TOXICOLOGICAL PROFILE FOR ALPHA-, BETA-, GAMMA-, AND DELTA-HEXACHLOROCYCLOHEXANE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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DISCLAIMER

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UPDATE STATEMENT

A Toxicological Profile for Hexachlorocyclohexane, Draft for Public Comment was released in September 2003. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
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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 the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous 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 public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. 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 protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

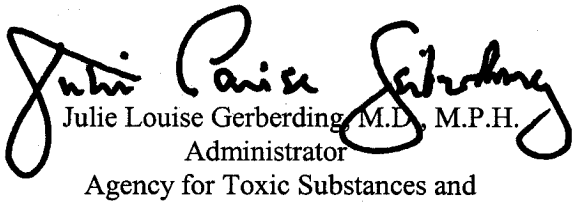
(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

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

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff 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 was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



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*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on November 7, 2003 (68 FR 63098) . For prior versions of the list of substances, see *Federal Register* notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17,1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); October 21, 1999(64 FR 56792) and October 25, 2001 (66 FR 54014). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

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 will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6	**How Can (Chemical X) Affect Children?**
Section 1.7	**How Can Families Reduce the Risk of Exposure to (Chemical X)?**
Section 3.7	**Children's Susceptibility**
Section 6.6	**Exposures of Children**

Other Sections of Interest:

Section 3.8	**Biomarkers of Exposure and Effect**
Section 3.11	**Methods for Reducing Toxic Effects**

ATSDR Information Center

Phone:	1-888-42-ATSDR or (404) 498-0110	***Fax:***	(770) 488-4178
E-mail:	atsdric@cdc.gov	***Internet***:	http://www.atsdr.cdc.gov

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental*

Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity; and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

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.

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, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-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.

Referrals

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.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific Minimal Risk Levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

PEER REVIEW

A peer review panel was assembled for hexachlorocyclohexane. The panel consisted of the following members:

1. C. Clifford Conaway, Ph.D., DABT, Associate Research Scientist, Institute for Cancer Prevention, Valhalla, NY 10595

2. Lucio Costa, Ph.D., Professor, Department of Environmental Health, University of Washington, Seattle, WA 98195

3. Raghubir Sharma, Ph.D., Fred C. Davidson Distinguished Chair in Toxicology, Department of Physiology and Pharmacology, University of Georgia, Athens, GA 30602

These experts collectively have knowledge of hexachlorocyclohexane 's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about alpha- (α), beta- (β), gamma- (γ), and delta- (δ) hexachlorocyclohexane (HCH) and the effects of exposure.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites are then placed on the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. α-, β-, γ-, and δ-HCH has been found in at least 146, 159, 189, and 126, respectively of the 1,662 current or former NPL sites. Although the total number of NPL sites evaluated for these substances is not known, the possibility exists that the number of sites at which HCH is found may increase in the future as more sites are evaluated. This information is important because these sites may be sources of exposure and exposure to these substances may harm you.

When a substance is released either from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. Such a release does not always lead to exposure. You can be exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact.

If you are exposed to HCH, many factors will determine whether you will be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider any other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS HEXACHLOROCYCLOHEXANE?

Hexachlorocyclohexane (HCH), formally known as benzene hexachloride (BHC), is a synthetic chemical that exists in eight chemical forms called isomers. The different isomers are named according to the position of the hydrogen atoms in the structure of the chemical. One of these forms, gamma-HCH (or γ-HCH, commonly called lindane), is produced and used as an

insecticide on fruit, vegetables, and forest crops, and animals and animal premises. It is a white solid whose vapor may evaporate into the air. The vapor is colorless and has a slight musty odor when it is present at 12 or more parts HCH per million parts air (ppm). γ-HCH has not been produced in the United States since 1976. However, imported γ-HCH is available in the United States for insecticide use as a dust, powder, liquid, or concentrate. It is also available as a prescription medicine (lotion, cream, or shampoo) to treat and/or control scabies (mites) and head lice in humans.

Technical-grade HCH, a mixture of several chemical forms of HCH, was also once used as an insecticide in the United States and typically contained about 10–15% of γ-HCH as well as the alpha (α), beta (β), delta (δ), and epsilon (ε) forms of HCH. Virtually all of the insecticidal properties reside in the gamma isomer. Technical-grade HCH has not been produced or used in the United States for more than 20 years.

The scope of this profile includes information on technical-grade HCH, as well as the α, β, γ, and δ isomers. Available information on the ε isomer is limited and is not included in this profile. Chapter 4 contains more information on the chemical and physical properties of HCH.

1.2 WHAT HAPPENS TO HEXACHLOROCYCLOHEXANE WHEN IT ENTERS THE ENVIRONMENT?

Although technical-grade HCH is no longer used as an insecticide in the United States, α-, β-, γ-, and δ-HCH have been found in the soil and surface water at hazardous waste sites because they persist in the environment. In air, the different forms of HCH can be present as a vapor or attached to small particles such as soil and dust; the particles may be removed from the air by rain or degraded by other compounds found in the atmosphere. HCH can remain in the air for long periods and travel great distances depending on the environmental conditions. In soil, sediments, and water, HCH is broken down to less toxic substances by algae, fungi, and bacteria, but this process can take a long time. Chapter 6 contains more information about the presence of HCH in the environment.

1.3 HOW MIGHT I BE EXPOSED TO HEXACHLOROCYCLOHEXANE?

You will be directly exposed to γ-HCH if you use a prescription medication that contains this compound in order to treat and/or control scabies and head lice. You can also be exposed to small amounts of γ-HCH and the other isomers (α-, β-, and δ-HCH) by eating foods that may be contaminated with these compounds. Exposure to the HCH isomers is also possible from ingesting contaminated drinking water, breathing contaminated air, or having contact with soil or water at hazardous waste sites that may contain these compounds. Exposure to α-, β-, and δ-HCH is less frequent than exposure to γ-HCH because these compounds are no longer used in the United States. Although γ-HCH is no longer made in the United States, it is still imported into the United States and formulated into products that are used here. Therefore, workers involved in the formulation or application of these products can be exposed to γ-HCH.

For more information on exposure to HCH, refer to Chapter 6.

1.4 HOW CAN HEXACHLOROCYCLOHEXANE ENTER AND LEAVE MY BODY?

γ-HCH and the other isomers of HCH can enter your body when you eat food or drink water contaminated with HCH. Inhaling γ-HCH or other isomers of HCH in air can also lead to entry of these chemicals into the lungs. γ-HCH can be absorbed through the skin when it is used as a lotion, cream, or shampoo for the treatment and/or control of scabies and body lice. In general, HCH isomers and the products formed from them in the body can be temporarily stored in body fat. Among the HCH isomers, β-HCH leaves the body the most slowly. α-HCH, δ-HCH, and γ-HCH, and the products formed from them in the body, are more rapidly excreted in the urine; small amounts leave in the feces and expired air. HCH breaks down in the body to many other substances; these include various chlorophenols, some of which have toxic properties. Chapter 3 gives more information on how HCH enters and leaves the body.

