples collected from 15 deep wells; not detected (<20 ng/L) in 5 wells; mean and ranges do not reflect samples reported as not detected/below detection limit	Law et al. 2004

Table 5-9. Water Monitoring Data for Hexachlorocyclohexanes (HCHs)

Locations	Geographic type	Date(s)	Range[a]	Mean[a]	Notes	Reference
Northeastern Florida	Surface water near active pesticide reformulating and packaging facility	2000	660–680 ng/L	670 ng/L	Three samples collected from creek adjacent to the site; not detected (<20 ng/L) in one sample; mean and ranges do not reflect samples reported as not detected/below detection limit	Law et al. 2004
β-HCH						
United States	Surface water	1982–2006	$2.4x10^{-5}$–80,000 ng/L	340 ng/L	Data collected by USGS monitoring stations across the United States; mean and ranges do not reflect samples reported as not detected/below detection limit	WQP 2021
United States	Surface water	2007–2018	$1.6x10^{-4}$–410 ng/L	9 ng/L	Data collected by USGS monitoring stations across the United States; mean and ranges do not reflect samples reported as not detected/below detection limit	WQP 2021
United States	Groundwater	1981–2006	0.94–$2.5x10^{6}$ ng/L	7,200 ng/L	Data collected by USGS monitoring stations across the United States; mean and ranges do not reflect samples reported as not detected/below detection limit	WQP 2021
United States	Groundwater	2007–2020	50–500 ng/L	290 ng/L	Data collected by USGS monitoring stations across the United States; mean and ranges do not reflect samples reported as not detected/below detection limit	WQP 2021
Northeastern Florida	Groundwater below active pesticide reformulating and packaging facility	2000	30–43,000 ng/L	12,000 ng/L	Samples collected from 19 shallow wells; not detected (<20 ng/L) in 8 wells; mean and ranges do not reflect samples reported as not detected/below detection limit	Law et al. 2004
Northeastern Florida	Groundwater below active pesticide reformulating and packaging facility	2000	82–820 ng/L	340 ng/L	Samples collected from 15 deep wells; not detected (<20 ng/L) in 8 wells; mean and ranges do not reflect samples reported as not detected/below detection limit	Law et al. 2004

Table 5-9. Water Monitoring Data for Hexachlorocyclohexanes (HCHs)

Locations	Geographic type	Date(s)	Range[a]	Mean[a]	Notes	Reference
Northeastern Florida	Surface water near active pesticide reformulating and packaging facility	2000	38–440 ng/L	300 ng/L	Three samples collected from creek adjacent to the site	Law et al. 2004
γ-HCH						
New Jersey	Wells	Not reported (1981 or earlier)	NR–900 ng/L		1,076 wells, not detected in around half of samples	Page 1981
Chesterfield County, South Carolina	Rural drinking water	Not reported (1978 or earlier)	0–93 ng/L	23 ng/L		Sandhu et al. 1978
Hampton, South Carolina	Rural drinking water	Not reported (1978 or earlier)	0–319 ng/L	147 ng/L		Sandhu et al. 1978
Cincinnati, Ohio	Drinking water	Not reported (1976 or earlier)		0.01 ng/L		Keith et al. 1976
Oahu, Hawaii	Drinking water	1970–1971		0.2 ng/L		Bevenue et al. 1972
Ozark Plateaus Province of Arkansas, Kansas, Missouri, and Oklahoma	Groundwater	April–September 1993	28 and 32 ng/L		Detected in two samples from domestic wells	Adamski and Pugh 1996
Connecticut	Drinking water well	Not reported (1999 or earlier)		60 ng/L		Eitzer and Chevalier 1999

Table 5-9. Water Monitoring Data for Hexachlorocyclohexanes (HCHs)

Locations	Geographic type	Date(s)	Range[a]	Mean[a]	Notes	Reference
United States	Drinking water	1998–2005	1–690 ng/L	62 ng/L	Samples collected from 44 states across the United States; ranges and averages do not include samples reported to be below the method reporting level.	EPA 2010
Washington, D.C. and Denver, Colorado	Surface water	Not reported (1984 or earlier)	52–100 ng/L			Cole et al. 1984
Niagara River	Surface water	1980–1981		2.1 ng/L	Mean of 99% samples	Kuntz and Warry 1983
Lake Michigan tributary streams	Surface water	Not reported (1974 or earlier)	ND–150 ng/L			EPA 1974
United States	Surface water	Not reported (1985 or earlier)		Median: 20 ng/L	Detected in 27% of 4,505 samples	Staples et al. 1985
Lake Ontario	Surface water	1983	0.806–1.85 ng/L			Biberhofer and Stevens 1987
Patuxent River	Surface water	1995	1.0 ng/L			Harman-Fetcho et al. 1999
Lake Superior	Surface water	Spring 1997		0.38 ng/L		Marvin et al. 2004
Lake Erie	Surface water	Spring 1998		0.32 ng/L		Marvin et al. 2004
Lake Ontario	Surface water	Spring 1998		0.24 ng/L		Marvin et al. 2004
York River estuary	Surface water	June 1998–April 1999	~0.04–0.21 ng/L		Concentrations were higher in freshwater areas than areas with higher salinity	Padma and Dickhut 2002
Northeastern Florida	Groundwater below active pesticide reformulating and packaging facility	2000	110–6.6×10^5 ng/L	99,000 ng/L	Samples collected from 19 shallow wells; not detected (<20 ng/L) in 11 wells; mean and ranges do not reflect samples reported as not detected/below detection limit	Law et al. 2004

Table 5-9. Water Monitoring Data for Hexachlorocyclohexanes (HCHs)

Locations	Geographic type	Date(s)	Range[a]	Mean[a]	Notes	Reference
Northeastern Florida	Groundwater below active pesticide reformulating and packaging facility	2000	120–$3.6x10^5$ ng/L	73,000 ng/L	Samples collected from 15 deep wells; not detected (<20 ng/L) in 10 wells; mean and ranges do not reflect samples reported as not detected/below detection limit	Law et al. 2004
Northeastern Florida	Surface water near active pesticide reformulating and packaging facility	2000	440–470 ng/L	460 ng/L	Three samples collected from creek adjacent to the site; not detected (<20 ng/L) in one sample; mean and ranges do not reflect samples reported as not detected/below detection limit	Law et al. 2004
δ-HCH						
Northeastern Florida	Groundwater below active pesticide reformulating and packaging facility	2000	40–$5.7x10^5$ ng/L	74,000 ng/L	Samples collected from 19 shallow wells; not detected (<20 ng/L) in 8 wells; mean and ranges do not reflect samples reported as not detected/below detection limit	Law et al. 2004
Northeastern Florida	Groundwater below active pesticide reformulating and packaging facility	2000	36–$2.9x10^5$ ng/L	26,000 ng/L	Samples collected from 15 deep wells; not detected (<20 ng/L) in 3 wells; mean and ranges do not reflect samples reported as not detected/below detection limit	Law et al. 2004
Northeastern Florida	Surface water near active pesticide reformulating and packaging facility	2000	55–970 ng/L	640 ng/L	Three samples collected from creek adjacent to the site	Law et al. 2004
HCH, mixture						
Northeastern Florida	Groundwater below contaminated site	Not reported (2015 or earlier)	30,000–$4.2x10^5$ ng/L		Range reported for α-, γ-, and δ-HCH	Chartrand et al. 2015

[a]Liquid unit conversion: 1 ng/L = 1 ppt = 0.001 ppb.

USGS = U.S. Geological Survey

5.5.3 Sediment and Soil

HCH has been detected in soil and sediment as a result of agricultural use. Soil and sediment monitoring data are presented in Table 5-10. Data from the EPA's WQP has been divided into two categories to reflect potential detection decreases as a result of the γ-HCH pesticide cancellation in 2006 (WQP 2021). A clear trend could not be discerned from the data, possibly due to the large ranges reflecting differences in land use. Most recent monitoring data report concentrations at the parts per billion range.

5.5.4 Other Media

HCH isomers have been detected in aquatic organisms; the results of these monitoring studies are summarized in Table 5-11. Data on terrestrial organism monitoring were not located. Schmitt et al. (1985) reported the results of a monitoring study of fish tissues from 107 freshwater stations in the United States from 1976 to 1981, which supported a decline in tissue occurrence of detectable α- and γ-HCH residues in aquatic organisms. α- and β-HCH have been detected in organisms as recently as 2018, however (WQP 2021). The most recent monitoring studies have detected HCH isomers in aquatic organisms in the parts per billion range.

Historically, as a result of pesticide use, γ-HCH was detected in meat, vegetables, and other food items, both imported to and produced in the United States. Due to the discontinued agricultural use of γ-HCH by the United States and many other countries, residues are typically no longer detected in food products. γ-HCH was detected in 5 out of 612 imported rice samples at a maximum concentration of 0.03 ppm during an FDA pesticide monitoring study conducted in 1993–1994 (Roy et al. 1997). A 10-year (1982–1991) FDA study of ready-to-eat foods commonly consumed in the United States showed that α-, β-, δ-, and γ-HCH were frequently detected (Rogers et al. 1995). The results of this study reported average concentrations of 0.0010, 0.0027, 0.0030, and 0.0012 ppm for α-, β-, δ-, and γ-HCH isomers, respectively, in 243 ready-to-eat foods. HCH isomers were also detected in the following feed types formulated for infants and toddlers and in adult diet foodstuffs: whole milk and other dairy products; meat, fish, and poultry; oils and fats; vegetables; and sugars and adjuncts (Gartrell et al. 1986a, 1986b).

Table 5-10. Soil and Sediment Monitoring Data for Hexachlorocyclohexanes (HCHs)

Locations	Geographic type	Date(s)	Range[a]	Mean[a]	Notes	Reference
α-HCH						
Alabama	Soil	Not reported (1999 or earlier)	0–0.269 µg/kg		Detected in 26 of 39 soils from 6 regions	Harner et al. 1999
Sequoia National Park, Rocky Mountain National Park, Mt. Rainier National Park, Denali National Park, Noatak National Preserve, and Gates of the Arctic National Park and Preserve	Sediment core from deepest point in several lakes	2003–2005	<0.8 µg/kg		Not detected	Genualdi et al. 2011
United States	Soil and sediment	1982–2006	4.0×10^{-5}–3,800 µg/kg	5.7 µg/kg	Data collected by USGS monitoring stations across the United States; mean and ranges do not reflect samples reported as not detected/below detection limit	WQP 2021
United States	Soil and sediment	2007–2020	1.2×10^{-2}–1,060 µg/kg	2.7 µg/kg	Data collected by USGS monitoring stations across the United States; mean and ranges do not reflect samples reported as not detected/below detection limit	WQP 2021
β-HCH						
United States	Soil and sediment	1989–2006	4.0×10^{-5}–4,230 µg/kg	8.8 µg/kg	Data collected by USGS monitoring stations across the United States; mean and ranges do not reflect samples reported as not detected/below detection limit	WQP 2021

Table 5-10. Soil and Sediment Monitoring Data for Hexachlorocyclohexanes (HCHs)

Locations	Geographic type	Date(s)	Range[a]	Mean[a]	Notes	Reference
United States	Soil and sediment	2007–2020	$1.3x10^{-2}$–9,390 µg/kg	11 µg/kg	Data collected by USGS monitoring stations across the United States; mean and ranges do not reflect samples reported as not detected/below detection limit	WQP 2021
γ-HCH						
Alabama, Arkansas, Georgia, Illinois, Iowa	Soil	Not reported (1974 or earlier)	10–150 µg/kg	52 µg/kg		Crockett et al. 1974
Alabama	Soil	Not reported (1999 or earlier)	0–1.07 µg/kg		Detected in 26 of 39 soils from 6 regions	Harner et al. 1999
Niagara River	Suspended sediment	Not reported (1983 or earlier)		2 µg/kg	Detection frequency 33%	Kuntz and Warry 1983
Lake Ontario	Settling particulates	1982		2.4 µg/kg		Oliver and Charlton 1984
James River, Virginia	Creek sediments	1976	7.3–8.5 µg/kg			Saleh et al. 1978
Gulf of Mexico	Sediment	1987	<0.02–1.74 µg/kg	0.07 µg/kg	Detection frequency 19%	Sericano et al. 1990
Around the Great Lakes	Sediment	May 1989	<0.10–0.99 µg/kg wet weight			Verbrugge et al. 1991
Indian River Lagoon, Florida	Sediment from impoundments along the river	Not reported (1992 or earlier)	9.4–34.4 µg/kg		33 sediment samples from 11 impoundment	Wang et al. 1992

Table 5-10. Soil and Sediment Monitoring Data for Hexachlorocyclohexanes (HCHs)

Locations	Geographic type	Date(s)	Range[a]	Mean[a]	Notes	Reference
HCH, mixture						
South Carolina	0–10 cm surface soils from cotton fields	November 1999	0.1–0.54 µg/kg dry weight	0.27 µg/kg dry weight	Reported as sum of α-, β-, and γ-isomers; not detected (<0.1 µg/kg dry weight) in 10 of 16 samples; mean and ranges do not reflect samples reported as not detected/below detection limit	Kannan et al. 2003
Georgia	0–10 cm surface soils from cotton fields	December 1999	0.16–0.49 µg/kg dry weight	0.33 µg/kg dry weight	Reported as sum of α-, β-, and γ-isomers; not detected (<0.1 µg/kg dry weight) in 14 of 16 samples; mean and ranges do not reflect samples reported as not detected/below detection limit	Kannan et al. 2003
United States	Sediment	2008	2.1–11 µg/kg	6.03 µg/kg	HCH isomer or mixture not specified; data collected by USGS monitoring stations across the United States; mean and ranges do not reflect samples reported as not detected/below detection limit	WQP 2021
United States	Sediment	2017	0.47–1.26 µg/kg	0.75 µg/kg	HCH isomer or mixture not specified; data collected by USGS monitoring stations across the United States; mean and ranges do not reflect samples reported as not detected/below detection limit	WQP 2021

[a]Solid unit conversion: 1 µg/kg = 1 ppb.

USGS = U.S. Geological Survey

Table 5-11. Organism Monitoring Data for Hexachlorocyclohexanes (HCHs)

Locations	Species	Date(s)	Range	Mean	Notes	Reference
α-HCH						
Southwestern and Midwestern United States	Freshwater Fish	1980–1981	0.03–0.04 ng/g		Highest concentrations detected from 107 monitoring stations across the United States	Schmitt et al. 1985
United States	Freshwater fish	1984	NR–10 ng/g	<10 ng/g		Schmitt et al. 1990
Louisiana section of the Mississippi River	Blue crab, cobia, flathead catfish, freshwater drum, long-nose gar, red drum, red snapper, river shrimp, small-mouth buffalo, spotted gar	1990–1994		Not detected		Watanabe et al. 2003
Louisiana section of the Mississippi River	Bigmouth buffalo	1990–1994		2.4 ng/g	Average detection in 1 of 3 sampling years; not detected in other years	Watanabe et al. 2003
Louisiana section of the Mississippi River	Blue catfish	1990–1994	0.333–26.3 ng/g		Range of average detections in 3 of 4 sampling years; not detected in other years	Watanabe et al. 2003
Louisiana section of the Mississippi River	Carp	1990–1994		31.1 ng/g	Range of average detections in 3 of 4 sampling years; not detected in other years	Watanabe et al. 2003
Louisiana section of the Mississippi River	Channel catfish	1990–1994	1.83–7.23 ng/g		Range of average detections in 2 of 3 sampling years; not detected in other years	Watanabe et al. 2003
Louisiana section of the Mississippi River	Crawfish	1990–1994		4.25 ng/g	Average detection in 1 of 1 sampling years	Watanabe et al. 2003
Louisiana section of the Mississippi River	Largemouth bass	1990–1994		1.00 ng/g	Average detection in 1 of 2 sampling years; not detected in other years	Watanabe et al. 2003
Louisiana section of the Mississippi River	Striped bass	1990–1994		2.88 ng/g	Average detection in 1 of 2 sampling years; not detected in other years	Watanabe et al. 2003

Table 5-11. Organism Monitoring Data for Hexachlorocyclohexanes (HCHs)

Locations	Species	Date(s)	Range	Mean	Notes	Reference
Louisiana section of the Mississippi River	White bass	1990–1994		1.44 ng/g	Average detection in 1 of 3 sampling years; not detected in other years	Watanabe et al. 2003
Louisiana section of the Mississippi River	White crappie	1990–1994		1.75 ng/g	Average detection in 1 of 3 sampling years; not detected in other years	Watanabe et al. 2003
Southwestern Michigan	Adult green frogs	1998		0.02 ng/g	0.04 ppb detected in juvenile frogs	Gilliland et al. 2001
Gulf of California	Clams (*Chione californiensis*)	Not reported (2015 or earlier)	<0.005–1.77 ng/g wet weight		Detection frequency 16.7% in 1 of 3 study areas, not detected in other areas; adipose tissue samples; surrounding area has primarily agricultural activity	Vargas-Gonzalez et al. 2016
Lake Apopka, Florida	Largemouth bass (*Micropterus salmoides*)	March 2013		Not detected	Limit of quantification 0.1–0.5 ng/g wet weight	Dang et al. 2016
United States	Freshwater fish	2018	2–150 ng/g wet weight	17 ng/g wet weight	Data collected by USGS monitoring stations across the United States; mean and ranges do not reflect samples reported as not detected/below detection limit	WQP 2021
β-HCH						
Upper Steele Bayou, Mississippi	Fish	1988	ND–20 ng/g wet weight			Ford and Hill 1991
Upper Steele Bayou, Mississippi	Snakes	1988	ND			Ford and Hill 1991
Southwestern Michigan	Adult green frogs	1998		0.01 ng/g	Not detected in juvenile frogs	Gilliland et al. 2001
Louisiana section of the Mississippi River	Cobia, long-nose gar, red drum, red snapper	1990–1994		Not detected		Watanabe et al. 2003
Louisiana section of the Mississippi River	Bigmouth buffalo	1990–1994	2.25–11.2 ng/g		Range of average detection in 3 of 3 sampling years	Watanabe et al. 2003

Table 5-11. Organism Monitoring Data for Hexachlorocyclohexanes (HCHs)

Locations	Species	Date(s)	Range	Mean	Notes	Reference
Louisiana section of the Mississippi River	Blue catfish	1990–1994	3.67–8.33 ng/g		Range of average detection in 3 of 4 sampling years; not detected in other year	Watanabe et al. 2003
Louisiana section of the Mississippi River	Blue crab	1990–1994	4.00–11.0 ng/g		Range of average detections in 2 of 2 sampling years	Watanabe et al. 2003
Louisiana section of the Mississippi River	Carp	1990–1994	5.00–11.3 ng/g		Range of average detections in 2 of 3 sampling years; not detected in other years	Watanabe et al. 2003
Louisiana section of the Mississippi River	Channel catfish	1990–1994	0.333–7.77 ng/g		Range of average detections in 3 of 4 sampling years; not detected in other years	Watanabe et al. 2003
Louisiana section of the Mississippi River	Crawfish	1990–1994		27.5 ng/g	Average detection in 1 of 1 sampling years	Watanabe et al. 2003
Louisiana section of the Mississippi River	Flathead catfish	1990–1994		0.500 ng/g	Average detection in 1 of 1 sampling years	Watanabe et al. 2003
Louisiana section of the Mississippi River	Freshwater drum	1990–1994		0.333 ng/g	Average detection in 1 of 1 sampling years	Watanabe et al. 2003
Louisiana section of the Mississippi River	Largemouth bass	1990–1994		2.00 ng/g	Average detection in 1 of 2 sampling years; not detected in other year	Watanabe et al. 2003
Louisiana section of the Mississippi River	River shrimp	1990–1994		8.67 ng/g	Average detection in 1 of 1 sampling years	Watanabe et al. 2003
Louisiana section of the Mississippi River	Small-mouth buffalo	1990–1994	0.25–2.00 ng/g		Range of average detection in 3 of 4 sampling years; not detected in other years	Watanabe et al. 2003
Louisiana section of the Mississippi River	Spotted gar	1990–1994		39.0 ng/g	Average detection in 1 of 1 sampling years	Watanabe et al. 2003
Louisiana section of the Mississippi River	Striped bass	1990–1994	5.50–57.9 ng/g		Range of average detection in 2 of 2 sampling years	Watanabe et al. 2003
Louisiana section of the Mississippi River	White bass	1990–1994		3.11 ng/g	Average detection in 1 of 3 sampling years; not detected in other years	Watanabe et al. 2003

Table 5-11. Organism Monitoring Data for Hexachlorocyclohexanes (HCHs)

Locations	Species	Date(s)	Range	Mean	Notes	Reference
Louisiana section of the Mississippi River	White crappie	1990–1994	1.00–11.0 ng/g		Range of average detection in 2 of 3 sampling years; not detected in other years	Watanabe et al. 2003
Gulf of California	Clams (*C. californiensis*)	Not reported (2015 or earlier)		Not detected	Limit of detection 0.01 ng/g wet weight Adipose tissue samples; surrounding area has primarily agricultural activity	Vargas-Gonzalez et al. 2016
Lake Apopka, Florida	Largemouth bass (*M. salmoides*)	March 2013		Not detected	Limit of quantification 0.1–0.5 ng/g wet weight	Dang et al. 2016
United States	Freshwater fish	2018	1–53 ng/g wet weight	10 ng/g wet weight	Data collected by USGS monitoring stations across the United States; mean and ranges do not reflect samples reported as not detected/below detection limit	WQP 2021
γ-HCH						
Gulf of Mexico	Oyster	1987	<0.25–9.06 ng/g	1.74 ng/g	Detection frequency 80%	Sericano et al. 1990
United States	Freshwater fish	1980–1981	0.02–0.03 ng/g		Whole body concentrations were >0.01 ng/g at 1 of 107 monitoring stations	Schmitt et al. 1985
United States	Freshwater fish	1984	NR–40 ng/g	<10 ng/g		Schmitt et al. 1990
Southwestern Michigan	Adult green frogs	1998		0.07 ng/g	Not detected in juvenile frogs	Gilliland et al. 2001
Louisiana section of the Mississippi River	Blue crab, channel catfish, cobia, crawfish, flathead catfish, freshwater drum, long-nose gar, red drum,	1990–1994		Not detected		Watanabe et al. 2003
Louisiana section of the Mississippi River	Bigmouth buffalo	1990–1994	1.00–1.80 ng/g		Range of average detection in 2 of 3 sampling years not detected in other year	Watanabe et al. 2003

Table 5-11. Organism Monitoring Data for Hexachlorocyclohexanes (HCHs)

Locations	Species	Date(s)	Range	Mean	Notes	Reference
Louisiana section of the Mississippi River	Blue catfish	1990–1994	2.25–26.5 ng/g		Range of average detection in 3 of 4 sampling years; not detected in other year	Watanabe et al. 2003
Louisiana section of the Mississippi River	Carp	1990–1994	0.714–5.00 ng/g		Range of average detections in 2 of 3 sampling years; not detected in other years	Watanabe et al. 2003
Louisiana section of the Mississippi River	Largemouth bass	1990–1994		1.00 ng/g	Average detection in 1 of 2 sampling years; not detected in other year	Watanabe et al. 2003
Louisiana section of the Mississippi River	Red snapper	1990–1994		0.333 ng/g	Average detection in 1 of 1 sampling years	Watanabe et al. 2003
Louisiana section of the Mississippi River	River shrimp	1990–1994		1.67 ng/g	Average detection in 1 of 1 sampling years	Watanabe et al. 2003
Louisiana section of the Mississippi River	Small-mouth buffalo	1990–1994	0.250–7.00 ng/g		Range of average detection in 4 of 4 sampling years	Watanabe et al. 2003
Louisiana section of the Mississippi River	Spotted gar	1990–1994		857 ng/g	Average detection in 1 of 1 sampling years	Watanabe et al. 2003
Louisiana section of the Mississippi River	Striped bass	1990–1994	0.500–1.25 ng/g		Range of average detection in 2 of 2 sampling years	Watanabe et al. 2003
Louisiana section of the Mississippi River	White bass	1990–1994		7.56 ng/g	Average detection in 1 of 3 sampling years; not detected in other years	Watanabe et al. 2003
Louisiana section of the Mississippi River	White crappie	1990–1994	0.750–1.20 ng/g		Range of average detection in 2 of 3 sampling years; not detected in other years	Watanabe et al. 2003
Gulf of California	Clams (*C. californiensis*)	Not reported (2015 or earlier)		Not detected	Limit of detection 0.005 ng/g wet weight; adipose tissue samples; surrounding area has primarily agricultural activity	Vargas-Gonzalez et al. 2016

Table 5-11. Organism Monitoring Data for Hexachlorocyclohexanes (HCHs)

Locations	Species	Date(s)	Range	Mean	Notes	Reference
Lake Apopka, Florida	Largemouth bass (*M. salmoides*)	March 2013		0.8 ng/g wet weight (gastrointestinal tract) 1.6 ng/g wet weight (liver) 2.6 ng/g wet weight (kidney) 0.8 ng/g wet weight (spleen) 4.8 ng/g wet weight (brain) 1.8 ng/g wet weight (gonad) 1.3 ng/g wet weight (muscle)	117.8 ng/g lipid (gastrointestinal tract) 29.4 ng/g lipid (liver) 742.6 ng/g lipid (kidney) 102.0 ng/g lipid (spleen) 144.1 ng/g lipid (brain) 77.6 ng/g lipid (gonad) 125.2 ng/g lipid (muscle)	Dang et al. 2016
δ-HCH						
Southwestern Michigan	Adult green frogs	1998		0.03 ng/g	Not detected in juvenile frogs	Gilliland et al. 2001
Gulf of California	Clams (*C. californiensis*)	Not reported (2015 or earlier)	<0.01–1.97 ng/g wet weight		Detection frequency 16.7% in 1 of 3 study areas, not detected in other areas; adipose tissue samples; surrounding area has primarily agricultural activity	Vargas-Gonzalez et al. 2016
Lake Apopka, Florida	Largemouth bass (*M. salmoides*)	March 2013		Not detected	Limit of quantification 0.1–0.5 ng/g wet weight	Dang et al. 2016

[a]Organism concentration unit conversion: 1 ng/g = 1 ppb.

NR = not reported; USGS = U.S. Geological Survey

γ-HCH residues were detected in fat samples of domestic farm animals collected in Ontario, Canada, in 1986–1988. Mean concentrations in fat from chickens, turkeys, beef, lamb, and pork ranged from 0.012 to 0.032 ppm; the mean concentration in hen eggs was 0.008 ppm (Frank et al. 1990). A pesticide residue screening program carried out by the H.E.B. Food Stores of San Antonio between 1989 and 1991 detected γ-HCH in 4 of 429 onion samples (detection limit 0.02 ppm); however, none of the positive samples exceeded the action level for this commodity (Schattenberg and Hsu 1992). γ-HCH was detected at levels of ≤10 ppm in 6 out of 5,784 fruit and vegetable commodities analyzed in Canada from 1992 to 1994 (Neidert and Saschenbrecker 1996). α-, β-, and γ-HCH were detected in butter samples from the United States at mean levels of 0.38, 0.42, and 0.78 ppb, respectively (Kalantzi et al. 2001). HCH isomers were also detected in butter samples from 20 other countries, with the highest levels being observed in a single butter sample from India with reported concentrations of 98, 108, and 164 ppb for α-, β-, and γ-HCH, respectively (Kalantzi et al. 2001).

Based on the most recent pesticide residue monitoring results published by the FDA from 2018, no γ-HCH residues were detected on food products produced in or imported to the United States (FDA 2020a). The products sampled were broadly encompassing of domestic and imported food and agricultural commodities, and included fruits, vegetables, grains, beans, nuts, honey, milk, and meat, amongst many other categories. A recent study, however, detected averages of 0.22 ppb α-HCH and 0.77 ppb γ-HCH in tobacco products (n=20; cigarettes from one pack were pooled for analysis) purchased in the United States (Quadroni and Bettinetti 2019). It is unclear if these products were domestic or imported.

Strategies exist to reduce pesticide residues on food products. γ-HCH residues on tomatoes decreased by 23.9% 15 days after application of the pesticide (from 0.1956 to 0.1488 ppm). Processing the tomatoes (e.g., pureeing, making tomato juice) reduced the residue levels by 100% after the waiting period; however, washing the tomatoes reduced the residues by up to 55.9% (Bessar et al. 1991). An analysis of pesticide residues in green coffee and after roasting indicated that technical-grade HCH was found in green coffee at concentrations ranging from <0.005 to 0.204 ppm. However, storage and roasting reduced the pesticide residues by 60–67% and up to 98%, respectively, with darker roasting resulting in the greatest reduction (McCarthy et al. 1992).

5.6 GENERAL POPULATION EXPOSURE

Exposure of the general population to HCH has declined steadily since its use as a pesticide was discontinued. Human exposure to γ-HCH may result from environmental exposures to contaminated water or soil, or possible ingestion of small amounts in drinking water. Historically, γ-HCH and its most persistent metabolite, β-HCH, have been detected in blood, adipose tissue, and breast milk. Based on the most recent U.S. population survey, γ-HCH is generally no longer detected in blood, but β-HCH still is (CDC 2019). This is consistent with the decreased general population exposure to γ-HCH as a pesticide. Medicinal exposure to γ-HCH can occur from prescription scabies and lice treatments. An analysis of data from 238 families in Missouri between June 1989 and March 1990 indicated that 9.2% of the families reported using Kwell shampoo (contains γ-HCH) for lice control on children (Davis et al. 1992). In general, accidental or intentional ingestion of these products would lead to the highest exposures. Worker exposure constitutes the next highest exposure population, although worker exposure is decreasing in both the number of workers exposed and the levels of exposure. Lastly, the general population receives the lowest levels, which occur mainly from ingestion of foods and water with γ-HCH residues. Living near a waste disposal site contaminated with γ-HCH will also increase the likelihood of exposure.

Ingestion of food containing pesticide residue, historically a significant route of exposure, is no longer expected to be a likely route of non-medicinal human exposure to γ-HCH. During studies conducted between 1982 and 1991, γ-HCH was detected in 4–6% of the foods collected in eight market basket surveys from different regions of the United States (Gunderson 1988, 1995a, 1995b). The most recent results of this survey reported no detections (limit of detection 0.4–2.8 ppb) in foods surveyed in 2017 for α-, β-, γ-, or δ-HCH (FDA 2020b). γ-HCH was also not detected in domestic or imported food products in the United States by the FDA (FDA 2020a). Foods representative of consumption patterns by eight infant and adult population groups were prepared for consumption prior to analysis in a revision to FDA's Total Diet Studies methodology. The estimated mean daily intakes (ng/kg body weight/day) of α-, β-, and γ-HCH for these groups continuously decreased between all study periods (1982–1984, 1984–1986, and 1986–1991). From 1986 to 1991 daily intakes ranged from 0.5 to 2.7 ng/kg/day for α-HCH, were all <1 ng/kg/day for β-HCH, and ranged from 0.6 to 3.2 ng/kg/day for γ-HCH (Gunderson 1988, 1995a, 1995b). An estimated γ-HCH daily dietary intake based on 2003 FDA pesticide residue monitoring data for fruits and vegetables was determined to be trace only for domestic produce and 0.00754 ng/kg/day for imported produce (Katz and Winter 2009). Because γ-HCH and its isomers were not detected in most recently available food monitoring data, current daily intake can be assumed to be negligible.

A small degree of exposure to γ-HCH from drinking water may be possible. α- and β-HCH have been detected in recent surface water and groundwater samples, from 2007 to 2020, although these samples may not represent drinking water sources (WQP 2021). γ-HCH was detected in drinking water samples collected for the 1998 to 2005 EPA 6-year review of drinking water quality (EPA 2010). Data for HCH were not reported for the most recent available period, 2006–2011.

Contaminated soils, which have been sampled as recently as 2020, may present another exposure pathway (WQP 2021). Studies in which soils containing 10 ppm radiolabeled γ-HCH were added to human skin samples at quantities that exceeded monolayer coverage (5 mg soil/cm^2 skin) demonstrated mean γ-HCH absorptions of 1.04% from sandy soils and 1.64% from silt soils (Duff and Kissel 1996). However, data from soil absorption studies can vary due to factors such as the amount of soil added to skin, exposure time, and possible evaporation of the contaminant.

The results of biomonitoring studies can be used as indicators of human exposures to HCH. The National Human Adipose Tissue Survey (NHATS) conducted in 1982 showed that β-HCH (the most prevalent HCH isomer in fatty tissue) was detected in 87% of 46 composite samples at concentrations <19–570 ng/g (ppb) (EPA 1986). It was detected most often in postmortem samples collected from individuals from the southern United States. In another survey conducted in 1970–1975, β-HCH was detected in >90% of the postmortem human adipose tissue samples at an average level of 300 ppb (Kutz et al. 1979). In a review of the NHATS data available from 1970 to 1983, EPA (1985c) reported that the estimated 1983 national median level of β-HCH was 80 ppb, in comparison to the historic level of 140 ppb. The median level had decreased over time, but the compound continued to be detected in nearly 100% of the population surveyed. Median levels were highest in the South census region and tended to increase with age but had not been found to differ across the sexes or racial groups. A further analysis of the NHATS data indicated that average β-HCH concentrations in fat had decreased from 0.45 ppm in 1970 to approximately 0.16 ppm since 1981 (Kutz et al. 1991). In a similar study in Japan, levels of HCHs in the adipose tissue of Japanese males increased from the late 1940s to 1966, coinciding with an increased annual production of HCH, and began dropping when HCHs were banned in 1971, with only the only the more persistent β-HCH isomer detected after 1974 (Loganathan et al. 1993). Recent adipose tissue concentrations in the United States were not located, but the trend towards lower concentrations may have continued following the discontinued use of γ-HCH as a pesticide.

A comparison of the levels of α- and β-HCH in the whole blood and biopsy fat of 25 patients showed median levels of <0.04 ng/g (maximum, <0.04 ng/g [LOD]) and 0.13 ng/g (maximum, 2.60 ng/g) for the blood and 1.1 ng/g (maximum, 9.6 ng/g) and 18.0 ng/g (maximum, 748.6 ng/g) for the fat tissue, respectively (Mes 1992). A further comparison of β-HCH levels in breast milk and adipose tissue samples was made for populations living near the Great Lakes (Canada only) and in other Canadian regions. Mean β-HCH levels in breast milk (0.6 ng/g, n=70 samples) and adipose tissue (23.4 ng/g, n=16 samples) were lower near the Great Lakes than in other parts of Canada (0.8 [n=305 samples] and 30.8 ng/g [n=90 samples], respectively) (Mes and Malcolm 1992). In addition, studies indicate that γ-HCH can also be present in breast milk at a previously reported average level of 0.006 ppm in Alberta, Canada (Currie et al. 1979). In a study of 50 donors of breast milk in Oahu, Hawaii, Takahashi et al. (1981) demonstrated HCH in 82% of the samples at a mean level of 81 ppb within a range of 0–480 ppb, expressed in terms of extractable lipid.

γ-HCH was one of the most frequently detected pesticides in the blood of Virginia residents, although the number of individuals sampled was not identified (Griffith and Blanke 1975). γ-HCH blood concentrations were the highest in residents of the middle age group (41–60 years). Some of the frequency of γ-HCH occurrence in the state was attributed to its common use in commercial vaporizers and its presence in cigarette smoke (Griffith and Blanke 1975). NHANES analyzed blood and urine specimens for the presence of HCH isomers. β-HCH was detected in approximately 13.9% of the U.S. population (12–74 years) in the Northeast, Midwest, and South. The median level for the 91% quantifiable positive results was 1.7 ppb (Murphy and Harvey 1985).

In a more recent study (1999–2000) of pesticide serum concentrations in pregnant Latina women living in an agricultural community in California, median serum levels were 36.9 ng/g lipid for β-HCH and 1.1 ng/g lipid for γ-HCH (Bradman et al. 2007). The median serum concentration of β-HCH was 5.9 ng/g lipid in 48 mothers enrolled in the California Childhood Leukemia Study in 2006–2007 (Whitehead et al. 2015). Maternal and blood cord samples were collected predominantly from Latina women, who were in their second or third trimester of pregnancy, as part of a study from October 2010 to June 2011 in San Francisco, California. Sixty-seven percent of maternal blood samples were above the method detection limit for β-HCH (5 ng/L wet weight). The lipid adjusted median cord:maternal serum ratio was 1.0, suggesting equivalent exposures for the fetus and the mother. (Morello-Frosch et al. 2016). In another study of 10 whole blood samples obtained from a blood donation center in Palo Alto, California, α-HCH was detected in all samples, β- and δ-HCH were detected in 60% of samples, and γ-HCH was detected in

80% of samples. Whole blood concentrations were 0.291–0.828, 0.544–1.15, 0.250–0.694, and 0.550–1.26 ng/g for α-, β-, γ-, and δ-HCH, respectively (Hao et al. 2020).

The Centers for Disease Control and Prevention (CDC) completed its Fourth National Report on Human Exposure to Environmental Chemicals that was derived from data obtained from NHANES (CDC 2019). The first report on 27 chemicals was issued in March 2001. This fourth report, released in January 2019, presents blood and urine levels of environmental chemicals from a sample of people who represent the noninstitutionalized, civilian U.S. population during 2-year study periods over 1999–2014. Lipid serum levels of β- and γ-HCH from the most recent available study period, 2013–2014 and 2011–2012, respectively, are summarized in Table 5-12. Serum monitoring was not conducted in the following NHANES study periods.

Table 5-12. Geometric Mean of the Serum Concentration (ng/g) of β-Hexachlorocyclohexane (β-HCH) (2013–2014) and γ-Hexachlorocyclohexane (γ-HCH) (2011–2012) in the U.S. Population

Population group (sex, age)	Geometric mean	Unadjusted standard error	Sample size (pools)[a]
β-HCH			
Non-Hispanic white			
Male, 12–19 years	NA[b]	NA	8
Male, 20–39 years	NA	NA	14
Male, 40–59 years	NA	NA	14
Male, ≥60 years	3.67	1.05	16
Female, 12–19 years	NA	NA	6
Female, 20–39 years	NA	NA	15
Female, 40–59 years	3.29	0.45	14
Female, ≥60 years	18.4	5.2	20
Non-Hispanic black			
Male, 12–19 years	NA	NA	6
Male, 20–39 years	NA	NA	7
Male, 40–59 years	3.70	1.11	7
Male, ≥60 years	6.90	1.67	9
Female, 12–19 years	NA	NA	6
Female, 20–39 years	NA	NA	8
Female, 40–59 years	5.61[c]	1.73	8
Female, ≥60 years	32.9	8.1	8
Mexican American			
Male, 12–19 years	NA	NA	7
Male, 20–39 years	5.52[c]	3.05	5
Male, 40-59 years	4.54	1.08	5

Table 5-12. Geometric Mean of the Serum Concentration (ng/g) of β-Hexachlorocyclohexane (β-HCH) (2013–2014) and γ-Hexachlorocyclohexane (γ-HCH) (2011–2012) in the U.S. Population

Population group (sex, age)	Geometric mean	Unadjusted standard error	Sample size (pools)[a]
Male, ≥60 years	8.64	1.27	4
Female, 12–19 years	1.35	0.25	7
Female, 20–39 years	8.28	1.76	5
Female, 40–59 years	11.4	1.1	6
Female, ≥60 years	44.4	9.6	5
All Hispanic			
Male, 12–19 years	NA	NA	10
Male, 20–39 years	4.38[c]	2.08	8
Male, 40–59 years	4.35	0.98	9
Male, ≥60 years	10.7	1.4	7
Female, 12–19 years	NA	NA	10
Female, 20–39 years	5.58	1.46	9
Female, 40–59 years	10.3	1.5	10
Female, ≥60 years	37.8	6.9	9
Asian			
Male, 12–19 years	23.0[c]	17.7	3
Male, 20–39 years	25.7	0.7	4
Male, 40–59 years	143	22	4
Male, ≥60 years	57.4[c]	41	3
Female, 12–19 years	9.01[c]	5.74	3
Female, 20–39 years	44.7[c]	14.1	5
Female, 40–59 years	227[c]	115	7
Female, ≥60 years	242[c]	101	3
γ-HCH			
Non-Hispanic white			
Male, 12–19 years	NA	NA	6
Male, 20–39 years	NA	NA	12
Male, 40–59 years	NA	NA	12
Male, ≥60 years	NA	NA	12
Female, 12–19 years	NA	NA	5
Female, 20–39 years	NA	NA	13
Female, 40–59 years	NA	NA	11
Female, ≥60 years	NA	NA	14
Non-Hispanic black			
Male, 12–19 years	NA	NA	7
Male, 20–39 years	NA	NA	9
Male, 40–59 years	NA	NA	7
Male, ≥60 years	NA	NA	9
Female, 12–19 years	NA	NA	6

Table 5-12. Geometric Mean of the Serum Concentration (ng/g) of β-Hexachlorocyclohexane (β-HCH) (2013–2014) and γ-Hexachlorocyclohexane (γ-HCH) (2011–2012) in the U.S. Population

Population group (sex, age)	Geometric mean	Unadjusted standard error	Sample size (pools)[a]
Female, 20–39 years	NA	NA	8
Female, 40–59 years	NA	NA	8
Female, ≥60 years	NA	NA	8
Mexican American			
Male, 12–19 years	NA	NA	5
Male, 20–39 years	NA	NA	4
Male, 40–59 years	NA	NA	4
Male, ≥60 years	NA	NA	2
Female, 12–19 years	NA	NA	4
Female, 20–39 years	NA	NA	4
Female, 40–59 years	NA	NA	3
Female, ≥60 years	NA	NA	3
All Hispanic			
Male, 12–19 years	NA	NA	7
Male, 20–39 years	NA	NA	8
Male, 40–59 years	NA	NA	7
Male, ≥60 years	NA	NA	6
Female, 12–19 years	NA	NA	7
Female, 20–39 years	NA	NA	8
Female, 40–59 years	NA	NA	7
Female, ≥60 years	NA	NA	7
Asian			
Male, 12–19 years	NA	NA	3
Male, 20–39 years	NA	NA	6
Male, 40–59 years	NA	NA	6
Male, ≥60 years	NA	NA	4
Female, 12–19 years	NA	NA	4
Female, 20–39 years	NA	NA	6
Female, 40–59 years	NA	NA	6
Female, ≥60 years	NA	NA	3

[a]Each pool contained serum from eight people.
[b]NA = not available; proportion of results below limit of detection (1.3 ng/g lipid for β-HCH and 0.92 ng/g lipid for γ-HCH).was too high to provide a valid result.
[c]Standard error of the mean is >30%.

[a]Source: CDC 2019

Factors such as age, dietary habits, and residence can influence the body burden of γ-HCH in exposed individuals. In one study, it was shown that women between the ages of 26 and 34 years who lived in a

rural area of India and were nonvegetarians tended to show higher body levels of γ-HCH than other Indian women who lived in an urban area or who were vegetarians (Saxena et al. 1981a). The higher levels of γ-HCH in women at an older child-bearing age suggest that a longer life span may cause a greater accumulation of pesticide in the body. Higher pesticide levels were found in mutton, eggs, and chicken, which are common in nonvegetarian meals; therefore, there tended to be a higher level of γ-HCH in the bodies of nonvegetarians. In another study, when corrected for age and BMI, vegans had an almost statistically significantly lower (p=0.076) mean β-HCH plasma concentration, not adjusted for lipids, than omnivores. Mean β-HCH plasma concentrations were 6.151 ng/g lipid for vegans and 5.720 ng/g lipid for omnivores (Arguin et al. 2010). In a study of hair samples, 460 ng/g γ-HCH was detected in samples from people who worked as pesticide applicators and 40 ng/g γ-HCH was detected in samples from people who lived close to farms in Atlanta, Georgia. Hair collected from people in Houston, Texas, representing urban environmental exposure, had 1,500 ng/g γ-HCH detected (Smith-Baker and Saleh 2011). The study authors did not suggest an explanation for the higher levels in the samples from environmentally exposed persons in Houston, Texas compared with levels in pesticide applicators in Atlanta, Georgia; however, the sample sizes were very small (eight applicators and eight each environmentally exposed persons in Atlanta and Houston). In addition, the ages of the volunteers from whom hair samples were collected were not reported, and hair from older individuals could have higher accumulation of γ-HCH. Further, there was no information on whether any volunteers had previous exposure to γ-HCH applied to the scalp for treatment of lice.

A study conducted in Colorado indicated, in general, that no quantitative relationships were demonstrated between pesticide levels in household dust and pesticide levels in blood. However, γ-HCH levels in blood sera in a pesticide formulator (16.8 ng/g) and his wife (5 ng/g) were found to be elevated in a household in which dust levels measured 5.85 ng/g (Starr et al. 1974). It is possible that the γ-HCH found in the wife's blood and in the household came from the clothes and person of the pesticide formulator.

The Nonoccupational Pesticide Exposure Study (NOPES) conducted by EPA was based on the Total Exposure Assessment Methodology (TEAM) approach to exposure estimation. NOPES was designed to provide estimates of nonoccupational exposure to 32 household pesticides in the United States. Samples were collected at two locations: (1) Jacksonville, Florida, an area representative of high pesticide usage; and (2) Springfield/Chicopee, Massachusetts, an area of low-to-moderate pesticide usage. Detectable levels of γ-HCH were found in the personal air samples of 32–70% of the Jacksonville sample population; the range of mean concentrations in the air samples was 7–22 ng/m^3. For the Springfield population,

detectable levels of γ-HCH were found in personal air samples collected from 8–10% of the population, with mean concentrations of 0.7–5 ng/m^3 (EPA 1990).

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

The populations with the most potential for chronic exposure to HCH are workers who work at facilities that produce, process, or use γ-HCH. Exposure of the general population to γ-HCH tends to be low because federal regulations limiting its use have taken effect. However, γ-HCH is available in some prescription medications (e.g., shampoos, lotions), and the possibility of exposure may arise from use of these products. Individuals living near hazardous waste sites contaminated with HCH may also be exposed.

Historically, the largest occupational exposures came from people who work with pesticides. A study on occupational pesticide exposure of commercial seed-treating applicators was conducted in Montana (Grey et al. 1983). No exposure was detectable on the chest and arm pads, but γ-HCH was detected on the hands and on the respirator pads. Workers involved with γ-HCH application complained of nasal irritation if they did not wear a respirator or mask. The α-, β-, γ-, and δ-isomers of HCH have been detected in the blood serum and adipose tissue of individuals occupationally exposed to HCH in pesticide formulation. Serum levels of <0.5 ppb–1 ppm α-HCH, <0.9 ppb–0.72 ppm β-HCH, <0.7 ppb–0.17 ppm γ-HCH, and 0.002–0.16 ppm δ-HCH have been detected in exposed workers (Baumann et al. 1980; Kashyap 1986; Morgan and Lin 1978; Nigam et al. 1986). Mean adipose tissue levels of 5.8 mg α-HCH/kg, 45.6 mg β-HCH/kg, and 3.1 mg γ-HCH/kg have also been reported in exposed workers (Baumann et al. 1980).

A number of case reports (e.g., Bhalla and Thami 2004; Daud et al. 2010; Juan et al. 2004; Paul et al. 2013; Shah et al. 2013; Ramabhatta et al. 2014; Wiles et al. 2015; Yu et al. 2015) have documented toxic effects in humans overexposed to γ-HCH through excessive dermal application or accidental or intentional ingestion of products used to treat scabies and head lice; effects observed in these studies are described in Chapter 2.

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 INFORMATION ON HEALTH EFFECTS

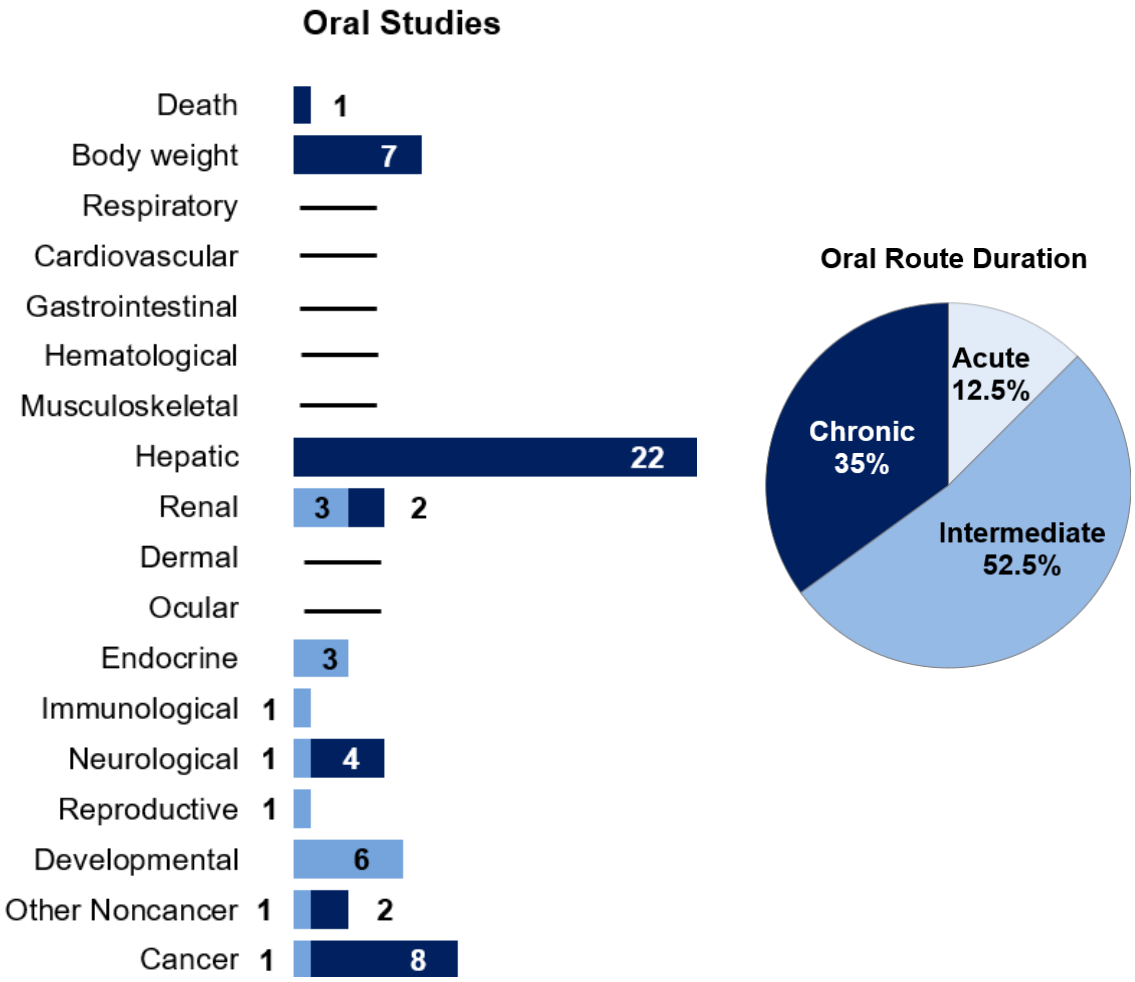
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to HCH that are discussed in Chapter 2 are summarized in Figures 6-1, 6-2, and 6-3. The purpose of these figures is to illustrate the information concerning the health effects of HCH. The number of human 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, and 6-3 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*

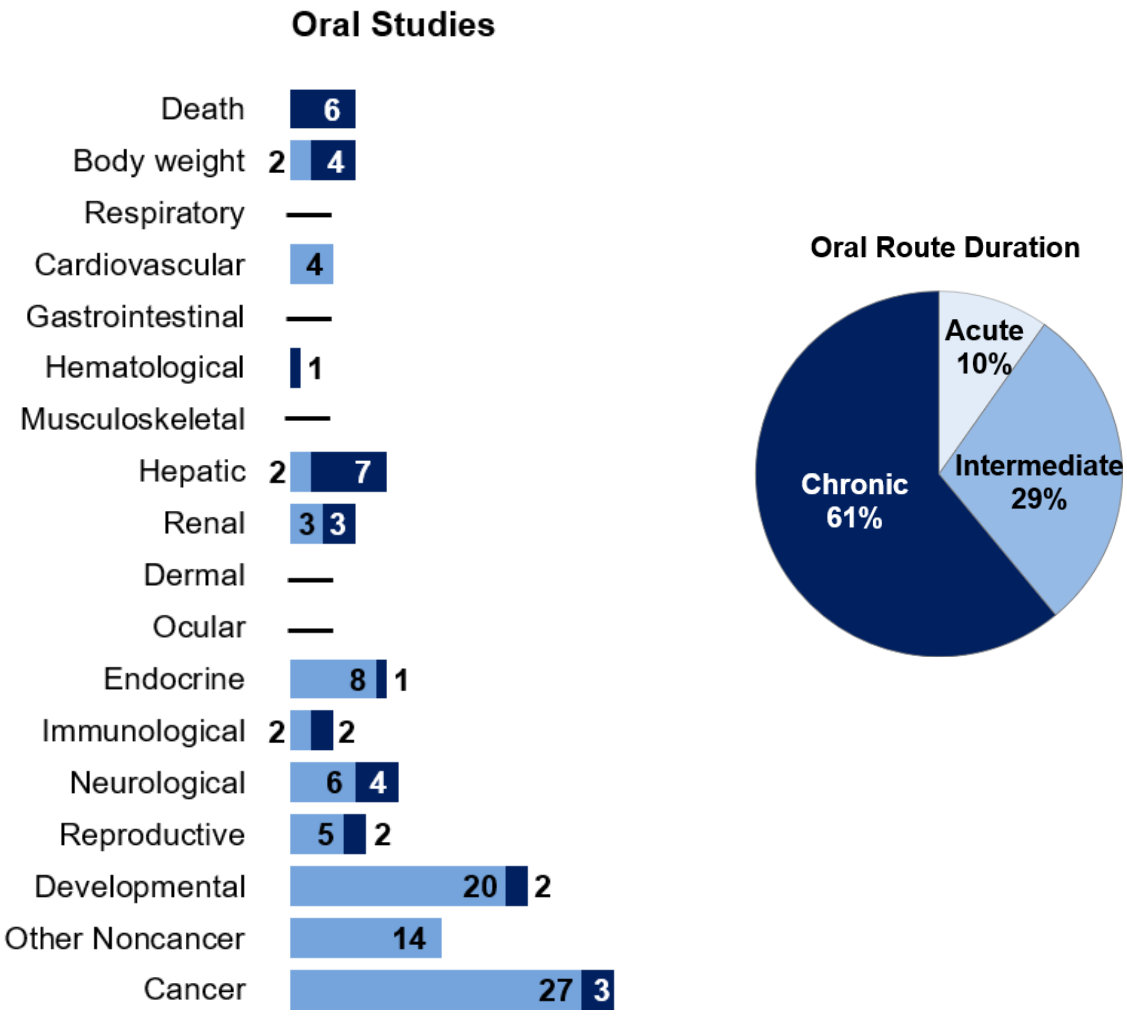
Potential body weight, liver, and cancer effects were the most studied endpoints
The majority of the studies examined oral exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. No inhalation or dermal studies in humans or animals were located.

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**)

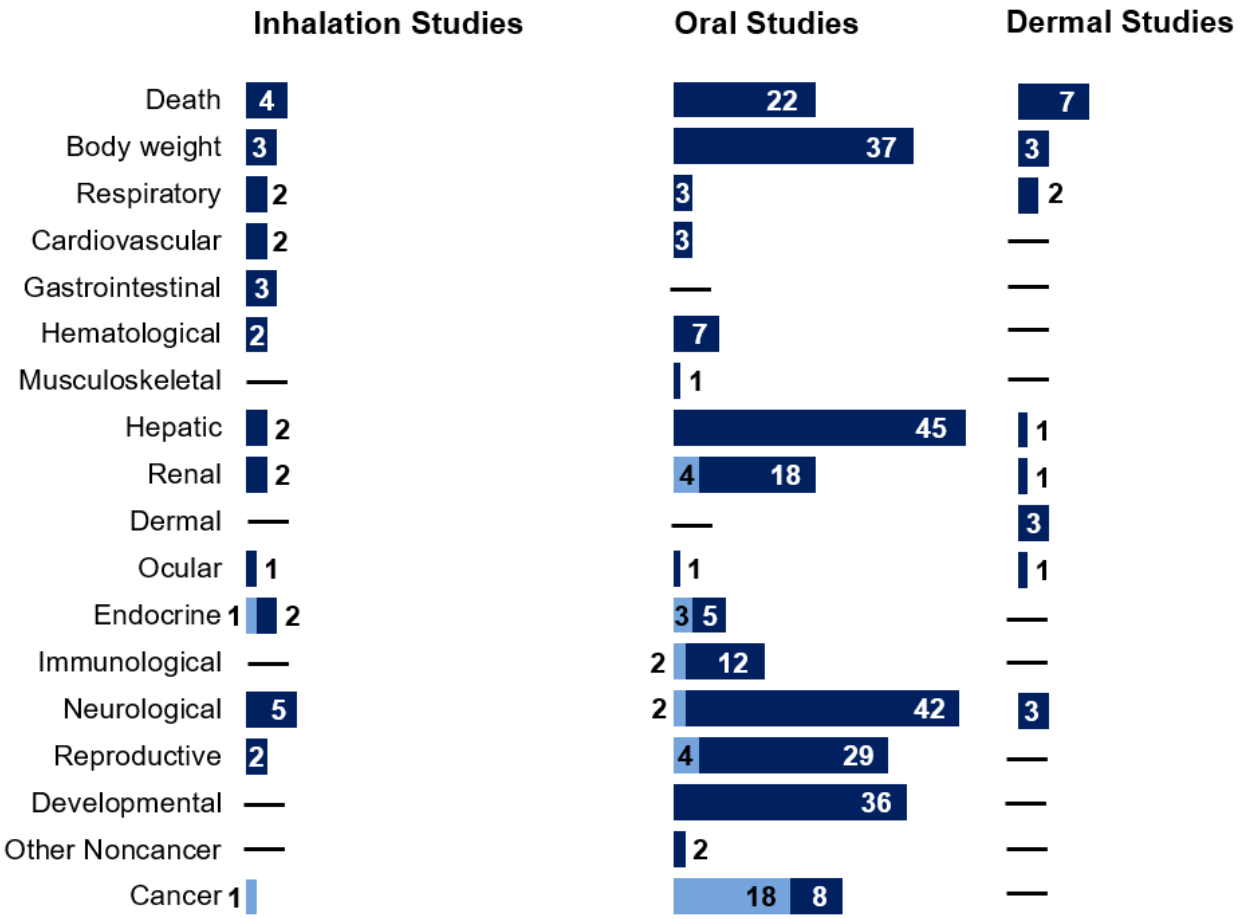


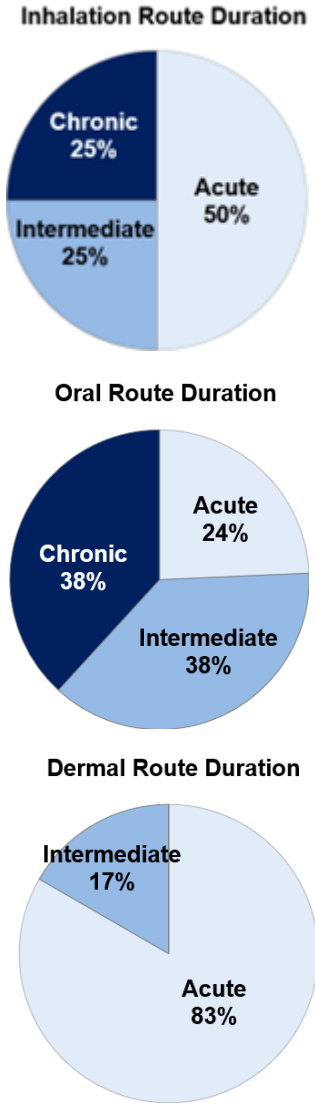
*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. No inhalation or dermal studies in humans or animals were located.

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.

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 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 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 oral exposure to α- and β-HCH, all durations of oral exposure to δ-HCH, and inhalation exposure 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. 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 it 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 ectoparasite 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 are 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

There is one ongoing study evaluating potential adverse effects of HCH in humans, as shown in Table 6-1. This study is focused on the association between organic pollutants and diabetes among Latinos.

Table 6-1. Ongoing Studies on HCH

Investigator	Affiliation	Research description	Sponsor
Persky, Victoria W	University of Illinois at Chicago	Persistent organic pollutants, endogenous hormones, and diabetes in Latinos	NIEHS

NIEHS = National Institute of Environmental Health Sciences

Source: RePORTER 2021

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding HCH in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs, which are substance-specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1.3 and Appendix A for detailed information on the MRLs for HCH.

Table 7-1. Regulations and Guidelines Applicable to Hexachlorocyclohexane (HCH)

Agency	Description	Information	Reference
	Air		
EPA	RfC	Not evaluated	IRIS 1987a, IRIS 1987b, IRIS 1987c, IRIS 1987d, IRIS 1987f
WHO	Air quality guidelines	No data	WHO 2010
	Water & Food		
EPA	Drinking water standards and health advisories		EPA 2018a
	γ-HCH		
	1-Day health advisory (10-kg child)	1 mg/L	
	10-Day health advisory (10-kg child)	1 mg/L	
	DWEL	0.2 mg/L	
	National primary drinking water regulations		EPA 2009
	γ-HCH		
	MCL and MCLG	0.0002 mg/L	
	RfD		
	β-HCH	0.00006 mg/kg/day	EPA 2006c
	γ-HCH	$3x10^{-4}$ mg/kg/day	IRIS 1987c
WHO	Drinking water quality guidelines		WHO 2017
	γ-HCH		
	Guideline value	0.002 mg/L	
	ADI	0–0.005 mg/kg body weight	
FDA	Substances added to food[a]	Not listed	FDA 2021
	Allowable level in bottled water		FDA 2017
	γ-HCH	0.0002 mg/L	

Table 7-1. Regulations and Guidelines Applicable to Hexachlorocyclohexane (HCH)

Agency	Description	Information	Reference
	Cancer		
HHS	Carcinogenicity classification		NTP 2016
	γ-HCH, technical HCH and other HCH isomers	Reasonably anticipated to be human carcinogens	
EPA	Carcinogenicity classification		
	α-HCH	Group B2[b]	IRIS 1987a
	β-HCH	Group C[c]	IRIS 1987b
	γ-HCH	Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential	EPA 2002
	δ-HCH	Group D[d]	IRIS 1987d
	Technical HCH	Group B2[b]	IRIS 1987f
	Inhalation unit risk		
	α-HCH	1.8×10^{-3} per µg/m^3	IRIS 1987a
	β-HCH	5.3×10^{-4} per µg/m^3	IRIS 1987b
	Technical HCH	5.1×10^{-4} per µg/m^3	IRIS 1987f
	Oral slope factor		
	α-HCH	6.3 per mg/kg/day	IRIS 1987a
	β-HCH	1.8 per mg/kg/day	IRIS 1987b
	Technical HCH	1.8 per mg/kg/day	IRIS 1987f
IARC	Carcinogenicity classification		
	γ-HCH	Group 1[e]	IARC 2018
	HCH	Group 2B[f]	IARC 1987
	Occupational		
OSHA	PEL (8-hour TWA) for general industry, shipyards, and construction		OSHA 2020a, 2020b, 2020c
	γ-HCH	0.5 mg/m^3 [g]	
NIOSH	REL (up to 10-hour TWA)		NIOSH 2019
	γ-HCH	0.5 mg/m^3 [g]	
	IDLH		NIOSH 1994
	γ-HCH	50 mg/m^3	
	Emergency Criteria		
EPA	AEGLs-air	No data	EPA 2018b

Table 7-1. Regulations and Guidelines Applicable to Hexachlorocyclohexane (HCH)

Agency	Description	Information	Reference
DOE	PACs-air		DOE 2018a
	γ-HCH		
	PAC-1[h]	9.1 mg/m^3	
	PAC-2[h]	100 mg/m^3	
	PAC-3[h]	1,000 mg/m^3	

[a]The Substances Added to Food inventory replaces EAFUS and contains the following types of ingredients: food and color additives listed in FDA regulations, flavoring substances evaluated by FEMA or JECFA, GRAS substances listed in FDA regulations, substances approved for specific uses in food prior to September 6, 1958, substances that are listed in FDA regulations as prohibited from use in food, delisted color additives, and some substances "no longer FEMA GRAS."
[b]Group B2: probable human carcinogen.
[c]Group C: possible human carcinogen.
[d]Group D: not classifiable as to human carcinogenicity.
[e]Group 1: carcinogenic to humans.
[f]Group 2B: possibly carcinogenic to humans.
[g]Skin notation.
[h]Definitions of PAC terminology are available from DOE (2018b).

ADI = acceptable daily intake; AEGL = acute exposure guideline levels; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FAO = Food and Agriculture Organization; FDA = Food and Drug Administration; FEMA = Flavor and Extract Manufacturers Association of the United States; GRAS = generally recognized as safe; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; JECFA = Joint FAO/WHO Expert Committee on Food Additives; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

Abd El-Moneam NM, Shreadah MA, El-Assar SA, et al. 2017. Protective role of antioxidants capacity of Hyrtios aff. Erectus sponge extract against mixture of persistent organic pollutants (POPs)-induced hepatic toxicity in mice liver: biomarkers and ultrastructural study. Environ Sci Pollut Res Int 24(27):22061-22072. http://doi.org/10.1007/s11356-017-9805-8.

Abolhassani M, Asadikaram G, Paydar P, et al. 2019. Organochlorine and organophosphorous pesticides may induce colorectal cancer; A case-control study. Ecotoxicol Environ Saf 178:168-177. http://doi.org/10.1016/j.ecoenv.2019.04.030.

Adamski JC, Pugh AL. 1996. Occurrence of pesticides in ground water of the Ozark Plateaus Province. Water Res Bull 31:97-105.

Agrahari A, Singh A, Srivastava A, et al. 2019. Overexpression of cerebral cytochrome P450s in prenatally exposed offspring modify the toxicity of lindane in rechallenged offspring. Toxicol Appl Pharmacol 371:20-37. http://doi.org/10.1016/j.taap.2019.03.022.

Ahamed M, Anand M, Kumar A, et al. 2006. Childhood aplastic anaemia in Lucknow, India: incidence, organochlorines in the blood and review of case reports following exposure to pesticides. Clin Biochem 39(7):762-766. http://doi.org/10.1016/j.clinbiochem.2006.03.021.

Ahdaya SM, Monroe RJ, Guthrie FE. 1981. Absorption and distribution of intubated insecticides in fasted mice. Pestic Biochem Physiol 16:38-46.

Ahmed FE, Hart RW, Lewis NJ. 1977. Pesticide induced DNA damage and its repair in cultured human cells. Mutat Res 42:161-174.

Ahmed RS, Suke SG, Seth V, et al. 2008. Protective effects of dietary ginger (Zingiber officinales Rosc.) on lindane-induced oxidative stress in rats. Phytother Res 22(7):902-906. http://doi.org/10.1002/ptr.2412.

Akhlaq M, Gupta AK, Yunus M. 2006. Effect of lindane pretreatment on the onset of acetaminophen induced hepatic damage in the rat. Chem Environ Res 15(1-2):93-102.

Akkina J, Reif J, Keefe T, et al. 2004. Age at natural menopause and exposure to organochlorine pesticides in Hispanic women. J Toxicol Environ Health A 67(18):1407-1422. http://doi.org/10.1080/15287390490483845.

Aks SE, Krantz A, Hryhorczuk DO. 1995. Acute accidental lindane ingestion in toddlers. Ann Emerg Med 26(5):647-651.

Alavanja MC, Hofmann JN, Lynch CF, et al. 2014. Non-Hodgkin lymphoma risk and insecticide, fungicide and fumigant use in the agricultural health study. PLoS ONE 9(10):e109332. http://doi.org/10.1371/journal.pone.0109332.

Albertson TE, Joy RM, Stark LG. 1985. Facilitation of kindling in adult rats following neonatal exposure to lindane. Dev Brain Res 17:263-266.

Albro PW, Thomas R. 1974. Intestinal absorption of hexachlorobenzene and hexachlorocyclohexane isomers in rats. Bull Environ Contam Toxicol 12:289-294.

Al-Hussaini TK, Abdelaleem AA, Elnashar I, et al. 2018. The effect of follicullar fluid pesticides and polychlorinated biphenyls concentrations on intracytoplasmic sperm injection (ICSI) embryological and clinical outcome. Eur J Obstet Gynecol Reprod Biol 220:39-43. http://doi.org/10.1016/j.ejogrb.2017.11.003.

Ali SS, Shakoori AR. 1998. Studies on the toxicity of lindane in albino rat: Histopathological effects in liver. Punjab Univ J Zool 13:149-166.

Ali U, Bajwa A, Iqbal Chaudhry MJ, et al. 2016. Significance of black carbon in the sediment-water partitioning of organochlorine pesticides (OCPs) in the Indus River, Pakistan. Ecotoxicol Environ Saf 126:177-185. http://doi.org/10.1016/j.ecoenv.2015.12.024.

Allen RH, Mage DT, Gondy G, et al. 2006. Investigation of job-related pesticide exposure in the third national health and nutrition examination survey. Arch Environ Occup Health 61(2):75-86. http://doi.org/10.3200/AEOH.61.2.75-86.

8. REFERENCES

Allsup T, Walsh D. 1982. Gas chromatographic analysis of chlorophenylmercapturic acid lindane metabolites. J Chromatogr 236:421-428.

Alvarado-Hernandez DL, Montero-Montoya R, Serrano-Garcia L, et al. 2013. Assessment of exposure to organochlorine pesticides and levels of DNA damage in mother-infant pairs of an agrarian community. Environ Mol Mutagen 54(2):99-111. http://doi.org/10.1002/em.21753.

Alvarez-Pedrerol M, Ribas-Fitó N, Torrent M, et al. 2008a. Thyroid disruption at birth due to prenatal exposure to beta-hexachlorocyclohexane. Environ Int 34(6):737-740. http://doi.org/10.1016/j.envint.2007.12.001.

Alvarez-Pedrerol M, Ribas-Fitó N, Torrent M, et al. 2008b. Effects of PCBs, p,p'-DDT, p,p'-DDE, HCB and beta-HCH on thyroid function in preschool children. Occup Environ Med 65(7):452-457. http://doi.org/10.1136/oem.2007.032763.

Alvarez-Pedrerol M, Guxens M, Ibarluzea J, et al. 2009. Organochlorine compounds, iodine intake, and thyroid hormone levels during pregnancy. Environ Sci Technol 43(20):7909-7915. http://doi.org/10.1021/es9007273.

Amyes SJ. 1990. Lindane: Combined oncogenicity and toxicity study by dietary administration to Wistar rats for 104 weeks. Suffolk, England: Life Science Research Limited. LSR Report No. 90/CIL002/0839.

Anand M, Taneja A. 2020. Organochlorine pesticides residue in placenta and their influence on anthropometric measures of infants. Environ Res 182:109106. http://doi.org/10.1016/j.envres.2019.109106.

Anand M, Gupta GSD, Gopal K, et al. 1991. Influence of dietary protein deficiency on EEG neurotransmitters and neurobehavior after chronic exposure to HCH. Toxicol Environ Chem 34:1-11.

Anand M, Meera P, Kumar R, et al. 1995. Possible role of calcium in the cardiovascular effects of prolonged administration of gamma-HCH (lindane) in rats. J Appl Toxicol 15(4):245-248.

Anand M, Singh L, Agarwal P, et al. 2019. Pesticides exposure through environment and risk of pre-term birth: a study from Agra city. Drug Chem Toxicol 42(5):471-477. http://doi.org/10.1080/01480545.2017.1413107.

Andrews JE, Gray LE. 1990. The effects of lindane and linuron on calcium metabolism, bone morphometry and the kidney in rats. Toxicology 60:99-107.

Angerer J, Heinrich R, Laudehr H. 1981. Occupational exposure to hexachlorocyclohexane. V. Gas chromatographic determination of monohydroxychlorobenzenes (chlorophenols) in urine. Int Arch Occup Environ Health 48:319-324.

Angerer J, Maass R, Heinrich R. 1983. Occupational exposure to hexachlorocyclohexane. VI. Metabolism of g-hexachlorocyclohexane in man. Int Arch Occup Environ Health 52:59-67.

Angsubhakorn S, Bhamarapravati N, Romruen K, et al. 1981. Further study of α-benzene hexachloride inhibition of aflatoxin B1 hepatocarcinogenesis in rats. Br J Cancer 43:881-883.

Anilakumar KR, Saritha V, Khanum F, et al. 2009. Ameliorative effect of ajwain extract on hexachlorocyclohexane-induced lipid peroxidation in rat liver. Food Chem Toxicol 47(2):279-282. http://doi.org/10.1016/j.fct.2008.09.061.

Appenzeller BMR, Hardy EM, Grova N, et al. 2017. Hair analysis for the biomonitoring of pesticide exposure: comparison with blood and urine in a rat model. Arch Toxicol 91(8):2813-2825. http://doi.org/10.1007/s00204-016-1910-9.

Arguin H, Sanchez M, Bray GA, et al. 2010. Impact of adopting a vegan diet or an olestra supplementation on plasma organochlorine concentrations: results from two pilot studies. Br J Nutr 103(10):1433-1441. http://doi.org/10.1017/S000711450999331X.

Arisi ACM, Simizu K, Kogake M, et al. 1994. Brain and liver lipid peroxidation levels following acute and short-term lindane administration in the rat. Toxicol Lett 74:61-68.

Aronson KJ, Wilson JW, Hamel M, et al. 2010. Plasma organochlorine levels and prostate cancer risk. J Expo Sci Environ Epidemiol 20(5):434-445. http://doi.org/10.1038/jes.2009.33.

8. REFERENCES

Arrebola JP, Pumarega J, Gasull M, et al. 2013. Adipose tissue concentrations of persistent organic pollutants and prevalence of type 2 diabetes in adults from Southern Spain. Environ Res 122:31-37. http://doi.org/10.1016/j.envres.2012.12.001.

Arrebola JP, Ocaña-Riola R, Arrebola-Moreno AL, et al. 2014. Associations of accumulated exposure to persistent organic pollutants with serum lipids and obesity in an adult cohort from Southern Spain. Environ Pollut 195:9-15. http://doi.org/10.1016/j.envpol.2014.08.003.

Arrebola JP, Belhassen H, Artacho-Cordon F, et al. 2015a. Risk of female breast cancer and serum concentrations of organochlorine pesticides and polychlorinated biphenyls: a case-control study in Tunisia. Sci Total Environ 520:106-113. http://doi.org/10.1016/j.scitotenv.2015.03.045.

Arrebola JP, Fernandez MF, Martin-Olmedo P, et al. 2015b. Historical exposure to persistent organic pollutants and risk of incident hypertension. Environ Res 138:217-223. http://doi.org/10.1016/j.envres.2015.02.018.

Arrebola JP, Ramos JJ, Bartolomé M, et al. 2019. Associations of multiple exposures to persistent toxic substances with the risk of hyperuricemia and subclinical uric acid levels in BIOAMBIENT.ES study. Environ Int 123:512-521. http://doi.org/10.1016/j.envint.2018.12.030.

Atkins DHF, Eggleton AEJ. 1971. Studies of atmospheric washout and deposition of γ-HHC, dieldrin, and p,p-DDT using radiolabelled pesticides. In: Nuclear techniques in environmental pollution: Proceedings of a symposium on use of nuclear techniques in the measurement and control of environmental pollution held by the International Atomic Energy Agency in Salzburg, 26-30 October 1970. Vienna: International Atomic Energy Agency, 521-533.

Atlas E, Giam CS. 1988. Ambient concentrations and precipitation scavenging of atmospheric organic pollutants. Water Air Soil Pollut 38:19-36.

ATSDR. 1989. Decision guide for identifying substance-specific data needs related to toxicological profiles; Notice. Agency for Toxic Substances and Disease Registry. Fed Regist 54(174):37618-37634.

ATSDR. 2018. Draft guidance for the preparation of toxicological profiles. Agency for Toxic Substances and Disease Registry. https://www.atsdr.cdc.gov/toxprofiles/guidance/profile_development_guidance.pdf. September 29, 2022.

ATSDR. 2019. Hexachlorocyclohexane. Full SPL data. Substance priority list (SPL) resource page. Agency for Toxic Substances and Disease Registry.

Attia AM, Richardson BA, Rodriguez C, et al. 1991. Lindane may enhance nocturnal pineal N-acetyltransferase activity via β-adrenergic receptors. Brain Res 554:253-256.

Attia AM, El-Banna SG, Nomeir FR, et al. 2011. Lindane-induced biochemical perturbations in rat serum and attenuation by omega-3 and Nigella sativa seed oil. Indian J Biochem Biophys 48(3):184-190.

Aulakh RS, Bedi JS, Gill JP, et al. 2007. Occurrence of DDT and HCH insecticide residues in human biopsy adipose tissues in Punjab, India. Bull Environ Contam Toxicol 78(5):330-334. http://doi.org/10.1007/s00128-007-9187-6.

Baker MT, Nelson RM, Van DR. 1985. The formation of chlorobenzene and benzene by the reductive metabolism of lindane in rat liver microsomes. Arch Biochem Biophys 236:506-514.

Band PR, Abanto Z, Bert J, et al. 2011. Prostate cancer risk and exposure to pesticides in British Columbia farmers. Prostate 71(2):168-183. http://doi.org/10.1002/pros.21232.

Banerjee BD, Koner BC, Ray A, et al. 1996. Influence of subchronic exposure to lindane on humoral immunity in mice. Indian J Exp Bio 34:1109-1113.

Barnes DG, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessments. Regul Toxicol Pharmacol 8:471-486.

Barros SB, Simizu K, Junqueira VB. 1991. Liver lipid peroxidation-related parameters after short-term administration of hexachlorocyclohexane isomers to rats. Toxicol Lett 56:137-144.

8. REFERENCES

Barry KH, Koutros S, Berndt SI, et al. 2011. Genetic variation in base excision repair pathway genes, pesticide exposure, and prostate cancer risk. Environ Health Perspect 119(12):1726-1732. http://doi.org/10.1289/ehp.1103454.

Bashir S, Hitzfeld KL, Gehre M, et al. 2015. Evaluating degradation of hexachlorocyclohexane (HCH) isomers within a contaminated aquifer using compound-specific stable carbon isotope analysis (CSIA). Water Res 71:187-196. http://doi.org/10.1016/j.watres.2014.12.033.

Bassig BA, Shu XO, Sjodin A, et al. 2020. Prediagnostic blood levels of organochlorines and risk of non-Hodgkin lymphoma in three prospective cohorts in China and Singapore. Int J Cancer 146(3):839-849. http://doi.org/10.1002/ijc.32350.

Baumann K, Angerer J, Heinrich R, et al. 1980. Occupational exposure to hexachlorocyclohexane. I. Body burden of HCH-isomers. Int Arch Occup Health 47:119-127.

Beard AP, Rawlings NC. 1998. Reproductive effects in mink (Mustela vison) exposed to the pesticides lindane, carbofuran and pentachlorophenol in a multigenerational study. J Reprod Fertil 113:93-104.

Beard AP, Rawlings NC. 1999. Thyroid function and effects on reproduction in ewes exposed to the organochlorine pesticides lindane or pentachlorophenol (PCP) from conception. J Toxicol Environ Health A 58:509-530.

Beard AP, McRae AC, Rawlings NC. 1997. Reproductive efficiency in mink (Mustela vison) treated with the pesticides lindane, carbofuran and pentachlorophenol. J Reprod Fertil 111:21-28.

Beard AP, Bartleweski PM, Rawlings NC. 1999b. Endocrine and reproductive function in ewes exposed to the organochlorine pesticides lindane or pentachlorophenol. J Toxicol Environ Health 56(1):23-46. http://doi.org/10.1080/009841099158213.

Beard AP, Bartlewski PM, Chandolia RK, et al. 1999a. Reproductive and endocrine function in rams exposed to the organochlorine pesticides lindane and pentachlorophenol from conception. J Reprod Fertil 115:303-314.

Bedi JS, Gill JP, Aulakh RS, et al. 2013. Pesticide residues in human breast milk: risk assessment for infants from Punjab, India. Sci Total Environ 463-464:720-726. http://doi.org/10.1016/j.scitotenv.2013.06.066.

Bemy PJ, Veniat A, Mazallon M. 2003. Bioaccumulation of lead, cadmium, and lindane in zebra mussels (Dreissena polymorpha) and associated risk for bioconcentration in tufted duck (Aythia fuligula). Bull Environ Contam Toxicol 71(1):90-97. http://doi.org/10.1007/s00128-003-0135-9.

Benjamin N, Kushwah A, Sharma RK, et al. 2006. Histopathological changes in liver, kidney and muscles of pesticides exposed malnourished and diabetic rats. Indian J Exp Biol 44(3):228-232.

Berg GL. 1988. Lindane. In: Farm chemicals handbook. Willoughby, OH: Meister Publishing Co.,

Berny P, Lachaux O, Buronfosse T, et al. 2002. Zebra mussels (Dreissena polymorpha) as indicators of freshwater contamination with lindane. Environ Res 90(2):142-151. http://doi.org/10.1006/enrs.2002.4371.

Berry DH, Brewster MA, Watson R, et al. 1987. Untoward effects associated with lindane abuse [letter]. Am J Dis Child 141:125-126.

Bessar BAA, Korany K, Szabo AS. 1991. Effect of home preparative procedures and technological processes on lindane residues in tomato. Acta Aliment 20:25-30.

Bevenue A, Hylin JW, Kawano Y, et al. 1972. Pesticides in water: Organochlorine pesticide residues in water, sediment, algae and fish: Hawaii 1970-1971. Pestic Monit J 6:56-72.

Bhalla M, Thami GP. 2004. Reversible neurotoxicity after an overdose of topical lindane in an infant. Pediatr Dermatol 21(5):597-599. http://doi.org/10.1111/j.0736-8046.2004.21515.x.

Bhatt DK, Bano M. 2009. Modulation of tricarboxylic acid cycle dehydrogenases during hepatocarcinogenesis induced by hexachlorocyclohexane in mice. Exp Toxicol Pathol 61(4):325-332. http://doi.org/10.1016/j.etp.2008.09.004.

Bhatt DK, Nagda G. 2012. Modulation of acid phosphatase and lactic dehydrogenase in hexachlorocyclohexane-induced hepatocarcinogenesis in mice. J Biochem Mol Toxicol 26(11):439-444. http://doi.org/10.1002/jbt.21441.

8. REFERENCES

Biberhofer J, Stevens RJJ. 1987. Organochlorine contaminants in ambient waters of Lake Ontario. Environment Canada, Inland Waters/Lands Director Scientific Series No. 159.

Boffa MJ, Brough PA, Ead RD. 1995. Lindane neurotoxicity. Br J Dermatol 133(6):1013.

Boll M, Weber LW, Stampfl A. 1995. The effect of γ-hexachlorocyclohexane (lindane) on the activities of liver lipogenic enzymes and on serum lipids in rats. Z Naturforsch C J Biosci 50(1-2):135-142. http://doi.org/10.1515/znc-1995-1-220.

Bosch AL. 1987a. Dermal absorption of 14C-lindane in male rats. Madison, WI: Hazelton Laboratories America, Inc. HLA Study No. 6188-103.

Bosch AL. 1987b. Dermal absorption of 14C-lindane in male rabbits. Madison, WI: Hazelton Laboratories America, Inc. HLA Study No. 6188-104.

Bradman AS, Schwartz JM, Fenster L, et al. 2007. Factors predicting organochlorine pesticide levels in pregnant Latina women living in a United States agricultural area. J Expo Sci Environ Epidemiol 17(4):388-399. http://doi.org/10.1038/sj.jes.7500525.

Brannen KC, Devaud LL, Liu J. 1998. Prenatal exposure to neurotoxicants dieldrin or lindane alters tert-butylbicyclophosphorothionate binding to GABA(A) receptors in fetal rat brainstem. Dev Neurosci 20:34-41.

Brassow HL, Baumann K, Lehnert G. 1981. Occupational exposure to hexachlorocyclohexane. II. Health conditions of chronically exposed workers. Int Arch Occup Environ Health 48:81-87.

Braun JM, Kalkbrenner AE, Just AC, et al. 2014. Gestational exposure to endocrine-disrupting chemicals and reciprocal social, repetitive, and stereotypic behaviors in 4- and 5-year-old children: the HOME study. Environ Health Perspect 122(5):513-520. http://doi.org/10.1289/ehp.1307261.

Brauner EV, Sorensen M, Gaudreau E, et al. 2012. A prospective study of organochlorines in adipose tissue and risk of non-Hodgkin lymphoma. Environ Health Perspect 120(1):105-111. http://doi.org/10.1289/ehp.1103573.

Bravo N, Grimalt JO, Chashchin M, et al. 2019. Drivers of maternal accumulation of organohalogen pollutants in Arctic areas (Chukotka, Russia) and 4,4'-DDT effects on the newborns. Environ Int 124:541-552. http://doi.org/10.1016/j.envint.2019.01.049.

Breton P, Bouvet S, Delamanche I, et al. 2005. Electrocorticogram disturbances detected in rats exposed from early stages of life to residual doses of lindane. Pestic Biochem Physiol 81(2):97-104. http://doi.org/10.1016/j.pestbp.2004.10.001.

Brubaker WW, Hites RA. 1998. Gas-phase oxidation products of biphenyl and polychlorinated biphenyls. Environ Sci Technol 32:3913-3918.

Buck Louis GM, Chen Z, Peterson CM, et al. 2012. Persistent lipophilic environmental chemicals and endometriosis: the ENDO Study. Environ Health Perspect 120(6):811-816. http://doi.org/10.1289/ehp.1104432.

Budavari S, O'Neil MJ, Smith A, et al. 1989. Lindane. In: The Merck index. Rahway, NJ: Merck & Co., Inc, 866-867.

Burns JS, Williams PL, Korrick SA, et al. 2014. Association between chlorinated pesticides in the serum of prepubertal Russian boys and longitudinal biomarkers of metabolic function. Am J Epidemiol 180(9):909-919. http://doi.org/10.1093/aje/kwu212.

Butte W, Fox K, Zauke GP. 1991. Kinetics of bioaccumulation and clearance of isomeric hexachlorocyclohexanes. Sci Total Environ 109-110:377-382.

Callan AC, Hinwood AL, Heyworth J, et al. 2016. Sex specific influence on the relationship between maternal exposures to persistent chemicals and birth outcomes. Int J Hyg Environ Health 219(8):734-741. http://doi.org/10.1016/j.ijheh.2016.09.018.

Cantor KP, Strickland PT, Brock JW, et al. 2003. Risk of non-Hodgkin's lymphoma and prediagnostic serum organochlorines: β-hexachlorocyclohexane, chlordane/heptachlor-related compounds, dieldrin, and hexachlorobenzene. Environ Health Perspect 111(2):179-183. http://doi.org/10.1289/ehp.4347.

Capt A, Luzy AP, Esdaile D, et al. 2007. Comparison of the human skin grafted onto nude mouse model with in vivo and in vitro models in the prediction of percutaneous penetration of three lipophilic pesticides. Regul Toxicol Pharmacol 47(3):274-287. http://doi.org/10.1016/j.yrtph.2006.11.008.

Caquet T, Thybaud E, Lebras S, et al. 1992. Fate and biological effects of lindane and deltamethrin in fresh-water mesocosms. Aquat Toxicol 23:261-278.

CDC. 2005. Unintentional topic lindane ingestions - United States, 1998-2003. Centers for Disease Control and Prevention. MMWR Rep 54(21):533-535.

CDC. 2019. Fourth national report on human exposure to environmental chemicals, updated tables. January 2019. Centers for Disease Control and Prevention. https://www.cdc.gov/exposurereport/. December 11, 2019.

Cerón JJ, Panizo CG, Montes A. 1995. Toxicological effects in rabbits induced by endosulfan, lindane, and methylparathion representing agricultural byproducts contamination. Bull Environ Contam Toxicol 54:258-265.

Chadwick RW, Freal JJ. 1972a. The identification of five unreported lindane metabolites recovered from rat urine. Bull Environ Contam Toxicol 7:137-146.

Chadwick RW, Freal JJ. 1972b. Comparative acceleration of lindane metabolism to chlorophenols by pretreatment of rats with lindane or with DDT and lindane. Food Cosmet Toxicol 10:789-795.

Chadwick R, Peoples A, Cranmer M. 1972. The effect of ascorbic acid deficiency and protein quality on stimulation of hepatic microsomal enzymes in guinea pigs. Toxicol Appl Pharmacol 22:308-309.

Chadwick RW, Copeland MF, Chadwick C. 1978a. Enhanced pesticide metabolism: A previously unreported effect of dietary fibre in mammals. Food Cosmet Toxicol 16:217-225.

Chadwick RW, Faeder EJ, King LC, et al. 1978b. Effect of acute and chronic Cd exposure on lindane metabolism. Ecotoxicol Environ Saf 2:301-316.

Chadwick RW, Freal JJ, Sovocool GW, et al. 1978c. The identification of three previously unreported lindane metabolites from mammals. Chemosphere 8:633-640.

Chadwick RW, Copeland MF, Mole ML, et al. 1981. Comparative effect of pretreatment with phenobarbital, Aroclor 1254, and β-naphthoflavone on the metabolism of lindane. Pestic Biochem Physiol 15:120-136.

Chadwick RW, Copeland MF, Wolff GL, et al. 1985. Effects of age and obesity on the metabolism of lindane by black a/a, yellow A^{vy}/a, and pseudoagouti A^{vy}/a phenotypes of (YS x VY) F_1 hybrid mice. J Toxicol Environ Health 16:771-796.

Chadwick RW, Cooper RL, Chang J, et al. 1988. Possible antiestrogenic activity of lindane in female rats. J Biochem Toxicol 3:147-158.

Chand B, Ramachandran M. 1980. Effect of dietary hexachlorocyclohexane on certain biochemical changes in albino rat. Indian J Exp Biol 18:735-736.

Chartrand M, Passeport E, Rose C, et al. 2015. Compound specific isotope analysis of hexachlorocyclohexane isomers: a method for source fingerprinting and field investigation of in situ biodegradation. Rapid Commun Mass Spectrom 29(6):505-514. http://doi.org/10.1002/rcm.7146.

Chen ZM, Zabik MJ, Leavitt RA. 1984. Comparative study of thin film photodegradative rates for 36 pesticides. Ind Eng Chem Prod Res Dev 23:5-11.

Chen Z, Zhao Y, Guo T, et al. 2013. Accumulation and phytoavailability of hexachlorocyclohexane isomers and cadmium in Allium sativum L. under the stress of hexachlorocyclohexane and cadmium. Bull Environ Contam Toxicol 90(2):182-187. http://doi.org/10.1007/s00128-012-0882-6.

Chen MW, Santos HM, Que DE, et al. 2018. Association between organochlorine pesticide levels in breast milk and their effects on female reproduction in a Taiwanese population. Int J Environ Res Public Health 15(5):931. http://doi.org/10.3390/ijerph15050931.

Chiou CT, McGroddy SE, Kile DE. 1998. Partition characteristics of polycyclic aromatic hydrocarbons on soils and sediments. Environ Sci Technol 32:264-269.

Cifone MA. 1990. Lindane (technical): In the in vitro rat primary hepatocyte unscheduled DNA synthesis assay. Kensington, MD: Hazelton Laboratories America, Inc. HLA Study No. 12024-0-447.

Clark DE, Smalley HE, Crookshank HR, et al. 1974. Residues in food and feed: Chlorinated hydrocarbon insecticide residues in feed and carcasses of feedlot cattle, Texas–1972. Pestic Monit J 8:180-183.

Clayton G, Clayton F, eds. 1981. Hexachlorocyclohexane. In: Patty's industrial hygiene and toxicology. Vol. IIB. 3rd ed. New York, NY: John Wiley & Sons, 3740-3749.

Clewell HJ, Andersen ME. 1985. Risk assessment extrapolations and physiological modeling. Toxicol Ind Health 1(4):111-131.

Cocco P, Brennan P, Ibba A, et al. 2008. Plasma polychlorobiphenyl and organochlorine pesticide level and risk of major lymphoma subtypes. Occup Environ Med 65(2):132-140. http://doi.org/10.1136/oem.2007.033548.

Cole RH, Frederick RE, Healy RP, et al. 1984. Preliminary findings of the priority pollutant monitoring project of the nationwide urban runoff program. J Water Pollut Control Fed 56:898-908.

Conley BE. 1952. Health hazards of electric vaporizing devices for insecticides. JAMA 149:367-369.

Cornacoff JB, Lauer LD, House RV, et al. 1988. Evaluation of the immunotoxicity of β-hexachlorocyclohexane (β-HCH). Fundam Appl Toxicol 11:293-299.

Cortes DR, Hites RA. 2000. Detection of statistically significant trends in atmospheric concentrations of semivolatile compounds. Environ Sci Technol 34:2826-2829.

Crockett AB, Wiersma GB, Tai H, et al. 1974. Pesticides in soil: Pesticide residue levels in soils and crops, FY-70 - National Soils Monitoring Program (II). Pestic Monit J 8:69-97.

Cupul-Uicab LA, Klebanoff MA, Brock JW, et al. 2013. Prenatal exposure to persistent organochlorines and childhood obesity in the US collaborative perinatal project. Environ Health Perspect 121(9):1103-1109. http://doi.org/10.1289/ehp.1205901.

Curren MS, Davis K, Liang CL, et al. 2014. Comparing plasma concentrations of persistent organic pollutants and metals in primiparous women from northern and southern Canada. Sci Total Environ 479-480:306-318. http://doi.org/10.1016/j.scitotenv.2014.01.017.

Currie RA, Kadis VW, Breitkreitz WE, et al. 1979. Pesticide residues in human milk, Alberta, Canada - 1966-1970, 1977-1978. Pestic Monit J 13:52-55.

Czeglédi-Jankó G, Avar P. 1970. Occupational exposure to lindane: Clinical and laboratory findings. Br J Ind Med 27:283-286.

Dallaire R, Dewailly E, Pereg D, et al. 2009. Thyroid function and plasma concentrations of polyhalogenated compounds in Inuit adults. Environ Health Perspect 117(9):1380-1386. http://doi.org/10.1289/ehp.0900633.

Dalsenter PR, Faqi AS, Chahoud I. 1997a. Serum testosterone and sexual behavior in rats after prenatal exposure to lindane. Bull Environ Contam Toxicol 59:360-366.

Dalsenter PR, Faqi AS, Webb J, et al. 1996. Reproductive toxicity and tissue concentrations of lindane in adult male rats. Hum Exp Toxicol 15:406-410.

Dalsenter PR, Faqi AS, Webb J, et al. 1997b. Reproductive toxicity and toxicokinetics of lindane in the male offspring of rats exposed during lactation. Hum Exp Toxiol 16:146-153.

Dang VD, Kroll KJ, Supowit SD, et al. 2016. Tissue distribution of organochlorine pesticides in largemouth bass (Micropterus salmoides) from laboratory exposure and a contaminated lake. Environ Pollut 216:877-883. http://doi.org/10.1016/j.envpol.2016.06.061.

Daniels SI, Chambers JC, Sanchez SS, et al. 2018. Elevated levels of organochlorine pesticides in South Asian immigrants are associated with an increased risk of diabetes. J Endocr Soc 2(8):832-841. http://doi.org/10.1210/js.2017-00480.

Danopoulos E, Melissinos K, Katsas G. 1953. Serious poisoning by hexachlorocyclohexane. Arch Ind Hyg 8:582-587.

Daud Y, Daud-ur-Rehman, Farooq U. 2010. Lindane toxicity in a 7 year old boy. J Ayub Med Coll Abbottabad 22(4):223.

Davies JE, Dedhia H, Morgade C, et al. 1983. Lindane poisonings. Arch Dermatol 119:142-144.

Davis JR, Brownson RC, Garcia R. 1992. Family pesticide use in the home, garden, orchard, and yard. Arch Environ Contam Toxicol 22:260-266.

8. REFERENCES

Debost-Legrand A, Warembourg C, Massart C, et al. 2016. Prenatal exposure to persistent organic pollutants and organophosphate pesticides, and markers of glucose metabolism at birth. Environ Res 146:207-217. http://doi.org/10.1016/j.envres.2016.01.005.

DeJongh J, Blaauboer BJ. 1997. Simulation of lindane kinetics in rats. Toxicology 122:1-9.

Desi I. 1974. Neurotoxicological effect of small quantities of lindane. Animal studies. Int Arch Arbeitsmed 33(2):153-162. http://doi.org/10.1007/BF00538999.

Desi I, Varga L, Farkas I. 1978. Studies on the immunosuppressive effect of organochlorine and organophosphoric pesticides in subacute experiments. J Hyg Epidemiol Microbiol Immunol Praha 22:115-122.

Dewan A, Gupta SK, Jani JP, et al. 1980. Effect of lindane on antibody response to typhoid vaccine in weanling rats. J Environ Sci Health B 15:395-402.

Dewan P, Jain V, Gupta P, et al. 2013. Organochlorine pesticide residues in maternal blood, cord blood, placenta, and breastmilk and their relation to birth size. Chemosphere 90(5):1704-1710. http://doi.org/10.1016/j.chemosphere.2012.09.083.

Di Consiglio E, De Angelis G, Traina ME, et al. 2009. Effect of lindane on CYP-mediated steroid hormone metabolism in male mice following in utero exposure. J Appl Toxicol 29(8):648-655. http://doi.org/10.1002/jat.1452.

Dick IP, Blain PG, Williams FM. 1997a. The percutaneous absorption and skin distribution of lindane in man. I. In vivo studies. Hum Exp Toxicol 16:645-651.

Dick IP, Blain PG, Williams FM. 1997b. The percutaneous absorption and skin distribution of lindane in man. II. In vitro studies. Hum Exp Toxicol 16:652-657.

Dietrich DR, Swenberg JA. 1990. Lindane induces nephropathy and renal accumulation of α2μ- globulin in male but not in female Fischer 344 rats or male NBR rats. Toxicol Lett 53:179-181.

Dietrich DR, Swenberg JA. 1991. NCI-Black-Reiter (NBR) male rats fail to develop renal disease following exposure to agents that induce α-2μ-globulin ($\alpha_{2\mu}$) nephropathy. Fundam Appl Toxicol 16:749-762.

Dikshith TSS, Chandra P, Datta KK. 1973. Effect of lindane on the skin of albino rats. Experientia 29:684-685.

Dikshith TS, Srivastava MK, Raizada RB. 1990. Fetotoxicity of hexachlorocyclohexane (HCH) in mice: Morphological, biochemical and residue evaluations. Vet Hum Toxicol 32:524-527.

Dikshith TSS, Raizada RB, Srivastava MK. 1991a. Long-term dietary study and development of no-observed-effect level (NOEL) of technical hexachlorocyclohexane to rats. J Toxicol Environ Health 34:495-507.

Dikshith TS, Srivastava MK, Raizada RB. 1991b. Response of young rats to repeated oral administration of technical hexachlorocyclohexane. Vet Hum Toxicol 33:235-237.

Dikshith TSS, Datta KK, Kushwah HS, et al. 1978. Histopathological and biochemical changes in guinea pigs after repeated dermal exposure to benzene hexachloride. Toxicology 10:55-66.

Dikshith TSS, Carrera G, Raizada RB, et al. 1989a. Interaction of hexachlorocyclohexane (HCH) and chloropropham (CIPC) in male rats. Toxicol Lett 45:281-288.

Dikshith TSS, Raizada RB, Srivastava MK, et al. 1989b. Dermal toxicity of hexachlorocyclohexane (HCH) in rabbit. Indian J Exp Biol 27:252-257.

Dikshith TS, Raizada RB, Singh V, et al. 1991c. Repeated dermal toxicity of technical HCH and methyl parathion (50EC) to female rats (Rattus norvigicus). Indian J Exp Biol 29:149-155.

Dimitriadou L, Malarvannan G, Covaci A, et al. 2016. Levels and profiles of brominated and chlorinated contaminants in human breast milk from Thessaloniki, Greece. Sci Total Environ 539:350-358. http://doi.org/10.1016/j.scitotenv.2015.08.137.

Doan TQ, Berntsen HF, Verhaegen S, et al. 2019. A mixture of persistent organic pollutants relevant for human exposure inhibits the transactivation activity of the aryl hydrocarbon receptor in vitro. Environ Pollut 254(Pt B):113098. http://doi.org/10.1016/j.envpol.2019.113098.