1.5 HOW CAN HEXACHLOROCYCLOHEXANE AFFECT MY HEALTH?

Scientists use many tests to protect the public from harmful effects of toxic chemicals and to find ways for treating persons who have been harmed.

One way to learn whether a chemical will harm people is to determine how the body absorbs, uses, and releases the chemical. For some chemicals, animal testing may be necessary. Animal testing may also help identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method for getting information needed to make wise decisions that protect public health. Scientists have the responsibility to treat research animals with care and compassion. Scientists must comply with strict animal care guidelines because laws today protect the welfare of research animals.

In humans, breathing toxic amounts of γ-HCH and/or α-, β-, and δ-HCH can result in blood disorders, dizziness, headaches, and possible changes in the levels of sex hormones in the blood. These effects have occurred in workers exposed to HCH vapors during pesticide manufacturing. People who have swallowed large amounts have had seizures; some have died. A few people who used very large amounts of γ-HCH or used it frequently on their skin developed blood disorders or seizures. However, no cause-and-effect relationship between exposure to γ-HCH and blood disorders in humans has been established. Animals that have been fed γ- and α-HCH have had convulsions, and animals fed β-HCH have become comatose. All isomers can produce liver and kidney effects. Reduced ability to fight infection was reported in animals fed γ-HCH, and injury to the ovaries and testes was reported in animals given γ-HCH or β-HCH. HCH isomers are changed by the body into other chemical products, some of which may be responsible for the harmful effects. Long-term oral administration of α-HCH, β-HCH, γ-HCH, or technical-grade HCH to laboratory rodents has been reported to result in liver cancer. The Department of Health and Human Services (DHHS) has determined that HCH (all isomers) may reasonably be anticipated to cause cancer in humans. The International Agency for Research on Cancer (IARC) has classified HCH (all isomers) as possibly carcinogenic to humans. The EPA has determined that there is suggestive evidence that lindane (γ-HCH) is carcinogenic, but the evidence is not sufficient to assess its human carcinogenic potential. The EPA has additionally

classified technical HCH and α-HCH as probable human carcinogens, β-HCH as a possible human carcinogen, and δ- and ε-HCH as not classifiable as to human carcinogenicity. Chapter 3 gives more information about the health effects of HCH isomers.

1.6 HOW CAN HEXACHLOROCYCLOHEXANE AFFECT CHILDREN?

This section discusses potential health effects in humans from exposures during the period from conception to maturity at 18 years of age.

The most likely source of exposure for children is from the use of shampoos and lotions containing HCH for the treatment of lice or scabies. HCH has also been found as a residue in food products; β-HCH isomer accumulates in animal tissue. In the body, α-, δ-, and γ-HCH are rapidly broken down and excreted. Although HCH is a restricted use pesticide in the United States, children could be exposed from eating foods grown in areas where HCH is still used or misused as a pesticide. HCH has also been detected in breast milk, resulting in a possible exposure pathway for infants and children.

It is not known for sure whether children are more susceptible than adults to health effects from exposure to γ-HCH. Limited information is available on the specific health effects resulting from HCH exposure in children. Health effects observed in adults should also be of potential concern for children. Children can experience convulsions from exposure to γ-HCH. Eating enough γ-HCH can kill a child. However, in a study performed on rabbits, young animals had higher death rates and greater sensitivity than adults when γ-HCH was applied to the skin.

It is not known whether HCH causes birth defects in humans. Technical-grade and γ-HCH do not cause significant birth defects in animals. Animals fed γ-HCH during pregnancy had an increased number of fetuses with extra ribs, which is a normal variation. HCH has been shown to cross the placenta in pregnant women. HCH is likely to be stored in fat. It has been measured in skin lipids and breast milk. In studies of rats, HCH has been shown to pass from the mother to newborns in the dam’s milk, causing neurological and hormonal effects. The male newborn

pups of female rats that had been fed HCH during lactation demonstrated a 50% reduction in testosterone levels and reduced testicular weight in adolescence and adulthood.

More information on how HCH can affect the health of children can be found in Sections 3.7 and 6.6.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO HEXACHLOROCYCLOHEXANE?

If your doctor finds that you have been exposed to substantial amounts of hexachlorocyclo-hexane, ask whether your children might also have been exposed. Your doctor might need to ask your state health department to investigate.

There are two primary pathways through which families can be exposed to HCH. γ-HCH, which may be labeled as lindane, is used in shampoos and lotions for the treatment of lice. It is normally safe if used as directed, but may be misused. If you use shampoos or lotions containing γ-HCH, follow the directions carefully. Products containing lindane should never be used on infants. Shampoos or lotions that contain lindane should be stored out of the reach of young children to prevent accidental poisoning. You may expose your child to lindane if you use products that contain lindane to treat lice or scabies on your child's head or skin. Alternative treatments are available that do not involve the use of lindane. You should consult with your physician to discuss appropriate alternative treatments.

γ-HCH is a restricted use pesticide. Its allowed uses are very limited. Your children may be exposed to γ-HCH if an unqualified person applies pesticides containing it around your home. In some cases, the improper use of pesticides banned for use in homes has turned homes into hazardous waste sites. Make sure that any person you hire is licensed and certified to apply pesticides. Your state licenses each person who is qualified to apply pesticides according to EPA standards and further certifies each person who is qualified to apply "restricted use" pesticides. Ask to see their license and certification. Also ask for the brand name of the pesticide, a Material Safety Data Sheet (MSDS), the name of the product's active ingredients, and the EPA

registration number. This information can be important if you or your family react to the product.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO HEXACHLOROCYCLOHEXANE?

HCH isomers can be measured in the blood, urine, and semen of exposed persons. Samples of these fluids can be collected in a doctor's office and sent to a laboratory that has the special equipment needed to measure the levels of HCH. Although the amount of HCH isomers in blood, urine, or semen can be measured, it is usually not possible to determine the environmental levels to which the person was exposed or to predict the health effects that are likely to occur from specific concentrations. The products of HCH that are formed in the body and then found in the urine have also been measured to find out whether a person was exposed to HCH. However, this method cannot yet be used to determine exposure to HCH alone because other environmental chemicals produce the same end products. Chapter 7 contains more information on ways to measure HCH in human blood and tissues.

1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations *can* be enforced by law. The EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA) are some federal agencies that develop regulations for toxic substances. Recommendations provide valuable guidelines to protect public health, but *cannot* be enforced by law. The Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH) are two federal organizations that develop recommendations for toxic substances.

Regulations and recommendations can be expressed as “not-to-exceed” levels, that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value that is usually based

on levels that affect animals; they are then adjusted to levels that will help protect humans. Sometimes these not-to-exceed levels differ among federal organizations because they used different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or other factors.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for HCH include the following:

γ-HCH is categorized by EPA as a restricted use pesticide. It can only be used by licensed and certified applicators. EPA has also recommended guidelines on how much HCH can be present in drinking water for specific periods without producing health effects. EPA advises that children should not have more than 1.2 milligrams HCH per liter of water (mg/L) for up to 10 days. For lifetime exposure in adults, EPA recommends that there should not be more than 0.0002 mg/L of HCH in drinking water. EPA has classified HCH as a hazardous waste that must meet certain disposal requirements.

OSHA regulates levels of γ-HCH in the workplace. The maximum allowable amount in workplace air during an 8-hour workday in a 40-hour work week is 0.5 mg per cubic meter of air.

Chapter 8 contains more information about regulations and guidelines concerning HCH.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below.

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles™ CD-ROM by calling the toll-free information and technical assistance number at 1-888-42ATSDR (1-888-422-8737), by e-mail at atsdric@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE
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Atlanta, GA 30333
Fax: 1-770-488-4178

Organizations for-profit may request copies of final Toxicological Profiles from the following:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: http://www.ntis.gov/

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO HEXACHLOROCYCLOHEXANE IN THE UNITED STATES

Hexachlorocyclohexane (HCH) is a synthetic chemical consisting of eight isomers. Only four of these isomers—α-HCH, β-HCH, γ-HCH, and δ-HCH—are of commercial significance. γ-HCH, commonly referred to as lindane, is used as seed treatment for barley, corn, oats, rye, sorghum, and wheat. It is also used in very small quantities as a prescription medication for the treatment of scabies and head lice in humans. The FDA does not recommend the use of γ-HCH in infants or in children or adults weighing less than 50 kg. In the past, γ-HCH was used in veterinary products to control mites, lice, and other pests, but recent data suggest that no products are currently registered in the United States for this use. Other HCH isomers, as well as technical-grade HCH, are used either as fungicides or in the synthesis of other chemicals. Technical-grade HCH is comprised of 60–70% α-HCH, 5–12% β-HCH, 10–15% γ-HCH, 6–10% δ-HCH, and 3–4% ε-HCH. Technical-grade HCH was banned for production and use in the United States in 1976, but still may be used in other countries in small quantities.

Monitoring data suggest that the general population is exposed to HCH through the inhalation of ambient air and the consumption of contaminated food and drinking water. The relatively high stability of the HCH isomers in the environment and their global use for many years has led to their continued detection in air, soil, surface water, groundwater, and drinking water. As worldwide use of HCH declines, however, the frequency of detection and the levels detected in the environment should continue to decrease. Very low levels of α- and γ-HCH in air have been detected in a study conducted in the 1990s. The average air levels of α-HCH at sites along Lake Michigan, Lake Superior, and Lake Erie were in the range of 0.110–0.140 ng/m^3 for samples collected during 1990–1997 and the average levels of γ-HCH were 0.024–0.062 ng/m^3 at the same sites. Similarly, fairly low levels of γ-HCH were detected in groundwater samples. γ-HCH was detected in two groundwater samples at levels of 0.028 and 0.032 μg/L during a groundwater monitoring study conducted in the Ozark Plateaus Province of Arkansas, Kansas, Missouri, and Oklahoma from April to September 1993. The estimated average daily dietary intakes of γ- and α-HCH were essentially the same in various adult age/sex groups in the United States, ranging from about 0.5 to 1.0 ng/kg/day for both isomers, whereas intake of β-HCH was <0.1 ng/kg/day (below the analytical detection limit in food).

HCH can be detected in the blood and urine of exposed individuals. In humans, the concentration of β-HCH in adipose tissue is typically higher than other HCH isomers. It has been estimated that approximately 100% of the U.S. population had detectable levels of β-HCH in adipose tissue in 1970; in 1980, 80% of the population had detectable levels. In a U.S. biomonitoring study conducted in 1999–2000, less than 50% of the studied population had detectable levels of β-HCH in serum; the geometric mean serum concentration was 9.68 ng/g lipid (95% confidence interval of <4.8–10.4 ng/g lipid). γ-HCH was only detected in 1.7% of the population surveyed in 1999–2000; the geometric mean serum concentration was below the detection limit of 7.5 ng/g of lipid.

2.2 SUMMARY OF HEALTH EFFECTS

Information on the toxicity of HCH comes from human exposure reports and experimental studies in animals. Most of the information on the health effects of HCH in humans comes from studies of individuals involved in the production or use of HCH products, reports of exposures to domestic products containing HCH, and intentional ingestion of HCH. Most of these studies involve exposure to technical HCH or γ-HCH and exposure levels are not available. Except for skin rashes observed in humans following topical application of γ-HCH, there is no evidence that the toxicity of HCH is route-dependent. In humans and animals, the main target of acute exposure to high amounts of HCH is the nervous system, and the effects consist of hyperexcitability, seizures, and convulsions that eventually may lead to death. Although the available reports on humans describe a wide array of effects associated with exposure to HCH, it is difficult to define a clear target organ or system for HCH toxicity, largely because of limitations of the studies, such as lack of exposure data and simultaneous exposure to other chemicals in occupational settings, or exposure to lethal or near lethal amounts, which caused generalized non-specific toxicities. Yet, vomiting and nausea are usual manifestations of γ-HCH ingestion and also have been reported after dermal exposure to γ-HCH. There are also reports of adverse hematological effects in humans exposed to γ-HCH following inhalation and/or dermal exposure to domestic products containing γ-HCH and following chronic occupational exposure. There is no evidence that HCH alters immunocompetence in humans, even though there is a report of increased serum IgM levels in a small study of workers exposed to technical-grade HCH. A study of 54 men occupationally exposed to γ-HCH reported an increase in serum luteinizing hormone among the exposed subjects, but this sole finding is clearly insufficient to make any inference regarding reproductive effects of HCH in humans. Similarly, a single report of an association between women with serum levels of HCH isomers and babies with intra-uterine growth retardation is insufficient to draw any conclusion regarding developmental effects of HCH

in humans, particularly since other organochlorine pesticides were also present. Studies of the cancer of HCH in humans have been inconclusive. Studies of the association between pesticide use and non-Hodgkin's lymphoma among U.S. farmers concluded that γ-HCH is not a major factor in the development of the disease, but may play some role. The majority of the studies of the general population have found no association between serum levels of HCH and breast cancer or breast tissue levels of HCH and breast cancer. In these studies, many other organochlorine chemicals were also detected. Results from studies of the genotoxic potential of HCH in humans have been inconclusive.