DOE. 2018a. Table 3: Protective action criteria (PAC) rev. 29a based on applicable 60-minute AEGLs, ERPGs, or TEELs. The chemicals are listed by CASRN. June 2018. U.S. Department of Energy. https://edms.energy.gov/pac/docs/Revision_29A_Table3.pdf. April 12, 2020.

DOE. 2018b. Protective action criteria (PAC) with AEGLs, ERPGs, & TEELs: Rev. 29A, June 2018. U.S. Department of Energy. https://edms.energy.gov/pac/. April 12, 2020.

Dorfler U, Schneider P, Scheunert I. 1991a. Volatilization rates of pesticides from soil and plant surfaces under controlled conditions. Toxicol Environ Chem 31-32:87-95.

Dorfler U, Adler-Koehler R, Schneider P, et al. 1991b. A laboratory model system for determining the volatility of pesticides from soil and plant surfaces. Chemosphere 23:485-496.

Duff RM, Kissel JC. 1996. Effect of soil loading on dermal absorption efficiency from contaminated soil. J Toxicol Environ Health 48:98-106.

Dzwonkowska A, Hubner H. 1986. Induction of chromosomal aberrations in the Syrian hamster by insecticides tested in vivo. Arch Toxicol 58:152-156.

Egeler P, Meller RM, Knacker T, et al. 1997. Bioaccumulation of lindane and hexachlorobenzene by tubificid sludgeworms (oligochaeta) under standardized laboratory conditions. Chemosphere 35(4):835- 852.

Eichler D, Heupt W, Paul W. 1983. Comparative study on the distribution of α- and g-hexachlorocyclohexane in the rat with particular reference to the problem of isomerization. Xenobiotica 13:639-647.

Eisenreich SJ, Looney BB, Thornton JD. 1981. Airborne organic contaminants in the Great Lakes ecosystem. Environ Sci Technol 15:30-38.

Eitzer BD, Chevalier A. 1999. Landscape care pesticide residues in residential drinking water wells. Bull Environ Contam Toxicol 62:420-427.

Elserougy S, Beshir S, Saad-Hussein A, et al. 2013. Organochlorine pesticide residues in biological compartments of healthy mothers. Toxicol Ind Health 29(5):441-448. http://doi.org/10.1177/0748233712436645.

Engst R, Macholz RH, Kujawa H. 1979. [Metabolism of lindane in microbial organisms, warm- blooded animals and humans]. Gig Sanit 10:64-65.

Engst R, Macholz R, Kujawa M, et al. 1976. The metabolism of lindane and its metabolites gamma-2,3,4,5,6-pentachlorocyclohexene, pentachlorobenzene, and pentachlorophenol in rats and the pathways of lindane metabolism. J Environ Sci Health B 11:95-117.

Ennaceur S. 2017. Study of the genotoxic and cytotoxic effects of the α-, β-, and γ-Hexachlorocyclohexane isomers in human lymphocyte cells using the cytokinesis-block micronucleus assay. Drug Chem Toxicol 40(1):85-89. http://doi.org/10.1080/01480545.2016.1175008.

EPA. 1974. Pesticide in the Illinois waters of Lake Michigan. Washington, DC: U.S. Environmental Protection Agency. EPA660374002.

EPA. 1975. Guidelines for the disposal of small quantities of unused pesticides. Washington, DC: U.S. Environmental Protection Agency. EPA670276057. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=300051QF.txt. May 5, 2021.

EPA. 1979. Water-related environmental fate of 129 priority pollutants. Volume I: Introduction and technical background, metals and inorganics, pesticides and PCBs. Washington, DC: U.S. Environmental Protection Agency. EPA440479029a.

EPA. 1980. Manual of analytical methods for the analysis of pesticides in humans and environmental samples. Research Triangle Park, NC: U.S. Environmental Protection Agency. EPA600880038. https://nepis.epa.gov/Exe/ZyPDF.cgi/20007QPD.PDF?Dockey=20007QPD.PDF. May 5, 2021.

EPA. 1982a. Aquatic fate process data for organic priority pollutants. Washington, DC: U.S. Environmental Protection Agency. EPA440481014.

EPA. 1982b. Retention and transformation of selected pesticides and phosphorous in soil-water systems: A critical review. Athens, GA: U.S. Environmental Protection Agency. EPA600382060.

EPA. 1985a. Drinking water criteria document for lindane. Cincinnati, OH: U.S. Environmental Protection Agency. EPA600X841821.

EPA. 1985b. Guidance for the reregistration of pesticide products containing lindane as the active ingredient. Washington, DC: U.S. Environmental Protection Agency. EPARS85027.

EPA. 1985c. Baseline estimates and time trends for beta-benzene hexachloride, hexachlorobenzene, and polychlorinated biphenyls in human adipose tissue: 1970-1983. Washington, DC: U.S. Environmental Protection Agency. EPA560585025.

EPA. 1986. Broad scan analysis of the FY82 national human adipose tissue survey specimens. Volume 1 - Executive summary. Washington, DC: U.S. Environmental Protection Agency.

EPA. 1988a. Data evaluation report: Lindane. 13-week dermal toxicity study (with interim kill and recovery period) in the rat. Hazelton UK. Submitted to the U.S. Environmental Protection Agency. Record No. 231696.

EPA. 1988b. Recommendations for and documentation of biological values for use in risk assessment. Washington, DC: U.S. Environmental Protection Agency. EPA600687008. https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=34855. May 5, 2021.

EPA. 1989a. List of hazardous substances and reportable quantities. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 302.4.

EPA. 1989b. Hydrolysis rate constants for enhancing property-reactivity relationships. Athens, GA: U.S. Environmental Protection Agency. EPA600389063. PB89220479.

EPA. 1990. Nonoccupational pesticide exposure study (NOPES): Final report. Research Triangle Park, NC: U.S. Environmental Protection Agency. EPA600390003.

EPA. 1991a. Data evaluation report: Lindane. Reproductive performance study in rats treated continuously through two successive generations: Final Report. Life Science Research, Ltd. Submitted to the U.S. Environmental Protection Agency. MRID42246101.

EPA. 1991b. Alpha-2μ-globulin: Association with chemically-induced renal toxicity and neoplasia in the male rat. Final draft. Washington, DC: U.S. Environmental Protection Agency. EPA625391019F.

EPA. 1993. Notice of receipt of requests for amendments to delete uses in certain pesticide registrations. U.S. Environmental Protection Agency. Fed Regist 58(220):60630-60631.

EPA. 1995. Method 508: Determination of chlorinated pesticides in water by gas chromatography with an electron capture device. Cincinnati, OH: U.S. Environmental Protection Agency. https://www.o2si.com/docs/epa-method-508.pdf. May 5, 2021.

EPA. 1999a. Data evaluation report: Lindane (gamma HCH). Neurotoxicity study by a single oral gavage administration to CD rats followed by a 14-day observation period. Huntingdon Life Sciences, Ltd. Submitted to the U.S. Environmental Protection Agency. MRID44769201.

EPA. 1999b. Data evaluation report: Lindane (gamma HCH). 13-week neurotoxicity study in rats by dietary administration. Huntingdon Life Sciences, Ltd. Submitted to the U.S. Environmental Protection Agency. MRID44781101.

EPA. 1999c. Data evaluation report: Lindane. Developmental neurotoxicity study in the Han Wistar rat by dietary administration. Huntingdon Life Sciences, Ltd. Submitted to the U.S. Environmental Protection Agency. MRID45073501.

EPA. 1999d. Compendium of methods for the determination of toxic organic compounds in ambient air. Second edition. Washington, DC: U.S. Environmental Protection Agency. EPA625R96010b. https://www.epa.gov/sites/production/files/2019-11/documents/tocomp99.pdf. April 2, 2021.

EPA. 2000a. Data evaluation report: Lindane. Oncogenicity feeding - mouse. Huntingdon Life Sciences, Ltd. Submitted to the U.S. Environmental Protection Agency. Project Identity No CIL/021. MRID No. 45291402.

EPA. 2000b. Method 1656, Revision A: Organo-halide pesticides in wastewater, soil, sludge, sediment, and tissue by GC/HSD. U.S. Environmental Protection Agency. EPA821R00017. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P1002CPW.txt. May 5, 2021.

EPA. 2001. Cancer assessment document. Evaluation of the carcinogenic potential of lindane. Final report. U.S. Environmental Protection Agency. https://hero.epa.gov/hero/index.cfm/reference/details/reference_id/628259. May 11, 2021.

EPA. 2002. Registration eligibility decision for lindane. Case 315. U.S. Environmental Protection Agency.

EPA. 2005. Toxic chemical release inventory reporting forms and instructions: Revised 2004 version. Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986). U.S. Environmental Protection Agency. EPA260B05001.

EPA. 2006a. Lindane; Notice of receipt of requests to voluntarily cancel lindane pesticide registrations. U.S. Environmental Protection Agency. Fed Regist 71:49445.

EPA. 2006b. Lindane; cancellation order. U.S. Environmental Protection Agency. Fed Regist 71:74905.

EPA. 2006c. Assessment of lindane and other hexachlorocyclohexane isomers. Washington, DC: U.S. Environmental Protection Agency. https://www.regulations.gov/document/EPA-HQ-OPP-2006-0034-0002. March 24, 2021.

EPA. 2007. Method 1699: Pesticides in water, soil, sediment, biosolids, and tissue by HRGC/HRMS Washington, DC: U.S. Environmental Protection Agency. EPA821R08001. https://www.epa.gov/sites/production/files/2015-10/documents/method_1699_2007.pdf. May 5, 2021.

EPA. 2009. National primary drinking water regulations. U.S. Environmental Protection Agency. EPA816F090004. https://www.epa.gov/sites/production/files/2016-06/documents/npwdr_complete_table.pdf. September 7, 2017.

EPA. 2010. Six-year review 2 contaminant occurrence data (1998-2005). U.S. Environmental Protection Agency. https://www.epa.gov/dwsixyearreview/six-year-review-2-contaminant-occurrence-data-1998-2005. May 5, 2021.

EPA. 2012. 2012 Chemical data reporting results. U.S. Environmental Protection Agency. February 20, 2019. https://www.epa.gov/chemical-data-reporting/access-cdr-data. May 5, 2021.

EPA. 2014. Applicability of treatment standards. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 268.40. https://www.ecfr.gov/cgi-bin/text-idx?node=pt40.29.268&rgn=div5. May 7, 2021.

EPA. 2016. 2016 Chemical data reporting results. U.S. Environmental Protection Agency. February 20, 2019. https://www.epa.gov/chemical-data-reporting/access-cdr-data. May 5, 2021.

EPA. 2018a. 2018 Edition of the drinking water standards and health advisories. Washington, DC: U.S. Environmental Protection Agency. EPA822S12001. https://www.epa.gov/sites/production/files/2018-03/documents/dwtable2018.pdf. July 25, 2018.

EPA. 2018b. Acute Exposure Guideline Levels (AEGLs) values. U.S. Environmental Protection Agency. https://www.epa.gov/sites/production/files/2018-08/documents/compiled_aegls_update_27jul2018.pdf. April 12, 2020.

EPA. 2020a. Initial list of hazardous air pollutants with modifications. U.S. Environmental Protection Agency. https://www.epa.gov/haps/initial-list-hazardous-air-pollutants-modifications. May 5, 2021.

EPA. 2020b. 2017 National emissions inventory (NEI) data. U.S. Environmental Protection Agency. https://www.epa.gov/air-emissions-inventories/2017-national-emissions-inventory-nei-data. March 30, 2021.

EPA. 2020c. List of lists. Consolidated list of chemicals subject to the Emergency Planning and Community Right To-Know Act (EPCRA), Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) and Section 112(r) of the Clean Air Act. U.S. Environmental Protection Agency. EPA550B20001. https://www.epa.gov/sites/production/files/2015-03/documents/list_of_lists.pdf. May 12, 2021.

EPA. 2021. Air toxics data. Ambient monitoring archive. U.S. Environmental Protection Agency. https://www3.epa.gov/ttnamti1/toxdat.html#data. April 2, 2021.

Etim OE, Farombi EO, Usoh IF, et al. 2006. The protective effect of aloe vera juice on lindane induced hepatotoxicity and genotoxicity. Pak J Pharm Sci 19(4):337-340.

Everett CJ, Matheson EM. 2010. Biomarkers of pesticide exposure and diabetes in the 1999-2004 national health and nutrition examination survey. Environ Int 36(4):398-401. http://doi.org/10.1016/j.envint.2010.02.010.

Everett CJ, Thompson OM. 2015. Association of DDT and heptachlor epoxide in human blood with diabetic nephropathy. Rev Environ Health 30(2):93-97. http://doi.org/10.1515/reveh-2015-0003.

Fabisiková A, Drobná B, Conka K, et al. 2012. The effect of prenatal and postnatal exposure to PCBs and some pesticides on mental and psychomotor development of infants at the age of 10 month. Organohalogen Compounds 74:948-951.

Fagan J. 1981. Henoch-Schonlein purpura and (γ)-benzene hexachloride [letter]. Pediatrics 67:310-311.

Fang J, Liu H, Zhao H, et al. 2019a. Association of prenatal exposure to organochlorine pesticides and birth size. Sci Total Environ 654:678-683. http://doi.org/10.1016/j.scitotenv.2018.10.384.

Fang J, Liu H, Zhao H, et al. 2019b. Association of in utero hexachlorocyclohexane exposure with gestational age. Ecotoxicol Environ Saf 174:263-269. http://doi.org/10.1016/j.ecoenv.2019.02.089.

Farm Chemicals Handbook. 1993. Lindane. In: Pesticide dictionary. Willoughby, OH: Meister Publishing Company, C204.

Fatih Fidan A, Hakk Cigerci I, Baysu-Sozbilir N, et al. 2008. The effects of the dose-dependent γ-hexachlorocyclohexane (lindane) on blood and tissue antioxidant defense systems, lipid peroxidation and histopathological changes in rats. J Anim Vet Adv 7(11):1480-1488.

Fazzalari FA. 1978. Compilation of odor and taste threshold values data (Committee E-18). Philadelphia, PA: American Society for Testing and Materials. ASTM Data Series DS 48A. http://doi.org/10.1520/DS48A-EB.

FDA. 2015. Lindane shampoo and lindane lotion. U.S. Food and Drug Administration. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/lindane-shampoo-and-lindane-lotion. May 5, 2021.

FDA. 2017. Subpart B - Requirements for specific standardized beverages. Bottled water. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR 165.110. https://www.gpo.gov/fdsys/pkg/CFR-2017-title21-vol2/pdf/CFR-2017-title21-vol2-sec165-110.pdf. September 7, 2017.

FDA. 2020a. Pesticide residue monitoring report and data for FY 2018. U.S. Food and Drug Administration. https://www.fda.gov/food/pesticides/pesticide-residue-monitoring-report-and-data-fy-2018. May 5, 2021.

FDA. 2020b. Analytical results of the total diet study. U.S. Food and Drug Administration. https://www.fda.gov/food/total-diet-study/analytical-results-total-diet-study. May 5, 2021.

FDA. 2021. Substances added to food. U.S. Food and Drug Administration. https://www.cfsanappsexternal.fda.gov/scripts/fdcc/?set=FoodSubstances. February 3, 2021.

Feldmann RJ, Maibach HI. 1974. Percutaneous penetration of some pesticides and herbicides in man. Toxicol Appl Pharmacol 28:126-132.

Fendinger NJ, Adams DD, Glotfelty DE. 1992. The role of gas ebullition in the transport of organic contaminants from sediments. Sci Total Environ 112:189-201.

Fenster L, Eskenazi B, Anderson M, et al. 2006. Association of in utero organochlorine pesticide exposure and fetal growth and length of gestation in an agricultural population. Environ Health Perspect 114(4):597-602. http://doi.org/10.1289/ehp.8423.

Fernandez MF, Olmos B, Granada A, et al. 2007. Human exposure to endocrine-disrupting chemicals and prenatal risk factors for cryptorchidism and hypospadias: a nested case-control study. Environ Health Perspect 115 Suppl 1:8-14. http://doi.org/10.1289/ehp.9351.

Ferrando MD, Alarcon V, Fernandez-Casalderrey A, et al. 1992. Persistence of some pesticides in the aquatic environment. Bull Environ Contam Toxicol 48:747-755.

Fischer TF. 1994. Lindane toxicity in a 24-year-old woman. Ann Emerg Med 24(5):972-974.

Fitzhugh OG, Nelson AA. 1947. The comparative chronic toxicities of fumaric, tartaric, oxalic, and maleic acids. J Am Pharm Assoc Am Pharm Assoc 36(7):217-219. http://doi.org/10.1002/jps.3030360708.

Fitzhugh OG, Nelson AA, Frawley JP. 1950. The chronic toxicities of technical benzene hexachloride and its alpha, beta and gamma isomers. J Pharmacol Exp Ther 100:59-66.

Fitzloff JF, Pan JC. 1984. Epoxidation of the lindane metabolite, β-PCCH, by human- and rat-liver microsomes. Xenobiotica 14:599-604.

Fitzloff JF, Portig J, Stein K. 1982. Lindane metabolism by human and rat liver microsomes. Xenobiotica 12:197-202.

Fonseca RG, Resende LAL, Silva MD, et al. 1993. Chronic motor neuron disease possibly related to intoxication with organochlorine insecticides. Acta Neurol Scand 88:56-58.

Ford WM, Hill EP. 1991. Organochlorine pesticides in soil sediments and aquatic animals in the Upper Steele Bayou watershed of Mississippi (USA). Arch Environ Contam Toxicol 20:160-167.

Forrester MB, Sievert JS, Stanley SK. 2004. Epidemiology of lindane exposures for pediculosis reported to Poison Centers in Texas, 1998-2002. J Toxicol Clin Toxicol 42(1):55-60. http://doi.org/10.1081/clt-120028745.

Frank R, Braun HE, Stonefield KI, et al. 1990. Organochlorine and organophosphorus residues in the fat of domestic farm animal species, Ontario, Canada 1986–1988. Food Addit Contam 7:629-636.

Franz TJ, Lehman PA, Franz SF, et al. 1996. Comparative percutaneous absorption of lindane and permethrin. Arch Dermatol 132(8):901-905.

Freire C, Koifman RJ, Koifman S. 2015. Hematological and hepatic alterations in Brazilian population heavily exposed to organochlorine pesticides. J Toxicol Environ Health A 78(8):534-548. http://doi.org/10.1080/15287394.2014.999396.

Freire C, Lopez-Espinosa MJ, Fernandez M, et al. 2011. Prenatal exposure to organochlorine pesticides and TSH status in newborns from Southern Spain. Sci Total Environ 409(18):3281-3287. http://doi.org/10.1016/j.scitotenv.2011.05.037.

Freire C, Koifman RJ, Sarcinelli P, et al. 2012. Long term exposure to organochlorine pesticides and thyroid function in children from Cidade dos Meninos, Rio de Janeiro, Brazil. Environ Res 117:68-74. http://doi.org/10.1016/j.envres.2012.06.009.

Freire C, Koifman RJ, Sarcinelli PN, et al. 2013. Long-term exposure to organochlorine pesticides and thyroid status in adults in a heavily contaminated area in Brazil. Environ Res 127:7-15. http://doi.org/10.1016/j.envres.2013.09.001.

Freire C, Koifman RJ, Sarcinelli PN, et al. 2014. Association between serum levels of organochlorine pesticides and sex hormones in adults living in a heavily contaminated area in Brazil. Int J Hyg Environ Health 217(2-3):370-378. http://doi.org/10.1016/j.ijheh.2013.07.012.

Friberg L, Martensson J. 1953. Case of panmyelophthisis after exposure to chlorophenothane and benzene hexachloride. AMA Arch Ind Hyg 8:166-169.

Fukata H, Omori M, Osada H, et al. 2005. Necessity to measure PCBs and organochlorine pesticide concentrations in human umbilical cords for fetal exposure assessment. Environ Health Perspect 113(3):297-303. http://doi.org/10.1289/ehp.7330.

Fytianos K, Vasilkiotis G, Weil L, et al. 1985. Preliminary study of organochlorine compounds in milk products, human milk, and vegetables. Bull Environ Contam Toxicol 34:504-508.

Gaines T. 1960. The acute toxicity of pesticides to rats. Toxicol Appl Pharmacol 2:88-99.

Gartrell MJ, Craun JC, Podrebarac DS, et al. 1986a. Pesticides, selected elements, and other chemicals in infant and toddler total diet samples, October 1980-March 1982. J AOAC 69:123-145.

Gartrell MJ, Craun JC, Podrebarac DS, et al. 1986b. Pesticides, selected elements, and other chemicals in adult total diet samples, October 1980-March 1982. J AOAC 69:146-161.

Gasull M, Pumarega J, Tellez-Plaza M, et al. 2012. Blood concentrations of persistent organic pollutants and prediabetes and diabetes in the general population of Catalonia. Environ Sci Technol 46(14):7799-7810. http://doi.org/10.1021/es300712g.

Gasull M, Castell C, Pallarès N, et al. 2018. Blood concentrations of persistent organic pollutants and unhealthy metabolic phenotypes in normal-weight, overweight, and obese individuals. Am J Epidemiol 187(3):494-506. http://doi.org/10.1093/aje/kwx267.

Gautam AK, Gandhi DN, Jani JP, et al. 1989. Histological and pharmacological changes in vas deferens of rats exposed to hexachlorocyclohexane. Res Commun Chem Pathol Pharmacol 63:463-466.

Genualdi SA, Hageman KJ, Ackerman LK, et al. 2011. Sources and fate of chiral organochlorine pesticides in western U.S. National Park ecosystems. Environ Toxicol Chem 30(7):1533-1538. http://doi.org/10.1002/etc.538.

Genuis SJ, Lane K, Birkholz D. 2016. Human elimination of organochlorine pesticides: Blood, urine, and sweat study. Biomed Res Int 2016:1624643. http://doi.org/10.1155/2016/1624643.

Gewin HM. 1939. Benzene hexachloride and aplastic anemia. JAMA 14:296-297.

Geyer H, Scheunert I, Bruggemann R, et al. 1997. Half-lives and bioconcentration of lindane (g-HCH) in different fish species and relationship with their lipid content. Chemosphere 35(1-2):343-351.

Ghosh R, Siddarth M, Singh N, et al. 2017. Organochlorine pesticide level in patients with chronic kidney disease of unknown etiology and its association with renal function. Environ Health Prev Med 22(1):49. http://doi.org/10.1186/s12199-017-0660-5.

Gilbert ME. 1995. Repeated exposure to lindane leads to behavioral sensitization and facilitates electrical kindling. Neurotoxicol Teratol 17:131-141.

Gilbert ME, Mack CM. 1995. Seizure thresholds in kindled animals are reduced by the pesticides lindane and endosulfan. Neurotoxicol Teratol 17:143-150.

Gilliland CD, Summer CL, Silliland MG, et al. 2001. Organochlorine insecticides, polychlorinated biphenyls, and metals in water, sediment, and green frogs from southwestern Michigan. Chemosphere 44:327-339.

Ginsburg CM, Lowry W, Reisch JS. 1977. Absorption of lindane (gamma benzene hexachloride) in infants and children. J Pediatrics 91:998-1000.

Gladen BC, Shkiryak-Nyzhnyk ZA, Chyslovska N, et al. 2003. Persistent organochlorine compounds and birth weight. Ann Epidemiol 13(3):151-157. http://doi.org/10.1016/S1047-2797(02)00268-5.

Goel A, McConnell LL, Torrents A, et al. 2010. Environmental factors affecting the levels of legacy pesticides in the airshed of Delaware and Chesapeake Bays, USA. Environ Toxicol Chem 29(9):1893-1906. http://doi.org/10.1002/etc.243.

Goldner WS, Sandler DP, Yu F, et al. 2013. Hypothyroidism and pesticide use among male private pesticide applicators in the agricultural health study. J Occup Environ Med 55(10):1171-1178. http://doi.org/10.1097/JOM.0b013e31829b290b.

Gopal K, Anand M, Khanna RN, et al. 1992. Some neurotoxicological consequences of hexachlorocyclohexane (HCH) stress in rats fed on protein deficient diet. Toxicol Environ Chem 36:57-63.

Gopalaswamy UV, Aiyar AS. 1984. Biotransformation of lindane in the rat. Bull Environ Contam Toxicol 32:148-156.

Govind R, Flaherty PA, Dobbs RA. 1991. Fate and effects of semivolatile organic pollutants during anaerobic digestion of sludge. Water Res 25:547-556.

Grabarczyk M, Kopec-Szlezak J, Szczepanska I, et al. 1990. The effect of gamma-hexachlorocyclohexane (lindane) on blood cells, kidney and liver tissues in rabbits. Haematologia 23:171-179.

Grey WE, Marthre DE, Rogers SJ. 1983. Potential exposure of commercial seed-treating applicators to the pesticides carboxin-thiram and lindane. Bull Environ Contam Toxicol 31:244-250.

Griffith FD, Blanke RV. 1975. Pesticides in people: Blood organochlorine pesticide levels in Virginia residents. Pestic Monit J 8:219-224.

Gunderson EL. 1988. FDA total diet study, April 1982–April 1984: Dietary intakes of pesticides, selected elements, and other chemicals. J AOAC 71:1200-1209.

Gunderson EL. 1995a. Dietary intakes of pesticides, selected elements, and other chemicals: FDA total diet study, June 1984-April 1986. J AOAC Int 78(4):910-921.

Gunderson EL. 1995b. FDA total diet study, July 1986-April 1991, dietary intakes of pesticides, selected elements, and other chemicals. J AOAC Int 78(6):1353-1363.

Guo H, Jin Y, Cheng Y, et al. 2014. Prenatal exposure to organochlorine pesticides and infant birth weight in China. Chemosphere 110:1-7. http://doi.org/10.1016/j.chemosphere.2014.02.017.

Gupta A, Agarwal R, Shukla GS. 1999. Functional impairment of blood–brain barrier following pesticide exposure during early development in rats. Hum Exp Toxicol 18(3):174-179.

Gupta C, Tripathi DN, Vikram A, et al. 2011. Quercetin inhibits diethylnitrosamine-induced hepatic preneoplastic lesions in rats. Nutr Cancer 63(2):234-241. http://doi.org/10.1080/01635581.2011.523806.

Haider K. 1979. Degradation and metabolization of lindane and other hexachlorocyclohexane isomers by anaerobic and aerobic soil microorganisms. Z Naturforsch C Biosci 34(11):1066-1069. http://doi.org/10.1515/znc-1979-1138.

Hall RC, Hall RC. 1999. Long-term psychological and neurological complications of lindane poisoning. Psychosomatics 40(6):513-517.

Hamada M, Kawano E, Kawamura S, et al. 1981. Radiation- and photo-induced degradation of five isomers of 1,2,3,4,5,6-hexachlorocyclohexane. Agric Biol Chem 45:659-665.

Han X, Meng L, Li Y, et al. 2019. Associations between exposure to persistent organic pollutants and thyroid function in a case-control study of East China. Environ Sci Technol 53(16):9866-9875. http://doi.org/10.1021/acs.est.9b02810.

Hanada M, Yutani C, Miyaji T. 1973. Induction of hepatoma in mice by benzene hexachloride. Gann 64:511-513.

Hanig JP, Yoder PD, Krop S. 1976. Convulsions in weanling rabbits after a single topical application of 1% lindane. Toxicol Appl Pharmacol 38:463-469.

Hansch C, Leo A. 1995. Hexachlorocyclohexane. In: Substituent constants for correlation analysis in chemistry and biology. New York, NY: John Wiley and Sons, 202.

Hao W, Kingston HM, Dillard A, et al. 2020. Quantification of persistent organic pollutants in human whole blood samples using stir bar sorptive extraction coupled with GC/MS/MS and isotope dilution mass spectrometry. Microchem J 153:104279. http://doi.org/10.1016/j.microc.2019.104279.

Hargrave BT, Vass WP, Erickson PE, et al. 1988. Atmospheric transport of organochlorines to the Arctic Ocean. Tellus 40B:480-493.

Harman-Fetcho JA, McConnell LL, Baker JE. 1999. Agricultural pesticides in the Patuxent River, a tributary of the Chesapeake Bay. J Environ Qual 28(3):928-938. http://doi.org/10.2134/jeq1999.00472425002800030025x.

Harner T, Wideman JL, Jantunen LM, et al. 1999. Residues of organochlorine pesticides in Alabama soils. Environ Pollut 106(3):323-332. http://doi.org/10.1016/s0269-7491(99)00110-4.

Harris CJ, Williford EA, Kemberling SR, et al. 1969. Pesticide intoxications in Arizona. Ariz Med 26:872-876.

Hassoun EA, Stohs SJ. 1996a. Comparative teratological studies on TCDD, endrin, and lindane in C57BL/6J and DBA/2J mice. Comp Biochem Physiol 113C(3):393-398.

Hassoun EA, Stohs SJ. 1996b. TCDD, endrin, and lindane induced oxidative stress in fetal and placental tissues of C57BL/6J and DBA/2J mice. Comp Biochem Physiol 115C(1):11-18.

Hassoun EA, Bagchi D, Stohs SJ. 1996. TCDD, endrin, and lindane induced increases in lipid metabolites in maternal sera and amniotic fluids of pregnant C57BL/6J and DBA/2J mice. Res Commun Mol Pathol Pharmacol 94(2):157-169.

Hauzenberger I, Perthen-Palmisano B, Hermann M. 2002. Lindane. Report presented at the third meeting of the POPs Expert Group in Geneva, Switzerland in June 2002.

Hayes WJ. 1982. Benzene hexachloride and lindane. In: Pesticides studied in man. Baltimore, MD: Williams and Wilkins, 211-228.

Heiberg OM, Wright HN. 1955. Benzene hexachloride poisoning. Arch Ind Health 11:457-458.

Heinisch E, Jonas K, Klein S. 1993. HCH isomers in soil and vegetation from the surroundings of an industrial landfill of the former GDR, 1971-1989. Sci Total Environ (Suppl Part 1):151-159.

Herbst M, Weisse I, Koellmer H. 1975. A contribution to the question of the possible hepatocarcinogenic effects of lindane. Toxicology 4(1):91-96. http://doi.org/10.1016/0300-483x(75)90025-6.

Hernik A, Struciński P, Buckley BT, et al. 2016. Relationship between paired cord blood and milk POPs levels as a tool for assessing perinatal exposure, a pilot study. Hum Ecol Risk Assess 22(7):1456-1468. http://doi.org/10.1080/10807039.2016.1185688.

Herrero-Mercado M, Waliszewski SM, Caba M, et al. 2010. Organochlorine pesticide levels in umbilical cord blood of newborn in Veracruz, Mexico. Bull Environ Contam Toxicol 85(4):367-371. http://doi.org/10.1007/s00128-010-0108-8.

Herrero-Mercado M, Waliszewski SM, Caba M, et al. 2011. Organochlorine pesticide gradient levels among maternal adipose tissue, maternal blood serum and umbilical blood serum. Bull Environ Contam Toxicol 86(3):289-293. http://doi.org/10.1007/s00128-011-0204-4.

Hfaiedh N, Murat J-C, Elfeki A. 2011. Protective effects of garlic (Allium sativum) extract upon lindane-induced oxidative stress and related damages in testes and brain of male rats. Pestic Biochem Physiol 100(2):187-192. http://doi.org/10.1016/j.pestbp.2011.03.009.

Hfaiedh N, Murat JC, Elfeki A. 2012. A combination of ascorbic acid and α-tocopherol or a combination of Mg and Zn are both able to reduce the adverse effects of lindane-poisoning on rat brain and liver. J Trace Elem Med Biol 26(4):273-278. http://doi.org/10.1016/j.jtemb.2012.04.002.

Hiskia A, Mylonas A, Tsipi D, et al. 1997. Photocatalytic degradation of lindane in aqueous solution. Pestic Sci 50:171-174.

Hitachi M, Yamada K, Takayama S. 1975. Brief communication: Cytologic changes induced in rat liver cells by short-term exposure to chemical substances. J Natl Cancer Inst 54(5):1245.

Hjermitslev MH, Long M, Wielsoe M, et al. 2020. Persistent organic pollutants in Greenlandic pregnant women and indices of foetal growth: The ACCEPT study. Sci Total Environ 698:134118. http://doi.org/10.1016/j.scitotenv.2019.134118.

Hoff RM, Muir DCG, Grift NP. 1992a. Annual cycle of polychlorinated biphenyls and organohalogen pesticides in air in southern Ontario. 1. Air concentration data. Environ Sci Technol 26:266-275.

Hoff RM, Muir DCG, Grift NP. 1992b. Annual cycle of polychlorinated biphenyls and organohalogen pesticides in air in southern Ontario. 2. Atmospheric transport and sources. Environ Sci Technol 26:276-283.

Hollifield HC. 1979. Rapid nephelometric estimate of water solubility of highly insoluble organic chemicals of environmental interest. Bull Environ Contam Toxicol 23:579-586.

Hong HL, Boorman GA. 1993. Residual myelotoxicity of lindane in mice. Fundam Appl Toxicol 21:500-507.

Howsam M, Grimalt JO, Guino E, et al. 2004. Organochlorine exposure and colorectal cancer risk. Environ Health Perspect 112(15):1460-1466. http://doi.org/10.1289/ehp.7143.

Hoyer A, Grandjean P, Jorgensen T, et al. 1998. Organochlorine exposure and risk of breast cancer. Lancet 352:1816-1820.

Hulth L, Hoglund L, Bergman A, et al. 1978. Convulsive properties of lindane, lindane metabolites, and the lindane isomer a-hexachlorocyclohexane: Effects on the convulsive threshold for pentylenetetrazol and the brain content of g-aminobutyric acid (GABA) in the mouse. Toxicol Appl Pharmacol 46:101-108.

Humphreys EH, Janssen S, Heil A, et al. 2008. Outcomes of the California ban on pharmaceutical lindane: clinical and ecologic impacts. Environ Health Perspect 116(3):297-302. http://doi.org/10.1289/ehp.10668.

IARC. 1979. Hexachlorocyclohexane. In: IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans: Some halogenated hydrocarbons. Vol. 20. Geneva, Switzerland: International Agency for Research on Cancer, 195-241.

IARC. 1987. Hexachlorocyclohexanes. IARC Monographs on the evaluation of carcinogenic risks to humans. Supplement 7. Overall evaluations of carcinogenicity: An updating of IARC monographs

volumes 1–42. Lyon, France: International Agency for Research on Cancer. 220-222. https://publications.iarc.fr/139. March 23, 2021.

IARC. 2018. DDT, lindane, and 2,4-D. Volume 113. IARC Monographs on the evaluation of carcinogenic risks to humans. Lyon, France: International Agency for Research on Cancer. https://publications.iarc.fr/550. March 23, 2021.

Ibarluzea JM, Fernandez MF, Santa-Marina L, et al. 2004. Breast cancer risk and the combined effect of environmental estrogens. Cancer Causes Control 15(6):591-600. http://doi.org/10.1023/B:CACO.0000036167.51236.86.

IRIS. 1987a. alpha-Hexachlorocyclohexane (alpha-HCH). CASRN 319-84-6. Integrated Risk Information System. Chemical assessment summary. U.S. Environmental Protection Agency. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0162_summary.pdf. March 22, 2021.

IRIS. 1987b. beta-Hexachlorocyclohexane (beta-HCH). CASRN 319-85-7. Integrated Risk Information System. Chemical assessment summary. U.S. Environmental Protection Agency. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0244_summary.pdf. March 22, 2021.

IRIS. 1987c. gamma-Hexachlorocyclohexane (gamma-HCH). CASRN 58-89-9. Integrated Risk Information System. Chemical assessment summary. U.S. Environmental Protection Agency. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0065_summary.pdf. March 22, 2021.

IRIS. 1987d. delta-Hexachlorocyclohexane (delta-HCH). CASRN 319-86-8. Integrated Risk Information System. Chemical assessment summary. U.S. Environmental Protection Agency. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0163_summary.pdf. March 22, 2021.

IRIS. 1987e. epsilon-Hexachlorocyclohexane (ε-HCH). CASRN 6108-10-7. Integrated Risk Information System. Chemical assessment summary. U.S. Environmental Protection Agency. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0164_summary.pdf. March 22, 2021.

IRIS. 1987f. Technical hexachlorocyclohexane (t-HCH). CASRN 608-73-1. Integrated Risk Information System. Chemical assessment summary. U.S. Environmental Protection Agency. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0165_summary.pdf. March 22, 2021.

Ishidate MJ, Odashima S. 1977. Chromosome tests with 134 compounds on Chinese hamster cells in vitro - a screening for chemical carcinogens. Mutat Res 49:337-354.

Ito N, Nagasaki H, Arai M, et al. 1973. Histologic and ultrastructural studies on the hepatocarcinogenicity of benzene hexachloride in mice. J Natl Cancer Inst 51:817-826.

Ito N, Nagasaki H, Aoe H, et al. 1975. Development of hepatocellular carcinomas in rats treated with benzene hexachloride. J Natl Cancer Inst 54:801-805.

Ito N, Hananouchi M, Sugihara S, et al. 1976. Reversibility and irreversibility of liver tumors in mice induced by the α isomer of 1,2,3,4,5,6-hexachlorocyclohexane. Cancer Res 36(7 pt 1):2227-2234.

Itoh H, Iwasaki M, Kasuga Y, et al. 2014. Association between serum organochlorines and global methylation level of leukocyte DNA among Japanese women: a cross-sectional study. Sci Total Environ 490:603-609. http://doi.org/10.1016/j.scitotenv.2014.05.035.

Iverson F, Ryan JJ, Lizotte R, et al. 1984. In vivo and in vitro binding of α- and g-hexachloro-cyclohexane to mouse liver macromolecules. Toxicol Lett 20:331-335.

Jacobsen BN, Nyholm N, Pedersen BM, et al. 1991. Microbial degradation of pentachlorophenol and lindane in laboratory-scale activated sludge reactors. Water Sci Technol 23:349-356.

Jantunen LM, Bidleman TF, Harner T, et al. 2000. Toxaphene, chlordane, and other organochlorine pesticides in Alabama air. Environ Sci Technol 34(24):5097-5105. http://doi.org/10.1021/es001197y.

Jeddy Z, Kordas K, Allen K, et al. 2018. Prenatal exposure to organochlorine pesticides and early childhood communication development in British girls. Neurotoxicology 69:121-129. http://doi.org/10.1016/j.neuro.2018.10.003.

Jenssen D, Ramel C. 1980. The micronucleus test as part of a short-term mutagenicity test program for the prediction of carcinogenicity evaluated by 143 agents tested. Mutat Res 75:191-202.

Johri A, Yadav S, Dhawan A, et al. 2007. Overexpression of cerebral and hepatic cytochrome P450s alters behavioral activity of rat offspring following prenatal exposure to lindane. Toxicol Appl Pharmacol 225(3):278-292. http://doi.org/10.1016/j.taap.2007.08.006.

Johri A, Yadav S, Dhawan A, et al. 2008. Responsiveness of cerebral and hepatic cytochrome P450s in rat offspring prenatally exposed to lindane. Toxicol Appl Pharmacol 231(1):10-16. http://doi.org/10.1016/j.taap.2008.03.019.

Jonnalagadda PR, Jahan P, Venkatasubramanian S, et al. 2012. Genotoxicity in agricultural farmers from Guntur district of South India--A case study. Hum Exp Toxicol 31(7):741-747. http://doi.org/10.1177/0960327111408151.

Joseph P, Shivanandappa T, Krishnakumari MK. 1992a. Influence of vitamin A on hexachlorocyclohexane (HCH) toxicity in the rat. J Nutr Biochem 3:408-414.

Joseph P, Viswanatha S, Krishnakumari MK. 1992c. Role of vitamin A in the haematotoxicity of hexachlorocyclohexane (HCH) in the rat. J Environ Sci Health B 27:269-280.

Joseph P, Shivanandappa T, Narasimhamurthy K, et al. 1992b. Effect of vitamin A on hexachlorocyclohexane (HCH) toxicity in the rat. Gen Pharmacol 23:1159-1164.

Joy RM, Stark LG, Albertson TE. 1982. Proconvulsant effects of lindane: Enhancement of amygdaloid kindling in the rat. Neurobehav Toxicol Teratol 4:347-354.

Juan WH, Yang LC, Hong HS. 2004. Acute generalized exanthematous pustulosis induced by topical lindane. Dermatology 209(3):239-240. http://doi.org/10.1159/000079899.

Jung D, Becher H, Edler L, et al. 1997. Elimination of β-hexachlorocyclohexane in occupationally exposed persons. J Toxicol Environ Health 51:23-34.

Junque E, Garcia S, Martinez MA, et al. 2020. Changes of organochlorine compound concentrations in maternal serum during pregnancy and comparison to serum cord blood composition. Environ Res 182:108994. http://doi.org/10.1016/j.envres.2019.108994.

Just AC, Hawker DW, Connell DW. 1990. Partitioning of lindane between sediment, water, and the crustacean Metapenaeus macleayi. Aust J Marine Freshwater Res 41:389-397.

Kachuri L, Beane Freeman LE, Spinelli JJ, et al. 2020. Insecticide use and risk of non-Hodgkin lymphoma subtypes: A subset meta-analysis of the North American Pooled Project. Int J Cancer 147(12):3370-3383. http://doi.org/10.1002/ijc.33164.

Kalantzi OI, Alcock RE, Johnston PA, et al. 2001. The global distribution of PCBs and organochlorine pesticides in butter. Environ Sci Technol 35:1013-1018.

Kalantzi OI, Hewitt R, Ford KJ, et al. 2004. Low dose induction of micronuclei by lindane. Carcinogenesis 25(4):613-622. http://doi.org/10.1093/carcin/bgh048.

Kalsch W, Knacker T, Robertz M, et al. 1998. Partitioning and mineralization of [^{14}C]lindane in a laboratory sediment-water system. Environ Toxicol Chem 17(4):662-669. http://doi.org/10.1002/etc.5620170420.

Kamal El-Dein EM, Aness LM, Elsayed Aly SM. 2016. Effects of α-lipoic acid on γ-radiation and lindane-induced heart toxicity in rats. Pak J Zool 48(5):1523-1529.

Kanja LW, Skaare JU, Ojwang SBO, et al. 1992. A comparison of organochlorine pesticide-residues in maternal adipose-tissue, maternal blood, cord blood, and human-milk from mother infant pairs. Arch Environ Contam Toxicol 22:21-24.

Kannan K, Battula S, Loganathan BG, et al. 2003. Trace organic contaminants, including toxaphene and trifluralin, in cotton field soils from Georgia and South Carolina, USA. Arch Environ Contam Toxicol 45(1):30-36. http://doi.org/10.1007/s00244-002-0267-7.

Kao CC, Que DE, Bongo SJ, et al. 2019. Residue levels of organochlorine pesticides in breast milk and its associations with cord blood thyroid hormones and the offspring's neurodevelopment. Int J Environ Res Public Health 16(8):1438. http://doi.org/10.3390/ijerph16081438.

Kar S, Singh PK. 1979a. Mutagenicity of pesticides carbofuran and hexachlorocyclohexane to blue-green alga Nostoc muscorum. Microbios Lett 12:79-82.

Kar S, Singh PK. 1979b. Detoxification of pesticides carbofuran and hexachlorocyclohexane by blue-green algae Nostoc muscorum and Wollea bharadwajae. Microbios Lett 10:111-114.

Karnik AB, Thakore KN, Nigam SR, et al. 1981. Studies on glucose-6-phosphatase, fructose-1,2-diphosphatase activity, glycogen distribution and endoplasmic reticulum changes during hexachlorocyclohexane induced hepato-carcinogenesis in pure inbred Swiss mice. Neoplasm 28:575-584.

Kashyap SK. 1986. Health surveillance and biological monitoring of pesticide formulators in India. Toxicol Lett 33:107-114.

Kashyap SK, Nigam SK, Gupta RC, et al. 1979. Carcinogenicity of hexachlorocyclohexane (BHC) in pure inbred Swiss mice. J Environ Sci Health B 14:305-318.

Katsumata K, Katsumata K. 2003. Norwegian scabies in an elderly patient who died after treatment with γBHC. Intern Med 42(4):367-369. http://doi.org/10.2169/internalmedicine.42.367.

Katz JM, Winter CK. 2009. Comparison of pesticide exposure from consumption of domestic and imported fruits and vegetables. Food Chem Toxicol 47(2):335-338. http://doi.org/10.1016/j.fct.2008.11.024.

Kaur N, Starling AP, Calafat AM, et al. 2020. Longitudinal association of biomarkers of pesticide exposure with cardiovascular disease risk factors in youth with diabetes. Environ Res 181:108916. http://doi.org/10.1016/j.envres.2019.108916.

Keerthinarayana S, Bandyopadhyay M. 1998. Assessment of equilibrium time and effect of co-solutes in lindane sorption. J Environ Sci Health 33(2):179-209. http://doi.org/10.1080/03601239809373138.

Keith LH, Garrison AW, Allen FR, et al. 1976. Identification and analysis of organic pollutants in drinking water from 13 U.S. cities. In: Keith LH, ed. Identification and analysis of organic pollutants in water. Ann Arbor, MI: Ann Arbor Science Publishers Inc, 329-373.

Kennedy DW, Aust SD, Bumpus JA. 1990. Comparative biodegradation of alkyl halide insecticides by the white rot fungus, Phanerochaete chrysosporium (BKM-F-1767). Appl Environ Microbiol 56:2347- 2353.

Khanjani N, Sim MR. 2006. Reproductive outcomes of maternal contamination with cyclodiene insecticides, hexachlorobenzene and β-benzene hexachloride. Sci Total Environ 368(2-3):557-564. http://doi.org/10.1016/j.scitotenv.2006.03.029.

Khanna RN, Das M, Anand M. 2002. Influence of phenobarbital and carbon tetrachloride on the modulation of tissue retention profile of hexachlorocyclohexane in rats. Biomed Environ Sci 15(2):119-129.

Khanna RN, Anband M, Gopal K, et al. 1988. Effect of repeated exposure to lindane and cadmium on lindane metabolism in rats. Toxicol Lett 42:177-182.

Khanna RN, Gupta R, Gupta GSD, et al. 1990. Effects of the level of dietary protein on the toxicity of hexachlorocyclohexane in rats. Toxicol Environ Chem 25:91-103.

Khare S, Rizvi A, Shukla O, et al. 1977. Epidemic outbreak of neuro-ocular manifestations due to chronic BHC poisoning. J Assoc Physicians India 25:215-222.

Khera KS, Whalen C, Trivett G, et al. 1979. Teratogenicity studies on pesticidal formulations of dimethoate, diuron, and lindane in rats. Bull Environ Contam Toxicol 22(4-5):522-529. http://doi.org/10.1007/BF02026981.

Khurana R, Mahipal S, Chauhan R. 1999. Effect of pesticides on delayed type hypersensitivity reaction in sheep. Indian J Anim Sci 69(11):0367-8318.

Kim S, Park J, Kim HJ, et al. 2013. Association between several persistent organic pollutants and thyroid hormone levels in serum among the pregnant women of Korea. Environ Int 59:442-448. http://doi.org/10.1016/j.envint.2013.07.009.

Kim KS, Lee YM, Kim SG, et al. 2014. Associations of organochlorine pesticides and polychlorinated biphenyls in visceral vs. subcutaneous adipose tissue with type 2 diabetes and insulin resistance. Chemosphere 94:151-157. http://doi.org/10.1016/j.chemosphere.2013.09.066.

Kim KS, Lee YM, Lee HW, et al. 2015. Associations between organochlorine pesticides and cognition in U.S. elders: National Health and Nutrition Examination Survey 1999-2002. Environ Int 75:87-92. http://doi.org/10.1016/j.envint.2014.11.003.

Kiraly J, Szentesi I, Ruzicska M, et al. 1979. Chromosome studies in workers producing organophosphate insecticides. Arch Environ Contam Toxicol 8:309-319.

Kirk ER, Othmer DF. 1985. Benzene hexachloride. In: Concise encyclopedia of chemical technology. New York, NY: John Wiley & Sons, 269-270.

Klonne DR, Kintigh WJ. 1988. Lindane technical: Fourteen-week dust aerosol inhalation study on mice. Export, PA: Bushy Run Research Center. BRRC #51-524. MetPath #14014.

Knap AH, Binkley KS. 1991. Chlorinated organic compounds in the troposphere over the western North Atlantic Ocean measured by aircraft. Atmos Environ 25:1507-1516.

Kokroko J, Kogut K, Harley K, et al. 2020. Prenatal β-hexachlorocyclohexane (β-HCH) exposure and 7-year child IQ in the CHAMACOS birth cohort. Neurotox Res 37(3):553-563. http://doi.org/10.1007/s12640-020-00160-w.

Koner BC, Banerjee BD, Ray A. 1998. Organochlorine pesticide-induced oxidative stress and immune suppression in rats. Indian J Exp Biol 36:395-398.

Kopec-Szlezak J, Goralczyk K, Wozniak J, et al. 1989. Changes in serum and internal organs during increased accumulation of gamma-hexachlorocyclohexane in adipose tissue of rabbits. Mater Med Pol 21:286-291.

Koutros S, Andreotti G, Berndt SI, et al. 2011. Xenobiotic-metabolizing gene variants, pesticide use, and the risk of prostate cancer. Pharmacogenet Genomics 21(10):615-623. http://doi.org/10.1097/FPC.0b013e3283493a57.

Kováčik J, Antoš V, Micalizzi G, et al. 2018. Accumulation and toxicity of organochlorines in green microalgae. J Hazard Mater 347:168-175. http://doi.org/10.1016/j.jhazmat.2017.12.056.

Kramer MS, Hutchison TA, Rudnick SA, et al. 1980. Operational criteria for adverse drug reactions in evaluating suspected toxicity of a popular scabicide. Clin Pharmacol Ther 27:149-155.

Krishnan K, Andersen ME, Clewell HJ, et al. 1994. Physiologically based pharmacokinetic modeling of chemical mixtures. In: Yang RSH, ed. Toxicology of chemical mixtures: Case studies, mechanisms, and novel approaches. San Diego, CA: Academic Press, 399-437.

Kujawa M, Engst R, Macholz R. 1977. On the metabolism of lindane. In: Zaidi SH, ed. Environmental pollution and human health: Proceedings of the international symposium on industrial toxicology, November 4-7, 1975. Lucknow: Industrial Toxicology Research Centre, 661-672.

Kumar D, Khan PK, Sinha SP. 1995. Cytogenetic toxicity and no-effect limit dose of pesticides. Food Chem Toxicol 33:309-314.