Studies in animals (mostly, but not exclusively, rats exposed orally) confirm the nervous system as a toxicity target for acute exposure to high amounts of HCH, regardless of the route of exposure. In addition to hyperexcitability and convulsions, treatment of animals with HCH has produced neurochemical alterations in the brain, behavioral alterations in adult animals, and in the offspring of animals exposed to HCH. Decreased numbers of red and white blood cells and hemoglobin have been reported in rats following repeated administration of γ-HCH or technical-grade HCH. Most HCH isomers were shown to increase cytochrome P-450 content and the activities of associated enzymes in rodents and also produced liver necrosis and degeneration with higher doses. γ- and β-HCH produced immunosuppression in intermediate-duration studies in rodents. HCH isomers have altered reproductive parameters in male and female animals including mink, rabbits, and rats. Effects included alterations in estrous cycle, embryotoxicity, and testicular and sperm alterations. Exposure of female rats to γ-HCH during lactation altered the development of the reproductive system of male offspring. Results of studies aimed to test whether γ-HCH and other HCH isomers are endocrine disruptors have yielded mixed results. Exposure to technical-grade HCH and γ-HCH during gestation caused fetotoxicity in mice. Teratogenicity of HCH has not been conclusively demonstrated. Numerous studies have examined the carcinogenicity of HCH in animals exposed orally. α-HCH induced liver tumors in mice and rats, β-HCH induced liver tumors in mice, and technical grade HCH induced liver tumors in mice; inconclusive results have been obtained with γ- and ε-HCH, and negative results were obtained with δ-HCH. In genotoxicity assays, HCH isomers exhibited no genotoxic activity or weak activity at best.

A greater detailed discussion of HCH-induced hepatic, immunological, neurological, reproductive, and carcinogenic effects follows. The reader is referred to Section 3.2, Discussion of Health Effects by Route of Exposure, for additional information on other health effects.

Hepatic Effects. Hepatic effects, such as increased liver enzymes, have been reported in humans exposed to technical-grade HCH principally by inhalation in a pesticide formulating plant; but there are

no liver data reported for individuals who ingested HCH or applied γ-HCH to their skin. An increase in cytochrome P-450 concentration has been reported in rats following inhalation exposure. Animal studies have also reported that ingestion of α-, β-, and γ-HCH isomers, individually or as technical-grade HCH, has resulted in some degree of liver toxicity including increased microsomal activity, increased liver weight, mild-to-moderate liver necrosis and fatty degeneration, and liver cancer. Biochemical or gross hepatic changes often were not accompanied by histopathological changes. Hepatic effects in animals following dermal exposure to γ-HCH or technical-grade HCH were similar to those observed with oral exposure. Although available human data are limited, effects on liver enzymes following exposure to technical-grade HCH were similar to those observed in animal studies. The observation of serious hepatic effects in animals (e.g., fatty degeneration and necrosis) suggests that the same results could potentially occur in workers following prolonged occupational exposure. Liver toxicity was used as the basis for an intermediate-duration oral MRL for β-HCH and a chronic-duration oral MRL for α-HCH. As detailed in Section 2.3 and Appendix A, the intermediate oral MRL for β-HCH is based on a lowest-observed-adverse-effect level (LOAEL) of 0.18 mg/kg/day for liver effects in rats (centrilobular hyalinization, with periportal fatty changes and focal necrosis at ≥4.5 mg/kg/day) exposed for 13 weeks. The chronic oral MRL for α-HCH is based on a hepatic no-observed-adverse-effect level (NOAEL) of 0.8 mg/kg/day in rats exposed for up to 107 weeks. Liver effects at higher doses of α-HCH progressed from slight histological changes at 3.5–4 mg/kg/day to hepatic cell atrophy, fatty degeneration, and focal necrosis at 56–64 mg/kg/day.

Immunological Effects. A significant increase in the level of IgM was observed in workers exposed to technical-grade HCH. Although there is no evidence of an increase in immunoglobulins in animals, antibody response has been reported to be depressed in rats, rabbits, and mice exposed to γ-HCH. Biphasic effects on immunosuppression were reported in mice fed γ-HCH. This is suggestive evidence that HCH may affect the human immune system.

Immunotoxicity was used as the basis for an intermediate-duration MRL for oral exposure to γ-HCH. As detailed in Section 2.3 and Appendix A, the intermediate oral MRL for γ-HCH is based on a LOAEL of 0.012 mg/kg/day for immunological effects in mice exposed for up to 24 weeks. Effects observed at ≥0.012 mg/kg/day included changes in delayed-type hypersensitivity reaction to sheep red blood cells (SRBC), response of IgM antibody forming cells in spleen to SRBC or lipopolysaccharide, and post-treatment histology of the spleen (reductions in lymphoid follicles and overall cellularity), lymph nodes (reduced lymphocyte population and size of medullary cords), and thymus (necrosis in the medulla).

Neurological Effects. In humans, neurological effects, including paresthesia of the face and extremities, headaches, vertigo, abnormal EEG patterns, and often seizures and convulsions, have been reported in individuals occupationally exposed to γ-HCH or in individuals exposed accidentally or intentionally to large amounts of γ-HCH by ingestion or dermal application. Acute- and intermediate-duration exposure of animals to high oral or dermal doses of γ- or β-HCH affects the central nervous system as evidenced by behavior disorders, decreased nerve conduction velocity, neurochemical changes, convulsions, seizures, and coma. Results of acute, intermediate, and developmental neurotoxicity test batteries in rats found that γ-HCH caused effects such as decreased motor activity, decreased habituation, and increased forelimb grip strength at lower doses and hypersensivity to touch, hunched posture, tremors, and convulsions at higher doses. There is evidence that exposure to γ-HCH caused functional impairment (reduced permeability) of the developing blood brain barrier in young rats. The effects in humans and animals suggest that exposure of humans to high air concentrations or large oral doses could potentially result in neurotoxic effects. An effect level for neurotoxicity in rats was used as the basis for an acute-duration oral MRL for β-HCH, as detailed in Section 2.3 and Appendix A.

Reproductive Effects. Information on the potential reproductive toxicity of HCH in humans is limited. An increase in serum luteinizing hormone levels was observed in male workers, but other reproductive hormone levels were not significantly altered. Additionally, increased blood levels of γ-HCH and total HCH isomers were detected in women experiencing spontaneous abortion or premature delivery. Because the women were exposed to multiple organochlorine pesticides, it is difficult to establish a causal relationship between HCH exposure and adverse reproductive outcomes.

Adverse reproductive effects have been observed in male and female laboratory animals orally exposed to γ-, β-, or technical-grade HCH. In male rats, exposure to >1 mg/kg/day γ-HCH resulted in decreases in the number of sperm and/or spermatids. This effect was observed following exposure of mature animals and in animals exposed during gestation or lactation. A decrease in sperm count was also observed in rats exposed to technical-grade HCH. At higher doses of γ-, β-, or technical-grade HCH, degeneration of the seminiferous tubules or testicular atrophy were also observed in rats and mice. An acute-duration oral MRL for γ-HCH is based on the reproductive effects observed in the offspring of rats exposed to γ-HCH during lactation, as detailed in Section 2.3 and Appendix A.

Effects in female rats, mice, and rabbits exposed to γ- or β-HCH include ovarian atrophy, increased length of estrous cycle, disruption of ovarian cycling, and decreased ovulation rate. In general, the effects in the females occurred at higher doses than in the males. Although a number of reproductive effects have been

observed in male and female rats, two multigeneration studies did not find alterations in fertility following exposure to 13.1 mg/kg/day γ-HCH or 32 mg/kg/day technical-grade HCH.

Cancer. Use of γ-HCH pesticides by farmers was associated with a 50% increased risk of non-Hodgkin's lymphoma. However, a causal relationship could not be determined due to confounding effects such as use of other pesticides. Several studies have examined the possible relationship between elevated blood levels of HCH and risk of breast cancer; one study found an association and three studies did not find associations. With oral exposure, α-, β-, γ-, and technical-grade HCH have been found to be carcinogenic in mice following long-term exposure. Hepatocellular carcinoma is the most frequently reported tumor type, although in many studies, the liver was the only organ under investigation. Benign lung adenomas were also increased in mice following chronic exposure to γ-HCH. In general, mice appear to be more susceptible to the carcinogenic effects of HCH isomers, even though some strains have a high background level of liver tumors; and rats generally developed cancer following longer exposure or exposure to higher doses. In addition, a study reported that α-, β-, and γ-HCH promoted tumor development in rats exposed to a single dose of *N*-nitrosomorpholine. A metabolite of γ-HCH, 2,4,6-trichlorophenol, accounts for 10–20% of γ-HCH-derived excretion products; this metabolite is carcinogenic in animals and might account for some or all of the carcinogenic activity observed in animals. A stable halogenated epoxide of another γ-HCH metabolite, pentachlorocyclohexene, could also contribute to the hepatocarcinogenicity of γ-HCH.

The available animal data suggest that liver cancer may be of potential concern to individuals exposed to HCH isomers for prolonged periods of time. The Department of Health and Human Services (DHHS) has determined that γ-HCH and other HCH isomers may reasonably be anticipated to cause cancer in humans. The International Agency for Research on Cancer (IARC) has determined that HCH is possibly carcinogenic to humans. The Environmental Protection Agency (EPA) has classified technical HCH and α-HCH as probable human carcinogens, β-HCH as a possible human carcinogen, and δ- and ε-HCH as not classifiable as to human carcinogenicity. The EPA has additionally classified lindane (γ-HCH) as having suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential.

2.3 MINIMAL RISK LEVELS

The general population is predominantly exposed to HCH by consumption of contaminated food, with minor exposures occurring from drinking water and ambient air. Average daily dietary intakes of HCH isomers in the U.S. adult population have been estimated to be in the range of 0.5–1.0 ng/kg/day for

α-HCH, 0.5–1.0 ng/kg/day for γ-HCH, and <0.1 ng/kg/day for β-HCH (Gunderson 1995b). Inhalation and dermal exposure to γ-HCH can also occur through occupational contact or at workplaces that formulate or use γ-HCH as a seed treatment. Additionally, a small percentage of the population can be dermally exposed to γ-HCH through pharmaceutical use, since this isomer is still available as a prescription lotion, cream, or shampoo medication for the treatment of head lice and mites.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for HCH. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. 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 within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

Sufficient health effects data are available to derive oral MRLs for the α-, β-, and γ-HCH isomers. Technical-grade HCH and the α- and β-HCH isomers are currently unavailable in the United States; therefore, exposure to these isomers is likely to occur only in or near hazardous waste sites at which technical-grade HCH was disposed. No MRLs were derived for technical-grade HCH. HCH is not found in the environment as technical-grade HCH, and analytical methods do not detect or measure technical-grade HCH, but rather, the individual isomers. When technical-grade HCH enters the environment, individual isomers partition into various media at different rates depending on the physical characteristics of each isomer. Some isomers may be more mobile in soil or water than others. Differences in partitioning and degradation would result in a different proportion of isomers than when initially spilled. Therefore, the development of an MRL(s) for technical grade HCH would not be relevant.

Inhalation MRLs

No inhalation MRLs could be developed for isomers of HCH due to insufficient data (Table 2-1).

Information on health effects following acute inhalation of γ-HCH in animals (Klonne and Kintigh 1988; Oldiges et al. 1980; Ullmann 1986b) is limited. Neurological effects following acute inhalation exposure to γ-HCH have included excitation, sedation, ataxia, and spasms (Ullmann 1986b). Acute inhalation studies for the other HCH isomers and technical-grade HCH are not available. Intermediate-duration inhalation studies of γ-HCH have been performed in rats with mortality reported (Klonne and Kintigh 1988). Inhalation of 5 mg/m^3 of γ-HCH for 90 days has not resulted in adverse respiratory, hematological, hepatic, or renal effects in rats (Oldiges et al. 1983), but the data are insufficient for developing an intermediate-duration inhalation MRL. No chronic-duration inhalation studies in animals are available for any HCH isomer. Due to the limitations of the database, additional information is needed on thresholds, dose-response relationships, and sensitive target organs for determining levels of significant human exposure to HCH and associated health effects following inhalation.

Oral MRLs

Five oral MRLs have been derived for α-, β-, and γ-HCH isomers of HCH, as discussed below, detailed in Appendix A, and summarized in Table 2-1.

α-HCH

- An MRL of 0.008 mg/kg/day has been derived for chronic-duration (365 days and longer) oral exposure to α-HCH.

The chronic oral MRL for α-HCH is based on a NOAEL of 0.8 mg/kg/day and LOAEL of 3.5 mg/kg/day for liver effects in rats (Fitzhugh et al. 1950) and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

The critical NOAEL was identified in a chronic toxicity study in which groups of 10 Wistar rats of each sex were exposed to α-HCH in the diet for up to 107 weeks at estimated doses of 0, 0.7, 3.5, 7, or 56 mg/kg/day in males and 0, 0.8, 4, 8, or 64 mg/kg/day in females (Fitzhugh et al. 1950). End points included clinical signs, body weight, food consumption, organ weights, gross pathology, and

Table 2-1. MRL Values for Hexachlorocyclohexane (HCH)

Isomer	Inhalation MRLs			Oral MRLs (mg/kg/day)		
	Acute	Intermediate	Chronic	Acute	Intermediate	Chronic
α-HCH	—	—	—	—	—	0.008
β-HCH	—	—	—	0.05	0.0006	—
γ-HCH	—	—	—	0.003	0.00001	—
δ-HCH	—	—	—	—	—	—
ε-HCH	—	—	—	—	—	—
Technical HCH	—	—	—	—	—	—

— Insufficient data

histopathology. No exposure-related changes occurred at the low dose in either sex, indicating that the highest NOAEL is 0.8 mg/kg/day in females. Liver effects were qualitatively described in both sexes at higher doses, progressing from very slight histological changes with no gross liver pathology at 3.5–4 mg/kg/day, slight histological changes with no gross pathology at 7–8 mg/kg/day, and moderate histological damage accompanied by moderate gross pathology at 56–64 mg/kg/day. The hepatic histopathological changes classified as moderate included hepatic cell atrophy, fatty degeneration, and focal necrosis. Non-hepatic effects included decreased body weight gain, slight kidney histopathology (focal nephritis), and reduced lifespan at 56–64 mg/kg/day.

β-HCH

- An MRL of 0.05 mg/kg/day has been derived for acute-duration (14 days or less) oral exposure to β-HCH.