Kumar V, Yadav CS, Singh S, et al. 2010. CYP 1A1 polymorphism and organochlorine pesticides levels in the etiology of prostate cancer. Chemosphere 81(4):464-468. http://doi.org/10.1016/j.chemosphere.2010.07.067.

Kuntz KW, Warry ND. 1983. Chlorinated organic contaminants in water and suspended sediments of the lower Niagara River. J Great Lakes Res 9:241-248.

Kurihara N, Tanaka K, Nakajima M. 1979. Mercapturic acid formation from lindane in rats. Pestic Biochem Physiol 10:137-150.

Kurihara N, Uchida M, Fujita T, et al. 1973. Studies on BHC isomers and related compounds. V. Some physicochemical properties of BHC isomers. Pestic Biochem Physiol 2(4):383-390. http://doi.org/10.1016/0048-3575(73)90050-3.

Kutz FW, Strassman SC, Spearling JF. 1979. Survey of selected organochlorine pesticides in the general population of the United States: Fiscal years 1970-1975. Ann NY Acad Sci 320:60-68.

Kutz FW, Wood PH, Bottimore DP. 1991. Organochlorine pesticides and polychlorinated biphenyls in human adipose tissue. Rev Environ Contam Toxicol 120:1-82.

La Sala G, Farini D, De Felici M. 2009. Proapoptotic effects of lindane on mouse primordial germ cells. Toxicol Sci 108(2):445-451. http://doi.org/10.1093/toxsci/kfp027.

Lahiri P, Chakravarty J, Sircar S. 1990. Residue accumulation in mice chronically fed lindane (g-HCH). Proc Indian Natl Sci Acad Part B Biol Sci 56:277-280.

Lakkad BC, Nigam SK, Karnik AB, et al. 1982. Dominant-lethal study of technical-grade hexachlorocyclohexane in Swiss mice. Mutat Res 101:315-320.

Lam T, Williams PL, Lee MM, et al. 2014. Prepubertal organochlorine pesticide concentrations and age of pubertal onset among Russian boys. Environ Int 73:135-142. http://doi.org/10.1016/j.envint.2014.06.020.

Lam T, Williams PL, Lee MM, et al. 2015. Prepubertal serum concentrations of organochlorine pesticides and age at sexual maturity in Russian boys. Environ Health Perspect 123(11):1216-1221. http://doi.org/10.1289/ehp.1409022.

Landgren O, Kyle RA, Hoppin JA, et al. 2009. Pesticide exposure and risk of monoclonal gammopathy of undetermined significance in the Agricultural Health Study. Blood 113(25):6386-6391. http://doi.org/10.1182/blood-2009-02-203471.

Lange M, Nitzche K, Zesch A. 1981. Percutaneous absorption of lindane by healthy volunteers and scabies patients: Dependency of penetration kinetics in serum upon frequency of application, time, and mode of washing. Arch Dermatol Res 271:387-399.

Lapertot ME, Pulgarin C. 2006. Biodegradability assessment of several priority hazardous substances: choice, application and relevance regarding toxicity and bacterial activity. Chemosphere 65(4):682-690. http://doi.org/10.1016/j.chemosphere.2006.01.046.

Laug EP, Nelson AA, Fitzhugh OG, et al. 1950. Liver cell alteration and DDT storage in the fat of the rat induced by dietary levels of 1 to 50 p.p.m. DDT. J Pharmacol Exp Ther 98(3):268-273.

Lauritzen HB, Larose TL, Oien T, et al. 2018. Prenatal exposure to persistent organic pollutants and child overweight/obesity at 5-year follow-up: a prospective cohort study. Environ Health 17(1):9. http://doi.org/10.1186/s12940-017-0338-x.

Law SA, Bidleman TF, Martin MJ, et al. 2004. Evidence of enantioselective degradation of α-hexachlorocyclohexane in groundwater. Environ Sci Technol 38(6):1633-1638. http://doi.org/10.1021/es030508c.

Laws SC, Carey SA, Hart DW, et al. 1994. Lindane does not alter the estrogen receptor or the estrogen-dependent induction of progesterone receptors in sexually immature or ovariectomized adult rats. Toxicology 92:127-142.

Lebov JF, Engel LS, Richardson D, et al. 2015. Pesticide exposure and end-stage renal disease risk among wives of pesticide applicators in the Agricultural Health Study. Environ Res 143(Pt A):198-210. http://doi.org/10.1016/j.envres.2015.10.002.

Lee B, Groth P. 1977. Scabies: Transcutaneous poisoning during treatment [letter]. Pediatrics 59:643.

Lee DH, Jacobs DR, Porta M. 2007. Association of serum concentrations of persistent organic pollutants with the prevalence of learning disability and attention deficit disorder. J Epidemiol Community Health 61(7):591-596. http://doi.org/10.1136/jech.2006.054700.

Lee HA, Park SH, Hong YS, et al. 2016. The effect of exposure to persistent organic pollutants on metabolic health among Korean children during a 1-year follow-up. Int J Environ Res Public Health 13(3):270. http://doi.org/10.3390/ijerph13030270.

Lee YM, Ha CM, Kim SA, et al. 2017. Low-dose persistent organic pollutants impair insulin secretory function of pancreatic β-cells: Human and in vitro evidence. Diabetes 66(10):2669-2680. http://doi.org/10.2337/db17-0188.

Lee YM, Kim SA, Choi GS, et al. 2018a. Association of colorectal polyps and cancer with low-dose persistent organic pollutants: A case-control study. PLoS ONE 13(12):e0208546. http://doi.org/10.1371/journal.pone.0208546.

Lee JY, Lee KM, Lee DH, et al. 2018b. Association of low-dose exposure to persistent organic pollutants with E-cadherin promoter methylation in healthy Koreans. Biomarkers 23(3):293-298. http://doi.org/10.1080/1354750X.2017.1417482.

Leeder JS, Kearns GL. 1997. Pharmacogenetics in pediatrics: Implications for practice. Ped Clin North America 44:55-77.

Lenters V, Iszatt N, Forns J, et al. 2019. Early-life exposure to persistent organic pollutants (OCPs, PBDEs, PCBs, PFASs) and attention-deficit/hyperactivity disorder: A multi-pollutant analysis of a Norwegian birth cohort. Environ Int 125:33-42. http://doi.org/10.1016/j.envint.2019.01.020.

Lerro CC, Jones RR, Langseth H, et al. 2018. A nested case-control study of polychlorinated biphenyls, organochlorine pesticides, and thyroid cancer in the Janus Serum Bank cohort. Environ Res 165:125-132. http://doi.org/10.1016/j.envres.2018.04.012.

Lewis RG, Lee RE. 1976. Air pollution from pesticides: Sources, occurrence [sic], and dispersion. In: Lee RE, ed. Air pollution from pesticides and agricultural processes. Cleveland, OH: CRC Press, 5-50.

Li J, Jiang S, Chang Y, et al. 2013. Association among serum organochlorine pesticide residues, glutathione S-transferase M1 genetic polymorphism and female breast cancer. Adv Breast Cancer Res 2:19-23. http://doi.org/10.4236/abcr.2013.22005.

Li C, Cheng Y, Tang Q, et al. 2014. The association between prenatal exposure to organochlorine pesticides and thyroid hormone levels in newborns in Yancheng, China. Environ Res 129:47-51. http://doi.org/10.1016/j.envres.2013.12.009.

Li S, Wang X, Yang L, et al. 2016. Interaction between β-hexachlorocyclohexane and ADIPOQ genotypes contributes to the risk of type 2 diabetes mellitus in East Chinese adults. Sci Rep 6:37769. http://doi.org/10.1038/srep37769.

Lide DR. 1991. Hexachlorocyclohexane. In: CRC handbook of chemistry and physics: A ready-reference book of chemical and physical data. Boston, MA: CRC Press, 35-195.

Lifshitz M, Gavrilov V. 2002. Acute lindane poisoning in a child. Isr Med Assoc J 4(9):731-732.

Lim JE, Nam C, Yang J, et al. 2017. Serum persistent organic pollutants (POPs) and prostate cancer risk: A case-cohort study. Int J Hyg Environ Health 220(5):849-856. http://doi.org/10.1016/j.ijheh.2017.03.014.

Lindenau A, Fischer B, Seiler P, et al. 1994. Effects of persistent chlorinated hydrocarbons on reproductive tissues in female rabbits. Hum Reprod 9:772-780.

Liu PT, Morgan DP. 1986. Comparative toxicity and biotransformation of lindane in C57BL/6 and DBA/2 mice. Life Sci 39:1237-1244.

Llorens J, Tusell JM, Sunol C, et al. 1989. Effects of lindane on spontaneous behavior of rats analyzed by multivariate statistics. Neurotoxicol Teratol 11:145-151.

Llorens J, Tusell JM, Sunol C, et al. 1990. On the effects of lindane on the plus-maze model of anxiety. Nerutoxicol Teratol 12:643-647.

Loganathan BG, Tanabe S, Hidaka Y, et al. 1993. Temporal trends of persistent organochlorine residues in human adipose tissue from Japan, 1928-1985. Environ Pollut 81:31-39.

Loge JP. 1965. Aplastic anemia following exposure to benzene hexachloride (lindane). JAMA 193:104-108.

Lopez-Carrillo L, Lopez-Cervantes M, Torres-Sanchez L, et al. 2002. Serum levels of beta-hexachlorocyclohexane, hexachlorobenzene and polychlorinated biphenyls and breast cancer in Mexican women. Eur J Cancer 11(2):129-135.

Lopez-Espinosa MJ, Granada A, Carreno J, et al. 2007. Organochlorine pesticides in placentas from southern Spain and some related factors. Placenta 28(7):631-638. http://doi.org/10.1016/j.placenta.2006.09.009.

Lopez-Espinosa MJ, Vizcaino E, Murcia M, et al. 2010. Prenatal exposure to organochlorine compounds and neonatal thyroid stimulating hormone levels. J Expo Sci Environ Epidemiol 20(7):579-588. http://doi.org/10.1038/jes.2009.47.

Lopez-Espinosa MJ, Murcia M, Iniguez C, et al. 2011. Prenatal exposure to organochlorine compounds and birth size. Pediatrics 128(1):e127-e134. http://doi.org/10.1542/peds.2010-1951.

Luebeck EG, Graslkraupp B, Timmermanntrosiener I, et al. 1995. Growth kinetics of enzyme-altered liver foci in rats treated with phenobarbital or α-hexachlorocyclohexane. Toxicol Appl Pharmacol 130(2):304-315. http://doi.org/10.1006/taap.1995.1035.

Macholz RM, Kujawa M. 1985. Recent state of lindane metabolism: Part III. Res Rev 94:119-149.

Macholz RM, Knoll R, Lewerenz HJ, et al. 1982a. Metabolism of alpha-hexachlorocyclohexane: Free metabolites in urine and organs of rats. Xenobiotica 12(4):277-231.

Macholz RM, Knoll R, Lewerenz HJ, et al. 1982b. Biodegradation of beta-hexachlorocyclohexane: Free metabolites in rat urine and organs. Arch Toxicol 50:85-88.

Mackay D, Leinonen PJ. 1975. Rate of evaporation of low-solubility contaminants from water bodies to atmosphere. Environ Sci Technol 9:1178-1180.

Malaiyandi M, Muzika K, Benoit FM. 1982. Isomerization of γ-hexachlorocyclohexane to its α-isomer by ultra-violet light irradiation. J Environ Sci Health A 17:299-311.

Maranghi F, Rescia M, Macrì C, et al. 2007. Lindane may modulate the female reproductive development through the interaction with ER-β: an in vivo-in vitro approach. Chem Biol Interact 169(1):1-14. http://doi.org/10.1016/j.cbi.2007.04.008.

Marsalek J, Schroeter H. 1988. Annual loadings of toxic contaminants in urban runoff from the Canadian Great Lakes basin. Water Pollut Res J Can 23:360-378.

Martinez AO, Martinez-Conde E. 1995. The neurotoxic effects of lindane at acute and subchronic dosages. Ecotoxicol Environ Saf 30:101-105.

Martinez E, de Vera N, Artigas F. 1991. Differential response of rat brain polyamines to convulsant agents. Life Sci 48:77-84.

Marvin C, Painter S, Williams D, et al. 2004. Spatial and temporal trends in surface water and sediment contamination in the Laurentian Great Lakes. Environ Pollut 129(1):131-144. http://doi.org/10.1016/j.envpol.2003.09.029.

Mathur AK, Narang S, Gupta BN, et al. 1992. Effect of dermal exposure to LAS detergent and HCH pesticide in guinea pigs: Biochemical and histopathologic changes in liver and kidney. J Toxicol Cutaneous Ocul Toxicol 11(1):3-13. http://doi.org/10.3109/15569529209042589.

Mathur AK, Narang S, Gupta BN, et al. 1993. Interaction of linear alkylbenzene sulfonate and hexachlorocyclohexane in guinea pigs after dermal application. J Toxicol Cutaneous Ocul Toxicol 12(1):25-34. http://doi.org/10.3109/15569529309057656.

Matsumura F, Benezet HJ. 1973. Studies on the bioaccumulation and microbial degradation of 2,3,7,8-tetrachlorodibenzo-p-dioxin. Environ Health Perspect 5:253-258.

Matsuoka LY. 1981. Convulsions following application of gamma-benzene hexachloride [letter]. J Am Acad Dermatol 5:98-99.

Matsuura I, Saitoh T, Tani E, et al. 2005. Evaluation of a two-generation reproduction toxicity study adding endpoints to detect endocrine disrupting activity using lindane. J Toxicol Sci 30 Spec No.:135-161. http://doi.org/10.2131/jts.30.s135.

Mattioli F, Robbiano L, Adamo D, et al. 1996. Genotoxic effects of α-hexachlorocyclohexane in primary cultures of rodent and human hepatocytes. Mutagenesis 11(1):79-83.

McCarthy JP, Adinolfi J, McMullin SL, et al. 1992. NCA survey of pesticide residues in brewed coffees. Colloq Sci Int Cafe 14:175-181.

McCready D, Aronson KJ, Chu W, et al. 2004. Breast tissue organochlorine levels and metabolic genotypes in relation to breast cancer risk Canada. Cancer Causes Control 15(4):399-418. http://doi.org/10.1023/B:CACO.0000027505.32564.c2.

McGlynn KA, Quraishi SM, Graubard BI, et al. 2008. Persistent organochlorine pesticides and risk of testicular germ cell tumors. J Natl Cancer Inst 100(9):663-671. http://doi.org/10.1093/jnci/djn101.

McNamara BP, Krop S. 1948. Observations on the pharmacology of the isomers of hexachlorocyclohexane. J Pharmacol Exp Ther 92:140-146.

McQueen EG, Brosnan C, Ferry DG. 1968. Poisoning from a rose spray containing lindane and malathion. N Z Med J 67:533-537.

McTernan WF, Pereira JA. 1991. Biotransformation of lindane and 2,4-D in batch enrichment cultures. Water Res 25:1417-1423.

Medehouenou TCM, Ayotte P, Carmichael PH, et al. 2019. Exposure to polychlorinated biphenyls and organochlorine pesticides and risk of dementia, Alzheimer's disease and cognitive decline in an older population: a prospective analysis from the Canadian Study of Health and Aging. Environ Health 18(1):57. http://doi.org/10.1186/s12940-019-0494-2.

Mediratta PK, Tanwar K, Reeta KH, et al. 2008. Attenuation of the effect of lindane on immune responses and oxidative stress by Ocimum sanctum seed oil (OSSO) in rats. Indian J Physiol Pharmacol 52(2):171-177.

Meera P, Rao PR, Shanker R, et al. 1992. Immunomodulatory effects of γ-HCH (lindane) in mice. Immunopharmacol Immunotoxicol 14:261-282.

Melancon SM, Pollard JE, Hern SC. 1986. Evaluation of SESOIL, PRZM and PESTAN in a laboratory column leaching experiment. Environ Toxicol Chem 5:865-878.

Mendeloff AI, Smith DE. 1955. Exposure to insecticides, bone marrow failure, gastrointestinal bleeding, and uncontrollable infections. Am J Med 9:274-284.

Mendez MA, Garcia-Esteban R, Guxens M, et al. 2011. Prenatal organochlorine compound exposure, rapid weight gain, and overweight in infancy. Environ Health Perspect 119(2):272-278. http://doi.org/10.1289/ehp.1002169.

Meng G, Feng Y, Nie Z, et al. 2016. Internal exposure levels of typical POPs and their associations with childhood asthma in Shanghai, China. Environ Res 146:125-135. http://doi.org/10.1016/j.envres.2015.12.026.

Mes J. 1992. Organochlorine residues in human blood and biopsy fat and their relationship. Bull Environ Contam Toxicol 48:815-820.

Mes J, Malcolm S. 1992. Comparison of chlorinated hydrocarbon residues in human populations from the Great Lakes and other regions of Canada. Chemosphere 25:417-424.

Michalakis M, Tzatzarakis M, Alegakis A, et al. 2012. Pesticides levels (DDTs, HCHs and DAPs) in blood and hair samples of children diagnosed with hypospadias. Toxicol Lett 211:S187. http://doi.org/10.1016/j.toxlet.2012.03.673.

Mill T. 1999. Predicting photoreaction rates in surface waters. Chemosphere 38:1379-1390.

Min JY, Cho JS, Lee KJ, et al. 2011. Potential role for organochlorine pesticides in the prevalence of peripheral arterial diseases in obese persons: results from the National Health and Nutrition Examination Survey 1999-2004. Atherosclerosis 218(1):200-206. http://doi.org/10.1016/j.atherosclerosis.2011.04.044.

Minh NH, Someya M, Minh TB, et al. 2004. Persistent organochlorine residues in human breast milk from Hanoi and Hochiminh City, Vietnam: contamination, accumulation kinetics and risk assessment for infants. Environ Pollut 129(3):431-441. http://doi.org/10.1016/j.envpol.2003.11.012.

Mladenović D, Hrnčić D, Vucević D, et al. 2007. Ethanol suppressed seizures in lindane-treated rats. Electroencephalographic and behavioral studies. J Physiol Pharmacol 58(4):641-656.

Mørck TA, Erdmann SE, Long M, et al. 2014. PCB concentrations and dioxin-like activity in blood samples from Danish school children and their mothers living in urban and rural areas. Basic Clin Pharmacol Toxicol 115(1):134-144. http://doi.org/10.1111/bcpt.12214.

Morello-Frosch R, Cushing LJ, Jesdale BM, et al. 2016. Environmental chemicals in an urban population of pregnant women and their newborns from San Francisco. Environ Sci Technol 50(22):12464-12472. http://doi.org/10.1021/acs.est.6b03492.

Morgan DP, Lin LI. 1978. Blood organochlorine pesticide concentrations, clinical hematology, and biochemistry in workers occupationally exposed to pesticides. Arch Environ Contam Toxicol 7:423-447.

Morgan MK, Wilson NK, Chuang JC. 2014. Exposures of 129 preschool children to organochlorines, organophosphates, pyrethroids, and acid herbicides at their homes and daycares in North Carolina. Int J Environ Res Public Health 11(4):3743-3764. http://doi.org/10.3390/ijerph110403743.

Morgan DP, Roberts RJ, Walter AW, et al. 1980. Anemia associated with exposure to lindane. Arch Environ Health 35:307-310.

Moriya M, Ohta T, Watanabe K, et al. 1983. Further mutagenicity studies on pesticides in bacterial reversion assay systems. Mutat Res 116:185-216.

Mortazavi N, Asadikaram G, Ebadzadeh MR, et al. 2019. Organochlorine and organophosphorus pesticides and bladder cancer: A case-control study. J Cell Biochem 120(9):14847-14859. http://doi.org/10.1002/jcb.28746.

Mougin C, Pericaud C, Malosse C, et al. 1996. Biotransformation of the insecticide lindane by the white rot basidiomycete Phanerochaete chrysosporium. Pestic Sci 47:51-59.

Mougin C, Pericaud C, Dubroca J, et al. 1997. Enhanced mineralization of lindane in soils supplemented with the white rot basidiomycete Phanerochaete chrysosporium. Soil Biol Biochem 29(9):1321-1324.

Mudawal A, Srivastava A, Singh A, et al. 2018. Proteomic approaches to investigate age related vulnerability to lindane induced neurodegenerative effects in rats. Food Chem Toxicol 115:499-510. http://doi.org/10.1016/j.fct.2018.03.049.

Muller D, Klepel H, Macholz RM, et al. 1981. Electroneurophysiological studies on neurotoxic effects of hexachlorocyclohexane isomers and gamma-pentachlorocyclohexene. Bull Environ Contam Toxicol 27(5):704- 706. http://doi.org/10.1007/BF01611085.

Mullins DE, Young RW, Hetzel GH, et al. 1992. Wastewater cleanup using demulsification, sorption, and filtration followed by chemical and biological degradation. ACS Symp Ser 510:166-176.

Munir KM, Soman CS, Bhide SV. 1983. Hexachlorocyclohexane-induced tumorigenicity in mice under different experimental conditions. Tumori 69:383-386.

Munk ZM, Nantel A. 1977. Acute lindane poisoning with development of muscle necrosis. Can Med Assoc J 117:1050-1054.

Murli H. 1990. Lindane (technical): In an in vitro cytogenetic assay measuring chromosomal aberration frequencies in Chinese Hamster Ovary (CHO) cells with multiple harvests under conditions of metabolic activation. Kensington, MD: Hazelton Laboratories America, Inc. HLA Study No. 12024-0-437C.

Murphy R, Harvey C. 1985. Residues and metabolites of selected persistent halogenated hydrocarbons in blood specimens from a general population survey. Environ Health Perspect 60:115-120.

Mustafa MD, Banerjee BD, Ahmed RS, et al. 2013. Gene-environment interaction in preterm delivery with special reference to organochlorine pesticides. Mol Hum Reprod 19(1):35-42. http://doi.org/10.1093/molehr/gas039.

Mustieles V, Fernandez MF, Martin-Olmedo P, et al. 2017. Human adipose tissue levels of persistent organic pollutants and metabolic syndrome components: Combining a cross-sectional with a 10-year longitudinal study using a multi-pollutant approach. Environ Int 104:48-57. http://doi.org/10.1016/j.envint.2017.04.002.

Naeher LP, Barr DB, Rithmire N, et al. 2009. Pesticide exposure resulting from treatment of lice infestation in school-aged children in Georgia. Environ Int 35(2):358-362. http://doi.org/10.1016/j.envint.2008.09.001.

Nagaraja TN, Desiraju T. 1994. Brain regional variations in the levels of biogenic amines, glutamate, GABA and glutamate decarboxylase activity in developing and adult rats exposed chronically to hexachlorocyclohexane. Biog Amines 10:141-149.

Nagasaki H, Kawabata H, Miyata K, et al. 1975. Effect of various factors on induction of liver tumors in animals by the α-isomer of benzene hexachloride. Gann 66:185-191.

Nagda G, Bhatt DK. 2011. Alleviation of lindane induced toxicity in testis of Swiss mice (Mus musculus) by combined treatment with vitamin C, vitamin E and α-lipoic acid. Indian J Exp Biol 49(3):191-199.

Nagy Z, Mile I, Antoni F. 1975. The mutagenic effect of pesticides on Escherichia coli WP2 try. Acta Microbiol Acad Sci Hung 22(3):309-314.

Nair A, Mandapati R, Dureja P, et al. 1996. DDT and HCH load in mothers and their infants in Delhi, India. Bull Environ Contam Toxicol 56:58-64.

Namulanda G, Maisonet M, Taylor E, et al. 2016. In utero exposure to organochlorine pesticides and early menarche in the Avon Longitudinal Study of parents and children. Environ Int 94:467-472. http://doi.org/10.1016/j.envint.2016.06.001.

Nantel A, Ayotte L, Benedatti JL, et al. 1977. A group of adults acutely poisoned by food contaminated with lindane. Acta Pharmacol Toxicol 41(Suppl 2):250.

NAS/NRC. 1989. Report of the oversight committee. In: Biologic markers in reproductive toxicology. Washington, DC: National Academy of Sciences, National Research Council, 15-35.

NCI. 1977. Bioassay of lindane for possible carcinogenicity. Bethesda, MD: National Cancer Institute. DHEW publication no. (NIH) 77-814.

Neidert E, Saschenbrecker PW. 1996. Occurrence of pesticide residues in selected agricultural food commodities available in Canada. J AOAC Int 79:549-566.

Neururer H, Womastek R. 1991. [Pesticides in the air]. Bodenkultur 42:57-70. (German)

Nigam SK, Lakkad BC, Karnick AB, et al. 1979. Effect of hexachlorocyclohexane feeding on testicular tissue of pure inbred Swiss mice. Bull Environ Contam Toxicol 23(4-5):431-437. http://doi.org/10.1007/BF01769983.

Nigam SK, Karnik AB, Majumder SK, et al. 1986. Serum hexachlorocyclohexane residues in workers engaged at a HCH manufacturing plant. Int Arch Occup Environ Health 57:315-320.

NIOSH. 1994. Lindane. Immediately dangerous to life or health concentrations (IDLH). National Institute for Occupational Safety and Health. https://www.cdc.gov/niosh/idlh/58899.html. March 23, 2021.

NIOSH. 2019. Lindane. NIOSH pocket guide to chemical hazards. National Institute for Occupational Safety and Health. https://www.cdc.gov/niosh/npg/npgd0370.html. March 23, 2021.

NLM. 2021. PubChem: Lindane. National Library of Medicine. https://pubchem.ncbi.nlm.nih.gov/compound/727. May 11, 2021.

Noegrohati S, Hammers WE. 1992. Sorption-desorption kinetics of some organochlorine insecticides in silt-water suspensions. Toxicol Environ Chem 34:187-206.

Nordmeyer H, Pestemer W, Rahman A. 1992. Sorption and transport behavior of some pesticides in groundwater sediments. Stygologia 7:5-11.

Nordt SP, Chew G. 2000. Acute lindane poisoning in three children. J Emerg Med 18(1):51-53.

NTP. 1984. National Toxicology Program fiscal year 1984 annual plan. Research Triangle Park, NC: National Toxicology Program.

NTP. 2013. Draft OHAT approach for systematic review and evidence integration for literature-based health assessments – February 2013. National Toxicology Program. https://ntp.niehs.nih.gov/ntp/ohat/evaluationprocess/draftohatapproach_february2013.pdf. May 5, 2021.

NTP. 2015. OHAT risk of bias rating tool for human and animal studies. National Toxicology Program. https://ntp.niehs.nih.gov/ntp/ohat/pubs/riskofbiastool_508.pdf. March 19, 2019.

NTP. 2016. Lindane, hexachlorocyclohexane (technical grade), and other hexachlorocyclohexane isomers. In: Report on carcinogens. 14th ed. National Toxicology Program, https://ntp.niehs.nih.gov/ntp/roc/content/profiles/lindane.pdf. March 23, 2021.

Nybom N, Knutsson B. 1947. Investigations on C-mitosis in Allium cepa. Hereditus 33:220-234.

Nyholm N, Jacobsen BN, Pedersen BM, et al. 1992. Removal of organic micropollutants at ppb levels in laboratory activated-sludge reactors under various operating-conditions: biodegradation. Water Res 26:339-353.

Ociepa-Zawal M, Rubis B, Wawrzynczak D, et al. 2010. Accumulation of environmental estrogens in adipose tissue of breast cancer patients. J Environ Sci Health A Tox Hazard Subst Environ Eng 45(3):305-312. http://doi.org/10.1080/10934520903468038.

Oesch F, Friedberg T, Herbst M, et al. 1982. Effects of lindane treatment on drug metabolizing enzymes and liver weight of CF1 mice in which it evoked hepatomas and in non-susceptible rodents. Chem Biol Interact 40:1-14.

Oldiges H, Takenaka S, Hochrainer D. 1980. Inhalation study with lindane (γ-hexachlorocyclohexane) to determine the LC50. Schmallenberg, Germany: Fraunhofer-Institut, Institute for Toxicology and Aerosol Research. Celamerck Document No. 111AA-423-002.

Oldiges H, Hertel R, Kördel W, et al. 1983. 90-day inhalation study with lindane. Schmallenberg, Germany: Fraunhofer-Institut, Institute for Toxicology and Aerosol Research. Celamerck Document No. 111AC-435-005.

Olgun S, Misra HP. 2006. Pesticides induced oxidative stress in thymocytes. Mol Cell Biochem 290(1-2):137-144. http://doi.org/10.1007/s11010-006-9178-7.

Olgun S, Gogal RM, Adeshina F, et al. 2004. Pesticide mixtures potentiate the toxicity in murine thymocytes. Toxicology 196(3):181-195. http://doi.org/10.1016/j.tox.2003.09.007.

Oliver BG, Charlton MN. 1984. Chlorinated organic contaminants on settling particulates in the Niagara River vicinity of Lake Ontario. Environ Sci Technol 18:903-908.

Orr JW. 1948. Absence of carcinogenic activity of benzene hexachloride (‘gammexane'). Nature 162(4109):189-189. http://doi.org/10.1038/162189a0.

Ortega P, Hayes WJ, Durham WF. 1957. Pathologic changes in the liver of rats after feeding low levels of various insecticides. AMA Arch Pathol 64:614-622.

OSHA. 2020a. Occupational safety and health standards. Subpart Z - Toxic and hazardous substances. Air contaminants. Table Z-1: Limits for air contaminants. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000. https://www.osha.gov/laws-regs/regulations/standardnumber/1910/1910.1000TABLEZ1. September 28, 2020.

OSHA. 2020b. Occupational safety and health standards for shipyard employment. Subpart Z - Toxic and hazardous substances. Air contaminants. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1915.1000. https://www.osha.gov/laws-regs/regulations/standardnumber/1915/1915.1000. September 28, 2020.

OSHA. 2020c. Safety and health regulations for construction. Subpart D - Occupational health and environment controls. Gases, vapors, fumes, dusts, and mists. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1926.55 Appendix A. https://www.osha.gov/laws-regs/regulations/standardnumber/1926/1926.55AppA. September 28, 2020.

Padma TV, Dickhut RM. 2002. Spatial and temporal variation in hexachlorocyclohexane isomers in a temperate estuary. Mar Pollut Bull 44(12):1345-1353. http://doi.org/10.1016/s0025-326x(02)00171-6.

Page GW. 1981. Comparison of groundwater and surface water for patterns and levels of contamination by toxic substances. Environ Sci Technol 15:1475-1481.

Pages N, diBlasi-Vouvet S, Schlatter J, et al. 2000. Hormone disruptive effects of residual doses of lindane in male rats exposed at prenatal and postnatal periods [Abstract]. Hum Exp Toxicol 19(8):479.

Pahwa P, Karunanayake CP, Dosman JA, et al. 2011. Soft-tissue sarcoma and pesticides exposure in men: results of a Canadian case-control study. J Occup Environ Med 53(11):1279-1286. http://doi.org/10.1097/JOM.0b013e3182307845.

Palmer AK, Bottomley AM, Worden AN, et al. 1978. Effect of lindane on pregnancy in the rabbit and rat. Toxicology 9:239-247.

Pankow JF, Isabelle LM, Asher WE. 1984. Trace organic compounds in rain. 1. Sampler design and analysis by adsorption/thermal desorption (ATD). Environ Sci Technol 18:310-318.

Parmar D, Yadav S, Dayal M, et al. 2003. Effect of lindane on hepatic and brain cytochrome P450s and influence of P450 modulation in lindane induced neurotoxicity. Food Chem Toxicol 41(8):1077-1087. http://doi.org/10.1016/s0278-6915(03)00045-0.

8. REFERENCES

Paul R, Talukdar A, Bhattacharya R, et al. 2013. γ-Benzene hexachloride poisoning leading to acute hepatorenal decompensation. BMJ Case Rep 2013:9851. http://doi.org/10.1136/bcr-2013-009851.

Pestana D, Fernandes V, Faria G, et al. 2011. Persistent organic pollutant (POPs) levels in human visceral and subcutaneous adipose tissue on an obese Portuguese population-Metabolic improvement after bariatric surgery versus POPs burden. Toxicol Lett 205:S75-S76. http://doi.org/10.1016/j.toxlet.2011.05.284.

Petersen MS, Halling J, Bech S, et al. 2008. Impact of dietary exposure to food contaminants on the risk of Parkinson's disease. Neurotoxicology 29(4):584-590. http://doi.org/10.1016/j.neuro.2008.03.001.

Philip GH, Sriraman PK, Ramamurthi R. 1989. Histopathological changes in liver and kidney of *Mus booduga* following oral benzenehexachloride (BHC) feeding. Bull Environ Contam Toxicol 42(4):499-502. http://doi.org/10.1007/BF01700228.

Pi N, Chia SE, Ong CN, et al. 2016. Associations of serum organohalogen levels and prostate cancer risk: Results from a case-control study in Singapore. Chemosphere 144:1505-1512. http://doi.org/10.1016/j.chemosphere.2015.10.020.

Piccoli C, Cremonese C, Koifman RJ, et al. 2016. Pesticide exposure and thyroid function in an agricultural population in Brazil. Environ Res 151:389-398. http://doi.org/10.1016/j.envres.2016.08.011.

Pierik FH, Klebanoff MA, Brock JW, et al. 2007. Maternal pregnancy serum level of heptachlor epoxide, hexachlorobenzene, and β-hexachlorocyclohexane and risk of cryptorchidism in offspring. Environ Res 105(3):364-369. http://doi.org/10.1016/j.envres.2007.04.005.

Pius J, Shivanandappa T, Krishnakumari MK. 1990. Protective role of vitamin A in the male reproductive toxicity of hexachlorocyclohexane (HCH) in the rat. Reprod Toxicol 4:325-330.

Ploteau S, Cano-Sancho G, Volteau C, et al. 2017. Associations between internal exposure levels of persistent organic pollutants in adipose tissue and deep infiltrating endometriosis with or without concurrent ovarian endometrioma. Environ Int 108:195-203. http://doi.org/10.1016/j.envint.2017.08.019.

Pool-Zobel BL, Lotzman N, Knoll M, et al. 1994. Detection of genotoxic effects in human gastric and nasal mucosa cells isolated from biopsy samples. Environ Mol Mutagen 24:23-45.

Porta M, Jariod M, López T, et al. 2009. Correcting serum concentrations of organochlorine compounds by lipids: alternatives to the organochlorine/total lipids ratio. Environ Int 35(7):1080-1085. http://doi.org/10.1016/j.envint.2009.06.004.

Portig J, Stein K, Vohland HW. 1989. Preferential distribution of α-hexachlorocyclohexane into cerebral white matter. Xenobiotica 19:123-130.

Powell GM. 1980. Toxicity of lindane [letter]. Central Afr J Med 26:170.

Prasad AK, Pant N, Srivastava SC, et al. 1995. Effect of dermal application of hexachlorocyclohexane (HCH) on male reproductive system of rat. Hum Exp Toxicol 14:484-488.

Prasad WL, Srilatha C, Sailaja N, et al. 2016. Amelioration of gamma-hexachlorocyclohexane (lindane) induced renal toxicity by Camellia sinensis in Wistar rats. Vet World 9(11):1331-1337. http://doi.org/10.14202/vetworld.2016.1331-1337.

Presutti R, Harris SA, Kachuri L, et al. 2016. Pesticide exposures and the risk of multiple myeloma in men: An analysis of the North American Pooled Project. Int J Cancer 139(8):1703-1714. http://doi.org/10.1002/ijc.30218.

Purdue MP, Hoppin JA, Blair A, et al. 2007. Occupational exposure to organochlorine insecticides and cancer incidence in the Agricultural Health Study. Int J Cancer 120(3):642-649. http://doi.org/10.1002/ijc.22258.

Quadroni S, Bettinetti R. 2019. An unnoticed issue: Organochlorine pesticides in tobacco products around the world. Chemosphere 219:54-57. http://doi.org/10.1016/j.chemosphere.2018.12.009.

Quansah R, Bend JR, Abdul-Rahaman A, et al. 2016. Associations between pesticide use and respiratory symptoms: A cross-sectional study in Southern Ghana. Environ Res 150:245-254. http://doi.org/10.1016/j.envres.2016.06.013.

Quintana PJ, Delfino RJ, Korrick S, et al. 2004. Adipose tissue levels of organochlorine pesticides and polychlorinated biphenyls and risk of non-Hodgkin's lymphoma. Environ Health Perspect 112(8):854-861. http://doi.org/10.1289/ehp.6726.

Quintero JC, Moreira MT, Feijoo G, et al. 2005. Effect of surfactants on the soil desorption of hexachlorocyclohexane (HCH) isomers and their anaerobic biodegradation. J Chem Technol Biotechnol 80(9):1005-1015. http://doi.org/10.1002/jctb.1277.

Raaschou-Nielsen O, Pavuk M, Leblanc A, et al. 2005. Adipose organochlorine concentrations and risk of breast cancer among postmenopausal Danish women. Cancer Epidemiol Biomarkers Prev 14(1):67-74.

Radomski JL, Astolfi E, Deichmann WB, et al. 1971a. Blood levels of organochlorine pesticides in Argentina: Occupationally and nonoccupationally exposed adults, children and newborn infants. Toxicol Appl Pharmacol 20:186-193.

Radomski JL, Deichmann WB, Rey AA, et al. 1971b. Human pesticide blood levels as a measure of body burden and pesticide exposure. Toxicol Appl Pharmacol 20:175-185.

Radosavljević T, Mladenović D, Vucević D, et al. 2008. Effect of acute lindane and alcohol intoxication on serum concentration of enzymes and fatty acids in rats. Food Chem Toxicol 46(5):1739-1743. http://doi.org/10.1016/j.fct.2008.01.011.

Raizada RB, Srivastava MK, Sarin S. 1993. Impact of technical hexachlorocyclohexane (HCH) on biogenic amines and locomotor activity of rat. Natl Acad Sci Letts Indian 16(2):73-76.

Raizada RB, Misra P, Saxena I, et al. 1980. Weak estrogenic activity of lindane in rats. J Toxicol Environ Health 6:483-492.

Ramabhatta S, Sunilkumar GR, Somashekhar C. 2014. Lindane toxicity following accidental oral ingestion. Indian J Dermatol Venereol Leprol 80(2):181-182. http://doi.org/10.4103/0378-6323.129419.

Ramachandran M, Banerjee BD, Gulati M, et al. 1984. DDT and HCH residues in the body fat and blood samples from some Delhi hospitals. Indian J Med Res 80:590-593.

Ramamoorthy S. 1985. Competition of fate processes in the bioconcentration of lindane. Bull Environ Contam Toxicol 34:349-358.

Ramchander V, Cameron ES, Reid HF. 1991. Lindane toxicity in an infant. West Indian Med J 40:41-43.

Rauch AE, Kowalsky SF, Lesar TS, et al. 1990. Lindane (Kwell)-induced aplastic anemia. Arch Intern Med 150:2393-2395.

Ravinder P, Srinivasan K, Radhakrishnamurty R. 1989. Biochemical toxicity of hexachlorocyclohexane and its γ-isomer in albino mice. Indian J Exp Biol 27:248-251.

Ravinder P, Srinivasan K, Radhakrishnamurty R. 1990. Dietary hexachlorocyclohexane induced changes in blood and liver lipids in albino mice. Indian J Exp Biol 28:155-157.

Reinhart DR, Pohland FG. 1991. The assimilation of organic hazardous wastes by municipal solid waste landfills. J Ind Microbiol 8:193-200.

Reinhart DR, Pohland FG, Gould JP, et al. 1991. The fate of selected organic pollutants codisposed with municipal refuse. Res J Water Pollut Control Fed 63:780-788.

RePORTER. 2021. Hexachlorocyclohexanes. National Institutes of Health, Research Portfolio Online Reporting Tools. http://projectreporter.nih.gov/reporter.cfm. March 15, 2021.

Ribas-Fito N, Sala M, Cardo E, et al. 2003. Organochlorine compounds and concentrations of thyroid stimulating hormone in newborns. Occup Environ Med 60(4):301-303. http://doi.org/10.1136/oem.60.4.301.

Richardson JR, Shalat SL, Buckley B, et al. 2009. Elevated serum pesticide levels and risk of Parkinson disease. Arch Neurol 66(7):870-875. http://doi.org/10.1001/archneurol.2009.89.

Richardson JR, Roy A, Shalat SL, et al. 2011. β-Hexachlorocyclohexane levels in serum and risk of Parkinson's disease. Neurotoxicology 32(5):640-645. http://doi.org/10.1016/j.neuro.2011.04.002.

Rippen G, Ilgenstein M, Klöpffer W, et al. 1982. Screening of the adsorption behavior of new chemicals: Natural soils and model adsorbents. Ecotoxicol Environ Saf 6(3):236-245. http://doi.org/10.1016/0147-6513(82)90014-8.

Rivera S, Sanfeliu C, Sunol C, et al. 1991. Regional effects on the cerebral concentration of noradrenaline, serotonin, and dopamine in suckling rats after a single dose of lindane. Toxicology 69:43- 54.

Rivera S, Rosa R, Marinez E, et al. 1998. Behavioral and monoaminergic changes after lindane exposure in developing rats. Neurotoxicol Teratol 20(2):155-160.

Rivett KF, Chesterman H, Kellett DN, et al. 1978. Effects of feeding lindane to dogs for periods of up to 2 years. Toxicology 9:273-289.

Rocchi P, Perocco P, Alberghini W, et al. 1980. Effect of pesticides on scheduled and unscheduled DNA synthesis of rat thymocytes and human lymphocytes. Arch Toxicol 45:101-108.

Rogers WM, Kendall DC, Salmon GD, et al. 1995. Accumulated pesticide and industrial chemical findings from a ten-year study of ready-to-eat foods. J AOAC Int 78:614-631.

Rooney AA, Boyles AL, Wolfe MS, et al. 2014. Systematic review and evidence integration for literature-based environmental health science assessments. Environ Health Perspect 122(7):711-718. http://doi.org/10.1289/ehp.1307972.

Roy RR, Wilson P, Laski RR, et al. 1997. Monitoring of domestic and imported apples and rice by the U.S. Food and Drug Administration Pesticide Program. J AOAC Int 80:883-894.

Roy Chowdhury A, Gautam AK. 1990. BHC induced testicular impairments in rats. Indian J Physiol Pharmacol 34:215-217.

Rüdel H. 1997. Volatilisation of pesticides from soil and plant surfaces. Chemosphere 38(1-2):143-152.

Rugman FP, Cosstick R. 1990. Aplastic anaemia associated with organochlorine pesticide: Case reports and review of evidence. J Clin Pathol 43:98-101.

Rupa DS, Reddy PP, Reddi OS. 1989a. Analysis of sister-chromatid exchanges, cell kinetics and mitotic index in lymphocytes of smoking pesticide sprayers. Mutat Res 223:253-258.

Rupa DS, Reddy PP, Reddi OS. 1989b. Chromosomal aberrations in peripheral lymphocytes of cotton field workers exposed to pesticides. Environ Res 49:1-6.

Rupa DS, Reddy PP, Reddi OS. 1989c. Frequencies of chromosomal aberrations in smokers exposed to pesticides in cotton fields. Mutat Res 222:37-41.

Rupa DS, Reddy PP, Reddi OS. 1989d. Genotoxic effect of benzene hexachloride in cultured human lymphocytes. Hum Genet 83:271-273.

Rupa DS, Rita P, Reddy PP, et al. 1988. Screening of chromosomal aberrations and sister chromatid exchanges in peripheral lymphocytes of vegetable garden workers. Hum Toxicol 7:333-336.

Rylander C, Sandanger TM, Nost TH, et al. 2015. Combining plasma measurements and mechanistic modeling to explore the effect of POPs on type 2 diabetes mellitus in Norwegian women. Environ Res 142:365-373. http://doi.org/10.1016/j.envres.2015.07.002.

Ryu DH, Yu HT, Kim SA, et al. 2018. Is chronic exposure to low-dose organochlorine pesticides a new risk factor of t-cell immunosenescence? Cancer Epidemiol Biomarkers Prev 27(10):1159-1167. http://doi.org/10.1158/1055-9965.Epi-17-0799.

Safe SH. 1993. Toxic aromatics. In: Kroschwitz JI, Howe-Grant M, eds. Kirk-Othmer's encyclopedia of chemical technology. New York, NY: John Wiley & Sons, 127-139.

Sahaya K, Mahajan P, Mediratta PK, et al. 2007. Reversal of lindane-induced impairment of step-down passive avoidance and oxidative stress by neurosteroids in rats. Toxicology 239(1-2):116-126. http://doi.org/10.1016/j.tox.2007.07.002.

Sahoo A, Samanta L, Das A, et al. 1999. Hexachlorocyclohexane-induced behavioral and neurochemical changes in rat. J Appl Toxicol 19(1):13-18.

Sahu SK, Patnaik KK, Bhuyan S, et al. 1993. Degradation of soil-applied isomers of hexachlorocyclohexane by a Pseudomonas SP. Soil Biol Biochem 25(3):387-391. http://doi.org/10.1016/0038-0717(93)90139-3.

Saleh FY, Lee GF, Butler JS. 1978. Kepone and other selected chlorinated hydrocarbon pesticides and PCBs behavior during hydraulic dredging of the James River near Hopewell, Virginia. J Environ Sci Health A 13:261-294.

Saleh FY, Dickson KL, Rodgers JH. 1982. Fate of lindane in the aquatic environment: Rate constants of physical and chemical processes. Environ Toxicol Chem 1:289-297.

Salo HM, Koponen J, Kiviranta H, et al. 2019. No evidence of the role of early chemical exposure in the development of β-cell autoimmunity. Environ Sci Pollut Res Int 26(2):1370-1378. http://doi.org/10.1007%2Fs11356-018-3659-6.

Samanta L, Chainy GBN. 1997. Comparison of hexachlorocyclohexane-induced oxidative stress in the testis of immature and adult rats. Comp Biochem Physiol 118C(3):319-327.

Samanta L, Sahoo A, Chainy GB. 1999. Age-related changes in rat testicular oxidative stress parameters by hexachlorocyclohexane. Arch Toxicol 73(2):96-107.

Samuel T, Pillai MKK. 1990. Effect of temperature and sunlight exposure on the fate of soil-applied [^{14}C]-gamma-hexachlorocyclohexane. Arch Environ Contam Toxicol 19:214-220.

Sandhu SS, Warren WJ, Nelson P. 1978. Pesticidal residue in rural potable water. J Am Water Works Assoc 70:41-45.

Saradha B, Mathur PP. 2006. Induction of oxidative stress by lindane in epididymis of adult male rats. Environ Toxicol Pharmacol 22(1):90-96. http://doi.org/10.1016/j.etap.2005.12.008.

Sasaki K, Ishizaka T, Suzuki T, et al. 1991. Organochlorine chemicals in skin lipids as an index of their accumulation in the human body. Arch Environ Contam Toxicol 21(2):190-194. http://doi.org/10.1007/bf01055336.

Sauviat M-P, Godeau G, Pages N. 2007. Alterations of offspring heart muscle electrical activity transferred by rat male genitors chronically treated with lindane (γ-hexachlorocyclohexane) trace concentrations. Pestic Biochem Physiol 87(2):131-137. http://doi.org/10.1016/j.pestbp.2006.07.002.

Sauviat MP, Bouvet S, Godeau G, et al. 2005. Electrical activity alterations induced by chronic absorption of lindane (γ-hexachlorocyclohexane) trace concentrations in adult rat heart. Can J Physiol Pharmacol 83(3):243-251. http://doi.org/10.1139/y04-132.

Sawada N, Iwasaki M, Inoue M, et al. 2010. Plasma organochlorines and subsequent risk of prostate cancer in Japanese men: a nested case-control study. Environ Health Perspect 118(5):659-665. http://doi.org/10.1289/ehp.0901214.

Sawyer ME, Evans MV, Wilson CA, et al. 2016. Development of a human physiologically based pharmacokinetic (PBPK) model for dermal permeability for lindane. Toxicol Lett 245:106-109. http://doi.org/10.1016/j.toxlet.2016.01.008.

Saxena DK, Murthy RC, Chandra SV. 1986. Embryotoxic and teratogenic effects of interaction of cadmium and lindane in rats. Acta Pharmacol Toxicol 59:175-178.

Saxena MC, Siddiqui MKJ, Bhargava AK, et al. 1980. Role of chlorinated hydrocarbon pesticides in abortions and premature labour. Toxicology 17:323-331.

Saxena MC, Siddiqui MKJ, Seth TD, et al. 1981a. Organochlorine pesticides in specimens from women undergoing spontaneous abortion, premature or full-term delivery. J Anal Toxicol 5:6-9.

Saxena MC, Siddiqui MKJ, Bhargava AK, et al. 1981b. Placental transfer of pesticides in humans. Arch Toxicol 48:127-134.

Scascitelli M, Pacchierotti F. 2003. Effects of lindane on oocyte maturation and preimplantation embryonic development in the mouse. Reprod Toxicol 17(3):299-303. http://doi.org/10.1016/s0890-6238(03)00008-x.

Schattenberg HJ, Hsu JP. 1992. Pesticide residue survey of produce from 1989 to 1991. J AOAC Int 75:925-933.

Schimmel SC, Patrick JM, Forester J. 1977. Toxicity and bioconcentration of BHC and lindane in selected estuarine animals. Arch Environ Contam Toxicol 6:355-363.

Schmitt CJ, Zajicek JL, Ribick MA. 1985. National pesticide monitoring program: Residues of organochlorine chemicals in freshwater fish, 1980-1981. Arch Environ Contam Toxicol 14:225-260.

Schmitt CJ, Zajicek JL, Peterman PH. 1990. National contaminant biomonitoring program: Residues of organochlorine chemicals in U.S. Freshwater Fish, 1976-1984. Arch Environ Contam Toxicol 19(5):748-781. http://doi.org/10.1007/bf01183992.

Schmitt M, Gellert G, Ludwig J, et al. 2005. Assessment of cyto- and genotoxic effects of a variety of chemicals using Saccharomyces cerevisiae. Acta Hydrochim Hydrobiol 33(1):56-63. http://doi.org/10.1002/aheh.200300554.

Schröter C, Parzefall W, Schröter H, et al. 1987. Dose-response studies on the effects of α-, β-, and g-hexachlorocyclohexane on putative preneoplastic foci, monooxygenases, and growth in rat liver. Cancer Res 47:80-88.

Seiler P, Fischer B, Lindenau A, et al. 1994. Effects of persistent chlorinated hydrocarbons on fertility and embryonic development in the rabbit. Hum Reprod 9:1920-1926.