The acute oral MRL for β-HCH is based on a NOAEL of 4.5 mg/kg/day and LOAEL of 22.5 mg/kg/day for clinical signs of ataxia in rats (Van Velsen et al. 1986) and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

The principal study, Van Velsen et al. (1986), is a 13-week toxicity study in which groups of 10 Wistar rats of each sex were exposed to estimated dietary doses of 0, 0.18, 0.9, 4.5, or 22.5 mg/kg/day in males, or 0, 0.2, 1.0, 5, or 25 mg/kg/day in females. At week 2 of the study, two male and two female rats receiving the highest dose (22.5 and 25 mg/kg/day, respectively) exhibited clinical signs of ataxia and became progressively inactive. Within 3 days of the first signs of ataxia, the animals became comatose and were sacrificed. The investigators did not report adverse clinical signs at the other dose levels; thus, the 4.5 mg/kg/day (in males and 5 mg/kg/day in females) dose is considered a NOAEL.

Similar neurotoxic effects were observed in an immunotoxicity study in which groups of six female B6C3F_1 mice were exposed to β-HCH in the diet at estimated doses of 0, 19, 57, or 190 mg/kg/day for up to 30 days (Cornacoff et al. 1988). Mice receiving 57 or 190 mg/kg/day showed signs of ataxia within the first week of exposure. The signs resolved in a few days in the 57 mg/kg/day group, whereas approximately 80% of the 190 mg/kg/day mice became laterally recumbent and moribund. No ataxia or other signs of neurotoxicity occurred at 19 mg/kg/day. Other effects in this study included immunological alterations at 57 mg/kg/day (e.g., decreased lymphoproliferative responses to T-cell mitogens and decreased natural killer cell activity), but these end points were only evaluated after 30 days and are therefore not considered to be consequences of acute duration exposure. Support for neuro-

toxicity as the critical effect for acute oral exposure to β-HCH is provided by the Cornacoff et al. (1988) study reporting ataxia after 1 week of exposure to 57 mg/kg/day and a study by Muller et al. (1981) reporting a significant reduction in tail nerve motor conduction velocity in rats exposed to 66 mg/kg/day β-HCH for 30 days.

- An MRL of 0.0006 mg/kg/day has been derived for intermediate-duration oral exposure to β-HCH.

The intermediate oral MRL for β-HCH is based on a LOAEL of 0.18 mg/kg/day for liver effects in rats (Van Velsen et al. 1986) and an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

The critical LOAEL was identified in a 13-week subchronic toxicity study in which groups of 10 Wistar rats of each sex were exposed to estimated dietary doses of 0, 0.18, 0.9, 4.5, or 22.5 mg/kg/day in males, or 0, 0.2, 1.0, 5, or 25 mg/kg/day in females (Van Velsen et al. 1986). End points that were examined included body weight, food consumption, hematology, blood biochemistry, organ weights, gross pathology, and histopathology. Hepatic effects were observed that included hyalinization of centrilobular cells in males at ≥0.18 mg/kg/day and females at 25 mg/kg/day; increased absolute and relative liver weight in both sexes at ≥0.9 mg/kg/day in males and ≥1.0 mg/kg/day in females; periportal fat accumulation, increased mitosis, and/or focal liver cell necrosis in males at ≥4.5 mg/kg/day and females at ≥5 mg/kg/day; and centrilobular hepatocytic hypertrophy, proliferation of smooth endoplasmic reticulum, increased microsomal activity, and/or increased glycogen content in males at 22.5 mg/kg/day and females at 25 mg/kg/day. Other systemic effects included increased absolute and/or kidney weight in females at ≥2.0 mg/kg/day and males at ≥4.5 mg/kg/day; renal medulla calcinosis in males at 22.5 mg/kg/day; and clinical signs (ataxia progressing to inactivity and coma), hematologic and splenic changes indicative of anemia (decreased red blood cells and hemoglobin, increased extramedullar hematopoiesis), and reduced body weight in males at 22.5 mg/kg/day and females at 25 mg/kg/day.

Due to the dose-related nature and progression in severity of the hepatic effects, and the mild, reversible nature of the changes at the lowest dose level, 0.18 mg/kg/day is considered to be a minimal LOAEL based on hyalinization of centrilobular cells. The liver is an established target of β-HCH in other subchronic and chronic studies in rats and mice (Fitzhugh et al. 1950; Ikegami et al. 1991a, 1991b; Ito et al. 1973; Schoter et al. 1987).

γ-HCH (lindane)

- An MRL of 0.003 mg/kg/day has been derived for acute-duration oral exposure to γ-HCH.

The acute oral MRL for γ-HCH is based on a minimal LOAEL of 1 mg/kg/day for developmental/ reproductive effects in rats (Dalsenter et al. 1997b) and an uncertainty factor of 300 (3 for extrapolation from a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

The critical LOAEL was identified in a study that assessed reproductive toxicity in male offspring of rats that were exposed during lactation (Dalsenter et al. 1997b). Groups of nine Bor:spf females 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. Actual doses to the offspring were not determined. The control group was administered the oil vehicle alone on days 9–14 of lactation. Male offspring (10 or 20/group) were terminated on postnatal day (pnd) 65 (puberty) or 140 (adulthood) and evaluated for the following end points: 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 end points (numbers of litters, implantations/litters, fetuses/litter, resorptions), and testicular histology (6 mg/kg offspring only). Effects observed in the 1 mg/kg/day offspring included statistically significant ($p<0.05$) reductions in relative testicular weight at pnd 140 (6.4% less than controls), relative epididymis weight at pnd 65 (7.1%), spermatid number at pnd 65 and 140 (29.0 and 12.8%, respectively), sperm number at pnd 140 (13.2%), serum testosterone at pnd 65 (30.0%), 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 exposed on gestation day 9 or 14, including significantly reduced relative testicular weight at pnd 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 mg/kg/day or 6 mg/kg offspring as shown by the mating, pregnancy, and fertility indices or other pregnancy end points. Because no significant alterations in fertility were observed, the significant changes observed for relative organ weights, sperm number, hormone levels, and intromission incidence are considered minimally adverse. 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.