Sericano JL, Atlas EL, Wade TL, et al. 1990. NOAA's status and trends mussel watch program: Chlorinated pesticides and PCBs in oysters (Crassostrea virginica) and sediments from the Gulf of Mexico, 1986-1987. Mar Environ Res 29:161-203.

Serrano MT, Vendrell M, Rivera S, et al. 1990. Effect of lindane on the myelination process in the rat. Neurotoxicol Teratol 12:577-583.

Seth V, Ahmad RS, Suke SG, et al. 2005. Lindane-induced immunological alterations in human poisoning cases. Clin Biochem 38(7):678-680. http://doi.org/10.1016/j.clinbiochem.2005.03.009.

Sexton K, Ryan AD. 2012. Using exposure biomarkers in children to compare between-child and within-child variance and calculate correlations among siblings for multiple environmental chemicals. J Expo Sci Environ Epidemiol 22(1):16-23. http://doi.org/10.1038/jes.2011.30.

Sexton K, Ryan AD, Adgate JL, et al. 2011. Biomarker measurements of concurrent exposure to multiple environmental chemicals and chemical classes in children. J Toxicol Environ Health A 74(14):927-942. http://doi.org/10.1080/15287394.2011.573745.

Shah HK, Sharma T, Banerjee BD. 2020. Organochlorine pesticides induce inflammation, ROS production, and DNA damage in human epithelial ovary cells: An in vitro study. Chemosphere 246:125691. http://doi.org/10.1016/j.chemosphere.2019.125691.

Shah PR, Kute VB, Gumber MR, et al. 2013. Benzene hexachloride poisoning with rhabdomyolysis and acute kidney injury. Indian J Nephrol 23(1):80-81. http://doi.org/10.4103/0971-4065.107222.

Shahin MM, von Borstel RC. 1977. Mutagenic and lethal effects of α-benzene hexachloride, dibutyl phthalate, and trichloroethylene in Saccharomyces cerevisiae. Mutat Res 48:173-180.

Sharma P, Singh R. 2010. Protective role of curcumin on lindane induced reproductive toxicity in male Wistar rats. Bull Environ Contam Toxicol 84(4):378-384. http://doi.org/10.1007/s00128-010-9942-y.

Sharma H, Zhang P, Barber DS, et al. 2010. Organochlorine pesticides dieldrin and lindane induce cooperative toxicity in dopaminergic neurons: role of oxidative stress. Neurotoxicology 31(2):215-222. http://doi.org/10.1016/j.neuro.2009.12.007.

Sharma E, Mustafa M, Pathak R, et al. 2012. A case control study of gene environmental interaction in fetal growth restriction with special reference to organochlorine pesticides. Eur J Obstet Gynecol Reprod Biol 161(2):163-169. http://doi.org/10.1016/j.ejogrb.2012.01.008.

Sharma T, Banerjee BD, Mustafa M, et al. 2013. Gene environment interaction in preterm delivery with special reference to organochlorine pesticide: a case control study. Int J Biochem Mol Biol 4(4):209-214.

Sharma T, Banerjee BD, Thakur GK, et al. 2019. Polymorphism of xenobiotic metabolizing gene and susceptibility of epithelial ovarian cancer with reference to organochlorine pesticides exposure. Exp Biol Med 244(16):1446-1453. http://doi.org/10.1177/1535370219878652.

Sharom MS, Miles JRW, Harris CR, et al. 1980. Persistence of 12 insecticides in water. Water Res 14:1089-1093.

Shen L, Wania F, Lei YD, et al. 2004. Hexachlorocyclohexanes in the North American atmosphere. Environ Sci Technol 38(4):965-975. http://doi.org/10.1021/es034998k.

Shen H, Main KM, Virtanen HE, et al. 2007. From mother to child: investigation of prenatal and postnatal exposure to persistent bioaccumulating toxicants using breast milk and placenta biomonitoring. Chemosphere 67(9):S256-262. http://doi.org/10.1016/j.chemosphere.2006.05.106.

Shimazu H, Shiraishi N, Akematsu T, et al. 1972. Carcinogenicity screening tests on induction of chromosomal aberrations in rat bone marrow cells in vivo [abstract]. Mutat Res 38:347.

Shirasu Y, Moriya M, Kato K, et al. 1976. Mutagenicity screening of pesticides in the microbial system. Mutat Res 40:19-30.

Shivanandappa T, Krishnakumari MK. 1983. Hexachlorocyclohexane-induced testicular dysfunction in rats. Acta Pharmacol Toxicol 52:12-17.

Siddarth M, Datta SK, Mustafa M, et al. 2014. Increased level of organochlorine pesticides in chronic kidney disease patients of unknown etiology: role of GSTM1/GSTT1 polymorphism. Chemosphere 96:174-179. http://doi.org/10.1016/j.chemosphere.2013.10.029.

Siddiqui MKJ, Saxena M, Krishna MC. 1981. Storage of DDT and BHC in adipose tissue of Indian males. Int J Environ Anal Chem 10:197-204.

Siddiqui MK, Srivastava S, Srivastava SP, et al. 2003. Persistent chlorinated pesticides and intra-uterine foetal growth retardation: a possible association. Int Arch Occup Environ Health 76(1):75-80. http://doi.org/10.1007/s00420-002-0393-6.

Sidorova TS, Matesic DF. 2008. Protective effect of the natural product, chaetoglobosin K, on lindane- and dieldrin-induced changes in astroglia: identification of activated signaling pathways. Pharm Res 25(6):1297-1308. http://doi.org/10.1007/s11095-007-9487-x.

Simon-Giavarotti KA, Giavarotti L, Gomes LF, et al. 2002. Enhancement of lindane-induced liver oxidative stress and hepatotoxicity by thyroid hormone is reduced by gadolinium chloride. Free Radic Res 36(10):1033-1039. http://doi.org/10.1080/1071576021000028280.

Sineli P, Benimeli CS, Amoroso MJ, et al. 2014. Biodegradation of alpha- and beta-Hexachlorocyclohexane by Indigenous Actinobacteria. In: Alvarez A, Polti M, eds. Bioremediation in Latin America. Switzerland: Springer International Publishing, 279-288. http://doi.org/10.1007/978-3-319-05738-5_18.

Singh R, Sharma P. 2011. Hepatoprotective effect of curcumin on lindane-induced oxidative stress in male Wistar rats. Toxicol Int 18(2):124-129. http://doi.org/10.4103/0971-6580.84264.

Singh G, Kathpal TS, Spencer WF, et al. 1991. Dissipation of some organochlorine insecticides in cropped and uncropped soil. Environ Pollut 70:219-240.

Singh NK, Chhillar N, Banerjee BD, et al. 2012. Gene-environment interaction in Alzheimer's disease. Am J Alzheimers Dis Other Demen 27(7):496-503. http://doi.org/10.1177/1533317512456067.

Singh N, Chhillar N, Banerjee B, et al. 2013. Organochlorine pesticide levels and risk of Alzheimer's disease in north Indian population. Hum Exp Toxicol 32(1):24-30. http://doi.org/10.1177/0960327112456315.

Singh NK, Banerjee BD, Bala K, et al. 2014. Polymorphism in cytochrome P450 2D6, glutathione S-transferases Pi I Genes, and organochlorine pesticides in Alzheimer disease: A case-control study in north Indian population. J Geriatr Psychiatry Neurol 27(2):119-127. http://doi.org/10.1177/0891988714522698.

Sinha C, Shukla GS. 2003. Species variation in pesticide-induced blood-brain barrier dysfunction. Hum Exp Toxicol 22(12):647-652. http://doi.org/10.1191/0960327103ht405oa.

Sipes IG, Gandolfi AJ. 1991. Biotransformation of toxicants. In: Amdur MO, Doull J, Klaassen CD, eds. Toxicology: The basic science of poisons. 4th ed. New York, NY: Pergamon Press, 86-126.

Sircar S, Lahiri P. 1989. Lindane (g-HCH) causes reproductive failure and fetotoxicity in mice. Toxicology 59:171-177.

Sisto R, Moleti A, Palkovicova Murinova L, et al. 2015. Environmental exposure to organochlorine pesticides and deficits in cochlear status in children. Environ Sci Pollut Res Int 22(19):14570-14578. http://doi.org/10.1007/s11356-015-4690-5.

Šmídová K, Hofman J, Ite AE, et al. 2012. Fate and bioavailability of ^{14}C-pyrene and ^{14}C-lindane in sterile natural and artificial soils and the influence of aging. Environ Pollut 171:93-98. http://doi.org/10.1016/j.envpol.2012.07.031.

Šmídová K, Šerá J, Bielská L, et al. 2015. Influence of feeding and earthworm density on compound bioaccumulation in earthworms Eisenia andrei. Environ Pollut 207:168-175. http://doi.org/10.1016/j.envpol.2015.09.025.

Smith AG. 1991. Chlorinated hydrocarbon insecticides. In: Handbook of pesticide toxicology. Vol. 2. San Diego, CA: Academic Press, 731-743, 791-816, 868-915.

Smith MT, Guyton KZ, Gibbons CF, et al. 2016. Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. Environ Health Perspect 124(6):713-721. http://doi.org/10.1289/ehp.1509912.

Smith-Baker C, Saleh MA. 2011. Hair as a marker for pesticides exposure. J Environ Sci Health B 46(7):648-653. http://doi.org/10.1080/03601234.2012.597701.

Solomon L, Faherer L, West D. 1977a. Gamma benzene hexachloride toxicity. Arch Dermatol 113:353-357.

Solomon L, West D, Fitzloff J, et al. 1977b. Gamma benzene hexachloride in guinea-pig brain after topical application. J Invest Dermatol 68:310-312.

Solomon BA, Haut SR, Carr EM, et al. 1995. Neurotoxic reaction to lindane in an HIV-seropositive patient: An old medication's new problem. J Fam Pract 40:291-295.

Song S, Ma X, Pan M, et al. 2018. Excretion kinetics of three dominant organochlorine compounds in human milk within the first 6 months postpartum. Environ Monit Assess 190(8):457. http://doi.org/10.1007/s10661-018-6850-9.

Srinivasan K, Radhakrishnamurty R. 1983. Studies on the distribution of β- and g-isomers of hexachlorocyclohexane in rat tissues. J Environ Sci Health B 18:401-418.

Srinivasan K, Radhakrishnamurty R. 1988. Biochemical changes produced by β- and g-hexachlorocyclohexane isomers in albino rats. J Environ Sci Health 23:367-386.

Srinivasan K, Ramesh HP, Radhakrishnamurty R. 1984. Renal tubular dysfunction caused by dietary hexachlorocyclohexane (HCH) isomers. J Environ Sci Health 19:453-466.

Srinivasan K, Mahadevappa KL, Radhakrishnamurty R. 1991. Effect of maternal dietary hexachlorocyclohexane exposure on pup survival and growth in albino rats. J Environ Sci Health B 26:339-349.

Srivastava MK, Raizada RB. 1993. Prenatal effects of technical hexachlorocyclohexane in mice. J Toxicol Environ Health 40(1):105-115. http://doi.org/10.1080/15287399309531778.

Srivastava MK, Raizada RB. 2000. A limited three-generation reproduction study on hexachlorocyclohexane (HCH) in rats. Food Chem Toxicol 38:195-201.

Srivastava A, Shivanandappa T. 2014. Prevention of hexachlorocyclohexane-induced neuronal oxidative stress by natural antioxidants. Nutr Neurosci 17(4):164-171. http://doi.org/10.1179/1476830513y.0000000075.

Srivastava A, Srivastava AK, Mishra M, et al. 2019. A proteomic approach to investigate enhanced responsiveness in rechallenged adult rats prenatally exposed to lindane. Neurotoxicology 74:184-195. http://doi.org/10.1016/j.neuro.2019.07.004.

Stachel B, Dougherty RC, Lahl U, et al. 1989. Toxic environmental chemicals in human semen: Analytical method and case studies. Andrologia 21:282-291.

Stanley CW, Barney JE, Helton MR, et al. 1971. Measurement of atmospheric levels of pesticides. Environ Sci Technol 5:430-435.

Staples CA, Werner A, Hoogheem T. 1985. Assessment of priority pollutant concentrations in the United States using STORET database. Environ Toxicol Chem 4:131-142.

Starr HJ, Clifford NJ. 1972. Acute lindane intoxication. A case study. Arch Environ Health 25:374-375.

Starr HG, Aldrich FD, McDougall WD, et al. 1974. Contribution of household dust to the human exposure to pesticides. Pest Monit J 8:209-212.

Steenland K, Mora AM, Barr DB, et al. 2014. Organochlorine chemicals and neurodegeneration among elderly subjects in Costa Rica. Environ Res 134:205-209. http://doi.org/10.1016/j.envres.2014.07.024.

Storen G. 1955. Lethal poisoning with the moth- and insecticide 'Jacutin'. Nord J Hyg 36:77-81.

Strachan WMJ. 1988. Toxic contaminants in rainfall in Canada: 1984. Environ Toxicol Chem 7:871-877.

Sturgeon S, Broxk J, Potischman N, et al. 1998. Serum concentrations of organochlorine compounds and endometrial cancer risk (United States). Cancer Causes Control 9:417-424.

Sudakin DL. 2007. Fatality after a single dermal application of lindane lotion. Arch Environ Occup Health 62(4):201-203. http://doi.org/10.3200/aeoh.62.4.201-203.

Sulik M, Deregowski K, Kemona A. 1988. Distribution and excretion of lindane-14C in acute intoxication in rats. Mater Med Pol 20:92-94.

Sullivan K, Krengel M, Bradford W, et al. 2018. Neuropsychological functioning in military pesticide applicators from the Gulf War: Effects on information processing speed, attention and visual memory. Neurotoxicol Teratol 65:1-13. http://doi.org/10.1016/j.ntt.2017.11.002.

Sumida K, Saito K, Oeda K, et al. 2007. A comparative study of gene expression profiles in rat liver after administration of alpha-hexachlorocyclohexane and lindane. J Toxicol Sci 32(3):261-288. http://doi.org/10.2131/jts.32.261.

Sunder Ram Rao CV, Shreenivas R, Singh V, et al. 1988. Disseminated intravascular coagulation in a case of fatal lindane poisoning. Vet Hum Toxicol 30:132-134.

Sunyer J, Alvarez-Pedrerol M, To-Figueras J, et al. 2008. Urinary porphyrin excretion in children is associated with exposure to organochlorine compounds. Environ Health Perspect 116(10):1407-1410. http://doi.org/10.1289/ehp.11354.

Suter P. 1983. Three months toxicity study in rats with lindane. Itingen, Switzerland: Research and Consulting Company AG. RCC project no. 005220.

Sweeney RA. 1969. Metabolism of lindane by unicellular algae. In: Proceedings of the 12th Conference on Great Lakes Research. International Association for Great Lakes Research, 98-102.

Szeto SY, Price PM. 1991. Persistence of pesticide residues in mineral and organic soils in the Fraser Valley of British Columbia. J Agric Food Chem 39:1679-1684.

Szokolay A, Rosival L, Uhnak J, et al. 1977. Dynamics of benzene hexachloride (BHC) isomers and other chlorinated pesticides in the food chain and in human fat. Ecotoxicol Environ Safety 1:349-359.

Szymczynski GA, Waliszewski SM. 1981. Comparison of the content of chlorinated pesticide residues in human semen, testicles and fat tissues. Andrologia 13:250-252.

Takahashi W, Saidin D, Takei G, et al. 1981. Organochlorine pesticide residues in human milk in Hawaii, 1979-1980. Bull Environ Contam Toxicol 27:506-511.

Tan J, Loganath A, Chong YS, et al. 2009. Exposure to persistent organic pollutants in utero and related maternal characteristics on birth outcomes: a multivariate data analysis approach. Chemosphere 74(3):428-433. http://doi.org/10.1016/j.chemosphere.2008.09.045.

Tanabe S, Tatsukawa R, Kawano M, et al. 1982. Global distribution and atmospheric transport of chlorinated hydrocarbons: HCH (BHC) isomers and DDT compounds in the western Pacific, eastern Indian and Antarctic Oceans. J Oceanogr Soc Jpn 38:137-148.

Tanaka K, Kurihara N, Nakajima N. 1979. Oxidative metabolism of lindane and its isomers with microsomes from rat liver and house fly abdomen. Pestic Biochem Physiol 10:96-103.

Tao S, Lu Y, Zhang D, et al. 2009. Assessment of oral bioaccessibility of organochlorine pesticides in soil using an in vitro gastrointestinal model. Environ Sci Technol 43(12):4524-4529. http://doi.org/10.1021/es900188c.

Telch J, Jarvis DA. 1982. Acute intoxication with lindane (gamma benzene hexachloride). Can Med Assoc J 126:662-663.

Tenenbein M. 1991. Seizures after lindane therapy. J Am Geriatr Soc 39:394-395.

Tewari A, Sethi RS, Banga HS, et al. 2017. Concomitant effect of low dose of lindane and intranasal lipopolysaccharide on respiratory system of mice. Hum Exp Toxicol 36(11):1201-1211. http://doi.org/10.1177/0960327116685889.

Tezak Z, Simic B, Kniewald J. 1992. Effect of pesticides on oestradiol-receptor complex formation in rat uterus cytosol. Food Chem Toxicol 30:879-885.

Thakore KN, Karnik AB, Nigam SK, et al. 1981. Sequential changes in lactate, isocitrate, and malate dehydrogenases in mice exposed to technical grade hexachlorocyclohexane (BHC) and their possible relationship to liver tumors. Pestic Biochem Physiol 15:262-266.

Thomas JC, Berger F, Jucquier M, et al. 1996. Isolation and characterization of a novel g-hexachlorocyclohexane-degrading bacterium. J Bacteriol 178(20):6049-6055.

Thorpe E, Walker AIT. 1973. The toxicology of dieldrin (HEOD). II. Comparative long-term oral toxicity studies in mice with dieldrin, DDT, phenobarbitone, β-BHC, and γ-BHC. Food Cosmet Toxicol 11:433-442.

Tilson HA, Shaw S, McLamb RL. 1987. The effects of lindane, DDT, and chlordecone on avoidance responding and seizure activity. Toxicol Appl Pharmacol 88:57-65.

Tochman AM, Kamiński R, Turski WA, et al. 2000. Protection by conventional and new antiepileptic drugs against lindane-induced seizures and lethal effects in mice. Neurotox Res 2(1):63-70. http://doi.org/10.1007/bf03033328.

Tomczak S, Baumann K, Lehnert G. 1981. Occupational exposure to hexachlorocyclohexane. IV. Sex hormone alterations in HCH-exposed workers. Int Arch Occup Environ Health 48:283-287.

Torres-Arreola L, Berkowitz G, Torres-Sanchez L, et al. 2003. Preterm birth in relation to maternal organochlorine serum levels. Ann Epidemiol 13(3):158-162. http://doi.org/10.1016/s1047-2797(02)00424-6.

Traina ME, Rescia M, Urbani E, et al. 2003. Long-lasting effects of lindane on mouse spermatogenesis induced by in utero exposure. Reprod Toxicol 17(1):25-35. http://doi.org/10.1016/s0890-6238(02)00101-6.

TRI21. 2022. TRI explorer: Providing access to EPA's toxics release inventory data. Washington, DC: Toxics Release Inventory. U.S. Environmental Protection Agency. https://enviro.epa.gov/triexplorer. December 19, 2022.

Trivedi NP, Rawal UM, Patel BP. 2007. Hepatoprotective effect of andrographolide against hexachlorocyclohexane-induced oxidative injury. Integr Cancer Ther 6(3):271-280. http://doi.org/10.1177/1534735407305985.

Trivedi NP, Rawal UM, Patel BP. 2009. Potency of andrographolide as an antitumor compound in BHC-induced liver damage. Integr Cancer Ther 8(2):177-189. http://doi.org/10.1177/1534735409335606.

Tryphonas L, Iverson F. 1983. Sequential histopathologic analysis of α-hexachlorocyclohexane-induced hepatic megalocytosis and adenoma formation in the HPB mouse. J Natl Cancer Inst 71:1307-1318.

Tsatsakis AM, Tzatzarakis MN, Tutudaki M, et al. 2008. Assessment of levels of organochlorine pesticides and their metabolites in the hair of a Greek rural human population. Hum Exp Toxicol 27(12):933-940. http://doi.org/10.1177/0960327108102047.

Tsezos M, Wang X. 1991a. Study on the kinetics of hazardous pollutants adsorption and desorption by biomass: Mechanistic considerations. J Chem Technol Biotechnol 50:507-521.

Tsezos M, Wang X. 1991b. A study on lindane: Biosorption and biodegradation interactions. BFE 8:120-125.

Tsukada H, Gotoh M, Mochizuki Y, et al. 1979. Changes in peroxisomes in preneoplastic liver and hepatoma of mice induced by α-benzene hexachloride. Cancer Res 39:1628-1634.

Tu CM. 1976. Utilization and degradation of lindane by soil microorganisms. Arch Microbiol 108:259-263.

Turner JC, Shanks V. 1980. Absorption of some organochlorine compounds by the rat small intestine - in vivo. Bull Environ Contam Toxicol 24:652-655.

Tusell JM, Sunol C, Gelpi E, et al. 1988. Effect of lindane at repeated low doses. Toxicology 49:375-379.

Tyagi V, Mustafa MD, Sharma T, et al. 2016. Association of organochlorine pesticides with the mRNA expression of tumour necrosis factor-alpha (TNF-α) & cyclooxygenase-2 (COX-2) genes in idiopathic preterm birth. Indian J Med Res 143(6):731-738. http://doi.org/10.4103/0971-5916.191986.

Ukropec J, Radikova Z, Huckova M, et al. 2010. High prevalence of prediabetes and diabetes in a population exposed to high levels of an organochlorine cocktail. Diabetologia 53(5):899-906. http://doi.org/10.1007/s00125-010-1683-2.

Ullmann L. 1986a. Acute dermal toxicity study with lindane in rats. Itingen, Switzerland: Research and Consulting Company AG. RCC Project No. 061648.

Ullmann L. 1986b. 4-Hour acute aerosol inhalation toxicity study with lindane in rats. Itingen, Switzerland: Research and Consulting Company AG. RCC Project No. 061637.

Ullmann L. 1986c. Primary eye irritation study with lindane in rabbits. Itingen, Switzerland: Research and Consulting Company AG. RCC Project No. 061672.

Ullmann L. 1986d. Primary skin irritation study with lindane in rabbits (4-hour occlusive application). Itingen, Switzerland: Research and Consulting Company AG. RCC Project No. 061661.

Uphouse L, Williams J. 1989. Diestrous treatment with lindane disrupts the female rat reproductive cycle. Toxicol Lett 48:21-28.

Upson K, De Roos AJ, Thompson ML, et al. 2013. Organochlorine pesticides and risk of endometriosis: findings from a population-based case-control study. Environ Health Perspect 121(11-12):1319-1324. http://doi.org/10.1289/ehp.1306648.

USGS. 2003. Methods of analysis of the U.S. Geological Survey National Water Quality Laboratory - Determination of organochlorine pesticides and polychlorinated biphenyls in bottom and suspended sediment by gas chromatography with electron-capture detection. Denver, CO: U.S. Geological Survey. Resources Investigations Report 03-4293. https://www.nemi.gov/methods/method_summary/8946/. May 5, 2021.

Valera B, Ayotte P, Poirier P, et al. 2013a. Associations between plasma persistent organic pollutant levels and blood pressure in Inuit adults from Nunavik. Environ Int 59:282-289. http://doi.org/10.1016/j.envint.2013.06.019.

Valera B, Jorgensen ME, Jeppesen C, et al. 2013b. Exposure to persistent organic pollutants and risk of hypertension among Inuit from Greenland. Environ Res 122:65-73. http://doi.org/10.1016/j.envres.2012.12.006.

Van Velsen FL, Danse LHJC, Van LFXR, et al. 1986. The subchronic oral toxicity of the β-isomer of hexachlorocyclohexane in rats. Fundam Appl Toxicol 6:697-712.

Vargas-Gonzalez HH, Mendez-Rodriguez LC, Garcia-Hernandez J, et al. 2016. Persistent organic pollutants (POPs) in populations of the clam Chione californiensis in coastal lagoons of the Gulf of California. J Environ Sci Health B 51(7):435-445. http://doi.org/10.1080/03601234.2016.1159455.

Varona-Uribe ME, Torres-Rey CH, Diaz-Criollo S, et al. 2016. Exposure to pesticide mixtures and DNA damage among rice field workers. Arch Environ Occup Health 71(1):3-9. http://doi.org/10.1080/19338244.2014.910489.

Veith G, Defoe D, Bergstedt B. 1979. Measuring and estimating the bioconcentration factor of chemicals in fish. J Fish Res Board Can 36:1040-1048.

Vendrell M, Tusell JM, Serratosa J. 1992a. c-fos Expression as a model for studying the action of hexachlorocyclohexane isomers in the CNS. J Neurochem 58:862-869.

Vendrell M, Tusell JM, Serratosa J. 1992b. Effect of γ-hexachlorocyclohexane and its isomers on proto-oncogene c-fos expression in brain. Neurotoxicology 13:301-308.

Verbrugge DA, Othoudt RA, Grzyb KR, et al. 1991. Concentrations of inorganic and organic contaminants in sediments of six harbors on the North American Great Lakes. Chemosphere 22:809-820.

Verma A, Pillai MK. 1991. Bioavailability of soil-bound residues of DDT and HCH to certain plants. Soil Biol Biochem 23(4):347-351. http://doi.org/10.1016/0038-0717(91)90190-u.

Verner M, Charbonneau M, López-Carrillo L, et al. 2008. Physiologically based pharmacokinetic modeling of persistent organic pollutants for lifetime exposure assessment: A new tool in breast cancer epidemiologic studies. Environ Health Perspect 116(7):886-892. http://doi.org/10.1289/ehp.10917.

Verner MA, Ayotte P, Muckle G, et al. 2009. A physiologically based pharmacokinetic model for the assessment of infant exposure to persistent organic pollutants in epidemiologic studies. Environ Health Perspect 117(3):481-487. http://doi.org/10.1289/ehp.0800047.

Verschueren K. 1983. alpha-Hexachlorocyclohexane. In: Handbook of environmental data of organic chemicals. 2nd ed. New York, NY: Van Nostrand Reinhold Co, 718-725.

Viel JF, Floret N, Deconinck E, et al. 2011. Increased risk of non-Hodgkin lymphoma and serum organochlorine concentrations among neighbors of a municipal solid waste incinerator. Environ Int 37(2):449-453. http://doi.org/10.1016/j.envint.2010.11.009.

Vijaya Padma V, Sowmya P, Arun Felix T, et al. 2011. Protective effect of gallic acid against lindane induced toxicity in experimental rats. Food Chem Toxicol 49(4):991-998. http://doi.org/10.1016/j.fct.2011.01.005.

Vijaya Padma V, Poornima P, Prakash C, et al. 2013. Oral treatment with gallic acid and quercetin alleviates lindane-induced cardiotoxicity in rats. Can J Physiol Pharmacol 91(2):134-140. http://doi.org/10.1139/cjpp-2012-0279.

Vijgen J, Abhilash PC, Li YF, et al. 2011. Hexachlorocyclohexane (HCH) as new Stockholm Convention POPs--a global perspective on the management of lindane and its waste isomers. Environ Sci Pollut Res Int 18(2):152-162. http://doi.org/10.1007/s11356-010-0417-9.

Viswanathan R, Ray S, Scheunert I, et al. 1988. Investigations on accumulation and biotransformation by earthworms of lindane occurring as soil contaminant. In: Abbou R, ed. Hazard Waste: Detection, Control, Treatment. Amsterdam, The Netherlands: Elsevier Science Publishers B.V., 759-765.

Vizcaino E, Grimalt JO, Carrizo D, et al. 2011. Assessment of prenatal exposure to persistent organohalogen compounds from cord blood serum analysis in two Mediterranean populations (Valencia and Menorca). J Environ Monit 13(2):422-432. http://doi.org/10.1039/c0em00483a.

Vodopick H. 1975. Cherchez la Chienne: Erythropoietic hypoplasia after exposure to g-benzene hexachloride. JAMA 24(8):850-851.

Wadaskar JV, Ekhe JD, Kale SP. 2006. Adsorption-desorption of HCH and endosulfan on a soil. Environ Technol 27(9):1011-1017. http://doi.org/10.1080/09593332708618709.

Waite DT, Gurprasad NP, Sproull JF, et al. 2001. Atmospheric movements of lindane (γ-hexachlorocyclohexane) from canola fields planted with treated seed. J Environ Qual 30:768-775.

Waite DT, Cabalo E, Chau D, et al. 2007. A comparison of flux chambers and ambient air sampling to measure γ-hexachlorocyclohexane volatilisation from canola (Brassica napus) fields. Chemosphere 68(6):1074-1081. http://doi.org/10.1016/j.chemosphere.2007.01.085.

Waliszewski SM. 1993. Residues of lindane, HCH isomers and HCB in the soil after lindane application. Environ Pollut 82:289-292.

Waliszewski SM, Bermudez MT, Infanzon RM, et al. 2005. Persistent organochlorine pesticide levels in breast adipose tissue in women with malignant and benign breast tumors. Bull Environ Contam Toxicol 75(4):752-759. http://doi.org/10.1007/s00128-005-0815-8.

Waliszewski SM, Melo-Santiesteban G, Villalobos-Pietrini R, et al. 2009. Breast milk excretion kinetic of β-HCH, pp'DDE and pp'DDT. Bull Environ Contam Toxicol 83(6):869-873. http://doi.org/10.1007/s00128-009-9796-3.

Wang F, Xu ZR, Sun JH. 2006. Effect of HCH contamination of diet on the growth performance and immune and antioxidant ability in growing/finishing pigs. Vet Res Commun 30(6):645-654. http://doi.org/10.1007/s11259-006-3327-z.

Wang TC, Hoffman ME, David J, et al. 1992. Chlorinated pesticide residue occurrence and distribution in mosquito control impoundments along the Florida Indian River Lagoon. Bull Environ Contam Toxicol 49:217-223.

Ward E, Sheulte P, Grajewski B, et al. 2000. Serum organochlorine levels with breast cancer: A nested case-control study of Norwegian women. Cancer Epidemiol Biomarkers Prev 9:1357-1367.

Warembourg C, Debost-Legrand A, Bonvallot N, et al. 2016. Exposure of pregnant women to persistent organic pollutants and cord sex hormone levels. Hum Reprod 31(1):190-198. http://doi.org/10.1093/humrep/dev260.

Warner M, Rauch S, Coker ES, et al. 2018. Obesity in relation to serum persistent organic pollutant concentrations in CHAMACOS women. Environ Epidemiol 2(4):e032. http://doi.org/10.1097/ee9.0000000000000032.

Watanabe KH, Desimone FW, Thiyagarajah A, et al. 2003. Fish tissue quality in the lower Mississippi River and health risks from fish consumption. Sci Total Environ 302(1-3):109-126. http://doi.org/10.1016/s0048-9697(02)00396-0.

Weber L, Song K, Boyle T, et al. 2018. Organochlorine levels in plasma and risk of multiple myeloma. J Occup Environ Med 60(10):911-916. http://doi.org/10.1097/jom.0000000000001387.

Weiss G. 1986. Benzene hexachloride. In: Hazardous chemicals data book. 2nd ed. Park Ridge, NJ: Noyes Data Corporation, 153.

Weisse I, Herbst M. 1977. Carcinogenicity study of lindane in the mouse. Toxicology 7(2):233-238. http://doi.org/10.1016/0300-483x(77)90069-5.

Wheatley GA, Hardman JA. 1965. Indications of the presence of organochlorine insecticides in rainwater in Central England. Nature 207(4996):486-487. http://doi.org/10.1038/207486a0.

Wheeler M. 1977. Gamma benzene hexachloride (Kwell) in a child. West J Med 127(6):518-521.

Whitehead TP, Crispo Smith S, Park JS, et al. 2015. Concentrations of persistent organic pollutants in California women's serum and residential dust. Environ Res 136:57-66. http://doi.org/10.1016/j.envres.2014.10.009.

WHO. 2010. Guidelines for indoor air quality: Selected pollutants. World Health Organization. http://www.euro.who.int/__data/assets/pdf_file/0009/128169/e94535.pdf. April 25, 2012.

WHO. 2017. Guidelines for drinking-water quality. Fourth edition incorporating the first addendum. World Health Organization. http://apps.who.int/iris/bitstream/10665/254637/1/9789241549950-eng.pdf?ua=1. February 28, 2017.

Wiberg K, Brorstrom-Lunden E, Wangberg I, et al. 2001. Concentrations and fluxes of hexachlorocyclohexanes and chiral composition of α-HCH in environmental samples from Southern Baltic Sea. Environ Sci Technol 35(24):4739-4746.

Wielsoe M, Kern P, Bonefeld-Jorgensen EC. 2017. Serum levels of environmental pollutants is a risk factor for breast cancer in Inuit: a case control study. Environ Health 16(1):56. http://doi.org/10.1186/s12940-017-0269-6.

Wild SR, Jones KC. 1992. Organic chemicals entering agricultural soils in sewage sludges: Screening for their potential to transfer to crop plants and livestock. Sci Total Environ 119:85-119.

Wiles DA, Russell JL, Olson KR, et al. 2015. Massive lindane overdose with toxicokinetics analysis. J Med Toxicol 11(1):106-109. http://doi.org/10.1007/s13181-014-0403-6.

Wittlinger R, Ballschmiter K. 1990. Studies of the global baseline pollution. XIII. C6-C14 organohalogens (α- and g-HCH, HCB, PCB 4,4'-DDT, 4,4'-DDE, cis- and trans-chlordane, trans-nonachlor, anisols) in the lower troposphere of the southern Indian Ocean. Fresenius J Anal Chem 336:193-200.

Wolff G, Roberts D, Morrissey R, et al. 1987. Tumorigenic responses to lindane in mice: Potentiation by a dominant mutation. Carcinogenesis 8:1889-1897.

Woodliff HJ, Connor PM, Scopa J. 1966. Aplastic anemia associated with insecticides. Med J Aust 1:628-629.

Woolley DE, Griffith JA. 1989. Kinetics and thresholds of several indices of lindane-induced toxicity. Pharmacol Biochem Behav 33:787-792.

WQP. 2021. Water Quality Portal data: alpha-Hexachlorocyclohexane, beta-hexachlorocyclohexane, 1,2,3,4,5,6 -Hexachlorocyclohexane. National Water Quality Monitoring Council. https://www.waterqualitydata.us/portal/. May 6, 2021.

Wu WZ, Xu Y, Schramm KW, et al. 1997. Study of sorption, biodegradation, and isomerization of HCH in stimulated sediment/water system. Chemosphere 35(9):1887-1894.

Xu X, Dailey AB, Talbott EO, et al. 2010. Associations of serum concentrations of organochlorine pesticides with breast cancer and prostate cancer in U.S. adults. Environ Health Perspect 118(1):60-66. http://doi.org/10.1289/ehp.0900919.

Xue M, Shen G, Yu J, et al. 2010. Dynamic changes of α-hexachlorocyclohexane and its enantiomers in various tissues of Japanese Rabbits (Oyctolagus cuniculus) after oral or dermal exposure. Chemosphere 81(11):1486-1491. http://doi.org/10.1016/j.chemosphere.2010.08.046.

Yaduvanshi SK, Srivastava N, Marotta F, et al. 2012. Evaluation of micronuclei induction capacity and mutagenicity of organochlorine and organophosphate pesticides. Drug Metab Lett 6(3):187-197. http://doi.org/10.2174/1872312811206030006.

Yalcin SS, Orun E, Yalcin S, et al. 2015. Organochlorine pesticide residues in breast milk and maternal psychopathologies and infant growth from suburban area of Ankara, Turkey. Int J Environ Health Res 25(4):364-372. http://doi.org/10.1080/09603123.2014.945515.

Yamazaki K, Itoh S, Araki A, et al. 2020. Associations between prenatal exposure to organochlorine pesticides and thyroid hormone levels in mothers and infants: The Hokkaido study on environment and children's health. Environ Res 189:109840. http://doi.org/10.1016/j.envres.2020.109840.

Yang X, Jiang X, Yu G, et al. 2007. Leaf-air transfer of organochlorine pesticides from three selected vegetables. Environ Pollut 148(2):555-561. http://doi.org/10.1016/j.envpol.2006.11.029.

Yang D, Li X, Tao S, et al. 2010. Enantioselective behavior of α-HCH in mouse and quail tissues. Environ Sci Technol 44(5):1854-1859. http://doi.org/10.1021/es9030134.

Yang Y, Zhang YB, Sheng W, et al. 2014. Influence of soy isoflavone on lindane cumulant in Sprague-Dawley rats. Biomed Environ Sci 27(8):637-640. http://doi.org/10.3967/bes2014.097.

Yang X, Zhang M, Lu T, et al. 2020. Metabolomics study and meta-analysis on the association between maternal pesticide exposome and birth outcomes. Environ Res 182:109087. http://doi.org/10.1016/j.envres.2019.109087.

Yin S, Zhang J, Guo F, et al. 2019. Transplacental transfer of organochlorine pesticides: Concentration ratio and chiral properties. Environ Int 130:104939. http://doi.org/10.1016/j.envint.2019.104939.

Yin S, Zhang J, Guo F, et al. 2020. Transplacental transfer mechanism of organochlorine pesticides: An in vitro transcellular transport study. Environ Int 135:105402. http://doi.org/10.1016/j.envint.2019.105402.

Yu Y, Wang B, Wang X, et al. 2013. Hexachlorocyclohexanes (HCHs) in placenta and umbilical cord blood and dietary intake for women in Beijing, China. Environ Pollut 179:75-80. http://doi.org/10.1016/j.envpol.2013.03.056.

Yu Y, Hung H, Alexandrou N, et al. 2015. Multiyear measurements of flame retardants and organochlorine pesticides in air in Canada's Western sub-Arctic. Environ Sci Technol 49(14):8623-8630. http://doi.org/10.1021/acs.est.5b01996.

Yuksel H, Karadas E, Keles H, et al. 2009. Effects of hexachlorocyclohexane (HCH-γ-isomer, lindane) intoxication on the proliferation and apoptosis in rat testes. Acta Vet Brno 78(4):615-620. http://doi.org/10.2754/avb200978040615.

Zesch A, Nitzsche K, Lange M. 1982. Demonstration of the percutaneous resorption of a lipophilic pesticide and its possible storage in the human body. Arch Dermatol Res 273:43-49.

Zhang N, Bashir S, Qin J, et al. 2014. Compound specific stable isotope analysis (CSIA) to characterize transformation mechanisms of α-hexachlorocyclohexane. J Hazard Mater 280:750-757. http://doi.org/10.1016/j.jhazmat.2014.08.046.

Zhang Y, Guo J, Zhang X, et al. 2016. Interaction effects between organochlorine pesticides and isoflavones in vitro and in vivo. Biomed Res Int 2016:6861702. http://doi.org/10.1155/2016/6861702.

Zhang X, Wu X, Lei B, et al. 2018. Transplacental transfer characteristics of organochlorine pesticides in paired maternal and cord sera, and placentas and possible influencing factors. Environ Pollut 233:446-454. http://doi.org/10.1016/j.envpol.2017.10.075.

8. REFERENCES

Zhao B, Shen H, Liu F, et al. 2012. Exposure to organochlorine pesticides is an independent risk factor of hepatocellular carcinoma: a case-control study. J Expo Sci Environ Epidemiol 22(6):541-548. http://doi.org/10.1038/jes.2011.29.

Zoeteman BCJ, Harmsen K, Linders JBHJ, et al. 1980. Persistent organic pollutants in river water and ground water of the Netherlands. Chemosphere 9:231-249.

Zong G, Valvi D, Coull B, et al. 2018. Persistent organic pollutants and risk of type 2 diabetes: A prospective investigation among middle-aged women in Nurses' Health Study II. Environ Int 114:334-342. http://doi.org/10.1016/j.envint.2017.12.010.

APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substances than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Office of Innovation and Analytics, Toxicology Section, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Office of Innovation and Analytics, Toxicology Section, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

HCH is a mixture of eight isomers, four of which are of commercial significance: α-HCH (CAS Registry Number 319-84-6), β-HCH (CAS Registry Number 319-85-7), γ-HCH (CAS Registry Number 58-89-9), and δ-HCH (CAS Registry Number 319-86-8). Technical HCH, which is used as an insecticide, is made up of the various isomers at different concentrations. The wide variations in isomer composition of technical HCH preclude the possibility of MRL derivation. MRL derivation was considered for the isomers included in this toxicological profile: α-, β-, γ-, and δ-HCH.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** α-HCH
CAS Number: 319-84-6
Date: January 2023
Profile Status: Draft for public comment
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL for α-HCH.

Rationale for Not Deriving an MRL: No acute-duration inhalation studies of α-HCH in humans or animals were located, precluding derivation of an acute-duration inhalation MRL.

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** α-HCH
CAS Number: 319-84-6
Date: January 2023
Profile Status: Draft for public comment
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL for α-HCH.

Rationale for Not Deriving an MRL: No intermediate-duration inhalation studies of α-HCH in humans or animals were located, precluding derivation of an intermediate-duration inhalation MRL.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** α-HCH
CAS Number: 319-84-6
Date: January 2023
Profile Status: Draft for public comment
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL for α-HCH.

Rationale for Not Deriving an MRL: No chronic-duration inhalation studies of α-HCH in humans or animals were located, precluding derivation of a chronic-duration inhalation MRL.

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** α-HCH
CAS Number: 319-84-6
Date: January 2023
Profile Status: Draft for public comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL for α-HCH.

Rationale for Not Deriving an MRL: No adequate exposure-response data were available for humans. Data on effects in laboratory animals exposed orally to α-HCH for acute durations are limited to a freestanding NOAEL of 20 mg/kg/day for body weight changes during the first 14 days of a 28-day study comparing gene expression profiles for α- and γ-HCH (Sumida et al. 2007). Increased relative liver weight (24%) and decreased serum ALP (19%) were seen at this dose after 14 days, but histopathology was not evaluated at this time, so reliable hepatic effect levels could not be determined for this study. Thus, this study did not provide an adequate basis for MRL derivation.

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** α-HCH
CAS Number: 319-84-6
Date: January 2023
Profile Status: Draft for public comment
Route: Oral
Duration: Intermediate
MRL: 0.002 mg/kg/day (2 µg/kg/day) (provisional)
Critical Effect: Increased liver weight and liver histopathology changes
Reference: Sumida et al. 2007
Point of Departure: 2 mg/kg/day (NOAEL)
Uncertainty Factor: 100
Modifying Factor: 10
LSE Graph Key: 6
Species: Rat

MRL Summary: A provisional intermediate-duration oral MRL of 0.002 mg/kg/day (2 µg/kg/day) was derived based on a NOAEL of 2 mg/kg/day for liver effects in a 28-day study in rats (Sumida et al. 2007). The NOAEL was divided by a total uncertainty factor of 100 (10 for human variability and 10 for animal to human extrapolation) and a modifying factor of 10 (for lack of studies examining developmental and immunological effects and limitations in available data on neurotoxicity).

Selection of the Critical Effect: No dose-response data are available for humans. In animal studies, hepatic effects (including cancers) occurred at lower doses than effects on body weight or kidneys. A single study found no effects on motor nerve conduction velocity in rats exposed to 106.2 mg/kg/day for 30 days (Muller et al. 1981). The α-hexachlorocyclohexane database only contains studies with body weight, renal, hepatic, neurological, and cancer endpoints; no other effects were evaluated in the available studies. Table A-1 summarizes the hepatic effects from intermediate-duration oral studies in laboratory animals exposed to doses up to 70 mg/kg/day.

Table A-1. Summary of NOAELs and LOAELs from Candidate Intermediate-Duration Studies in Laboratory Animals Orally Exposed to α-Hexachlorocyclohexane

Species	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Hepatic effects					
Mouse (dd) 20–40 M	24 weeks (F)	ND	18	33% relative liver weight increase; hepatocellular hypertrophy	Ito et al. 1973
Rat (Fischer-344) 4 M	28 days (GO)	2	20	Increased relative liver weight (25%); centrilobular hepatocellular hypertrophy	Sumida et al. 2007
Rat (W strain) 18–24 M	48 weeks (F)	ND	35	Hepatocellular hypertrophy	Ito et al. 1975
Rat (Wistar) 8 M	24 weeks (F)	ND	45	Mild liver cell hypertrophy; 2-fold increase in liver weight	Nagasaki et al. 1975

Table A-1. Summary of NOAELs and LOAELs from Candidate Intermediate-Duration Studies in Laboratory Animals Orally Exposed to α-Hexachlorocyclohexane

Species	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Hamster (Golden Syrian) 6–10 M	24 weeks (F)	ND	45	20–38% increase in liver weight; liver cell hypertrophy	Nagasaki et al. 1975
Rat (Wistar) 10 F, 10 M	6–9 months (F)	ND	60 M 70 F (serious LOAEL for decreased survival)	Decreased survival; moderate histopathology changes (focal necrosis, fatty degeneration); >2-fold increase in liver weight	Fitzhugh et al. 1950

Principal study for the MRL.

(F) = feed; F = female(s); (GO) = gavage in oil vehicle; LOAEL = lowest-observed-adverse-effect level; M = male(s); ND = not determined; NOAEL = no-observed-adverse-effect level

Selection of the Principal Study: As Table A-1 shows, the lowest effect level (18 mg/kg/day) was associated with a relative liver weight increase of 33% and hepatocellular hypertrophy in mice exposed via diet for 24 weeks (Ito et al. 1973). A NOAEL was not identified for this study. In a study of rats exposed by gavage for only 28 days (Sumida et al. 2007), a slightly higher LOAEL of 20 mg/kg/day was identified for similar hepatic effects; the NOAEL in that study was 2 mg/kg/day. All of the other studies identified hepatic effects at the lowest doses tested (no other NOAEL was identified). The study by Sumida et al. (2007) was selected as the principal study for MRL derivation because the NOAEL identified in the study was lower than the LOAELs identified in all other studies and because a NOAEL was not identified in the study by Ito et al. (1973). Although the LOAEL (18 mg/kg/day) from Ito et al. (1973) is slightly lower than the LOAEL (20 mg/kg/day) identified by Sumida et al. (2007), use of the LOAEL from Ito et al. (1973) as the point of departure (POD) would necessitate the use of an uncertainty factor of 10, while use of the NOAEL (2 mg/kg/day) from Sumida et al. (2007) does not. In addition, if the LOAEL from Ito et al. (1973) were used as the POD, it would be equivalent to the value derived based on the NOAEL from Sumida et al. (2007) (18 mg/kg/day divided by an uncertainty factor of 10 for use of a LOAEL yields 1.8 mg/kg/day, which rounds to 2 mg/kg/day).

Summary of the Principal Study:

Sumida K, Siato K, Oeda K, et al. 2007. A comparative study of gene expression profiles in rat liver after administration of α-hexachlorocyclohexane and lindane. J Toxicol Sci 32(3):261-288.

Groups of four male F344 rats were administered α-HCH (99% purity, in corn oil) by gavage at doses of 0 (corn oil control), 2, or 20 mg/kg/day for 28 consecutive days. The following parameters were evaluated: body weight, serum clinical chemistry (AST, ALT, ALP, and total bilirubin in blood collected at necropsy), liver weight, hepatic histopathology, and gene expression in the liver. There were no effects on body weight at any dose. After 28 days of exposure, small but statistically significant increases in AST and ALT were seen at 2 mg/kg/day, but not at 20 mg/kg/day. At the high dose, ALP was decreased by 19% at the end of 28 days. At 20 mg/kg/day, liver weights were increased by 20% (absolute) and 25% (relative) compared to controls. At 2 mg/kg/day, relative liver weight was increased by a small, but

statistically significant margin of 6%. Hepatocellular hypertrophy was observed in 4/4 animals at 20 mg/kg/day compared to 0/4 in control and 2 mg/kg/day groups. Based on the increase in liver weight and histological changes at 20 mg/kg/day, this dose is a LOAEL. No exposure-related changes occurred at the 2 mg/kg/day, indicating that this dose is a NOAEL.

Selection of the Point of Departure for the MRL: The NOAEL of 2 mg/kg/day was selected as the POD for derivation of the intermediate-duration oral MRL for α-HCH. Although quantitative data on histopathology findings in the liver were reported, the incidence data increased from 0/4 at 2 mg/kg/day to 4/4 at 20 mg/kg/day, so the data were not amenable to benchmark dose (BMD) modeling. BMD modeling of relative liver weight data was undertaken, but that dataset was also not amenable to BMD modeling, as neither the constant nor nonconstant variance models provide an adequate fit to the variance data. Thus, the NOAEL was selected as the POD.

Intermittent Exposure: Not applicable.

Uncertainty and Modifying Factor: The NOAEL of 2 mg/kg/day was divided by a total uncertainty factor (UF) of 100 and a modifying factor (MF) of 10:

- 10 for extrapolation from animals to humans
- 10 for human variability

A modifying factor of 10 was applied to the NOAEL to account for lack of data on developmental toxicity and immunotoxicity and limitations in available data on neurotoxicity. These are sensitive endpoints for other HCH isomers.

Provisional MRL = NOAEL ÷ (UF x MF)
2 mg/kg/day ÷ ((10 x 10) x 10) = 0.002 mg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Hepatic effects have been observed in rats, mice, and hamsters after intermediate- and chronic-duration oral exposures to α-HCH. Observed effects include increases in absolute and relative liver weight, hepatocellular hypertrophy and/or hyperplasia, focal necrosis, fatty degeneration, hepatomegaly, bile duct proliferation, oval cells, nodular hyperplasia, and megalocytosis (Fitzhugh et al. 1950; Ito et al. 1973, 1975, 1976; Nagasaki et al. 1975; Sumida et al. 2007; Tryphonas and Iverson 1983). Both rats and mice have also developed liver tumors at higher doses of α-HCH (Hanada et al. 1973; Ito et al. 1973, 1975, 1976; Nagasaki et al. 1975; Tryphonas and Iverson 1983; Tsukada et al. 1979).