Similar effects on testicular histology and sperm numbers occurred in adult male offspring of mice that were orally exposed to γ-HCH in doses ≥15 mg/kg/day (lower doses not tested) on gestation days 9–16 (Traina et al. 2003). Additionally, intermediate-duration studies of γ-HCH showed that testicular and other reproductive effects occurred in mink exposed to 1 mg/kg/day. 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 of age showed effects on reproductive efficiency that included reduced receptivity to mating and reduced whelping rate (Beard et al. 1997). The decreased fertility was primarily due to embryo mortality after implantation. Reductions in whelping rate, litter size, and testicular size were observed in a three-generation study of mink exposed to 1 mg/kg/day dietary γ-HCH (Beard and Rawlings 1998). Acute exposure to γ-HCH caused effects on neurological and other systemic end points at oral doses higher than the 1 mg/kg/day LOAEL for developmental/reproductive toxicity. Neurological effects of γ-HCH included enhanced susceptibility to kindling (induction of seizures by repeated subthreshold electrical stimulation of the brain) following a single 5-mg/kg dose (Gilbert and Mack 1995) or 3 mg/kg/day for 4 days (Joy et al. 1982), reduced brain serotonin level following 3 mg/kg/day for 6 days (Attia et al. 1991), and reduced brain barrier permeability in 10-day-old pups exposed to 2 mg/kg as a single dose or 8 daily doses (Gupta et al. 1999). The toxicological relevance of these effects is unclear because there were no concurrent tests of neurobehavioral function (as well as the unnatural method of seizure induction). A comprehensive neurotoxicity screening study was conducted in which groups of 10 male and 10 female Crl:CD BR rats were administered a single dose of γ-HCH by gavage at levels of 0, 6, 20, or 60 mg/kg (Hughes 1999a). This study is an unpublished Confidential Business Information (CBI) submission summarized by EPA (2000). End points included functional observational battery (FOB) and motor activity (MA) tests performed prior to treatment, within 3 hours of dosing, and on post-exposure days 7 and 14, as well as histopathology of nervous system tissues at study termination. No clinical signs or any other effects were observed at 6 mg/kg. Motor activity was decreased in females at ≥20 mg/kg and males at 60 mg/kg. Females also had increased forelimb grip strength and decreased grooming behavior at 20 mg/kg, as well as 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.

Other acute oral effects of γ-HCH included hematological and immunological changes in mice at 10–20 mg/kg/day (Hong and Boorman 1993), developmental changes in rats and mice at 20–45 mg/kg/day in

rats and mice (Dalsenter et al. 1997b; Hassoun and Stohs 1996a; Rivera et al. 1991), and liver and kidney changes in mice at 72 mg/kg/day (Srinivasan and Radhakrishnamurty 1988; Srinivasan et al. 1984).

- An MRL of 0.00001 mg/kg/day has been derived for intermediate-duration oral exposure to γ-HCH.

The intermediate oral MRL for γ-HCH is based on a LOAEL of 0.012 mg γ-HCH/kg/day for immunological/lymphoreticular effects in mice (Meera et al. 1992) and an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

The critical LOAEL was identified in an immunotoxicity study in which groups of six female Swiss mice were exposed to γ-HCH in measured dietary doses of 0, 0.012, 0.12, or 1.2 mg/kg/day for up to 24 weeks (Meera et al. 1992). End points that were evaluated throughout the study included delayed-type hypersensitivity reaction to sheep red blood cells (SRBC), lymphoproliferative response to mitogenic stimulation by concavalin A, mixed lymphocyte reactions, response of IgM antibody forming cells in spleen (plaque formation) to SRBC or lipopolysaccharide (LPS), and peritoneal macrophage phagocytic activity in response to LPS or *Staphylococcus aureus*. Histology of the thymus, peripheral lymph nodes, and spleen was evaluated at 4, 12, and 24 weeks post-treatment. Both the cell-mediated and humoral components of the immune system showed a biphasic response, characterized initially by stimulation followed by suppression in a dose-dependent manner at all dose levels, indicating that a NOAEL was not identified. Effects observed at ≥0.012 mg/kg/day included biphasic changes in delayed-type hypersensitivity reaction to SRBC (increased at 4–12 weeks and decreased at 12–24 weeks), IgM plaque formation to SRBC (increased at 4–8 weeks and decreased at 12–24 weeks), and plaque formation to LPS-SRBC (increased at 4 weeks at ≥0.12 mg/kg/day and decreased at 8-24 weeks at ≥0.012 mg/kg/day). Histological changes occurred in lymphoid organs of treated animals and were consistent with the biphasic immunomodulatory responses. Effects were observed in the spleen at ≥0.12 mg/kg/day, including no significant reaction except for active proliferation of megakaryocytes at 4 weeks post-treatment, an apparent reduction in lymphoid follicles at 12 weeks post-treatment, and considerable reduction in the overall cellularity of red pulp and white pulp areas at 24 weeks post-treatment. Histopathology at 1.2 mg/kg/day included effects in lymph nodes (reduced lymphocyte population and size of medullary cords) and thymus (necrosis in the medulla) at 12–24 weeks post-treatment at 1.2 mg/kg/day.

Immunotoxic effects have been observed in other oral studies of γ-HCH. Immunosuppression in the form of reduced antibody responses to *Salmonella* and typhoid vaccines occurred in rats exposed to

6.25 mg/kg/day for up to 5 weeks (Dewan et al. 1980). Exposure to 10 mg/kg/day for 10 days caused residual bone marrow damage and suppressed granulocyte-macrophage progenitor cells in mice, and atrophy of the thymus was observed in mice following 40 mg/kg/day for 3 days (Hong and Boorman 1993). Serum antibody response to SRBC was suppressed in rats exposed to 3.6 mg/kg/day for 8 weeks (Koner et al. 1998).

3. HEALTH EFFECTS

3.1 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.

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

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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 first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure 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 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 end point 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 end points. 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.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of HCH are indicated in Tables 3-2, 3-3, and 3-5 and Figures 3-2 and 3-3. Because cancer effects could occur at lower exposure levels, Figure 3-3 also shows a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

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

HCH exists as several isomers. The four major isomers discussed in this profile are alpha-HCH (α-HCH), beta-HCH (β-HCH), gamma-HCH (γ-HCH), and delta-HCH (δ-HCH). γ-HCH is also commonly known as lindane. Technical-grade HCH consists of at least five isomers (approximately 60–70% α-HCH, 5–12% β-HCH, 10–15% γ-HCH, 6–10% δ-HCH, and 3–4% ε-HCH). The toxicity of the isomers varies. With respect to acute exposure, γ-HCH is the most toxic, followed by α-, δ-, and β-HCH. With chronic exposure, however, β-HCH is the most toxic followed by α-, γ-, and δ-HCH. With chronic exposures, the increased toxicity of β-HCH is probably due to its longer biological half-life in the body and its accumulation in the body over time.

3.2.1 Inhalation Exposure

Studies examining the inhalation toxicity of HCH in humans are limited. Most of the available information is from case reports of acute poisoning in the home following accidental inhalation of pesticidal powder or from the use of γ-HCH vaporizers, whereby γ-HCH pellets are vaporized by

electrical warming of a ceramic jacket, and from studies of workers engaged in the manufacture and formulation of pesticides and fertilizers. Limitations inherent in these reports or studies include unquantified exposure concentrations and concomitant exposure to HCH mixtures, pyrolysis products from vaporizers, and other pesticides and chemicals. Studies that provide levels of significant exposure for inhalation exposure to γ-HCH are shown in Table 3-1 and Figure 3-1.