There are no studies on the effects of α-HCH on the developing organism or on the immune system. Studies of β- and γ-HCH have shown developmental effects (e.g., Di Consiglio et al. 2009; Hassoun and Stohs 1996a; La Sala et al. 2009; Rivera et al. 1998; Sauviat et al. 2005; Srinivasan et al. 1991), and for γ-HCH, these are the effects occurring at the lowest doses in animal studies. γ-HCH, and to a lesser extent β-HCH, have been demonstrated to induce suppression of the immune system in several species (e.g., Banerjee et al. 1996; Cornacoff et al. 1988; Desi et al. 1978; Dewan et al. 1980; Hong and Boorman 1993; Khurana et al. 1999; Koner et al. 1998; Mediratta et al. 2008; Meera et al. 1992; Van Velsen et al. 1986). Animal studies of γ-HCH indicate that these effects occur at lower doses than hepatic effects. Thus, the lack of developmental and immunotoxicity data for α-HCH is a significant limitation of the existing database for this isomer.

Data on the neurotoxicity of α-HCH are limited to a single study showing no change in motor nerve conduction velocity after 30 days of exposure (Muller et al. 1981). Both β- and γ-HCH have induced neurotoxic effects in laboratory rodents (e.g., Cornacoff et al. 1988; EPA 1999a; Gilbert and Mack 1995;

Parmar et al. 2003; Van Velsen et al. 1986), and γ-HCH has been shown to induce neurotoxicity in humans exposed orally (e.g., Davies et al. 1983; Harris et al. 1969; Munk and Nantel 1977; Nordt and Chew 2000; Powell 1980; Starr and Clifford 1972; Storen 1955).

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** α-HCH
CAS Number: 319-84-6
Date: January 2023
Profile Status: Draft for public comment
Route: Oral
Duration: Chronic
MRL: 0.0009 mg/kg/day (0.9 µg/kg/day) (provisional)
Critical Effect: Increased liver weight and liver histopathology changes
Reference: Fitzhugh et al. 1950
Point of Departure: 0.9 mg/kg/day (NOAEL)
Uncertainty Factor: 100
Modifying Factor: 10
LSE Graph Key: 14
Species: Rat

MRL Summary: A provisional chronic-duration oral MRL of 0.0009 mg/kg/day (0.9 µg/kg/day) was derived for α-HCH based on a NOAEL of 0.9 mg/kg/day and a LOAEL of 4 mg/kg/day for increased liver weight and liver histopathology changes in rats exposed to α-HCH in the diet for 107 weeks (Fitzhugh et al. 1950). A total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) and a modifying factor of 10 (for lack of immunotoxicity data and limitations in data on potential neurotoxicity) were applied to the NOAEL to derive the provisional MRL.

Selection of the Critical Effect: Two chronic-duration oral studies of α-HCH were located: Fitzhugh et al. (1950) and Ito et al. (1975). While Ito et al. (1975) examined only cancer endpoints, Fitzhugh et al. (1950) evaluated histopathology in a large number of organs and identified the liver as the most sensitive target of chronic oral exposure.

Selection of the Principal Study: Only Fitzhugh et al. (1950) evaluated endpoints other than cancer, so this study was selected for use in derivation of the chronic-duration oral MRL.

Summary of the Principal Study:

Fitzhugh OG, Nelson AA, Frawley JP. 1950. The chronic toxicities of technical benzene hexachloride and its α, β, and γ isomers. J Pharmacol Exp Ther 100:59-66.

Groups of 10 male and 10 female Wistar rats were treated with 0, 10, 50, 100, or 800 ppm α-HCH in food for life. ATSDR calculated doses corresponding to these concentrations using default food intake and body weight values for male and female Wistar rats in chronic studies as reported in EPA (1988b). Estimated doses were 0, 0.7, 4, 7, or 60 mg/kg/day in males and 0, 0.9, 4, 9, or 70 mg/kg/day in females. The lifetime of the animals sacrificed at the end of the experiment was taken as 107 weeks. Endpoints included clinical signs, body weight, food consumption, organ weights (liver, kidney, and spleen), gross pathology, and histopathology (lung, heart, liver, spleen, pancreas, stomach, small intestine, colon, kidney, adrenal, thyroid, leg muscles and bones, bone marrow, and testis or uterus and ovary). The numbers of animals per group evaluated for histopathology were 10, 8, 14, and 10 in the control through 100 ppm groups.

Survival was significantly reduced at the high dose (mean survival 35.9 weeks at 800 ppm [60–70 mg/kg/day] versus 58.3 weeks in controls), so effects in this group are considered to reflect intermediate-duration exposure. The mean age at death in the remaining groups did not differ from

controls (58.3, 54.6, 54.9, and 56.2 weeks for control through 100 ppm groups, respectively). Body weight gain through the first 6 months on study was tabulated for the 100 ppm (7–9 mg/kg/day) and 800 ppm (60–70 mg/kg/day) groups, but not for the 10 or 50 ppm groups. However, the text of the publication indicate that "lower experimental dosage levels had no effect on growth." Additionally, there was no significant difference in body weight gain in the 100 ppm (7–9 mg/kg/day) group, and no effect on food consumption in any group.

Histopathology findings were reported for the kidney, testes, and liver. Kidney pathological effects were not observed in groups receiving 10, 50, or 100 ppm, with the exception of slight brown pigmentation of the convoluted tubular epithelium at 100 ppm (7–9 mg/kg/day). The 800 ppm (60–70 mg/kg/day) group had slight to moderate kidney damage primarily consisting of tubular dilatation and/or atrophy, glomerular fibrosis and/or atrophy, and interstitial cell infiltration. The study authors reported a "questionable" increase in the degree of testicular atrophy in the group exposed to 800 ppm (60–70 mg/kg/day) α-HCH, but no further information was provided.

Significant increases in relative liver weight (both sexes grouped for analysis) were seen at 50 ppm (32%) and 100 ppm (44%). Gross and microscopic pathology findings were limited to the liver in the groups exposed for the full duration; there were no microscopic changes in the controls. Liver histopathology findings in treated animals were described qualitatively as very slight histological changes at 50 ppm (4 mg/kg/day) and slight histological changes at 100 ppm (7–9 mg/kg/day). The lesions were described as "characteristic of certain chlorinated cyclic compounds" with citation to earlier studies of dichloro-diphenyltrichloroethane (DDT). The earlier studies (e.g., Fitzhugh and Nelson 1947; Laug et al. 1950) characterized the histological changes as primarily centrilobular hepatocellular hypertrophy with increased cytoplasmic "oxyphilia" of these cells along with basophilia and margination of cytoplasmic granules and hyalinization of cytoplasm. There was evidence of increased severity in the group exposed to 800 ppm and surviving less than a year; these animals exhibited moderate histological damage including hepatic cell enlargement or atrophy, fatty degeneration, and focal necrosis.

Based on the increase in liver weight and histological changes at 50 ppm, this dose (4 mg/kg/day) is a LOAEL. No exposure-related changes occurred at the low dose in either sex, indicating that the NOAEL is 10 ppm (0.7–0.9 mg/kg/day).

Selection of the Point of Departure for the MRL: The NOAEL of 0.9 mg/kg/day (for females) was selected as the POD for MRL derivation (ATSDR policy is to select the highest NOAEL associated with the lowest LOAEL for the POD). BMD modeling of the liver weight data was not possible because the study did not report the numbers of animals per group evaluated for liver weights. Liver histology findings were reported qualitatively and without incidences, so BMD modeling was not feasible for these effects.

Intermittent Exposure: Not applicable.

Uncertainty and Modifying Factor: The NOAEL of 0.9 mg/kg/day was divided by a total uncertainty factor (UF) of 100:

- 10 for extrapolation from animals to humans
- 10 for human variability

A modifying factor of 10 was applied to the NOAEL to account for the limitations (no immune studies, one neurotoxicity study) in the toxicological database for α-HCH. Immune and nervous system effects are sensitive endpoints for other HCH isomers.

Provisional MRL = NOAEL ÷ (UF x MF)
0.9 mg/kg/day ÷ ((10 x 10) x 10) = 0.0009 mg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Hepatic effects have been observed in rats, mice, and hamsters after intermediate- and chronic-duration oral exposures to α-HCH. Observed effects include increases in absolute and relative liver weight, hepatocellular hypertrophy and/or hyperplasia, focal necrosis, fatty degeneration, hepatomegaly, bile duct proliferation, oval cells, nodular hyperplasia, and megalocytosis (Fitzhugh et al. 1950; Ito et al. 1973, 1975, 1976; Nagasaki et al. 1975; Sumida et al. 2007; Tryphonas and Iverson 1983). Both rats and mice have also developed liver tumors at higher doses of α-HCH (Hanada et al. 1973; Ito et al. 1973, 1975, 1976; Nagasaki et al. 1975; Tryphonas and Iverson 1983; Tsukada et al. 1979).

There are no studies on the effects of α-HCH on the immune system. Studies of γ-HCH, and a few studies of β-HCH, have shown suppression of the immune system (e.g., Banerjee et al. 1996; Cornacoff et al. 1988; Desi et al. 1978; Dewan et al. 1980; Hong and Boorman 1993; Khurana et al. 1999; Koner et al. 1998; Mediratta et al. 2008; Meera et al. 1992; Van Velsen et al. 1986) and for γ-HCH, these effects occur at lower doses than hepatic effects in animal studies. Thus, the lack of immunotoxicity data for α-HCH is a significant limitation of the existing database for this isomer.

Data on the neurotoxicity of α-HCH are limited to a single study showing no change in motor nerve conduction velocity after 30 days of exposure (Muller et al. 1981). Both β- and γ-HCH have induced neurotoxic effects in laboratory rodents (e.g., Cornacoff et al. 1988; EPA 1999a; Gilbert and Mack 1995; Parmar et al. 2003; Van Velsen et al. 1986), and γ-HCH has shown to induce neurotoxicity in humans exposed orally (e.g., Davies et al. 1983; Harris et al. 1969; Munk and Nantel 1977; Nordt and Chew 2000; Powell 1980; Starr and Clifford 1972; Storen 1955).

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** β-HCH
CAS Number: 319-85-7
Date: January 2023
Profile Status: Draft for public comment
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL for β-HCH.

Rationale for Not Deriving an MRL: No acute-duration inhalation studies of β-HCH in humans or animals were located, precluding derivation of an acute-duration inhalation MRL.

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** β-HCH
CAS Number: 319-85-7
Date: January 2023
Profile Status: Draft for public comment
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL for β-HCH.

Rationale for Not Deriving an MRL: No intermediate-duration inhalation studies of β-HCH in humans or animals were located, precluding derivation of an intermediate-duration inhalation MRL.

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** β-HCH
CAS Number: 319-85-7
Date: January 2023
Profile Status: Draft for public comment
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL for β-HCH.

Rationale for Not Deriving an MRL: No chronic-duration inhalation studies of β-HCH in humans or animals were located, precluding derivation of a chronic-duration inhalation MRL.

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** β-HCH
CAS Number: 319-85-7
Date: January 2023
Profile Status: Draft for public comment
Route: Oral
Duration: Acute
MRL: 0.08 mg/kg/day (provisional)
Critical Effect: Ataxia and hypoactivity
Reference: Van Velsen et al. 1986
Point of Departure: 8 mg/kg/day (NOAEL)
Uncertainty Factor: 100
LSE Graph Key: 2
Species: Rat

MRL Summary: A provisional acute-duration oral MRL of 0.08 mg/kg/day was derived for β-HCH based on a NOAEL of 8 mg/kg/day in the first few weeks of a 13-week study (Van Velsen et al. 1986); the higher dose in this study (38 mg/kg/day) was a serious LOAEL for a neurological endpoint of ataxia and hypoactivity progressing in some animals to coma. A total uncertainty factor of 100 (10 each for extrapolation from animals to humans and for human variability) was applied to the NOAEL to derive the provisional MRL.

Selection of the Critical Effect: Of the three studies reporting acute-duration oral exposure to β-HCH, two studies (Cornacoff et al. 1988; Van Velsen et al. 1986) identified clinical signs of neurotoxicity as the critical effect at doses of ≥38 mg/kg/day for 1–2 weeks. Renal effects were observed in the third study (Srinivasan et al. 1984) at a higher dose (72 mg/kg/day, the only dose tested).

Selection of the Principal Study: The lowest LOAEL for acute-duration oral exposure to β-HCH was 38 mg/kg/day for ataxia and hypoactivity signs observed in rats during for the first 2 weeks of a 13-week study (Van Velsen et al. 1986). At a dose of 8 mg/kg/day, no clinical signs of neurotoxicity were observed throughout the 13 weeks of exposure (NOAEL).

Summary of the Principal Study:

Van Velsen FL, Danse LHJC, Van Leeuwen FXR, et al. 1986. The subchronic oral toxicity of the β-isomer of hexachlorocyclohexane in rats. Fundam Appl Toxicol 6:697-712.

Groups of 10 male and 10 female Wistar rats were exposed to β-HCH in diets containing 0, 2, 10, 50, or 250 mg/kg feed in a 13-week study. The animals were weanlings at study initiation. For the acute (first 2 weeks) portion of the study, ATSDR calculated dose values using food intake and body weight for male and female weanling Wistar rats from EPA (1988b) to arrive at 0, 0.3, 1.5, 8, and 38 mg/kg/day doses. Clinical signs of toxicity were noted in the first few weeks of the study. At the end of week 2, two male and two female rats receiving 38 mg/kg/day in the diet exhibited ataxia and hypoactive, progressing to coma within 3 days. The animals were humanely sacrificed, as were five additional males and six additional females that showed similar signs later in the study. No clinical signs were seen at lower doses of β-HCH at any time during the 13-week exposure period, nor were there histopathology changes in the brain, spinal cord, or sciatic nerve at any dose after 13 weeks of exposure.

Selection of the Point of Departure for the MRL: The NOAEL of 8 mg/kg/day was selected as the basis for the MRL. BMD modeling was not considered because the effects at the next highest dose (clinical signs of toxicity) reflected a serious LOAEL.

Intermittent Exposure: Not applicable.

Uncertainty Factor: The NOAEL of 8 mg/kg/day was divided by a total uncertainty factor of 100:

- 10 for extrapolation from animals to humans
- 10 for human variability

Provisional MRL = NOAEL ÷ (UF)
8 mg/kg/day ÷ (10 x10) = 0.08 mg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Mice treated with 60 or 200 mg/kg/day β-HCH in the diet in a 30-day study developed ataxia within the first week of treatment (Cornacoff et al. 1988). The animals receiving 60 mg/kg/day recovered within a few days, while those receiving 200 mg/kg/day became markedly worse, leading to humane sacrifice of 80% of the animals in this group (Cornacoff et al. 1988). Effects on peripheral nerves were reported by Muller et al. (1981), who observed a significant delay in tail nerve conduction velocity in rats fed 66.3 mg β-HCH/kg/day for 30 days.

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** β-HCH
CAS Number: 319-85-7
Date: January 2023
Profile Status: Draft for public comment
Route: Oral
Duration: Intermediate
MRL: 0.0006 mg/kg/day (0.6 µg/kg/day) (provisional)
Critical Effect: Hyalinization of centrilobular cells in the liver.
Reference: Van Velsen et al. 1986
Point of Departure: 0.18 mg/kg/day (minimal LOAEL)
Uncertainty Factor: 300
LSE Graph Key: 10
Species: Rat

MRL Summary: A provisional intermediate-duration oral MRL of 0.0006 mg/kg/day (0.6 µg/kg/day) was derived for β-HCH based on a minimal LOAEL of 0.18 mg/kg/day for liver histopathology changes (hyalinization of centrilobular cells) in a 13-week study of rats exposed via the diet (Van Velsen et al. 1986). A total uncertainty factor of 300 (10 each for extrapolation from animals to humans and for human variability, and 3 for use of a minimal LOAEL) was applied to the LOAEL to derive the provisional MRL.

Selection of the Critical Effect: Table A-2 provides a summary of the lowest effect levels in intermediate-duration animal studies of oral exposure to β-HCH. The lowest LOAEL was 0.18 mg/kg/day for hyalinization of centrilobular cells in the liver in male rats exposed for 13 weeks (Van Velsen et al. 1986); these effects increased with dose and are supported by the observation of β-HCH-induced liver effects at higher doses in other intermediate-duration oral studies in rats and mice (Hanada et al. 1973; Ito et al. 1973, 1975).

Table A-2. Summary of NOAELs and LOAELs from Candidate Intermediate-Duration Studies in Laboratory Animals Orally Exposed to β-Hexachlorocyclohexane

Species	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Hepatic effects					
Rat (Wistar) 10 M	13 weeks (F)	ND	0.18 M (minimal LOAEL)	Hyalinization of centrilobular cells	Van Velsen et al. 1986
Mouse (dd) 20–40 M	24 weeks (F)	ND	18	18% increase in relative liver weight	Ito et al. 1973
Rat (W strain) 18–24 M	24–48 weeks (F)		35	Hepatocellular hypertrophy after 48 weeks	Ito et al. 1975
Mouse (dd) 10–11 M, 10–11 F	32 weeks (F)	20	60 F 50 M	Nuclear irregularities in foci of enlarged hepatocytes	Hanada et al. 1973

Table A-2. Summary of NOAELs and LOAELs from Candidate Intermediate-Duration Studies in Laboratory Animals Orally Exposed to β-Hexachlorocyclohexane

Species	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Developmental effects					
Rat (Wistar) 6 F	GDs 0–21 LDs 1–28 (F)	ND	5 20 (serious LOAEL)	Increased liver weight in pups exposed during gestation and lactation 48% pup mortality by PND 5	Srinivasan et al. 1991

Principal study for the MRL.

(F) = feed; F = female(s); GD = gestation day; LD = lactation day; LOAEL = lowest-observed-adverse-effect level; M = male(s); ND = not determined; NOAEL = no-observed-adverse-effect level; PND = postnatal day

Selection of the Principal Study: Van Velsen et al. (1986) was selected as the principal study because it identified the lowest LOAEL among intermediate-duration oral studies.

Summary of the Principal Study:

Van Velsen FL, Danse LHJC, Van Leeuwen FXR, et al. 1986. The subchronic oral toxicity of the β-isomer of hexachlorocyclohexane in rats. Fundam Appl Toxicol 6:697-712.

Groups of 10 male and 10 female Wistar rats were exposed to β-HCH in diets containing 0, 2, 10, 50, or 250 mg/kg feed (>98% pure) for 13 weeks. ATSDR calculated doses corresponding to these concentrations using food factor values for male and female Wistar rats in subchronic studies as reported in EPA (1988b). Estimated dietary doses were 0, 0.18, 0.9, 4.5, or 22.5 mg/kg/day in males, and 0, 0.2, 1.0, 5, or 25 mg/kg/day in females. Clinical signs were monitored daily, and body weights and food intake were measured weekly. At sacrifice at the end of exposure, blood was collected for hematology and clinical chemistry. Necropsy evaluations included organ weights (liver, kidneys, spleen, thymus, adrenals, pituitary, testes, uterus, and ovaries), gross pathology, and comprehensive histopathology.

At the end of week 2, two male and two female rats receiving the highest dose exhibited ataxia and hypoactive, progressing to coma within 3 days. The animals were humanely sacrificed, as were five additional males and six additional females that showed similar signs later in the study. Terminal body weight was significantly reduced (15.5% relative to controls in both males and females) in the animals from this dose group that survived. Other effects seen at the highest dose (either in the early decedents or in survivors or both), but not at lower doses, included: centrilobular hepatocytic hypertrophy, proliferation of smooth endoplasmic reticulum, increased microsomal activity, and/or increased glycogen content in the livers; hematologic and splenic changes indicative of anemia (decreased red blood cells and hemoglobin, increased extramedullary hematopoiesis); depletion of splenic lymphoid tissue; thymic cortical atrophy; adrenal cortical hypertrophy in both sexes; testicular and ovarian atrophy; and epithelial hyperplasia, metaplasia, and dilation of endometrial glands in the uterus.

No clinical signs, and no reductions in body weight gain or food intake were seen at lower doses of β-HCH. The lower dose groups had increased food intake and increases in body weight, but terminal body weights did not differ significantly from controls. At doses of 0.2–5 mg/kg/day, reduced neutrophil

counts were seen in females, but there were no other significant hematology changes. Clinical chemistry did not show any effects of treatment on serum AST, ALT, ALP, urea, IgM, or IgG levels. Dose-related trends in lower serum lactate and pyruvate were seen, but the only significant difference from controls was for serum lactate in 4.5 mg/kg/day males. Relative, but not absolute, testes weights were reduced (~10%) at 4.5 mg/kg/day, but the difference may have resulted from increased body weight (10% higher than controls) at this dose. At the highest dose, both absolute and relative testes weights were markedly reduced and accompanied by testicular atrophy. Kidney weights were significantly increased at all doses in females, but the increase did not show dose-dependence. In males, significant increases were seen only at ≥4.5 mg/kg/day and were accompanied by renal medullary calcinosis at 22.5 mg/kg/day; this lesion was seen in females ≥5 mg/kg/day. Increased absolute and/or relative liver weights occurred at ≥0.9 mg/kg/day in males and ≥1.0 mg/kg/day in females. Increased incidences of hyalinization of centrilobular cells were observed in the livers of males at all doses, but not in females except in survivors at the highest dose (25 mg/kg/day). At the lowest dose (0.18 mg/kg/day), the hyalinization in males was characterized as slight. Females exhibited a low incidence of increased mitoses at 5 mg/kg/day. One male each in the 4.5 and 22.5 mg/kg/day groups exhibited focal liver cell necrosis. Periportal fat accumulation and/or focal liver cell necrosis occurred in males and females at ≥4.5 mg/kg/day. Based on the slight liver histopathology changes (hyalinization of centrilobular cells) seen in males at the lowest dose level, 0.18 mg/kg/day is considered to be a minimal LOAEL. A NOAEL could not be determined.

Selection of the Point of Departure for the MRL: The minimal LOAEL of 0.18 mg/kg/day was selected as the POD for MRL derivation because these effects occurred at the lowest dose (increased liver weights were seen at the next higher dose of 0.9–1.0 mg/kg/day). The histopathology findings in the liver did not exhibit a monotonic dose-response relationship and were thus not amenable to BMD modeling.

Intermittent Exposure: Not applicable.

Uncertainty Factor: The LOAEL of 0.18 mg/kg/day was divided by a total uncertainty factor of 300:

- 3 for use of a minimal LOAEL
- 10 for extrapolation from animals to humans
- 10 for human variability

Provisional MRL = NOAEL ÷ (UF)
0.18 mg/kg/day ÷ (3 x 10 x 10) = 0.0006 mg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The liver is an established target of β-HCH in other intermediate- and chronic-duration oral studies in rats and mice (Fitzhugh et al. 1950; Ito et al. 1973).

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** β-HCH
CAS Number: 319-85-7
Date: January 2023
Profile Status: Draft for public comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL for β-HCH.

Rationale for not deriving an MRL: Two chronic-duration oral studies of β-HCH were located: Fitzhugh et al. (1950) and Thorpe and Walker (1973). While Thorpe and Walker (1973) examined only cancer endpoints, Fitzhugh et al. (1950) evaluated histopathology in a large number of organs and identified the liver as the most sensitive target of chronic oral exposure. In this study, the lowest dose (0.7–0.9 mg/kg/day) was identified as a LOAEL based on increased in liver weight and histological changes. A NOAEL was not identified. Thus, the only available chronic LOAEL (0.7–0.9 mg/kg/day) is higher than the LOAEL (0.18 mg/kg/day based on liver effects in a study by Van Velsen et al. 1986) used as the POD for intermediate MRL derivation. Thus, a chronic MRL could not be derived based on the study by Fitzhugh et al. (1950).

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** γ-HCH
CAS Number: 58-89-9
Date: January 2023
Profile Status: Draft for public comment
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL for γ-HCH.

Rationale for Not Deriving an MRL: No acute-duration inhalation studies of γ-HCH in humans were located. Acute-duration inhalation studies in animals are shown in Table A-3, and include two studies of rats exposed for 4 hours (Oldiges et al. 1980; Ullmann 1986b) and data on clinical signs in mice in the first 2 weeks of an intermediate-duration study (Klonne and Kintigh 1988). Klonne and Kintigh (1988) observed 16% mortality in the first week of exposure to 10 mg/m3 γ-HCH (6 hours/day, 5 days/week). Other endpoints were not evaluated in the first few weeks of these studies (Klonne and Kintigh 1988; Oldiges et al. 1983). The rat studies of 4-hour exposures (Oldiges et al. 1980; Ullmann 1986b) identified freestanding LOAELs (101 or 237 mg/m^3). The available data are not adequate to identify sensitive targets of inhaled γ-HCH, precluding derivation of an acute-duration inhalation MRL for γ-HCH.

Table A-3. Summary of NOAELs and LOAELs from Acute-Duration Studies in Laboratory Animals Exposed to γ-Hexachlorocyclohexane by inhalation

Species	Exposure scenario	NOAEL (mg/m^3)	LOAEL (mg/m^3)	Effect	Reference
Mouse (CD-1) 45 M, 45 F	1 week 5 days/week 6 hours/day	ND	10 (serious LOAEL)	16% mortality during the first week	Klonne and Kintigh 1988
Rat (Wistar) 5 M, 5 F	4 hours	ND	101	Sedation	Ullmann 1986b
Rat (Wistar) 5 M, 5 F	4 hours	ND	237	Clinical signs of restlessness and hyperactivity	Oldiges et al. 1980

F = female(s); LOAEL = lowest-observed-adverse-effect level; M = male(s); ND = not determined; NOAEL = no-observed-adverse-effect level

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** γ-HCH
CAS Number: 58-89-9
Date: January 2023
Profile Status: Draft for public comment
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL for γ-HCH.

Rationale for Not Deriving an MRL: No intermediate-duration inhalation studies of γ-HCH in humans were located. Intermediate-duration inhalation studies in animals are shown in Table A-4, and include one study of rats exposed for 90 days (Oldiges et al. 1983) and a 14-week study of mice (Klonne and Kintigh 1988). The lowest LOAEL (0.5 mg/m^3) was identified for renal effects in male rats; a NOAEL for this endpoint was not identified (Oldiges et al. 1980). For the 14-week mouse study by Klonne and Kintigh (1988), a serious LOAEL of 1 mg/m^3 was identified for concentration-related increases in mortality. No deaths were observed at 0.3 mg/m^3, and there were no treatment-related effects on body weight, food and water intake, clinical chemistry, organ weight, bone marrow evaluations, ophthalmic evaluations, or gross or microscopic pathology (Klonne and Kintigh 1988). No studies evaluating developmental, neurological, immune system, or reproductive effects of γ-HCH in animals exposed by inhalation were located; these have been demonstrated to be sensitive endpoints of γ-HCH toxicity after oral exposure. The available data were not considered adequate for derivation of an intermediate duration due to the lack of studies on sensitive endpoints and because the lowest LOAEL (0.5 mg/m^3 in rats) is only one-half the serious LOAEL of 1 mg/mg3 for mortality in mice.

Table A-4. Summary of NOAELs and LOAELs from Intermediate-Duration Studies in Laboratory Animals Exposed to γ-Hexachlorocyclohexane by inhalation

Species	Exposure scenario	NOAEL (mg/m^3)	LOAEL (mg/m^3)	Effect	Reference
Rat (Wistar) 5 M, 5 F	90 days day/week NS 6 hours/day	ND	0.5	Dilated renal tubules with protein-containing contents; proliferated tubules in males	Oldiges et al. 1983
Mouse (CD-1) 45 M, 45 F	14 week 5 days/week 6 hours/day	0.3	1 (serious LOAEL)	1/45 males and 1/45 females died at 1 mg/m^3; 5/45 males and 15/45 females died at 5 mg/m^3	Klonne and Kintigh 1988
Rat (Wistar) 5 M, 5 F	90 days days/week NS 6 hours/day	0.5	5	Diarrhea; bone marrow myelogram changes	Oldiges et al. 1983

F = female(s); LOAEL = lowest-observed-adverse-effect level; M = male(s); ND = not determined; NOAEL = no-observed-adverse-effect level; NS = not specified

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** γ-HCH
CAS Number: 58-89-9
Date: January 2023
Profile Status: Draft for public comment
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL for γ-HCH.

Rationale for Not Deriving an MRL: No chronic-duration inhalation studies of γ-HCH in humans or animals were located, precluding derivation of a chronic-duration inhalation MRL.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** γ-HCH
CAS Number: 58-89-9
Date: January 2023
Profile Status: Draft for public comment
Route: Oral
Duration: Acute
MRL: 0.003 mg/kg/day (3 µg/kg/day)
Critical Effect: Effects on development of male reproductive tract
Reference: Dalsenter et al. 1997b
Point of Departure: 1 mg/kg/day (LOAEL)
Uncertainty Factor: 300
LSE Graph Key: 6
Species: Rat

MRL Summary: An acute-duration oral MRL of 0.003 mg/kg/day (3 µg/kg/day) was derived for γ-HCH based on a minimal LOAEL of 1 mg/kg/day for developmental effects (effects on developing reproductive system in male rat pups exposed during lactation) (Dalsenter et al. 1997b). A cumulative uncertainty factor of 300 (10 for extrapolation from animals to humans, 10 for human variability, and 3 for use of a minimal LOAEL) was applied to the LOAEL to obtain the MRL.

Selection of the Critical Effect: Table A-5 provides a summary of the lowest effect levels in acute-duration oral studies of γ-HCH exposure in animals. The lowest effect level was a LOAEL of 1 mg/kg/day for effects on the development of the male reproductive tract in rat pups exposed during LDs 9–14 (Dalsenter et al. 1997b). These effects were seen during assessments on PNDs 65 and 140, as follows. At PND 65, there was no significant effect on relative testicular weight; 7% reduction relative epididymis weight; 29% lower spermatid count; 12% lower sperm count; and 30% lower testosterone levels. At PND 140, the differences from control had declined: testicular weight was 6% lower than controls; spermatid and sperm counts were 13% lower than controls; and there were no significant differences in relative epididymal weights or serum testosterone concentration. There were no effects on mating or fertility. There was no NOAEL associated with the study. The findings in this study are consistent with adverse effects on developing male reproductive organs reported in other animal studies (Agrahari et al. 2019; Dalsenter et al. 1997a, 1997b; Di Consiglio et al. 2009; La Sala et al. 2009; Traina et al. 2003).

Table A-5. Summary of NOAELs and LOAELs from Candidate Acute-Duration Studies in Laboratory Animals Orally Exposed to γ-Hexachlorocyclohexane (Doses ≤10 mg/kg/day)

Species	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Developmental effects					
Rat (BOR: spf) 9 F	LDs 9–14 (GO)	ND	1 (minimal LOAEL)	In male pups, reduced relative testicular and epididymis weight (6–7%), spermatid and sperm counts (12–29%), and testosterone levels (8–30%) at maturity with no effect on fertility	Dalsenter et al. 1997b

Table A-5. Summary of NOAELs and LOAELs from Candidate Acute-Duration Studies in Laboratory Animals Orally Exposed to γ-Hexachlorocyclohexane (Doses ≤10 mg/kg/day)

Species	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Rat (BOR: spf) 9 F	LD 9 or 14 once (GO)	ND	6	In male pups, reduced relative testicular and epididymis weight (~10%), spermatid and sperm counts (~8–10%), testosterone levels (~30-50%), Leydig cell numbers, and spermatogenesis at maturity with no effect on fertility	Dalsenter et al. 1997b
Neurological effects					
Rat (Sprague-Dawley) 9 M	6 days (GO)	ND	3	Increased pineal N-acetyl-transferase, decreased serotonin levels	Attia et al. 1991
Rat (Sprague-Dawley) 7–14 M	4 days (GO)	1	3	Increased kindling acquisition	Joy et al. 1982
Rat (Long-Evans) 14 M	Once (GO)	ND	5	Myoclonic jerks and single clonic seizure in kindled animals	Gilbert and Mack 1995
Rat (Wistar) 5 M, 5 F	3 days (GO)	ND	5 (serious LOAEL)	Decreased myelin in developing brain	Serrano et al. 1990
Hepatic effects					
Rat (Wistar) 6 M	3 days (GO)	ND	5	Fatty degeneration, vacuolation, and necrosis of the liver	Hfaiedh et al. 2012
Hematological effects					
Mouse (B6C3F1) 7 M	10 days (GO)	ND	10	Transient decrease in marrow progenitor cell numbers	Hong and Boorman 1993
Immunological effects					
Rat (Wistar) 8 M	14 days (NS)	ND	10	Reduced delayed-type hypersensitivity (43% decrease in foot pad thickness)	Mediratta et al. 2008
Mouse (B6C3F1) 7 M	10 days (GO)	ND	10	Dose-related decrease in relative thymus and spleen weights	Hong and Boorman 1993

Principal study for the MRL.

F = female(s); (GO) = gavage in oil vehicle; LD = lactation day; LOAEL = lowest-observed-adverse-effect level; M = male(s); ND = not determined; NOAEL = no-observed-adverse-effect level; NS = not specified

Selection of the Principal Study: The study by Dalsenter et al. (1997b) was selected for use in deriving the MRL because the lowest LOAEL (1 mg/kg/day) was identified for developmental effects in this study.

Summary of the Principal Study:

Dalsenter PR, Faqi AS, Webb J, et al. 1997b. Reproductive toxicity and toxicokinetics of lindane in the male offspring of rats exposed during lactation. Hum Exp Toxicol 16:146-153.

Reproductive toxicity was evaluated in male offspring of groups of nine Bor:spf female rats that were administered γ-HCH in peanut oil by gavage as a single 6 mg/kg dose on day 9 or day 14 of lactation, or as daily 1 mg/kg/day doses on days 9–14 of lactation (Dalsenter et al. 1997b). A group of nine controls was administered the vehicle alone on days 9–14 of lactation. Male offspring (10 or 20/group) were terminated on PND 65 (puberty) or 140 (adulthood) and evaluated for the following endpoints: testis and epididymis weights, spermatid and sperm numbers, serum testosterone level, sexual behavior at 130 days of age during 1:1 mating with unexposed females (mount latency, intromission and ejaculatory latency, number and frequency of intromissions), mating index (number sperm positive females/number males mated x100), pregnancy index (number of males that made females pregnant/number of males that made females sperm-positive x100), fertility index (number of days elapsed until males fertilized their female partner), pregnancy endpoints (numbers of litters, implantations/litters, fetuses/litter, resorptions), and testicular histology (6 mg/kg offspring only).

Effects occurred in all treated groups. Findings in the 1 mg/kg/day offspring included statistically significant ($p<0.05$) reductions in relative testicular weight at PND 140 (6% less than controls), relative epididymis weight at PND 65 (7%), spermatid number at PNDs 65 and 140 (29 and 13%, respectively), sperm number at PND 140 (13%), serum testosterone at PND 65 (30%), and increased number of intromissions per minute up to ejaculation at PND 130 (45%). Effects were generally similar in type and magnitude in the 6 mg/kg offspring following exposure on GDs 9 or 14, including significantly reduced relative testicular weight at PNDs 65 and 140 (~10%), spermatid and sperm numbers at PND 140 (~8–10%), and serum testosterone at PND 140 (~50%). There were no significant effects on sexual behavior or fertility in the 1 or 6 mg/kg/day offspring as shown by the mating, pregnancy, and fertility indices or other pregnancy endpoints. Thus, the statistically significant changes observed for relative organ weights, sperm number, hormone levels, and intromission incidence are considered minimally effective for reproduction; their associated dose levels are considered minimal LOAELs. The testicular histological examinations of the 6 mg/kg/day offspring showed large areas of normal tissue, although some areas had distinct changes ranging from small alterations to a pronounced effect. The most affected areas were the tubules in which the effects included necrotic changes and reductions in Leydig cell numbers and spermatogenesis.

Selection of the Point of Departure for the MRL: The minimal LOAEL of 1 mg/kg/day for effects on the developing male reproductive tract (Dalsenter et al. 1997b) was selected as the POD for derivation of the acute-duration oral MRL for γ-HCH. BMD modeling was not possible as only a single exposed group was included in the experiment.

Intermittent Exposure: Not applicable.

Uncertainty Factor: The changes in relative organ weights, sperm number, hormone levels, and intromission incidence at the LOAEL were not associated with effects on sexual behavior or fertility; thus, the dose is considered a minimal LOAEL. Therefore, the LOAEL of 1 mg/kg/day was divided by a total uncertainty factor of 300:

- 10 for extrapolation from animals to humans
- 10 for human variability
- 3 for use of a minimal LOAEL

MRL = LOAEL ÷ (UF)
1 mg/kg/day ÷ (3 x 10 x 10) = 0.003 mg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: 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. 1997b; Di Consiglio et al. 2009; La Sala et al. 2009; Traina et al. 2003).

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** γ-HCH
CAS Number: 58-89-9
Date: January 2023
Profile Status: Draft for public comment
Route: Oral
Duration: Intermediate
MRL: $8x10^{-7}$ mg/kg/day (0.8 ng/kg/day) (provisional)
Critical Effect: Cardiac effects in offspring
Reference: Sauviat et al. 2005
Point of Departure: 0.000076 mg/kg/day (NOAEL)
Uncertainty Factor: 100
LSE Graph Key: 75
Species: Rat

MRL Summary: An intermediate-duration oral MRL of 0.0000008 ($8x10^{-7}$) mg/kg/day (0.8 ng/kg/day) was derived for γ-HCH based on a NOAEL of 0.000076 mg/kg/day for a developmental endpoint of cardiac effects in rat pups (Sauviat et al. 2005). A total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) was applied to the NOAEL to obtain the MRL.

Selection of the Critical Effect: Table A-6 provides a summary of the lowest effect levels in intermediate-duration studies of animals exposed to γ-HCH by oral administration. The lowest effect level (0.00015 mg/kg/day, minimal LOAEL) was identified for effects on cardiac electrophysiology in a rat pups exposed to γ-HCH in drinking water (Sauviat et al. 2005). A NOAEL of 0.000076 mg/kg/day was identified for this study. The effects at the LOAEL in this study were minimal, but additional evidence that the effects were adverse is provided by the serious findings of altered heart morphometry and cardiac histopathology changes at the higher dose of 0.0003 mg/kg/day. Histopathology evaluations were not conducted in rat pups receiving the lower doses.

Table A-6. Summary of NOAELs and LOAELs from Candidate Intermediate-Duration Studies in Laboratory Animals Orally Exposed to γ-Hexachlorocyclohexane (Doses ≤1 mg/kg/day)

Species	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Developmental effects					
Rat (Sprague-Dawley) NS F	~13 weeks (premating, mating, gestation, lactation and 3 weeks postweaning) (W)	0.000076	0.00015 (minimal LOAEL) 0.0003 (serious LOAEL)	LOAEL: altered ventricular electrophysiology. Serious LOAEL: 21% decrease in pup body weight; altered heart morphometry and electrophysiology; cardiac histopathology (hypertrophy in left ventricular area, unorganized collagen bundles and layers, fibroblast destruction)	Sauviat et al. 2005

Table A-6. Summary of NOAELs and LOAELs from Candidate Intermediate-Duration Studies in Laboratory Animals Orally Exposed to γ-Hexachlorocyclohexane (Doses ≤1 mg/kg/day)

Species	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Rat (Wistar) 13–14 F	GDs 5–21 (GO)	0.125	0.25	Persistent hyperactivity	Johri et al. 2007
Rat (Wistar) 25 F	GDs 5–21 (GO)	ND	0.25 (serious LOAEL)	Ultrastructural changes in the brain (moderately distorted mitochondria and demyelinated neurons)	Srivastava et al. 2019
Immunological effects					
Mouse (Swiss albino) 6 F	24 weeks (F)	ND	0.012	Changes in cell- and humoral-mediated immune system	Meera et al. 1992

Principal study for the MRL.

(F) = feed; F = female(s); GD =gestation day; (GO) = gavage in oil vehicle; (W) = water; LOAEL = lowest-observed-adverse-effect level; M = male(s); ND = not determined; NOAEL = no-observed-adverse-effect level; PND = postnatal day

Selection of the Principal Study: The lowest LOAEL (0.00015 mg/kg/day) and NOAEL (0.000076 mg/kg/day) for any effect of γ-HCH was identified in the study by Sauviat et al. (2005). These doses are much lower than those associated with other effects of γ-HCH.

Summary of the Principal Study:

Sauviat MP, Bouvet S, Godeau G, et al. 2005. Electrical activity alterations induced by chronic absorption of lindane (gamma-hexachlorocyclohexane) trace concentrations in adult rat heart. Can J Physiol Pharmacol 83:243-251.

Groups of female Sprague-Dawley rats (number not reported) were administered γ-HCH via "beverage" at doses of 0.5, 1, or 2 ppb. ATSDR estimated corresponding maternal doses of 0, 0.000076, 0.00015, and 0.00030 mg/kg/day using water intake and body weight for female Sprague-Dawley rats in subchronic studies as reported in EPA (1988b). Doses were administered prior to mating for four estrous cycles (~2 weeks); throughout mating (~2 weeks), gestation (3 weeks), lactation (3 weeks), and growth (3 weeks) until pups were 6 weeks of age for a total of ~13 weeks. Exposure of the pups after weaning was not described but assumed to occur via water at the same dose as the dams. Offspring were sacrificed at 6 weeks of age. The left ventricular papillary muscles (LVPM) were dissected from 18 control rats from 7 litters; 5 rats from 2 litters in the 0.000076 mg/kg/day group; 7 rats from 2 litters in the 0.00015 mg/kg/day group; and 18 rats from 7 litters in the 0.0003 mg/kg/day group. Dissected LVPMs were evaluated for the following electrophysiologic measurements: resting potential, action potential, plateau, action potential duration, overshoot, end of early repolarization, and end of terminal repolarization. Cardiac weight, lipid content, and morphometry, as well as left ventricular papillary muscle histopathology were evaluated in pups from the 0.0003 mg/kg/day and control groups only.

The study authors indicated that the high-dose offspring were less sensitive to anesthesia and more sensitive to noise than other groups, but details of these assessments and findings were not provided. Body weights of pups were significantly decreased by 21% in the 0.0003 mg/kg/day group, compared to controls; no significant body weight changes were observed in other groups.

Morphometry analysis showed that hearts from pups in the 0.0003 mg/kg/day group had a 9% increase in heart width (relative to controls), but no significant change in length, with a corresponding 9% decrease in length-to-width ratio. Heart weights and total lipid content were not significantly different in the 0.0003 mg/kg/day group compared to control. At 0.0003 mg/kg/day, offspring heart morphology was described as more round and "cherry like." The study authors reported that hearts of treated offspring showed hypertrophied area with thinning of the left ventricular wall and few developed papillary muscles. Histopathological examination in 0.0003 mg/kg/day offspring showed that the heart tissue muscle bundles and layers were unorganized and dissociated, with large hemorrhagic interspaces and dispersion of cell nuclei, destruction of fibroblasts, and dispersion and disorganization of collagen bundles, compared to control heart muscle. Incidences of changes were not reported, and these parameters were not assessed in pups from the 0.5 and 0.00015 mg/kg/day groups.

Electrophysiology changes were evident in LVPMs from animals exposed to 0.00015 mg/kg/day and 0.0003 mg/kg/day γ-HCH. Action potential durations were unchanged at 0.000076 mg/kg/day, but the plateau was shortened moderately at 0.00015 mg/kg/day, and significantly shortened at 0.0003 mg/kg/day. At 0.0003 mg/kg/day, the slow repolarizing phase was also significantly shortened.

The effects at the high dose (0.0003 mg/kg/day) represent a serious LOAEL for cardiac effects (histopathology and electrophysiology changes) and significant body weight decrements (21% decrease) in the developing rat. The only effect at the middle dose (0.00015 mg/kg/day) was shortened action potential duration at the initial plateau phase (measured at 0 millivolts); similar results were not observed in the early repolarization or terminal repolarization phases (measured at 40 and 10 millivolts, respectively). However, at the high dose (0.0003 mg/kg/day), there were effects in all three phases, suggesting a dose-response relationship. There was no assessment of cardiac morphometry or histopathology in offspring from the middle dose group. The electrophysiology changes observed at 0.00015 mg/kg/day are considered to represent a minimal LOAEL. The lowest dose (0.000076 mg/kg/day) was not associated with electrophysiology changes and is considered to be a NOAEL.

Selection of the Point of Departure for the MRL: The data on electrophysiology changes in the study by Sauviat et al. (2005) are not amenable to BMD modeling, as the authors did not report variability measures. Thus, the NOAEL of 0.000076 mg/kg/day was selected as the POD for MRL derivation.

Intermittent Exposure: Not applicable.

Uncertainty Factor: The NOAEL of 0.000076 mg/kg/day was divided by a total uncertainty factor (UF) of 100:

- 10 for extrapolation from animals to humans
- 10 for human variability

Provisional MRL = NOAEL ÷ (UF)
0.000076 mg/kg/day ÷ (10 x 10) ≈ 0.0000008 mg/kg/day (8×10^{-7} mg/kg/day)

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Sauviat et al. (2007) conducted a related study examining whether the cardiac effects seen after maternal exposure

could be induced by paternal exposure to γ-HCH in drinking water. In this study, male rats were exposed to a concentration of 2 μg/L for an unspecified "chronic" duration prior to mating with untreated females. The lack of information on exposure duration in the males precluded estimation of doses. In offspring sacrificed at 6 weeks of age, there were no effects on pup heart weight or shape or electrophysiology, but there were histopathology changes in the hearts similar to those reported by Sauviat et al. (2005) at the same drinking water concentration.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** γ-HCH
CAS Number: 58-89-9
Date: January 2023
Profile Status: Draft for public comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL for γ-HCH.

Rationale for Not Deriving an MRL: No adequate exposure-response data were available for humans. Chronic oral studies of γ-HCH that evaluated noncancer endpoints include a 2-year dog study (Rivett et al. 1978), 18-month and 2-year studies in rats (Ali and Shakoori 1998; Fitzhugh et al. 1950); and 78–80-week studies in mice (EPA 2000a; Herbst et al. 1975; Weisse and Herbst 1977). Table A-7 summarizes effect levels from these chronic studies. As the table shows, all of the effect levels are much higher than the POD (0.000076 mg/kg/day) used for derivation of the intermediate oral MRL for γ-HCH. Thus, the available oral chronic data were not considered adequate for MRL derivation.

Table A-7. Summary of NOAELs and LOAELs from Candidate Chronic-Duration Studies in Laboratory Animals Orally Exposed to γ-Hexachlorocyclohexane

Species	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Dog (Beagle) 4 M, 4 F	104 weeks (F)	2.92	ND	No body weight, hepatic, hematological, or ocular effects	Rivett et al. 1978
Rat (Wistar) 10 M, 10 F	107 weeks (F)	4	7 M	Increased liver weight (35%); very slight microscopic liver damage; very slight microscopic kidney damage	Fitzhugh et al. 1950
Rat (Sprague-Dawley) 3–5 NS	18 month (F)	ND	9	Increased cell, nucleus, and nucleolus size; extensive cytoplasmolysis; slight cytoplasmic degeneration; increasing nuclear distortion	Ali and Shakoori 1998
Mouse (CD-1) 50 M, 50 F	78 weeks (F)	5.2 M	20.5 M	Centrilobular hepatocyte hypertrophy	EPA 2000a
Mouse (NMRI) 50 M, 50 F	80 weeks (F)	8.2 M	ND	No body weight or liver effects	Herbst et al. 1975; Weisse and Herbst 1977

(F) = feed; F = female(s); LOAEL = lowest-observed-adverse-effect level; M = male(s); ND = not determined; NOAEL = no-observed-adverse-effect level; NS = not specified

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** δ-HCH
CAS Number: 319-86-8
Date: January 2023
Profile Status: Draft for public comment
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL for δ-HCH.

Rationale for Not Deriving an MRL: No acute-duration inhalation studies of δ-HCH in humans or animals were located, precluding derivation of an acute-duration inhalation MRL.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** δ-HCH
CAS Number: 319-86-8
Date: January 2023
Profile Status: Draft for public comment
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL for δ-HCH.

Rationale for Not Deriving an MRL: No intermediate-duration inhalation studies of δ-HCH in humans or animals were located, precluding derivation of an intermediate-duration inhalation MRL.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** δ-HCH
CAS Number: 319-86-8
Date: January 2023
Profile Status: Draft for public comment
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL for δ-HCH.

Rationale for Not Deriving an MRL: No chronic-duration inhalation studies of δ-HCH in humans or animals were located, precluding derivation of a chronic-duration inhalation MRL.

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** δ-HCH
CAS Number: 319-86-8
Date: January 2023
Profile Status: Draft for public comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL for δ-HCH.

Rationale for Not Deriving an MRL: No acute-duration oral studies of δ-HCH in humans or animals were located, precluding derivation of an acute-duration oral MRL.

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** δ-HCH
CAS Numbers: 319-86-8
Date: January 2023
Profile Status: Draft for public comment
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration oral MRL for δ-HCH.

Rationale for Not Deriving an MRL: No intermediate-duration oral studies of δ-HCH in humans were located. Two intermediate-duration oral studies of δ-HCH administered in feed were identified: a 48-week study in rats (Ito et al. 1975) and a 24-week study in mice (Ito et al. 1973). Both studies were focused on the evaluation of liver cancer, and only the liver was evaluated (organ weight and histopathology). Due to the lack of data pertaining to other potential target organs, these data are not considered adequate for derivation of an intermediate-duration oral MRL.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** δ-HCH
CAS Number: 319-86-8
Date: January 2023
Profile Status: Draft for public comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL for δ-HCH.

Rationale for Not Deriving an MRL: No chronic-duration oral studies of δ-HCH in humans or animals were located, precluding derivation of a chronic-duration oral MRL.

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR HCH

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to HCH.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for HCH. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of HCH have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of HCH are presented in Table B-1.

Table B-1. Inclusion Criteria for the Literature Search and Screen

Health Effects
Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects
Cardiovascular effects
Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Other noncancer effects

Table B-1. Inclusion Criteria for the Literature Search and Screen

Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals
Potential for human exposure
Releases to the environment
Air
Water
Soil
Environmental fate
Transport and partitioning
Transformation and degradation
Environmental monitoring
Air
Water
Sediment and soil
Other media
Biomonitoring
General populations
Occupation populations

B.1.1 Literature Search

The current literature search was intended to update the 2005 toxicological profile for HCH; thus, the literature search was restricted to studies published between January 2003 and October 2020. The following main databases were searched in October 2020:

- PubMed
- National Technical Reports Library (NTRL)
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for HCH. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures

and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to HCH were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
10/2020	((319-84-6[rn] OR 319-85-7[rn] OR YM80ODM9PD[rn] OR 319-86-8[rn] OR 58-89-9[rn] OR 59NEE7PCAB[rn] OR 608-73-1[rn] OR "Hexachlorocyclohexane"[mh]) AND (("Hexachlorocyclohexane/toxicity"[mh] OR "Hexachlorocyclohexane/adverse effects"[mh] OR "Hexachlorocyclohexane/poisoning"[mh] OR "Hexachlorocyclohexane/pharmacokinetics"[mh] OR "Hexachlorocyclohexane/blood"[mh] OR "Hexachlorocyclohexane/cerebrospinal fluid"[mh] OR "Hexachlorocyclohexane/urine"[mh] OR "Hexachlorocyclohexane/antagonists and inhibitors"[mh] OR ("Hexachlorocyclohexane/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh]))) OR ("Hexachlorocyclohexane"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("Hexachlorocyclohexane"[mh] AND toxicokinetics[mh:noexp]) OR ("Hexachlorocyclohexane"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Hexachlorocyclohexane"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Hexachlorocyclohexane"[mh] AND cancer[sb]) OR Hexachlorocyclohexane/pharmacology[majr]) AND 2003:3000[mhda]) OR ((("gamma-Lindane"[tw] OR "1,2,3,4,5,6-Hexachlorocyclohexane"[tw] OR "alpha-Benzene hexachloride"[tw] OR "alpha-Hexachlorocyclohexane"[tw] OR "beta-Benzene hexachloride"[tw] OR "beta-hexachlorocyclohexane"[tw] OR "delta-Benzene hexachloride"[tw] OR "delta-Benzenehexachloride"[tw] OR "delta-Hexachlorocyclohexane"[tw] OR "gamma-Benzene hexachloride"[tw] OR "gamma-Hexachlorocyclohexane"[tw] OR "1,2,3,4,5,6- Hexachlorocyclohexane"[tw] OR "A-Hexachlorocyclohexane"[tw] OR "alpha-Benzene hexachloride"[tw] OR "alpha-Benzenehexachloride"[tw] OR "alpha-Hexachlorocyclohexane"[tw] OR "alpha-Lindane"[tw] OR "Aalindan"[tw] OR "Aficide"[tw] OR "Agrocide"[tw] OR "Agronexit"[tw] OR "Ameisentod"[tw] OR "Aparasin"[tw] OR "Aphtiria"[tw] OR "Aplidal"[tw] OR "Arbitex"[tw] OR "B-Hexachlorocyclohexane"[tw] OR "Benzene hexachloride"[tw] OR "Benzenehexachloride"[tw] OR "beta-1,2,3,4,5,6-Hexachlorocyclohexane"[tw] OR "beta-Hexachloro-cyclohexane"[tw] OR "beta-Hexachlorocyclohexane"[tw] OR "beta-Lindane"[tw] OR "Ben-Hex"[tw] OR "Benhexol"[tw] OR "Bexol"[tw] OR "Celanex"[tw] OR

Table B-2. Database Query Strings

Database search date	Query string
	"Chloresene"[tw] OR "Codechine"[tw] OR "Cyclohexane, 1,2,3,4,5,6-hexachloro-"[tw] OR "delta-Benzene hexachloride"[tw] OR "delta-Benzenehexachloride"[tw] OR "delta-Hexachlorocyclohexane"[tw] OR "delta-Lindane"[tw] OR "Devoran"[tw] OR "Entomoxan"[tw] OR "Forst-Nexen"[tw] OR "Gallogama"[tw] OR "Gamacarbatox"[tw] OR "Gamacid"[tw] OR "Gamacide"[tw] OR "Gamaphex"[tw] OR "Gamene"[tw] OR "Gamiso"[tw] OR "gamma Benzene hexachloride"[tw] OR "gamma-1,2,3,4,5,6-Hexachlorocyclohexane"[tw] OR "gamma-Benzenehexachloride"[tw] OR "gamma-Benzohexachloride"[tw] OR "gamma-Hexachlorcyclohexanum"[tw] OR "gamma-Hexachloro-cyclohexane"[tw] OR "gamma-Hexachlorobenzene"[tw] OR "gamma-Hexachlorocyclohexane"[tw] OR "Gammalin"[tw] OR "Gammaterr"[tw] OR "Gammexane"[tw] OR "Geobilan"[tw] OR "Gexane"[tw] OR "HEXACHLORCYCLOHEXANE"[tw] OR "Hexachloro-cyclohexane"[tw] OR "Hexachlorocyclohexane"[tw] OR "hexachlorocyclohexanes"[tw] OR "Hexachlor"[tw] OR "Hexachlorcyclohexan"[tw] OR "Heclotox"[tw] OR "Hexachloran"[tw] OR "Hexachlorane"[tw] OR "Hexaverm"[tw] OR "Hexcidum"[tw] OR "Hexicide"[tw] OR "Hexyclan"[tw] OR "Hilbeech"[tw] OR "Hortex"[tw] OR "Hungaria L 7"[tw] OR "Hungaria L-7"[tw] OR "Jacutin"[tw] OR "Kokotine"[tw] OR "Kwell"[tw] OR "Lindane"[tw] OR "Lasochron"[tw] OR "Lendine"[tw] OR "Lentox"[tw] OR "Lidenal"[tw] OR "Lindafor"[tw] OR "Lindagam"[tw] OR "Lindagrain"[tw] OR "Lindagranox"[tw] OR "Lindan"[tw] OR "Lindanum"[tw] OR "Lindapoudre"[tw] OR "Lindatox"[tw] OR "Lindosep"[tw] OR "Lintox"[tw] OR "Linvur"[tw] OR "Lorexane"[tw] OR "Mszycol"[tw] OR "Neo-Scabicidol"[tw] OR "Nexol E"[tw] OR "Nexol-E"[tw] OR "Nicochloran"[tw] OR "Novigam"[tw] OR "Omnitox"[tw] OR "Ovadziak"[tw] OR "Owadziak"[tw] OR "Pedraczak"[tw] OR "Pflanzol"[tw] OR "Quellada"[tw] OR "Technical HCH"[tw] OR "technical grade HCH"[tw] OR "Scabene"[tw] OR "Silvanol"[tw] OR "Spritz-Rapidin"[tw] OR "Spritzlindane"[tw] OR "Spruehpflanzol"[tw] OR "Streunex"[tw] OR "α-Benzohexachloride"[tw] OR "α-Hexachlorocyclohexane"[tw] OR "α-Lindane"[tw] OR "β-1,2,3,4,5,6-Hexachlorocyclohexane"[tw] OR "β-Benzene hexachloride"[tw] OR "β-Hexachlorocyclohexane"[tw] OR "β-Lindane"[tw] OR "γ-1,2,3,4,5,6-Hexachlorocyclohexane"[tw] OR "γ-Benzene hexachloride"[tw] OR "γ-Benzohexachloride"[tw] OR "γ-Hexachlorobenzene"[tw] OR "γ-Hexachlorocyclohexane"[tw] OR "γ-Lindane"[tw] OR "δ-Benzene hexachloride"[tw] OR "δ-Hexachlorocyclohexane"[tw] OR "δ-Lindane"[tw] OR "alpha BHC"[tw] OR "alpha-BHC"[tw] OR "alpha-HCH"[tw] OR "beta BHC"[tw] OR "beta-BHC"[tw] OR "beta-HCH"[tw] OR "delta BHC"[tw] OR "delta-BHC"[tw] OR "delta-HCH"[tw] OR "Gamma-BHC"[tw] OR "gamma-HCH"[tw] OR "Nexit Stark"[tw] OR "Nexit-stark"[tw] OR "α-BHC"[tw] OR "α-HCH"[tw] OR "β-666"[tw] OR "β-BHC"[tw] OR "β-HCH"[tw] OR "γ-666"[tw] OR "γ-BHC"[tw] OR "γ-HCH"[tw] OR "δ-BHC"[tw] OR "δ-HCH"[tw] OR "total BHC"[tw] OR "α-666"[tw] OR "δ-666"[tw] OR "BHC-gamma"[tw] OR "α-Benzenehexachloride"[tw]) NOT medline[sb]) AND (2003:3000[crdt] OR 2003:3000[edat])) ("A-HCCH"[tw] OR "BHC alpha"[tw] OR "BHC beta"[tw] OR "BHC delta"[tw] OR "BHC-alpha"[tw] OR "BHC-beta"[tw] OR "BHC-delta"[tw] OR "D-BHC"[tw] OR "D-HCCH"[tw] OR "Detox 25"[tw] OR "Dol Granule"[tw] OR "Dolmix"[tw] OR "ENT 7,796"[tw] OR "ENT 9,232"[tw] OR "HCH (mixed isomers)"[tw] OR "TAP 85"[tw] OR "Tri-6 Dust No. 30"[tw] OR "(1.alpha.,2.alpha.,3.beta.,4.alpha.,5.alpha.,6.beta.)-1,2,3,4,5,6-Hexachlorocyclohexane"[tw] OR "(1.alpha.,2.alpha.,3.beta.,4.alpha.,5.beta.,6.beta.)1,2,3,4,5,6-Hexachlorocyclohexane"[tw] OR "(1.alpha.,2.beta.,3.alpha.,4.beta.,5.alpha.,6.beta.)-1,2,3,4,5,6-hexachloro-cyclohexane"[tw] OR "(1alpha,2alpha,3alpha,4beta,5alpha,6beta)-1,2,3,4,5,6-Hexachlorocyclohexane"[tw] OR "(1alpha,2alpha,3beta,4alpha,5beta,6beta)-1,2,3,4,5,6-

Table B-2. Database Query Strings

Database search date	Query string
	Hexachlorocyclohexane"[tw] OR "(1alpha,2beta,3alpha,4beta,5alpha,6beta)-1,2,3,4,5,6-Hexachlorocyclohexane"[tw] OR "(1r,2r,3r,4r,5r,6r)-1,2,3,4,5,6-Hexachlorocyclohexane"[tw] OR "(1R,2R,3R,4R,5S,6S)-1,2,3,4,5,6-Hexachlorocyclohexane"[tw] OR "(1R,2S,3r,4R,5S,6r)-1,2,3,4,5,6-Hexachlorocyclohexane"[tw] OR "(1R,2S,3r,4R,5S,6s)-1,2,3,4,5,6-Hexachlorocyclohexane"[tw] OR "alpha-hexachlorcyclohexane"[tw] OR "1,2,3,4,5,6-G-HEXACHLOROCYCLOHEXANE"[tw] OR "1,2,3,4,5,6-Hexachloro(1a,2a,3a,4b,5a,6b)cyclohexane"[tw] OR "1,2,3,4,5,6-Hexachloro(1a,2b,3a,4b,5a,6b)cyclohexane"[tw] OR "1,2,3,4,5,6-Hexachloro-(1.alpha.,2.alpha.,3.alpha.,4.beta.,5.alpha.,6.beta.) cyclohexane"[tw] OR "1-alpha,2-alpha,3-alpha,4-beta,5-alpha,6-beta-Hexachlorocyclohexane"[tw] OR "1-alpha,2-beta,3-alpha,4-beta,5-alpha,6-beta-Hexachlorocyclohexane"[tw] OR "1a,2a,3b,4a,5b,6b-Hexachlorocyclohexane"[tw] OR "1α,2α,3β,4α,5α,6β)-1,2,3,4,5,6-Hexachlorocyclohexane"[tw] OR "(1α,2α,3α,4β,5α,6.β)-1,2,3,4,5,6-Hexachlorocyclohexane"[tw] OR "(1α,2α,3α,4β,5α,6β)-1,2,3,4,5,6-Hexachlorcyclohexan"[tw] OR "(1α,2α,3α,4β,5α,6β)-1,2,3,4,5,6-hexachlorocyclohexane"[tw] OR "(1α,2α,3α,4β,5α,6β)-1,2,3,4,5,6-hexaclorociclohexano"[tw] OR "(1α,2α,3β,4α,5α,6β)-1,2,3,4,5,6-Hexachlorocyclohexane"[tw] OR "(1α,2α,3β,4α,5β,6β)-1,2,3,4,5,6-Hexachlorcyclohexan"[tw] OR "(1α,2α,3β,4α,5β,6β)-1,2,3,4,5,6-Hexachlorocyclohexane"[tw] OR "(1α,2α,3β,4α,5β,6β)-1,2,3,4,5,6-hexaclorociclohexano"[tw] OR "(1α,2β,3α,4β,5α,6β)-1,2,3,4,5,6-Hexachlorcyclohexan"[tw] OR "(1α,2β,3α,4β,5α,6β)-1,2,3,4,5,6-Hexachlorocyclohexane"[tw] OR "(1α,2β,3α,4β,5α,6β)-1,2,3,4,5,6-hexaclorociclohexano"[tw] OR "A-Benzene hexachloride"[tw] OR "ALPHA-1,2,3,4,5,6-HEXACHLORCYCLOHEXAN"[tw] OR "alpha-1,2,3,4,5,6-Hexachlorocyclohexane"[tw] OR "alpha-Hexachloran"[tw] OR "alpha-Hexachlorane"[tw] OR "Ameisenmittel merck"[tw] OR "Arcotal S"[tw] OR "B-Benzene hexachloride"[tw] OR "Bentox 10"[tw] OR "Benzene-1,2,3,4,5,6-hexachloride"[tw] OR "Bercema-Spritz-Lindan 50"[tw] OR "Benzanex"[tw] OR "BETA-1,2,3,4,5,6-HEXACHLORCYCLOHEXAN"[tw] OR "beta-Hexachloran"[tw] OR "beta-Hexachlorobenzene"[tw] OR "delta-(Aeeeee)-1,2,3,4,5,6-hexachlorocyclohexane"[tw] OR "Detmol Extract"[tw] OR "Fenoform forte"[tw] OR "Gamaxene"[tw] OR "Gamma-mean 400"[tw] OR "Gamoline"[tw] OR "Gamtox"[tw] OR "Geolin G 3"[tw] OR "Grammexene"[tw] OR "Gyben"[tw] OR "Hexablanc"[tw] OR "Hexachlorine cyclohexane"[tw] OR "Hexachlorzyklohexan"[tw] OR "Hexamul"[tw] OR "Hexapoudre"[tw] OR "Hungaria L7"[tw] OR "Isatox"[tw] OR "Kanodane"[tw] OR "Lidano"[tw] OR "Mglawik L"[tw] OR "Milbol 49"[tw] OR "Nexen FB"[tw] OR "Prodactif"[tw] OR "Sang gamma"[tw] OR "Sang-gamma"[tw] OR "Scabecid"[tw] OR "Submar"[tw] OR "trans-alpha-Benzenehexachloride"[tw] OR "Trives-T"[tw] OR "Verindal Ultra"[tw] OR "BHC, d-"[tw] OR "BHC, total"[tw] OR "HCH, technical grade"[tw] OR "Cyclohexane,1,2,3,4,5,6-hexachloro-(1.alpha.,2.alpha.,3.beta.,4.alpha.,5.alpha.,6.beta.)-"][tw] OR "Ciclohexano, 1,2,3,4,5,6-hexacloro-"[tw] OR "Cyclohexane, beta-1,2,3,4,5,6-hexachloro-"[tw] OR "Cyclohexane, delta-1,2,3,4,5,6-hexachloro-"[tw] OR "Cyclohexane, l,2,3,4,5,6-hexachloro-, (1alpha,2alpha,3beta,4alpha,5beta,6beta)-"[tw] OR "1,2,3,4,5,6-Benzenehexachloride"[tw] OR "1,2,3,4,5,6-Hexachlorohexane"[tw] OR "D-Benzene hexachloride"[tw] OR "D-Hexachlorocyclohexane"[tw] OR "delta-1,2,3,4,5,6-Hexachlorocyclohexane"[tw] OR "α-1,2,3,4,5,6-Hexachlorocyclohexane"[tw] OR "α-Hexachloran"[tw] OR "α-Hexachlorane"[tw] OR "α-Hexachlorcyclohexane"[tw] OR "β-Hexachloran"[tw] OR "β-Hexachlorobenzene"[tw] OR "γ-Hexachloran"[tw] OR "γ-Hexachlorane"[tw] OR "δ-1,2,3,4,5,6-Hexachlorocyclohexane"[tw])

Table B-2. Database Query Strings

Database search date	Query string
NTRL	
10/2020	Search Titles OR Keywords; date limit 2003-2020 "Hexachlorocyclohexane" OR "Benzene hexachloride" OR "Lindane" OR "Hexachlorane" OR "Benzenehexachloride"
Toxcenter	
10/2020	FILE 'TOXCENTER' ENTERED AT 15:53:54 ON 13 OCT 2020 CHARGED TO COST=EH038.05.01.LB.03 L1 34352 SEA 319-84-6 OR 319-85-7 OR 319-86-8 OR 58-89-9 OR 608-73-1 L2 34314 SEA L1 NOT TSCATS/FS L3 33618 SEA L2 NOT PATENT/DT L4 11648 SEA L3 AND PY>=2003 ACTIVATE TOXQUERY/Q --------- L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L10 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L11 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L12 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L13 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L15 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L16 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L17 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L18 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?) L19 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?) L20 QUE (ENDOCRIN? AND DISRUPT?) L21 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?) L22 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?) L23 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)

Table B-2. Database Query Strings

Database search date	Query string
	L24 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L25 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L26 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L27 QUE (NEPHROTOX? OR HEPATOTOX?)
	L28 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L29 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L30 QUE L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29
	L31 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L32 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L33 QUE L30 OR L31 OR L32
	L34 QUE (NONHUMAN MAMMALS)/ORGN
	L35 QUE L33 OR L34
	L36 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
	L37 QUE L35 OR L36

	L38 6058 SEA L4 AND L37
	L39 5151 SEA L4 AND L30
	L40 739 SEA L39 AND MEDLINE/FS
	L41 1022 SEA L39 AND BIOSIS/FS
	L42 3370 SEA L39 AND CAPLUS/FS
	L43 20 SEA L39 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L44 4143 DUP REM L40 L41 L43 L42 (1008 DUPLICATES REMOVED)
	L*** DEL 739 S L39 AND MEDLINE/FS
	L*** DEL 739 S L39 AND MEDLINE/FS
	L45 739 SEA L44
	L*** DEL 1022 S L39 AND BIOSIS/FS
	L*** DEL 1022 S L39 AND BIOSIS/FS
	L46 754 SEA L44
	L*** DEL 3370 S L39 AND CAPLUS/FS
	L*** DEL 3370 S L39 AND CAPLUS/FS
	L47 2631 SEA L44
	L*** DEL 20 S L39 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L*** DEL 20 S L39 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L48 19 SEA L44
	L49 3404 SEA (L45 OR L46 OR L47 OR L48) NOT MEDLINE/FS
	SAVE TEMP L49 HCH/A

Table B-2. Database Query Strings

Database search date	Query string
	D SCAN L49
	L50 773 SEA L49 NOT CAPLUS/FS
	D SCAN L50
	L51 2631 SEA L49 AND CAPLUS/FS
	D SCAN L51

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
10/2020	Compounds searched: 319-84-6, 319-85-7, 319-86-8, 58-89-9, 608-73-1
NTP	
10/2020	"Hexachlorocyclohexane" "Lindane" "Benzenehexachloride" "Benzene hexachloride" "Benzenehexachloride" "Hexachlorane" "319-84-6" "319-85-7" "319-86-8" "608-73-1"
Regulations.gov	
10/2020	Compounds searched: 319-84-6, 319-85-7, 319-86-8, 58-89-9, 608-73-1
NIH RePORTER	
03/2021	Text Search: ""gamma-Lindane"" OR ""1,2,3,4,5,6-Hexachlorocyclohexane"" OR ""alpha-Benzene hexachloride"" OR ""alpha-Hexachlorocyclohexane"" OR ""beta-Benzene hexachloride"" OR ""beta-hexachlorocyclohexane"" OR ""delta-Benzene hexachloride"" OR ""delta-Benzenehexachloride"" OR ""delta-Hexachlorocyclohexane"" OR ""gamma-Benzene hexachloride"" OR ""gamma-Hexachlorocyclohexane"" OR ""1,2,3,4,5,6- Hexachlorocyclohexane"" OR ""A-Hexachlorocyclohexane"" OR ""alpha-Benzene hexachloride"" OR ""alpha-Benzenehexachloride"" OR ""alpha-Hexachlorocyclohexane"" OR ""alpha-Lindane"" OR ""Aalindan"" OR ""Aficide"" OR ""Agrocide"" OR ""Agronexit"" OR ""Ameisentod"" OR ""Aparasin"" OR ""Aphtiria"" OR ""Aplidal"" OR ""Arbitex"" OR ""B-Hexachlorocyclohexane"" OR ""Benzene hexachloride"" OR ""Benzenehexachloride"" OR ""beta-1,2,3,4,5,6-Hexachlorocyclohexane"" OR ""beta-Hexachloro-cyclohexane"" OR ""beta-Hexachlorocyclohexane"" OR ""beta-Lindane"" OR ""Ben-Hex"" OR ""Benhexol"" OR ""Bexol"" OR ""Celanex"" OR ""Chloresene"" OR ""Codechine"" OR ""Cyclohexane, 1,2,3,4,5,6-hexachloro-"" OR ""delta-Benzene hexachloride"" OR ""delta-Benzenehexachloride"" OR ""delta-Hexachlorocyclohexane"" OR ""delta-Lindane"" OR ""Devoran"" OR ""Entomoxan"" OR ""Forst-Nexen"" OR ""Gallogama"" OR ""Gamacarbatox"" OR ""Gamacid"" OR ""Gamacide"" OR ""Gamaphex"" OR ""Gamene"" OR ""Gamiso"" OR ""gamma Benzene hexachloride"" OR ""gamma-1,2,3,4,5,6-Hexachlorocyclohexane"" OR ""gamma-Benzenehexachloride"" OR ""gamma-Benzohexachloride"" OR ""gamma-Hexachlorcyclohexanum"" OR ""gamma-Hexachloro-cyclohexane"" OR ""gamma-Hexachlorobenzene"" OR ""gamma-Hexachlorocyclohexane"" OR ""Gammalin"" OR ""Gammaterr"" OR ""Gammexane"" OR ""Geobilan"" OR ""Gexane"" OR ""HEXACHLORCYCLOHEXANE"" OR ""Hexachloro-cyclohexane"" OR ""Hexachlorocyclohexane"" OR ""hexachlorocyclohexanes"" OR ""Hexachlor"" OR ""Hexachlorcyclohexan"" OR

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	""Heclotox"" OR ""Hexachloran"" OR ""Hexachlorane"" OR ""Hexaverm"" OR ""Hexcidum"" OR ""Hexicide"" OR ""Hexyclan"" OR ""Hilbeech"" OR ""Hortex"" OR ""Hungaria L 7"" OR ""Hungaria L-7"" OR ""Jacutin"" OR ""Kokotine"" OR ""Kwell"" OR ""Lindane"" OR ""Lasochron"" OR ""Lendine"" OR ""Lentox"" OR ""Lidenal"" OR ""Lindafor"" OR ""Lindagam"" OR ""Lindagrain"" OR ""Lindagranox"" OR ""Lindan"" OR ""Lindanum"" OR ""Lindapoudre"" OR ""Lindatox"" OR ""Lindosep"" OR ""Lintox"" OR ""Linvur"" OR ""Lorexane"" OR ""Mszycol"" OR ""Neo-Scabicidol"" OR ""Nexol E"" OR ""Nexol-E"" OR ""Nicochloran"" OR ""Novigam"" OR ""Omnitox"" OR ""Ovadziak"" OR ""Owadziak"" OR ""Pedraczak"" OR ""Pflanzol"" OR ""Quellada"" OR ""Technical HCH"" OR ""technical grade HCH"" OR ""Scabene"" OR ""Silvanol"" OR ""Spritz-Rapidin"" OR ""Spritzlindane"" OR ""Spruehpflanzol"" OR ""Streunex"" (advanced) Limit to: Project Title, Project Terms, Project Abstracts Search Criteria Fiscal Year: Active Projects Text Search: "α-Benzohexachloride" OR "α-Hexachlorocyclohexane" OR "α-Lindane" OR "β-1,2,3,4,5,6-Hexachlorocyclohexane" OR "β-Benzene hexachloride" OR "β-Hexachlorocyclohexane" OR "β-Lindane" OR "γ-1,2,3,4,5,6-Hexachlorocyclohexane" OR "γ-Benzene hexachloride" OR "γ-Benzohexachloride" OR "γ-Hexachlorobenzene" OR "γ-Hexachlorocyclohexane" OR "γ-Lindane" OR "δ-Benzene hexachloride" OR "δ-Hexachlorocyclohexane" OR "δ-Lindane" OR "Nexit Stark" OR "Nexit-stark" OR "α-Benzenehexachloride" (advanced) Limit to: Project Title, Project Terms, Project Abstracts Search Criteria Fiscal Year: Active Projects Text Search: "Dol Granule" OR "Dolmix" OR "HCH (mixed isomers)" OR "Tri-6 Dust No. 30" OR "(1.alpha.,2.alpha.,3.beta.,4.alpha.,5.alpha.,6.beta.)-1,2,3,4,5,6-Hexachlorocyclohexane" OR "(1.alpha.,2.alpha.,3.beta.,4.alpha.,5.beta.,6.beta.)1,2,3,4,5,6-Hexachlorocyclohexane" OR "(1.alpha.,2.beta.,3.alpha.,4.beta.,5.alpha.,6.beta.)-1,2,3,4,5,6-hexachloro-cyclohexane" OR "(1alpha,2alpha,3alpha,4beta,5alpha,6beta)-1,2,3,4,5,6-Hexachlorocyclohexane" OR "(1alpha,2alpha,3beta,4alpha,5beta,6beta)-1,2,3,4,5,6-Hexachlorocyclohexane" OR "(1alpha,2beta,3alpha,4beta,5alpha,6beta)-1,2,3,4,5,6-Hexachlorocyclohexane" OR "(1r,2r,3r,4r,5r,6r)-1,2,3,4,5,6-Hexachlorocyclohexane" OR "(1R,2R,3R,4R,5S,6S)-1,2,3,4,5,6-Hexachlorocyclohexane" OR "(1R,2S,3r,4R,5S,6r)-1,2,3,4,5,6-Hexachlorocyclohexane" OR "(1R,2S,3r,4R,5S,6s)-1,2,3,4,5,6-Hexachlorocyclohexane" OR "alpha-hexachlorcyclohexane" OR "1,2,3,4,5,6-G-HEXACHLOROCYCLOHEXANE" OR "1,2,3,4,5,6-Hexachloro(1a,2a,3a,4b,5a,6b)cyclohexane" OR "1,2,3,4,5,6-Hexachloro(1a,2b,3a,4b,5a,6b)cyclohexane" OR "1,2,3,4,5,6-Hexachloro-(1.alpha.,2.alpha.,3.alpha.,4.beta.,5.alpha.,6.beta.) cyclohexane" OR "1-alpha,2-alpha,3-alpha,4-beta,5-alpha,6-beta-Hexachlorocyclohexane" OR "1-alpha,2-beta,3-alpha,4-beta,5-alpha,6-beta-Hexachlorocyclohexane" OR "1a,2a,3b,4a,5b,6b-Hexachlorocyclohexane" OR "1α,2α,3β,4α,5α,6β)-1,2,3,4,5,6-Hexachlorocyclohexane" OR "(1α,2α,3α,4β,5α,6.β)-1,2,3,4,5,6-Hexachlorocyclohexane" OR "(1α,2α,3α,4β,5α,6β)-1,2,3,4,5,6-Hexachlorcyclohexan" OR "(1α,2α,3α,4β,5α,6β)-1,2,3,4,5,6-hexachlorocyclohexane" OR "(1α,2α,3α,4β,5α,6β)-1,2,3,4,5,6-hexaclorociclohexano" OR "(1α,2α,3β,4α,5α,6β)-1,2,3,4,5,6-Hexachlorocyclohexane" OR "(1α,2α,3β,4α,5β,6β)-1,2,3,4,5,6-Hexachlorcyclohexan" OR "(1α,2α,3β,4α,5β,6β)-1,2,3,4,5,6-Hexachlorocyclohexane" OR "(1α,2α,3β,4α,5β,6β)-1,2,3,4,5,6-hexaclorociclohexano" OR "(1α,2β,3α,4β,5α,6β)-1,2,3,4,5,6-Hexachlorcyclohexan" OR "(1α,2β,3α,4β,5α,6β)-1,2,3,4,5,6-Hexachlorocyclohexane" (advanced) Limit to: Project Title, Project Terms, Project Abstracts

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	Search Criteria Fiscal Year: Active Projects Text Search: "(1α,2β,3α,4β,5α,6β)-1,2,3,4,5,6-hexaclorociclohexano" OR "A-Benzene hexachloride" OR "ALPHA-1,2,3,4,5,6-HEXACHLORCYCLOHEXAN" OR "alpha-1,2,3,4,5,6-Hexachlorocyclohexane" OR "alpha-Hexachloran" OR "alpha-Hexachlorane" OR "Ameisenmittel merck" OR "Arcotal S" OR "B-Benzene hexachloride" OR "Bentox 10" OR "Benzene-1,2,3,4,5,6-hexachloride" OR "Bercema-Spritz-Lindan 50" OR "Benzanex" OR "BETA-1,2,3,4,5,6-HEXACHLORCYCLOHEXAN" OR "beta-Hexachloran" OR "beta-Hexachlorobenzene" OR "delta-(Aeeeee)-1,2,3,4,5,6-hexachlorocyclohexane" OR "Detmol Extract" OR "Fenoform forte" OR "Gamaxene" OR "Gamma-mean 400" OR "Gamoline" OR "Gamtox" OR "Geolin G 3" OR "Grammexene" OR "Gyben" OR "Hexablanc" OR "Hexachlorine cyclohexane" OR "Hexachlorzyklohexan" OR "Hexamul" OR "Hexapoudre" OR "Hungaria L7" OR "Isatox" OR "Kanodane" OR "Lidano" OR "Mglawik L" OR "Milbol 49" OR "Nexen FB" OR "Prodactif" OR "Sang gamma" OR "Sang-gamma" OR "Scabecid" OR "Submar" OR "trans-alpha-Benzenehexachloride" OR "Trives-T" OR "Verindal Ultra" OR "BHC, total" OR "HCH, technical grade" OR "Cyclohexane,1,2,3,4,5,6-hexachloro-(1.alpha.,2.alpha.,3.beta.,4.alpha.,5.alpha.,6.beta.)-]" OR "Ciclohexano, 1,2,3,4,5,6-hexacloro-" OR "Cyclohexane, beta-1,2,3,4,5,6-hexachloro-" OR "Cyclohexane, delta-1,2,3,4,5,6-hexachloro-" OR "Cyclohexane, l,2,3,4,5,6-hexachloro-, (1alpha,2alpha,3beta,4alpha,5beta,6beta)-" OR "1,2,3,4,5,6-Benzenehexachloride" OR "1,2,3,4,5,6-Hexachlorohexane" OR "D-Benzene hexachloride" OR "D-Hexachlorocyclohexane" OR "delta-1,2,3,4,5,6-Hexachlorocyclohexane" OR "α-1,2,3,4,5,6-Hexachlorocyclohexane" OR "α-Hexachloran" OR "α-Hexachlorane" OR "α-Hexachlorcyclohexane" OR "β-Hexachloran" OR "β-Hexachlorobenzene" OR "γ-Hexachloran" OR "γ-Hexachlorane" OR "δ-1,2,3,4,5,6-Hexachlorocyclohexane" (advanced) Limit to: Project Title, Project Terms, Project Abstracts
Other	Identified throughout the assessment process

The 2020 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 4,732
- Number of records identified from other strategies: 92
- Total number of records to undergo literature screening: 4,824

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on HCH:

- Title and abstract screen
- Full text screen

Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

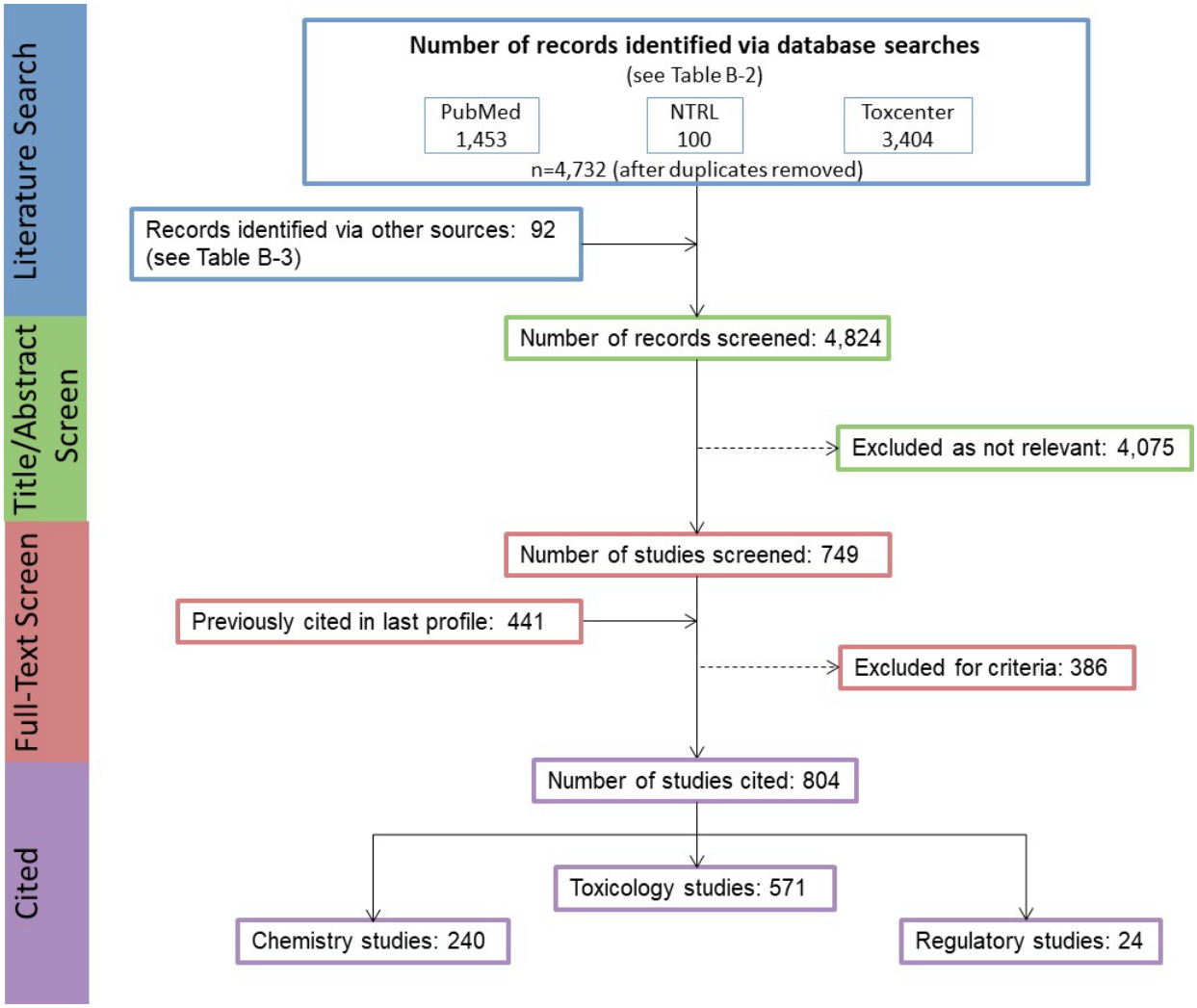
- Number of titles and abstracts screened: 4,824
- Number of studies considered relevant and moved to the next step: 749

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 749
- Number of studies cited in the pre-public draft of the toxicological profile: 441
- Total number of studies cited in the profile: 804

A summary of the results of the literature search and screening is presented in Figure B-1.

Figure B-1. October 2020 Literature Search Results and Screen for HCH



APPENDIX C. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR HCH

To increase the transparency of ATSDR's process of identifying, evaluating, synthesizing, and interpreting the scientific evidence on the health effects associated with exposure to HCH, ATSDR utilized a slight modification of NTP's Office of Health Assessment and Translation (OHAT) systematic review methodology (NTP 2013, 2015; Rooney et al. 2014). ATSDR's framework is an eight-step process for systematic review with the goal of identifying the potential health hazards of exposure to HCH:

- Step 1. Problem Formulation
- Step 2. Literature Search and Screen for Health Effects Studies
- Step 3. Extract Data from Health Effects Studies
- Step 4. Identify Potential Health Effect Outcomes of Concern
- Step 5. Assess the Risk of Bias for Individual Studies
- Step 6. Rate the Confidence in the Body of Evidence for Each Relevant Outcome
- Step 7. Translate Confidence Rating into Level of Evidence of Health Effects
- Step 8. Integrate Evidence to Develop Hazard Identification Conclusions

The systematic review for this profile is divided into four sections:

1. Steps 1, 2, and 3 for α-, β-, and γ-HCH (Sections C.1, C.2, and C.3)
2. Steps 4, 5, 6, 7, and 8 for α-HCH (Sections C.4, C.5, C.6, C.7, and C.8)
3. Steps 4, 5, 6, 7, and 8 for β-HCH (Sections C.9, C.10, C.11, C.12, and C.13)
4. Steps 4, 5, 6, 7, and 8 for γ-HCH (Sections C.14, C.15, C.16, C.17, and C.18)

C.1 PROBLEM FORMULATION

The objective of the toxicological profile and this systematic review was to identify the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to HCH. The inclusion criteria used to identify relevant studies examining the health effects of HCH are presented in Table C-1.

Data from human and laboratory animal studies were considered relevant for addressing this objective. Human studies were divided into two broad categories: observational epidemiology studies and controlled exposure studies. The observational epidemiology studies were further divided: cohort studies (retrospective and prospective studies), population studies (with individual data or aggregate data), and case-control studies.

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects
Cardiovascular effects
Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Other noncancer effects
Cancer

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen was conducted to identify studies examining the health effects of HCH. The literature search framework for the toxicological profile is discussed in detail in Appendix B.

C.2.1 Literature Search

As noted in Appendix B, the current literature search was intended to update the 2005 toxicological profile for HCH; thus, the literature search was restricted to studies published between January 2003 and October 2020. See Appendix B for the databases searched and the search strategy.

A total of 4,824 records relevant to all sections of the toxicological profile were identified (after duplicate removal).

C.2.2 Literature Screening

As described in Appendix B, a two-step process was used to screen the literature search to identify relevant studies examining the health effects of HCH.

Title and Abstract Screen. In the Title and Abstract Screen step, 4,824 records were reviewed; 141 documents were considered to meet the health effects inclusion criteria in Table C-1 and were moved to the next step in the process.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of 258 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 258 documents, 369 studies were included in the qualitative review.

The epidemiological database for HCH is extensive. To facilitate the selection and inclusion of human studies of greater utility in assessing the hazards of HCH, only studies meeting the criteria below were included in the Toxicological Profile.

- Exposure was assessed for individuals, either using a biomarker or through detailed individual history (i.e., ecological study designs were excluded);
- The study presented an effect estimate specific to one or more HCH isomers;
- The statistical analysis of the association was multivariate, with consideration of at least one potential covariate. Studies limited to bivariate analyses (i.e., Pearson or Spearman correlation coefficients) were not included, nor were studies in which the analysis was limited to a comparison between blood concentrations in cases and controls;
- The health outcomes evaluated in the study were not mechanistic in nature (e.g., oxidative stress, genotoxicity);
- Case reports and case series were included if there was clear evidence of exposure to one or more HCH isomers.

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

Relevant data extracted from the individual studies selected for inclusion in the systematic review were collected in customized data forms. A summary of the type of data extracted from each study is presented in Table C-2. For references that included more than one experiment or species, data extraction records were created for each experiment or species.

Table C-2. Data Extracted From Individual Studies

Citation
Chemical form
Route of exposure (e.g., inhalation, oral, dermal)
Specific route (e.g., gavage in oil, drinking water)
Species
Strain
Exposure duration category (e.g., acute, intermediate, chronic)
Exposure duration
Frequency of exposure (e.g., 6 hours/day, 5 days/week)
Exposure length
Number of animals or subjects per sex per group
Dose/exposure levels
Parameters monitored
Description of the study design and method
Summary of calculations used to estimate doses (if applicable)
Summary of the study results
Reviewer's comments on the study
Outcome summary (one entry for each examined outcome)

Table C-2. Data Extracted From Individual Studies

No-observed-adverse-effect level (NOAEL) value
Lowest-observed-adverse-effect level (LOAEL) value
Effect observed at the LOAEL value

A summary of the extracted data for each study is presented in the Supplemental Documents for HCH isomers and overviews of the results of the inhalation, oral, and dermal exposure studies are presented in Sections 2.2–2.18 of the profile and in the Levels Significant Exposures tables in Section 2.1 of the profile (Tables 2-1 through 2-2).

There was only a single study of δ-HCH, and inadequate data for derivation of an MRL, so a systematic review of the data for this isomer was not undertaken.

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN—α-HCH

Overviews of the potential health effect outcomes for α-HCH identified in human and animal studies are presented in Tables C-3 and C-4, respectively. There was a small number of human studies examining a handful of endpoints; the largest number of studies was devoted to developmental endpoints. The human studies used measures of α-HCH in blood or tissues to assess exposure, so the route is unknown; for the purpose of enumerations, these studies are considered to reflect oral exposure (e.g., through contaminated food). There were no inhalation or dermal animal studies of α-HCH, and very few oral studies. The available animal studies primarily examined liver effects and cancer. The most sensitive effect in animal studies were hepatic. Studies examining hepatic effects were carried through to Steps 4–8 of the systematic review. There were eight studies (published in six documents) examining these potential outcomes carried through to Steps 4–8 of the systematic review. There were no human studies examining hepatic effects of α-HCH.

APPENDIX C

Table C-3. Overview of the Health Outcomes for α-Hexachlorocyclohexane Evaluated In Human Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Cancer
Inhalation studies																	
Cohort																	
Case control																	
Population																	
Case series																	
Oral studies																	
Cohort																	
Case control								2 1				1 1	1		3 3	1	1
Population								1			3 1			1 1	3 2		
Case series																	
Dermal studies																	
Cohort																	
Case control																	
Population																	
Case series																	

Number of studies examining endpoint	0	1	2	3	4	5-9	≥10
Number of studies reporting outcome	0	1	2	3	4	5-9	≥10

APPENDIX C

Table C-4. Overview of the Health Outcomes for α-Hexachlorocyclohexane Evaluated in Experimental Animal Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological[a]	Neurological[a]	Reproductive[a]	Developmental	Other Noncancer	Cancer
Inhalation studies																	
Acute-duration																	
Intermediate-duration																	
Chronic-duration																	
Oral studies																	
Acute-duration	1						4 2						1			1 1	
Intermediate-duration	5 4						14 13	1 1					1				7 7
Chronic-duration							2 2	1 1									1 1
Dermal studies																	
Acute-duration																	
Intermediate-duration																	
Chronic-duration																	

Number of studies examining endpoint	0	1	2	3	4	5-9	≥10
Number of studies reporting outcome	0	1	2	3	4	5-9	≥10

[a]Number of studies examining endpoint includes studies evaluating histopathology, but not evaluating function.

C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES—α-HCH

C.5.1 Risk of Bias Assessment—α-HCH

The risk of bias of individual studies was assessed using OHAT's Risk of Bias Tool (NTP 2015). The risk of bias questions for observational epidemiology studies, human-controlled exposure studies, and animal experimental studies are presented in Tables C-5, C-6, and C-7, respectively. Each risk of bias question was answered on a four-point scale:

- **Definitely low risk of bias (++)**
- **Probably low risk of bias (+)**
- **Probably high risk of bias (-)**
- **Definitely high risk of bias (– –)**

In general, "definitely low risk of bias" or "definitely high risk of bias" were used if the question could be answered with information explicitly stated in the study report. If the response to the question could be inferred, then "probably low risk of bias" or "probably high risk of bias" responses were typically used.

Table C-5. Risk of Bias Questionnaire for Observational Epidemiology Studies

Selection bias
Were the comparison groups appropriate?
Confounding bias
Did the study design or analysis account for important confounding and modifying variables?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table C-6. Risk of Bias Questionnaire for Human-Controlled Exposure Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were the research personnel and human subjects blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?

Table C-6. Risk of Bias Questionnaire for Human-Controlled Exposure Studies

Selective reporting bias
Were all measured outcomes reported?

Table C-7. Risk of Bias Questionnaire for Experimental Animal Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were experimental conditions identical across study groups?
Were the research personnel blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

After the risk of bias questionnaires were completed for the health effects studies, the studies were assigned to one of three risk of bias tiers based on the responses to the key questions listed below and the responses to the remaining questions.

- Is there confidence in the exposure characterization? (only relevant for observational studies)
- Is there confidence in the outcome assessment?
- Does the study design or analysis account for important confounding and modifying variables? (only relevant for observational studies)

First Tier. Studies placed in the first tier received ratings of "definitely low" or "probably low" risk of bias on the key questions **AND** received a rating of "definitely low" or "probably low" risk of bias on the responses to at least 50% of the other applicable questions.

Second Tier. A study was placed in the second tier if it did not meet the criteria for the first or third tiers.

Third Tier. Studies placed in the third tier received ratings of "definitely high" or "probably high" risk of bias for the key questions **AND** received a rating of "definitely high" or "probably high" risk of bias on the response to at least 50% of the other applicable questions.

The results of the risk of bias assessment for the α-HCH health effects studies (animal experimental studies) are presented in Table C-8. There were no observational epidemiology or human controlled experimental studies of α-HCH.

Table C-8. Summary of Risk of Bias Assessment for α-Hexachlorocyclohexane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings										
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias		
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	Risk of bias tier	
Outcome: Hepatic effects											
Oral intermediate exposure											
Sumida et al. 2007 (rat; 28 days)	–	–	+	+	–	+	+	++	NA	First	
Ito et al. 1973 (mouse; 24 weeks)	–	–	+	+	+	++	+	++	NA	First	
Ito et al. 1975 (rat; 24 or 48 weeks)	–	–	+	+	–	++	+	++	NA	First	
Nagasaki et al. 1975 (rat; 24 weeks)	–	–	+	+	–	–	+	++	NA	Second	
Nagasaki et al. 1975 (mouse; 24 weeks)	–	–	+	+	–	–	+	++	NA	Second	
Nagasaki et al. 1975 (hamster; 24 weeks)	–	–	+	+	–	–	+	++	NA	Second	
Tryphonas and Iverson 1983 (mouse; 50 weeks)	–	–	+	+	++	+	+	++	NA	First	

Table C-8. Summary of Risk of Bias Assessment for α-Hexachlorocyclohexane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings										Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias		
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?		
Oral chronic exposure											
Fitzhugh et al. 1950 (rat; 72 weeks)	–	–	+	+	++	+	+	++	NA		First

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable

*Key question used to assign risk of bias tier

C.6 RATE THE CONFIDENCE IN THE BODY OF EVIDENCE FOR EACH RELEVANT OUTCOME—α-HCH

Confidence in the body of human and animal evidence were evaluated independently for each potential outcome. ATSDR did not evaluate the confidence in the body of evidence for carcinogenicity; rather, the Agency defaulted to the cancer weight-of-evidence assessment of other agencies including HHS, EPA, and IARC. The confidence in the body of evidence for an association or no association between exposure to HCH and a particular outcome was based on the strengths and weaknesses of individual studies. Four descriptors were used to describe the confidence in the body of evidence for effects or when no effect was found:

- **High confidence:** the true effect is highly likely to be reflected in the apparent relationship
- **Moderate confidence:** the true effect may be reflected in the apparent relationship
- **Low confidence:** the true effect may be different from the apparent relationship
- **Very low confidence:** the true effect is highly likely to be different from the apparent relationship

Confidence in the body of evidence for a particular outcome was rated for each type of study: case-control, case series, cohort, population, human-controlled exposure, and experimental animal. In the absence of data to the contrary, data for a particular outcome were collapsed across animal species, routes of exposure, and exposure durations. If species (or strain), route, or exposure duration differences were noted, then the data were treated as separate outcomes.

In the case of α-HCH, the only available type of study was experimental animal.

C.6.1 Initial Confidence Rating—α-HCH

In ATSDR's modification to the OHAT approach, the body of evidence for an association (or no association) between exposure to α-HCH and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions, which were customized for epidemiology, human controlled exposure, or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies, human controlled exposure studies, and experimental animal studies are presented in Tables C-9, C-10, and C-11, respectively. The initial confidence in the study was determined based on the number of key features present in the study design:

- **High Initial Confidence:** Studies in which the responses to the four questions were "yes".
- **Moderate Initial Confidence:** Studies in which the responses to only three of the questions were "yes".
- **Low Initial Confidence:** Studies in which the responses to only two of the questions were "yes".
- **Very Low Initial Confidence:** Studies in which the response to one or none of the questions was "yes".

Table C-9. Key Features of Study Design for Observational Epidemiology Studies

Exposure was experimentally controlled
Exposure occurred prior to the outcome
Outcome was assessed on individual level rather than at the population level
A comparison group was used

Table C-10. Key Features of Study Design for Human Controlled Exposure Studies

A comparison group was used or the subjects served as their own control
A sufficient number of subjects were tested
Appropriate methods were used to measure outcomes (i.e., clinically-confirmed outcome versus self-reported)
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

Table C-11. Key Features of Study Design for Experimental Animal Studies

A concurrent control group was used
A sufficient number of animals per group were tested
Appropriate parameters were used to assess a potential adverse effect
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

The presence or absence of the key features and the initial confidence levels for studies of hepatic effects observed in the animal experimental studies are presented in Table C-12.

Table C-12. Presence of Key Features of Study Design for α-Hexachlorocyclohexane—Experimental Animal Studies

	Key feature				
Reference	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Outcome: Hepatic effects					
Oral intermediate exposure					
Sumida et al. 2007 (rat; 28 days)	Yes	No	Yes	Yes	Moderate
Ito et al. 1973 (mouse; 24 weeks)	Yes	Yes	Yes	Yes	High

Table C-12. Presence of Key Features of Study Design for α-Hexachlorocyclohexane—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Ito et al. 1975 (rat; 24 or 48 weeks)	Yes	Yes	Yes	No	Moderate
Nagasaki et al. 1975 (rat; 24 weeks)	Yes	No	Yes	No	Low
Nagasaki et al. 1975 (mouse; 24 weeks)	Yes	Yes	Yes	No	Moderate
Nagasaki et al. 1975 (hamster; 24 weeks)	Yes	No	Yes	No	Low
Tryphonas and Iverson 1983 (mouse; 50 weeks)	Yes	Yes	Yes	Yes	High
Oral chronic exposure					
Fitzhugh et al. 1950 (rat; 72 weeks)	Yes	No	Yes	Yes	Moderate

A summary of the initial confidence ratings for each outcome is presented in Table C-13. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence; any exceptions were noted in Table C-13.

Table C-13. Initial Confidence Rating for α-HCH Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Hepatic effects		
Oral intermediate exposure		
Animal studies		
Sumida et al. 2007 (rat; 28 days)	Moderate	High
Ito et al. 1973 (mouse; 24 weeks)	High	
Ito et al. 1975 (rat; 24 or 48 weeks)	Moderate	
Nagasaki et al. 1975 (rat; 24 weeks)	Low	
Nagasaki et al. 1975 (mouse; 24 weeks)	Moderate	
Nagasaki et al. 1975 (hamster; 24 weeks)	Low	
Tryphonas and Iverson 1983 (mouse; 50 weeks)	High	
Oral chronic exposure		
Animal studies		
Fitzhugh et al. 1950	Moderate	Moderate

C.6.2 Adjustment of the Confidence Rating—α-HCH

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for hepatic effects are presented in Table C-14. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with α-HCH exposure is presented in Table C-15.

Five properties of the body of evidence were considered to determine whether the confidence rating should be downgraded:

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
    - No downgrade if most studies are in the risk of bias first tier
    - Downgrade one confidence level if most studies are in the risk of bias second tier
    - Downgrade two confidence levels if most studies are in the risk of bias third tier

- **Unexplained inconsistency.** Evaluation of whether there is inconsistency or large variability in the magnitude or direction of estimates of effect across studies that cannot be explained. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for unexplained inconsistency:
    - No downgrade if there is little inconsistency across studies or if only one study evaluated the outcome
    - Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect
    - Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direct of the effect

- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
    - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans
    - Directness of the endpoints to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects
    - Nature of the exposure in human studies and route of administration in animal studies—inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
    - Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

  Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for indirectness:
    - No downgrade if none of the factors are considered indirect
    - Downgrade one confidence level if one of the factors is considered indirect
    - Downgrade two confidence levels if two or more of the factors are considered indirect

- **Imprecision.** Evaluation of the narrowness of the effect size estimates and whether the studies have adequate statistical power. Data are considered imprecise when the ratio of the upper to lower 95% CIs for most studies is ≥10 for tests of ratio measures (e.g., odds ratios) and ≥100 for absolute measures (e.g., percent control response). Adequate statistical power is determined if the study can detect a potentially biologically meaningful difference between groups (20% change from control response for categorical data or risk ratio of 1.5 for continuous data). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for imprecision:
    - No downgrade if there are no serious imprecisions
    - Downgrade one confidence level for serious imprecisions
    - Downgrade two confidence levels for very serious imprecisions

- **Publication bias.** Evaluation of the concern that studies with statistically significant results are more likely to be published than studies without statistically significant results.
    - Downgrade one level of confidence for cases where there is serious concern with publication bias

Four properties of the body of evidence were considered to determine whether the confidence rating should be upgraded:

- **Large magnitude of effect.** Evaluation of whether the magnitude of effect is sufficiently large so that it is unlikely to have occurred as a result of bias from potential confounding factors.
    - Upgrade one confidence level if there is evidence of a large magnitude of effect in a few studies, provided that the studies have an overall low risk of bias and there is no serious unexplained inconsistency among the studies of similar dose or exposure levels; confidence can also be upgraded if there is one study examining the outcome, provided that the study has an overall low risk of bias

- **Dose response.** Evaluation of the dose-response relationships measured within a study and across studies. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
    - Upgrade one confidence level for evidence of a monotonic dose-response gradient
    - Upgrade one confidence level for evidence of a non-monotonic dose-response gradient where there is prior knowledge that supports a non-monotonic dose-response and a non-monotonic dose-response gradient is observed across studies

- **Plausible confounding or other residual biases.** This factor primarily applies to human studies and is an evaluation of unmeasured determinants of an outcome such as residual bias towards the null (e.g., "healthy worker" effect) or residual bias suggesting a spurious effect (e.g., recall bias). Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
    - Upgrade one confidence level for evidence that residual confounding or bias would underestimate an apparent association or treatment effect (i.e., bias toward the null) or suggest a spurious effect when results suggest no effect

- **Consistency in the body of evidence.** Evaluation of consistency across animal models and species, consistency across independent studies of different human populations and exposure scenarios, and consistency across human study types. Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:

- Upgrade one confidence level if there is a high degree of consistency in the database

Table C-14. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Hepatic effects:			
Human studies	NA	NA	NA
Animal studies	High	+1 consistency, +1 magnitude	High

Table C-15. Confidence in the Body of Evidence for α-Hexachlorocyclohexane

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Hepatic	NA	High

C.7 TRANSLATE CONFIDENCE RATING INTO LEVEL OF EVIDENCE OF HEALTH EFFECTS—α-HCH

In the seventh step of the systematic review of the health effects data for HCH, the confidence in the body of evidence for specific outcomes was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted. The level of evidence for health effects was rated on a five-point scale:

- **High level of evidence:** High confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Moderate level of evidence:** Moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Low level of evidence:** Low confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Evidence of no health effect:** High confidence in the body of evidence that exposure to the substance is not associated with the health outcome
- **Inadequate evidence:** Low or moderate confidence in the body of evidence that exposure to the substance is not associated with the health outcome OR very low confidence in the body of evidence for an association between exposure to the substance and the health outcome

A summary of the level of evidence of health effects for HCH is presented in Table C-16.

Table C-16. Level of Evidence of Health Effects for α-Hexachlorocyclohexane

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies		NA	
Animal studies			
Hepatic	High	Health Effect	High

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS—α-HCH

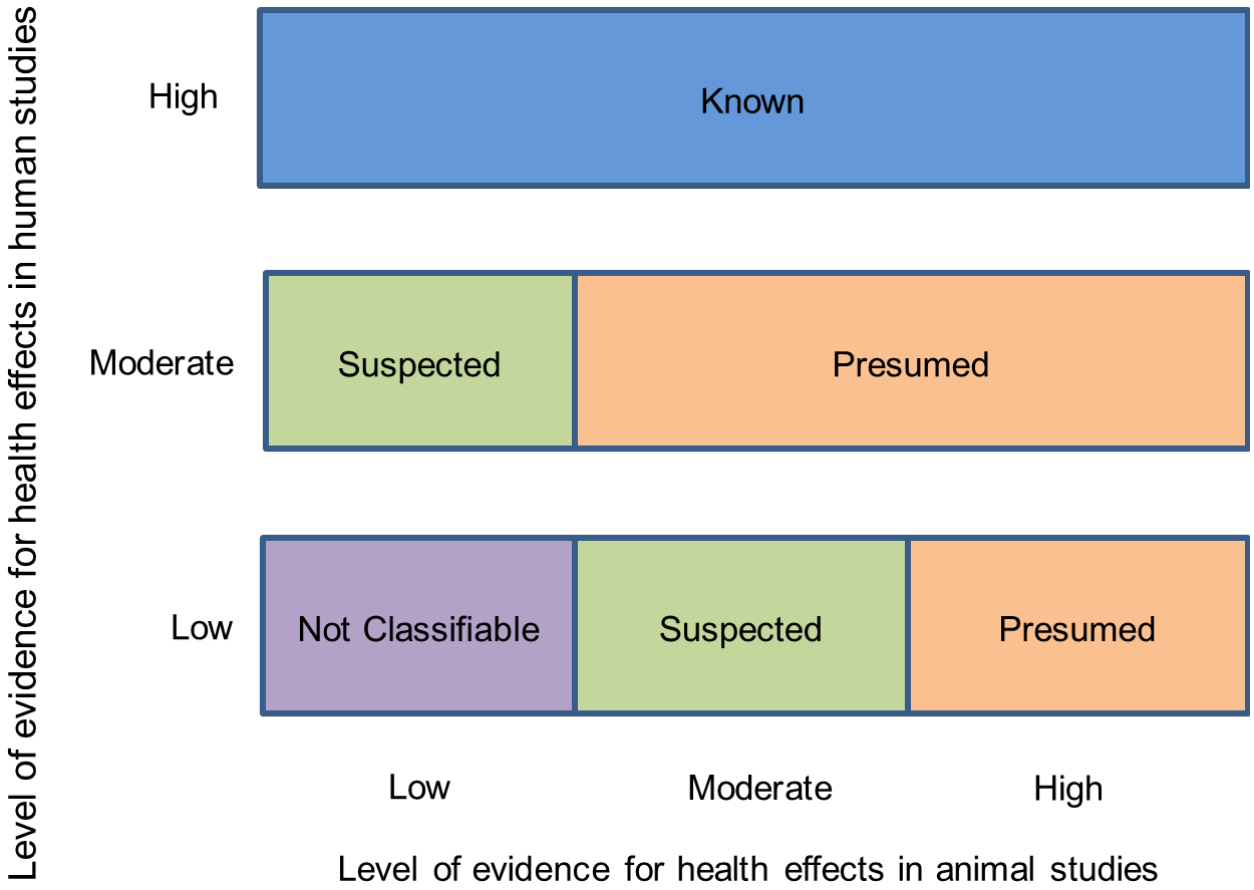
The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

The initial hazard identification was based on the highest level of evidence in the human studies and the level of evidence in the animal studies; if there were no data for one evidence stream (human or animal), then the hazard identification was based on the one data stream (equivalent to treating the missing evidence stream as having low level of evidence). The hazard identification scheme is presented in Figure C-1 and described below:

- **Known:** A health effect in this category would have:
  - High level of evidence for health effects in human studies **AND** a high, moderate, or low level of evidence in animal studies.
- **Presumed:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** high or moderate level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** high level of evidence in animal studies
- **Suspected:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** low level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** moderate level of evidence in animal studies
- **Not classifiable:** A health effect in this category would have:
  - Low level of evidence in human studies **AND** low level of evidence in animal studies

Figure C-1. Hazard Identification Scheme



Other relevant data such as mechanistic or mode-of-action data were considered to raise or lower the level of the hazard identification conclusion by providing information that supported or opposed biological plausibility.

Two hazard identification conclusion categories were used when the data indicated that there may be no health effect in humans:

- **Not identified** to be a hazard in humans
- **Inadequate** to determine hazard to humans

If the human level of evidence conclusion of no health effect was supported by the animal evidence of no health effect, then the hazard identification conclusion category of "not identified" was used. If the human or animal level of evidence was considered inadequate, then a hazard identification conclusion category of "inadequate" was used. As with the hazard identification for health effects, the impact of other relevant data was also considered for no health effect data.

The hazard identification conclusions for α-HCH are listed below and summarized in Table C-17.

Presumed Health Effects

- Hepatic
  - No information on hepatic effects in humans exposed to α-HCH.
  - High evidence level in animals including increased liver weight and histopathological lesions after oral exposure to α-HCH (Fitzhugh et al. 1950; Ito et al. 1973, 1975; Nagasaki et al. 1975; Sumida et al. 2007; Tryphonas and Iverson 1983).
  - Plausible mechanism based on increased oxidative stress markers in livers of animals exposed to low oral doses *in vivo* (Barros et al. 1991).

Table C-17. Hazard Identification Conclusions for α-Hexachlorocyclohexane

Outcome	Hazard identification
Hepatic effects	Presumed health effect

C.9 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN—β-HCH

Overviews of the potential health effect outcomes for β-HCH identified in human and animal studies are presented in Tables C-18 and C-19, respectively. Human studies examined a wide range of outcomes, with more studies of endocrine (thyroid hormone levels) developmental outcomes, other noncancer endpoints (diabetes and metabolic perturbations) and cancer than other outcomes. The human studies used measures of β-HCH in blood or tissues to assess exposure, so the route is unknown; for the purpose of enumerations, these studies are considered to reflect oral exposure (e.g., through contaminated food). Animal studies are limited to oral exposures, and the endpoints examined were limited. The animal data show that the liver and nervous system are sensitive effects of exposure to β-HCH; studies examining these potential outcomes were carried through to Steps 4–8 of the systematic review. There were 15 studies (published in 15 documents) examining these potential outcomes carried through to Steps 4–8 of the systematic review.

APPENDIX C

Table C-18. Overview of the Health Outcomes for β-Hexachlorocyclohexane Evaluated In Human Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Cancer
Inhalation studies																	
Cohort																	
Case control																	
Population																	
Case series																	
Oral studies																	
Cohort	1		1										1	1	2	2	3
	1		1											1	1		1
Case control								2			1	1	3	2	5	4	23
											1	1	3	2	1	4	7
Population	1		3				2	1			7	1	2	2	13	8	1
	1		1				1				5	1	1	2	8	4	1
Case series																	
Dermal studies																	
Cohort																	
Case control																	
Population																	
Case series																	

Number of studies examining endpoint	0	1	2	3	4	5-9	≥10
Number of studies reporting outcome	0	1	2	3	4	5-9	≥10

Table C-19. Overview of the Health Outcomes for β-Hexachlorocyclohexane Evaluated in Experimental Animal Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological[a]	Neurological[a]	Reproductive[a]	Developmental	Other Noncancer	Cancer
Inhalation studies																	
Acute-duration																	
Intermediate-duration																	
Chronic-duration																	
Oral studies																	
Acute-duration							1	1					2				1
								1					2				
Intermediate-duration	4				1		5	1			1	2	2	2	2		1
	2				1		5	1			1	2	2	2	2		
Chronic-duration							1	1									1
							1	1									1
Dermal studies																	
Acute-duration																	
Intermediate-duration																	
Chronic-duration																	

Number of studies examining endpoint	0	1	2	3	4	5-9	≥10
Number of studies reporting outcome	0	1	2	3	4	5-9	≥10

[a]Number of studies examining endpoint includes study evaluating histopathology, but not evaluating function.

C.10 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES—β-HCH

C.10.1 Risk of Bias Assessment—β-HCH

The risk of bias of individual studies was assessed using OHAT's Risk of Bias Tool (NTP 2015). The risk of bias questions for observational epidemiology studies, human-controlled exposure studies, and animal experimental studies were presented above in Tables C-5, C-6, and C-7, respectively. As described in Section C.5.1, each risk of bias question was answered on a four-point scale and studies were assigned to one of three risk of bias tiers.

The results of the risk of bias assessment for the different types of β-HCH health effects studies (observational epidemiology and animal experimental studies) are presented in Tables C-20 and C-21, respectively.

Table C-20. Summary of Risk of Bias Assessment for β-Hexachlorocyclohexane—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings: Selection bias — Comparison groups appropriate?	Confounding bias — **Study design or analysis account for important confounding and modifying variables?***	Attrition / exclusion bias — Outcome data complete without attrition or exclusion from analysis?	Detection bias — **Confidence in the exposure characterization?***	Detection bias — **Confidence in the outcome assessment?***	Selective reporting bias — All measured outcomes reported?	Risk of bias tier
Outcome: Neurological effects							
Cohort							
Medehouenou et al. 2019	++	++	+	++	++	++	First
Case-control							
Petersen et al. 2008	+	–	++	++	+	++	Second
Richardson et al. 2009, 2011	–	+	++	++	++	++	First
Singh et al. 2012, 2013, 2014	+	+	++	++	++	++	First
Cross-sectional							
Kim et al. 2015	++	++	+	++	++	++	First
Steenland et al. 2014	–	+	+	++	++	++	First
Outcome: Hepatic effects							
Cross-sectional							
Arrebola et al. 2014	++	++	–	++	++	++	First
Freire et al. 2015	++	++	–	++	++	++	First

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; NA = not applicable

*Key question used to assign risk of bias tier

Table C-21. Summary of Risk of Bias Assessment for β-Hexachlorocyclohexane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	
Outcome: Hepatic effects										
Oral intermediate exposure										
Van Velsen et al. 1986 (rat; 13 weeks)	–	–	+	+	++	++	+	++	NA	First
Hanada et al. 1973 (mouse; 32 weeks)	–	–	+	+	+	–	+	++	NA	First
Ito et al. 1973 (mouse; 24 weeks)	–	–	+	+	+	++	+	++	NA	First
Ito et al. 1975 (rat; 24–48 weeks)	–	–	+	+	–	++	+	++	NA	First
Oral chronic exposure										
Fitzhugh et al. 1950 (rat; 107 weeks)	–	–	+	+	++	+	+	++	NA	First
Outcome: Neurological effects										
Oral acute exposure										
Van Velsen et al. 1986 (rat; 2 weeks)	–	–	+	+	++	++	+	++	NA	First
Cornacoff et al. 1988 (mouse; 1 week)	–	–	+	+	–	++	+	++	NA	First

Table C-21. Summary of Risk of Bias Assessment for β-Hexachlorocyclohexane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	
Oral intermediate exposure										
Muller et al. 1981 (rat; 30 days)	–	–	+	+	–	–	+	++	NA	Second

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; NA = not applicable

*Key question used to assign risk of bias tier

C.11 RATE THE CONFIDENCE IN THE BODY OF EVIDENCE FOR EACH RELEVANT OUTCOME—β-HCH

As discussed in greater detail in Section C.6, confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome for each type of study: case-control, case series, cohort, population, human-controlled exposure, and experimental animal. In the absence of data to the contrary, data for a particular outcome were collapsed across animal species, routes of exposure, and exposure durations. If species (or strain), route, or exposure duration differences were noted, then the data were treated as separate outcomes.

C.11.1 Initial Confidence Rating—β-HCH

As discussed in greater detail in Section C.6.1, the body of evidence for an association (or no association) between exposure to β-HCH and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. Refer to Tables C-9, C-10, and C-11, respectively, for the key features for observational epidemiology (cohort, population, and case-control) studies, human controlled exposure studies, and experimental animal studies.

The presence or absence of the key features and the initial confidence levels for studies examining neurological and hepatic effects observed in the observational epidemiology and animal experimental studies are presented in Tables C-22 and C-23, respectively.

Table C-22. Presence of Key Features of Study Design for β-Hexachlorocyclohexane—Observational Epidemiology Studies

Reference	Key features				Initial study confidence
	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	
Outcome: Neurological effects					
Cohort					
Medehouenou et al. 2019	No	Yes	Yes	Yes	Moderate
Case-control					
Petersen et al. 2008	No	No	Yes	Yes	Low
Richardson et al. 2009, 2011	No	No	Yes	Yes	Low
Singh et al. 2012, 2013, 2014	No	No	Yes	Yes	Low
Cross-sectional					
Kim et al. 2015	No	No	Yes	Yes	Low
Steenland et al. 2014	No	No	Yes	Yes	Low
Outcome: Hepatic effects					
Cross-sectional					
Arrebola et al. 2014	No	No	Yes	Yes	Low
Freire et al. 2015	No	No	Yes	Yes	Low

Table C-23. Presence of Key Features of Study Design for β-Hexachlorocyclohexane—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Outcome: Hepatic effects					
Oral intermediate exposure					
Van Velsen et al. 1986 (rat; 13 weeks)	Yes	Yes	Yes	Yes	High
Hanada et al. 1973 (mouse; 32 weeks)	Yes	Yes	Yes	No	Moderate
Ito et al. 1973 (mouse; 24 weeks)	Yes	Yes	Yes	Yes	High
Ito et al. 1975 (rat; 48 weeks)	Yes	Yes	Yes	No	Moderate
Oral chronic exposure					
Fitzhugh et al. 1950 (rat; 107 weeks)	Yes	No	Yes	Yes	Moderate
Outcome: Neurological effects					
Oral acute exposure					
Van Velsen et al. 1986 (rat; 2 weeks)	Yes	Yes	Yes	No	Moderate
Cornacoff et al. 1988 (mouse; 1 week)	Yes	Yes	Yes	No	Moderate
Oral intermediate exposure					
Muller et al. 1981 (rat; 30 days)	Yes	Yes	Yes	Yes	High

A summary of the initial confidence ratings for each outcome is presented in Table C-24. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence; any exceptions were noted in Table C-24.

Table C-24. Initial Confidence Rating for β-Hexachlorocyclohexane Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Neurological effects		
Oral acute exposure		
Animal studies		
Van Velsen et al. 1986	Moderate	Moderate
Cornacoff et al. 1988	Moderate	
Oral intermediate exposure		
Animal studies		
Muller et al. 1981	High	High

Table C-24. Initial Confidence Rating for β-Hexachlorocyclohexane Health Effects Studies

	Initial study confidence	Initial confidence rating
Oral chronic exposure		
Human studies		
Medehouenou et al. 2019	Moderate	Moderate
Singh et al. 2012, 2013, 2014	Low	
Petersen et al. 2008	Low	
Richardson et al. 2009, 2011	Low	
Kim et al. 2015	Low	
Steenland et al. 2014	Low	
Outcome: Hepatic effects		
Oral intermediate exposure		
Animal studies		
Van Velsen et al. 1986 (rat; 13 weeks)	High	High
Hanada et al. 1973 (mouse; 32 weeks)	Moderate	
Ito et al. 1973 (mouse; 24 weeks)	High	
Ito et al. 1975 (rat; 48 weeks)	Moderate	
Oral chronic exposure		
Human studies		
Arrebola et al. 2014	Low	Low
Freire et al. 2015	Low	
Animal studies		
Fitzhugh et al. 1950	Moderate	Moderate

C.11.2 Adjustment of the Confidence Rating—β-HCH

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The five properties of the body of evidence that were considered to determine whether the confidence rating should be downgraded and the four properties of the body of evidence that were considered to determine whether the confidence rating should be upgraded are described above in Section C.6.2. The summaries of the assessment of the confidence in the body of evidence for neurological and hepatic effects are presented in Table C-25. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with β-HCH exposure is presented in Table C-26.

Table C-25. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Neurological effects			
Human studies	Moderate	+1 consistency, -1 indirectness	Moderate
Animal studies	High	-1 indirectness, +1 dose-response, +1 consistency	High
Hepatic effects			
Human studies	Low	-1 indirectness	Very low
Animal studies	High	+1 dose-response, +1 consistency	High

Table C-26. Confidence in the Body of Evidence for β-Hexachlorocyclohexane

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Neurological	Moderate	High
Hepatic	Very Low	High

C.12 TRANSLATE CONFIDENCE RATING INTO LEVEL OF EVIDENCE OF HEALTH EFFECTS—β-HCH

As described in Section C.7, the confidence in the body of evidence for specific outcomes was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted.

A summary of the level of evidence of health effects for β-HCH is presented in Table C-27.

Table C-27. Level of Evidence of Health Effects for β-Hexachlorocyclohexane

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Neurological	Moderate	Health effect	Moderate
Hepatic	Very Low	No health effect	Inadequate
Animal studies			
Neurological	High	Health effect	High
Hepatic	High	Health effect	High

C.13 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS– β-HCH

The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. Refer to Section C.8 for the four hazard identification conclusion categories for health effects, the hazard characterization scheme (see Figure C-1), and the hazard identification conclusion categories.

The hazard identification conclusions for β-HCH are listed below and summarized in Table C-28.

Presumed Health Effects

- Neurological
  - Moderate level of evidence in humans based on case-control studies reporting associations between serum β-HCH and risk of Parkinson and Alzheimer diseases (Petersen et al. 2008; Richardson et al. 2009, 2011; Singh et al. 2012, 2013, 2014) and a cross-sectional study showing an association between risk of cognitive deficits and β-HCH in blood (Kim et al. 2015).
  - High level of evidence in animals exposed orally based on clinical signs of neurotoxicity in rats and mice after acute durations (Cornacoff et al. 1988; Van Velsen et al. 1986) and reduced nerve conduction velocity in rats exposed for an intermediate duration (Muller et al. 1981). Clinical signs showed dose-related increase in severity.
  - Supported by evidence for neurological effects of γ-HCH in humans and animals (see Section 2.15).
- Hepatic
  - Very low level of evidence in humans based on two cross-sectional studies reporting no association between serum or adipose levels of β-HCH and hepatic clinical chemistry endpoints except for increased serum bilirubin in females (Arrebola et al. 2014; Freire et al. 2015).
  - High level of evidence in animals based on liver weight and histopathology changes in rats and mice exposed by dietary administration for intermediate and chronic durations (Fitzhugh et al. 1950; Hanada et al. 1973; Ito et al. 1973, 1975; Van Velsen et al. 1986).

Table C-28. Hazard Identification Conclusions for – β-HCHs

Outcome	Hazard identification
Neurological	Presumed health effect
Hepatic	Presumed health effect

C.14 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN—γ-HCH

Overviews of the potential health effect outcomes for γ-HCH identified in human and animal studies are presented in Tables C-29 and C-30, respectively. Most of the human studies evaluated developmental, reproductive, renal, endocrine, or cancer endpoints. Most of human studies of noncancer endpoints used measures of γ-HCH in blood or tissues to assess exposure, so the route is unknown; for the purpose of enumerations, these studies are considered to reflect oral exposure (e.g., through contaminated food). Studies of occupational exposure via pesticide application are considered to reflect primarily inhalation exposure. Most of the animal studies used oral administration, and the available studies examined comprehensive noncancer and cancer endpoints. The effects seen at the lowest doses in the animal studies were developmental and immune system effects. Studies examining these potential outcomes

were carried through to Steps 4–8 of the systematic review. There were 41 studies (published in 35 documents) examining these potential outcomes carried through to Steps 4–8 of the systematic review.

APPENDIX C

Table C-29. Overview of the Health Outcomes for γ-Hexachlorocyclohexane Evaluated In Human Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Caner
Inhalation studies																	
Cohort											1						1
											1						1
Case control																	
Population																	
Case series																	
Oral studies																	
Cohort								1				1	1	1	1		2
								0				0	1	1	0		1
Case control								2				1	1	1	4	1	16
								1				1	0	0	4	0	5
Population								1			3			2	2		
								0			1			1	1		
Case series																	
Dermal studies																	
Cohort																	
Case control																	
Population																	
Case series																	

Number of studies examining endpoint	0	1	2	3	4	5-9	≥10
Number of studies reporting outcome	0	1	2	3	4	5-9	≥10

APPENDIX C

Table C-30. Overview of the Health Outcomes for γ-Hexachlorocyclohexane Evaluated in Experimental Animal Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological[a]	Neurological[a]	Reproductive[a]	Developmental	Other Noncancer	Caner
Inhalation studies																	
Acute-duration	1			1									4		1		
	1			1									4		1		
Intermediate-duration	2	2	2	2	2		2	2		1	2		1	2	2	2	2
	0	0	0	1	1		0	0		0	0		0	0	0	0	0
Chronic-duration																	
Oral studies																	
Acute-duration	13				2		14	2			1	4	23	10	22		
	1				2		8	1			0	4	17	4	19		
Intermediate-duration	18	2	3		3	1	26	14			3	8	17	18	14	2	2
	4	1	2		0	1	22	12			2	7	16	14	9	2	1
Chronic-duration	6	1			2		5	2		1	1		2	1			6
	0	0			0		3	1		0	0		1	1			4
Dermal studies																	
Acute-duration	2	1							1	1			2				
	0	1							0	1			2				
Intermediate-duration	1	1					1	1	2				1				
	0	1					1	1	1				1				
Chronic-duration																	

Number of studies examining endpoint	0	1	2	3	4	5-9	≥10
Number of studies reporting outcome	0	1	2	3	4	5-9	≥10

[a]Number of studies examining endpoint includes study evaluating histopathology, but not evaluating function.

C.15 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES—γ-HCH

C.15.1 Risk of Bias Assessment—γ-HCH

The risk of bias of individual studies was assessed using OHAT's Risk of Bias Tool (NTP 2015). The risk of bias questions for observational epidemiology studies, human-controlled exposure studies, and animal experimental studies were presented above in Tables C-5, C-6, and C-7, respectively. As described in Section C.5.1, each risk of bias question was answered on a four-point scale and studies were assigned to one of three risk of bias tiers.

The results of the risk of bias assessment for the different types of γ-HCH health effects studies (observational epidemiology and animal experimental studies) are presented in Tables C-31 and C-32, respectively.

Table C-31. Summary of Risk of Bias Assessment for γ-Hexachlorocyclohexane—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings: Selection bias — Comparison groups appropriate?	Confounding bias — **Study design or analysis account for important confounding and modifying variables?***	Attrition / exclusion bias — Outcome data complete without attrition or exclusion from analysis?	Detection bias — **Confidence in the exposure characterization?***	Detection bias — **Confidence in the outcome assessment?***	Selective reporting bias — All measured outcomes reported?	Risk of bias tier
Outcome: Developmental effects							
Cohort							
Fenster et al. 2006	++	+	–	+	++	++	First
Case-control							
Fernandez et al. 2007	++	++	+	++	++	++	First
Mustafa et al. 2013	+	+	+	++	+	++	First
Sharma et al. 2012	+	+	+	++	++	++	First
Siddiqui et al. 2003	+	+	+	++	+	++	First
Cross-sectional							
Fang et al. 2019a, 2019b	++	+	++	++	+	++	First
Freire et al. 2011	++	+	–	++	–	++	Second
Outcome: Immunological effects							
Cohort							
Landgren et al. 2009	++	++	++	+	++	++	First
Case-control							
Meng et al. 2016	+	–	++	+	++	++	Second

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; NA = not applicable

*Key question used to assign risk of bias tier

Table C-32. Summary of Risk of Bias Assessment for γ-Hexachlorocyclohexane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Outcome: Developmental effects										
Oral acute exposure										
Dalsenter et al. 1997a (rat; once)	–	–	+	+	++	–	+	++	NA	First
Dalsenter et al. 1997b (rat; once)	–	–	+	+	–	+	+	++	NA	First
Dalsenter et al. 1997b (rat; LDs 8–14)	–	–	+	+	–	+	+	++	NA	First
Johri et al. 2008 (rat; once)	–	–	+	+	–	–	+	++	NA	Second
Khera et al. 1979 (rat; GDs 6–15)	–	–	+	+	+	+	+	++	NA	First
Palmer et al. 1978 (rat; GDs 6–15)	+	+	+	+	+	–	+	++	NA	First
Rivera et al. 1991 (rat; once)	+	+	+	+	–	+	+	++	NA	First
Rivera et al. 1998 (rat; once)	+	+	+	+	–	–	+	++	NA	First
Rivera et al. 1998 (rat; PNDs 8–14)	–	–	+	+	–	–	–	++	NA	Third
Serrano et al. 1990 (rat; PNDs 8–10)	+	+	+	+	–	–	+	++	NA	First
Di Consiglio et al. 2009 (mouse; GDs 9–16)	+	+	+	+	+	–	+	++	NA	First

Table C-32. Summary of Risk of Bias Assessment for γ-Hexachlorocyclohexane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Hassoun and Stohs 1996a (mouse, once)	–	–	+	+	++	–	+	++	NA	First
La Sala et al. 2009 (mouse; 3 days)	+	+	+	+	–	–	+	++	NA	First
Maranghi et al. 2007 (mouse, GDs 91–6)	+	+	+	+	++	–	+	++	NA	First
Traina et al. 2003 (mouse; GDs 9–16)	+	+	+	+	++	–	+	++	NA	First
Palmer et al. 1978 (rabbit; GDs 6–18)	+	+	+	+	+	–	+	++	NA	First
Oral intermediate exposure										
Breton et al. 2005 (rat; ~21 weeks (2-generation, premating–PND 98)	–	–	+	+	–	–	+	++	NA	First
EPA 1991a (rat; 2-generation, 70 days prior to mating until sacrifice)	+	+	+	+	+	+	++	++	NA	First
EPA 1999c (rat; GD 6–LD 10)	–	–	+	+	++	++	+	++	NA	First
Johri et al. 2007 (rat; GDs 5-21)	+	+	+	+	–	–	+	++	NA	First

Table C-32. Summary of Risk of Bias Assessment for γ-Hexachlorocyclohexane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias — Administered dose or exposure level adequately randomized?	Selection bias — Allocation to study groups adequately concealed?	Performance bias — Experimental conditions identical across study groups?	Performance bias — Research personnel blinded to the study group during the study?	Attrition/ exclusion bias — Outcome data complete without attrition or exclusion from analysis?	Detection bias — Confidence in the exposure characterization?	Detection bias — **Confidence in the outcome assessment?***	Selective reporting bias — All measured outcomes reported?	Other bias — Study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Johri et al. 2008 (rat; GDs 5–21 and PND 45)	+	+	+	+	–	–	+	++	NA	First
Matsuura et al. 2005 (rat; ~10 weeks (2-generation; premating–PND 21))	++	+	+	+	+	++	+	++	NA	First
Sauviat et al. 2005 (rat; ~13 weeks)	–	–	+	+	–	–	+	++	NA	Second
Srinivasan et al. 1991 (rat; GDs 0–21, LDs 1–28)	–	–	+	+	+	–	+	++	NA	First
Srivastava et al. 2019 (rat, GDs 5–21)	–	–	+	+	–	–	–	++	NA	Third
Seiler et al. 1994 (rabbit; 12–15 weeks, 3 days/week)	–	–	+	+	–	+	+	++	NA	First
Outcome: Immunological effects										
Oral acute exposure										
Mediratta et al. 2008 (rat; 14 days)	+	+	+	+	++	–	+	++	NA	First
Hong and Boorman 1993 (mouse; 10 days)	+	+	+	+	–	–	+	++	NA	First
Hong and Boorman 1993 (mouse; 3 days)	+	+	+	+	–	–	+	++	NA	First

Table C-32. Summary of Risk of Bias Assessment for γ-Hexachlorocyclohexane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Oral intermediate exposure										
Koner et al. 1998 (rat; 8 weeks)	+	+	+	+	–	++	+	++	NA	First
Mediratta et al. 2008 (rat; 21 days)	+	+	+	+	++	–	+	++	NA	First
Meera et al. 1992 (mouse; 24 weeks)	–	–	+	+	–	+	+	++	NA	First

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; NA = not applicable

*Key question used to assign risk of bias tier

C.16 RATE THE CONFIDENCE IN THE BODY OF EVIDENCE FOR EACH RELEVANT OUTCOME—γ-HCH

As discussed in greater detail in Section C.6, confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome for each type of study: case-control, case series, cohort, population, human-controlled exposure, and experimental animal. In the absence of data to the contrary, data for a particular outcome were collapsed across animal species, routes of exposure, and exposure durations. If species (or strain), route, or exposure duration differences were noted, then the data were treated as separate outcomes.

C.16.1 Initial Confidence Rating—γ-HCH

As discussed in greater detail in Section C.6.1, the body of evidence for an association (or no association) between exposure to γ-HCH and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. Refer to Tables C-9, C-10, and C-11, respectively, for the key features for observational epidemiology (cohort, population, and case-control) studies, human controlled exposure studies, and experimental animal studies.

The presence or absence of the key features and the initial confidence levels for studies examining developmental and immune system effects in the observational epidemiology and animal experimental studies are presented in Tables C-33 and C-34, respectively.

Table C-33. Presence of Key Features of Study Design for γ-Hexachlorocyclohexane—Observational Epidemiology Studies

Reference	Key features				Initial study confidence
	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	
Outcome: Developmental effects					
Cohort					
Fenster et al. 2006	No	Yes	Yes	Yes	Moderate
Case-control					
Fernandez et al. 2007	No	No	Yes	Yes	Low
Mustafa et al. 2013	No	No	Yes	Yes	Low
Sharma et al. 2012	No	No	Yes	Yes	Low
Siddiqui et al. 2003	No	No	Yes	Yes	Low
Cross-sectional					
Fang et al. 2019a, 2019b	No	No	Yes	Yes	Low
Outcome: Immunological effects					
Cohort					
Landgren et al. 2009	No	Yes	Yes	Yes	Moderate
Case-control					
Meng et al. 2016	No	No	Yes	Yes	Low

Table C-34. Presence of Key Features of Study Design for γ-Hexachlorocyclohexane—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Outcome: Developmental effects					
Oral acute exposure					
Dalsenter et al. 1997a (rat; once)	Yes	Yes	Yes	Yes	High
Dalsenter et al. 1997b (rat; once)	Yes	Yes	Yes	Yes	High
Dalsenter et al. 1997b (rat; LDs 8–14)	Yes	Yes	Yes	Yes	High
Johri et al. 2008 (rat; once)	Yes	Yes	Yes	Yes	High
Khera et al. 1979 (rat; GDs 6–15)	Yes	Yes	Yes	Yes	High
Palmer et al. 1978 (rat; GDs 6–15)	Yes	Yes	Yes	Yes	High
Rivera et al. 1991 (rat; once)	Yes	No	Yes	Yes	Moderate
Rivera et al. 1998 (rat; once)	Yes	No	Yes	Yes	Moderate
Rivera et al. 1998 (rat; PNDs 8–14)	Yes	No	Yes	Yes	Moderate
Serrano et al. 1990 (rat; PNDs 8–10)	Yes	Yes	Yes	No	Moderate
Di Consiglio et al. 2009 (mouse; GDs 9–16)	Yes	No	Yes	Yes	Moderate
Hassoun and Stohs 1996a (mouse, once)	Yes	Yes	Yes	Yes	High
La Sala et al. 2009 (mouse; 3 days)	Yes	No	Yes	Yes	Moderate
Maranghi et al. 2007 (mouse, GDs 91–6)	Yes	Yes	Yes	Yes	High
Traina et al. 2003 (mouse; GDs 9–16)	Yes	Yes	Yes	Yes	High
Palmer et al. 1978 (rabbit; GDs 6–18)	Yes	Yes	Yes	Yes	High
Oral intermediate exposure					
Breton et al. 2005 (rat; ~21 weeks, 2-generation, premating–PND 98)	Yes	No	Yes	Yes	Moderate
EPA 1991a (rat; 2-generation, 70 days prior to mating until sacrifice)	Yes	Yes	Yes	Yes	High
EPA 1999c (rat; GD 6–LD 10)	Yes	Yes	Yes	Yes	High
Johri et al. 2007 (rat; GDs 5–21)	Yes	Yes	Yes	Yes	High
Johri et al. 2008 (rat; GDs 5–21 and PND 45)	Yes	Yes	Yes	Yes	High
Matsuura et al. 2005 (rat; ~10 weeks, 2-generation; premating–PND 21)	Yes	Yes	Yes	Yes	High
Sauviat et al. 2005 (rat; ~13 weeks)	Yes	No	Yes	Yes	Moderate
Srinivasan et al. 1991 (rat; GDs 0–21, LDs 1–28)	Yes	No	Yes	Yes	Moderate
Srivastava et al. 2019 (rat, GDs 5–21)	Yes	Yes	Yes	Yes	High
Seiler et al. 1994 (rabbit; 12–15 weeks, 3 days/week)	Yes	No	Yes	Yes	Moderate

Table C-34. Presence of Key Features of Study Design for γ-Hexachlorocyclohexane—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Outcome: Immunological effects					
Oral acute exposure					
Mediratta et al. 2008 (rat; 14 days)	Yes	Yes	Yes	Yes	High
Hong and Boorman 1993 (mouse; 10 days)	Yes	Yes	Yes	Yes	High
Hong and Boorman 1993 (mouse; 3 days)	Yes	Yes	Yes	Yes	High
Oral intermediate exposure					
Koner et al. 1998 (rat; 8 weeks)	Yes	No	Yes	Yes	Moderate
Mediratta et al. 2008 (rat; 21 days)	Yes	No	Yes	Yes	Moderate
Meera et al. 1992 (mouse; 24 weeks)	Yes	Yes	Yes	Yes	High

A summary of the initial confidence ratings for each outcome is presented in Table C-35. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence; any exceptions were noted in Table C-35.

Table C-35. Initial Confidence Rating for γ-Hexachlorocyclohexane Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Developmental effects		
Oral acute exposure		
Animal studies		
Dalsenter et al. 1997a	High	High
Dalsenter et al. 1997b	High	
Dalsenter et al. 1997b	High	
Johri et al. 2008	High	
Khera et al. 1979	High	
Palmer et al. 1978	High	
Rivera et al. 1991	Moderate	
Rivera et al. 1998	Moderate	
Rivera et al. 1998	Moderate	
Serrano et al. 1990	Moderate	

Table C-35. Initial Confidence Rating for γ-Hexachlorocyclohexane Health Effects Studies

	Initial study confidence	Initial confidence rating
Di Consiglio et al. 2009	Moderate	
Hassoun and Stohs 1996a	High	
Hassoun and Stohs 1996a	Moderate	
La Sala et al. 2009	High	
Maranghi et al. 2007	High	
Traina et al. 2003	High	
Palmer et al. 1978	High	
Oral intermediate exposure		
Animal studies		
Breton et al. 2005	Moderate	
EPA 1991a	High	
EPA 1999c	High	
Johri et al. 2007	High	
Johri et al. 2008	High	High
Matsuura et al. 2005	High	
Sauviat et al. 2005	Moderate	
Srinivasan et al. 1991	Moderate	
Srivastava et al. 2019	High	
Seiler et al. 1994	Moderate	
Oral chronic exposure		
Human studies		
Fenster et al. 2006	Moderate	
Fernandez et al. 2007	Low	
Mustafa et al. 2013	Low	Moderate
Sharma et al. 2012	Low	
Siddiqui et al. 2003	Low	
Fang et al. 2019a, 2019b	Low	
Outcome: Immunological effects		
Oral acute exposure		
Animal studies		
Mediratta et al. 2008	High	
Hong and Boorman 1993	High	High
Hong and Boorman 1993	High	
Oral intermediate exposure		
Animal studies		
Koner et al. 1998	Moderate	
Mediratta et al. 2008	Moderate	High
Meera et al. 1992	High	
Oral chronic exposure		
Human studies		
Landgren et al. 2009	Moderate	Moderate
Meng et al. 2016	Low	

C.16.2 Adjustment of the Confidence Rating—γ-HCH

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The five properties of the body of evidence that were considered to determine whether the confidence rating should be downgraded and the four properties of the body of evidence that were considered to determine whether the confidence rating should be upgraded are described above in Section C.6.2. The summaries of the assessment of the confidence in the body of evidence for developmental and immune system effects are presented in Table C-36. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with γ-HCH exposure is presented in Table C-37.

Table C-36. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Developmental effects			
Human studies	Moderate	-1 imprecision	Low
Animal studies	High	+1 consistency	High
Immunological effects			
Human Studies	Moderate	-1 risk of bias	Low
Animal Studies	High	+1 consistency	High

Table C-37. Confidence in the Body of Evidence for γ-Hexachlorocyclohexane

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Developmental	Low	High
Immune	Low	High

C.17 TRANSLATE CONFIDENCE RATING INTO LEVEL OF EVIDENCE OF HEALTH EFFECTS—γ-HCH

As described in Section C.7, the confidence in the body of evidence for specific outcomes was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted.

A summary of the level of evidence of health effects for γ-HCH is presented in Table C-38.

Table C-38. Level of Evidence of Health Effects for γ-Hexachlorocyclohexane

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Developmental	Low	Health effect	Low
Immunological	Low	Health effect	Low
Animal studies			
Developmental	High	Health effect	High
Immunological	High	Health effect	High

C.18 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS—γ-HCH

The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. Refer to Section C.8 for the four hazard identification conclusion categories for health effects, the hazard characterization scheme (see Figure C-1), and the hazard identification conclusion categories.

The hazard identification conclusions for γ-HCH are listed below and summarized in Table C-39.

Presumed Health Effects

- Developmental
  - Low level of evidence in humans based on associations between γ-HCH in maternal or fetal blood (or tissue) and intrauterine growth retardation/fetal growth retardation in small case-control studies in India (Sharma et al. 2012; Siddiqui et al. 2003), decreased gestational age and increased preterm birth in a cross-sectional study in China (Fang et al. 2019a, 2019b) and a case-control study in India (Mustafa et al. 2013), and cryptorchidism or hypospadias in a nested case-control study in Spain (Fernandez et al. 2007).
  - High level of evidence in animals based on studies in a variety of species exposed to γ-HCH for acute or intermediate durations during gestation or postnatal development demonstrating effects on a wide range of developmental endpoints, including birth outcomes (Beard et al. 1997; EPA 1991a, 1999c; Hassoun and Stohs 1996a; Matsuura et al. 2005; Sauviat et al. 2005) and development of the male and female reproductive tracts (Agrahari et al. 2019; Dalsenter et al. 1997a, 1997b; Di Consiglio et al. 2009; La Sala et al. 2009; Maranghi et al. 2007; Matsuura et al. 2005; Traina et al. 2003), central nervous system (Albertson et al. 1985; Breton et al. 2005; EPA 1999c; Johri et al. 2007, 2008; Rivera et al. 1991, 1998; Srivastava et al. 2019), heart (Sauviat et al. 2005), liver (Srinivasan et al. 1991), and thymus and spleen (Hassoun et al. 1996; Matsuura et al. 2005).
- Immunological
  - Low level of evidence in humans based on association between asthma and plasma levels of γ-HCH in children (Meng et al. 2016) and no evidence for increased prevalence of monoclonal gammopathy of undetermined significance in cohort of male pesticide applicators followed for 9 years (Landgren et al. 2009).
  - High level of evidence in animals based on acute- and intermediate-duration studies of γ-HCH administered orally to rats, mice, rabbits, and sheep showing suppression of the immune system (Banerjee et al. 1996; Desi et al. 1978; Dewan et al. 1980; Khurana et al.

1999; Koner et al. 1998; Mediratta et al. 2008; Meera et al. 1992) and effects on thymus, spleen, and lymph node weights or histology (Hong and Boorman 1993; Meera et al. 1992).

Table C-39. Hazard Identification Conclusions for γ-Hexachlorocyclohexane

Outcome	Hazard identification
Developmental	Presumed health effect
Immunological	Presumed health effect

APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a

substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page D-5)

(1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Figure key. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), food intake (FI), gross necropsy (GN), hematology (HE), histopathology (HP), immune function (IX), lethality (LE), neurological function (NX), organ function (OF), ophthalmology (OP), organ weight (OW), reproductive function (RX), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page D-6)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(12) Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

(13) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(14) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(15) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(16) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(17) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

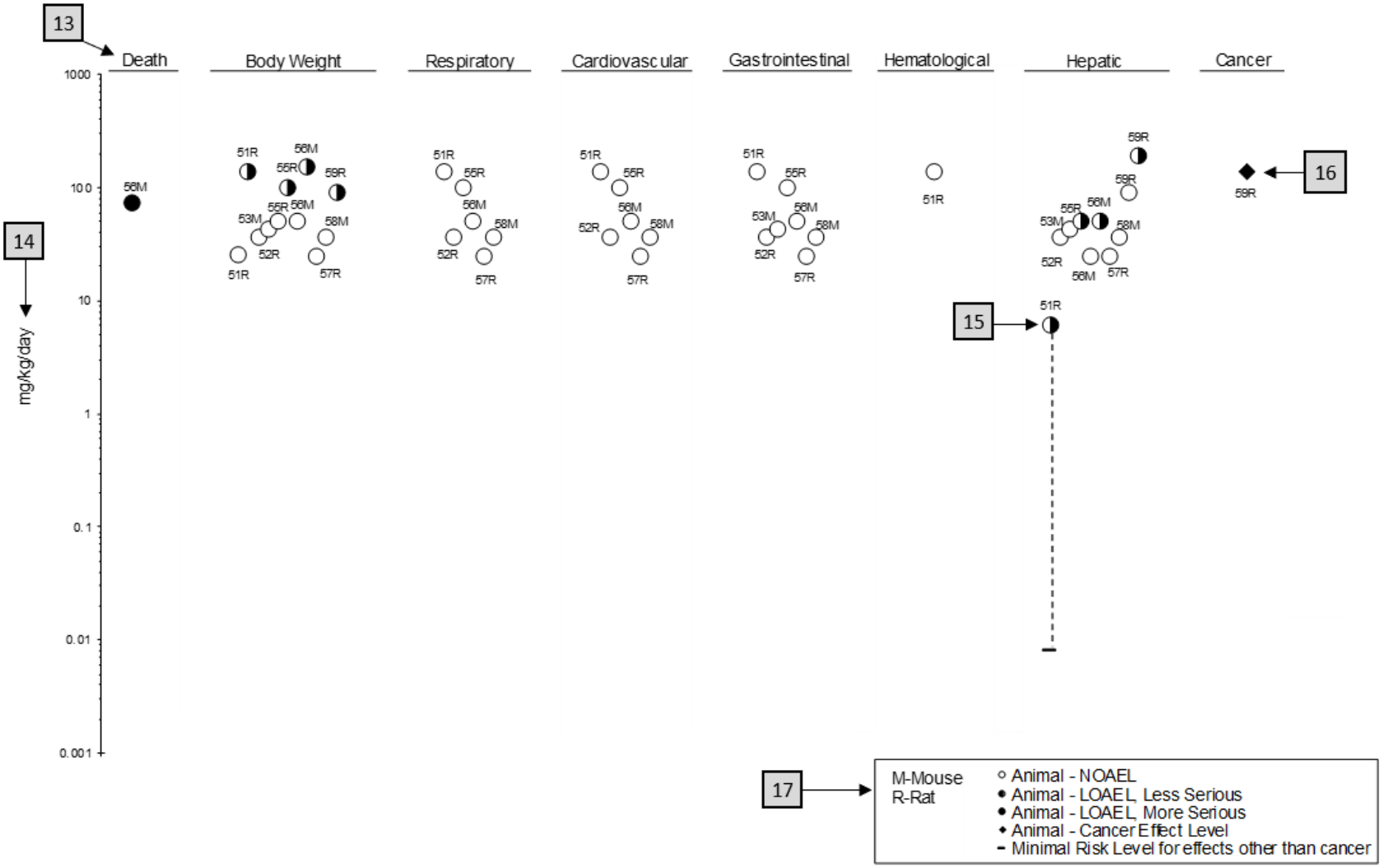
Figure key[a] (2)	Species (strain) No./group (3)	Exposure parameters (4)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE									
51 (10)	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	**Lifetime** (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

[a]The number corresponds to entries in Figure 2-x.

(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:

Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

ATSDR develops educational and informational materials for health care providers categorized by hazardous substance, clinical condition, and/or by susceptible population. The following additional materials are available online:

Physician Briefs discuss health effects and approaches to patient management in a brief/factsheet style. *Physician Overviews* are narrated PowerPoint presentations with Continuing Education credit available (see https://www.atsdr.cdc.gov/emes/health_professionals/index.html).

Managing Hazardous Materials Incidents is a set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.html).

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX F. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register

FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences

NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
REL-C	recommended exposure limit-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SLOAEL	serious lowest-observed-adverse-effect level
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey

USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
µm	micrometer
µg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result