3.2.1.1 Death

γ-HCH was once used in vaporizers, resulting in human exposure to unspecified levels via inhalation and dermal routes. Occasional deaths associated with the use of this product for several months or years have been reported, but in no case is it clear that γ-HCH was responsible for the deaths (Loge 1965). Two fatalities resulting from pulmonary edema were reported in toddlers inhaling and ingesting unknown quantities of γ-HCH-containing pesticidal powder (McQueen 1968). No human deaths from inhalation exposure to other isomers have been reported.

An acute study with rats exposed nose-only to γ-HCH aerosol for 4 hours, followed by a 22-day observation period, estimated the acute LC_{50} to be 1,560 mg/m^3 (Ullmann 1986b). Rats inhaling up to 603 mg/m^3 γ-HCH aerosol for 4 hours in whole-body exposure chambers exhibited no mortality throughout the 14-day observation period (Oldiges et al. 1980). In an intermediate-duration study with mice inhaling γ-HCH dust aerosol in whole-body exposure chambers, 16% mortality was observed after 1 week of exposure to 10 mg/m^3, while exposures of up to 14 weeks resulted in 22% mortality at 5 mg/m^3, 2% mortality at 1 mg/m^3, and no mortality at 0.3 mg/m^3 (Klonne and Kintigh 1988).

The lethal concentrations reported by Ullmann (1986b) and Klonne and Kintigh (1988) are presented in Table 3-1 and plotted in Figure 3-1.

3.2.1.2 Systemic Effects

No studies were located regarding gastrointestinal, musculo/skeletal, or dermal effects in humans or animals following inhalation exposure to HCH.

The highest NOAEL values and all NOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

Table 3-1 Levels of Significant Exposure to Gamma-hexachlorocyclohexane (lindane) - Inhalation

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
ACUTE EXPOSURE							
Death							
1	Rat (Wistar)	4 hr				1560 (LC50)	Ullmann 1986b lindane
2	Mouse (CD-1)	1 wk 5 d/wk 6 hr/d				10 (16% mortality)	Klonne and Kintigh 1988 lindane
Systemic							
3	Rat (Wistar)	4 hr	Resp	603			Oldiges et al. 1980 lindane
			Hepatic	603			
			Renal	603			
Neurological							
4	Rat (Wistar)	4 hr			101 (sedation)	642 (ataxia)	Ullmann 1986b lindane
INTERMEDIATE EXPOSURE							
Death							
5	Mouse (CD-1)	14 wk 5 d/wk 6 hr/d				1 (2% mortality)	Klonne and Kintigh 1988 lindane
Systemic							
6	Rat (Wistar)	90 d 6 hr/d	Resp	5			Oldiges et al. 1983 lindane
			Hemato	5			
			Hepatic	5			
			Renal	5			
			Bd Wt	5			

Table 3-1 Levels of Significant Exposure to Gamma-hexachlorocyclohexane (lindane) - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
Neurological							
7	Mouse (CD-1)	14 wk 5 d/wk 6 hr/d	Other	5			Klonne and Kintigh 1988 lindane

a The number corresponds to entries in Figure 3-1.

Bd Wt = body weight; d = day(s); Hemato = hematological; hr = hour(s); LC50, lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

Figure 3-1 Levels of Significant Exposure to Gamma-Hexachlorocyclohexane (Lindane) - Inhalation

Acute (≤14 days)

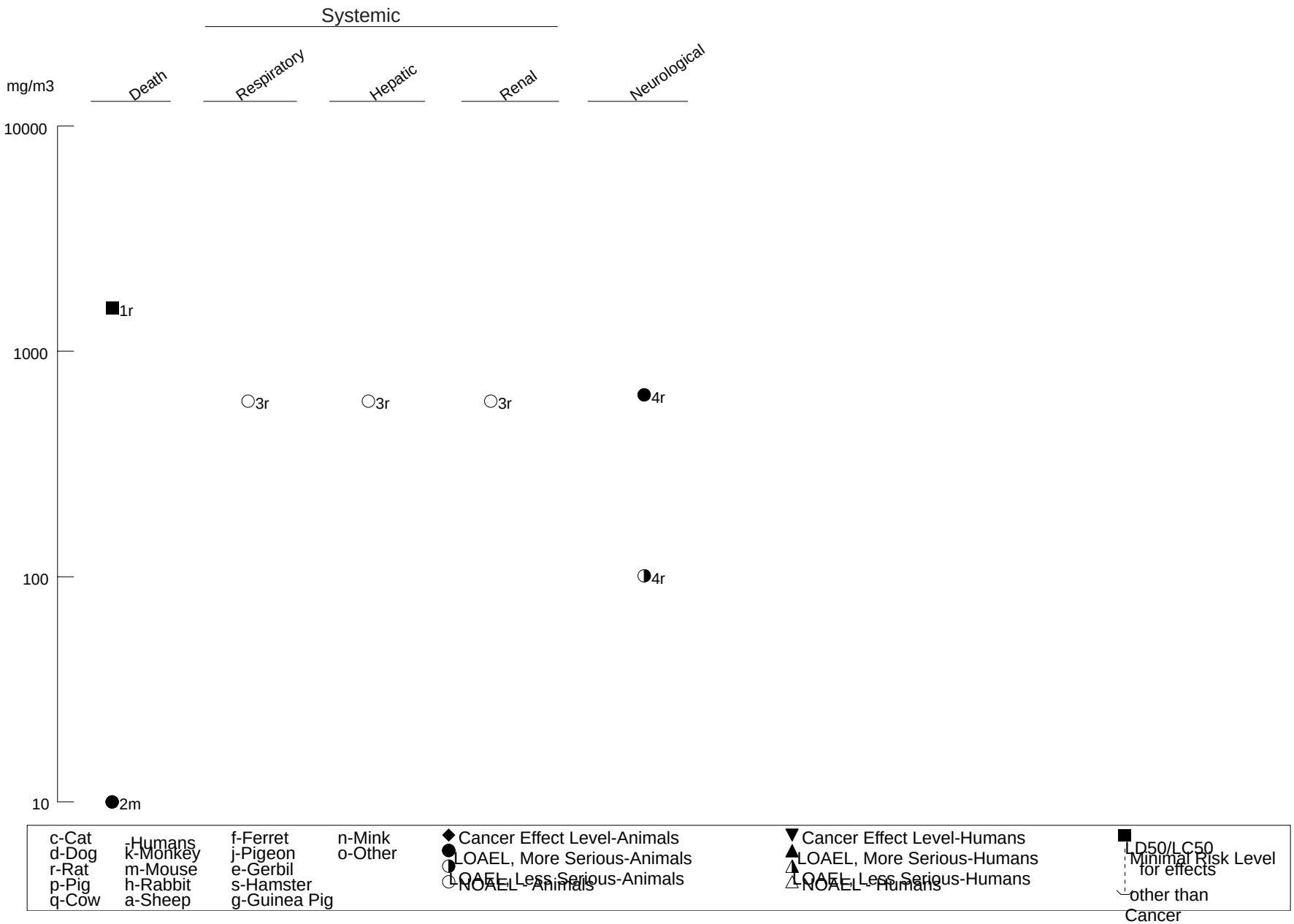
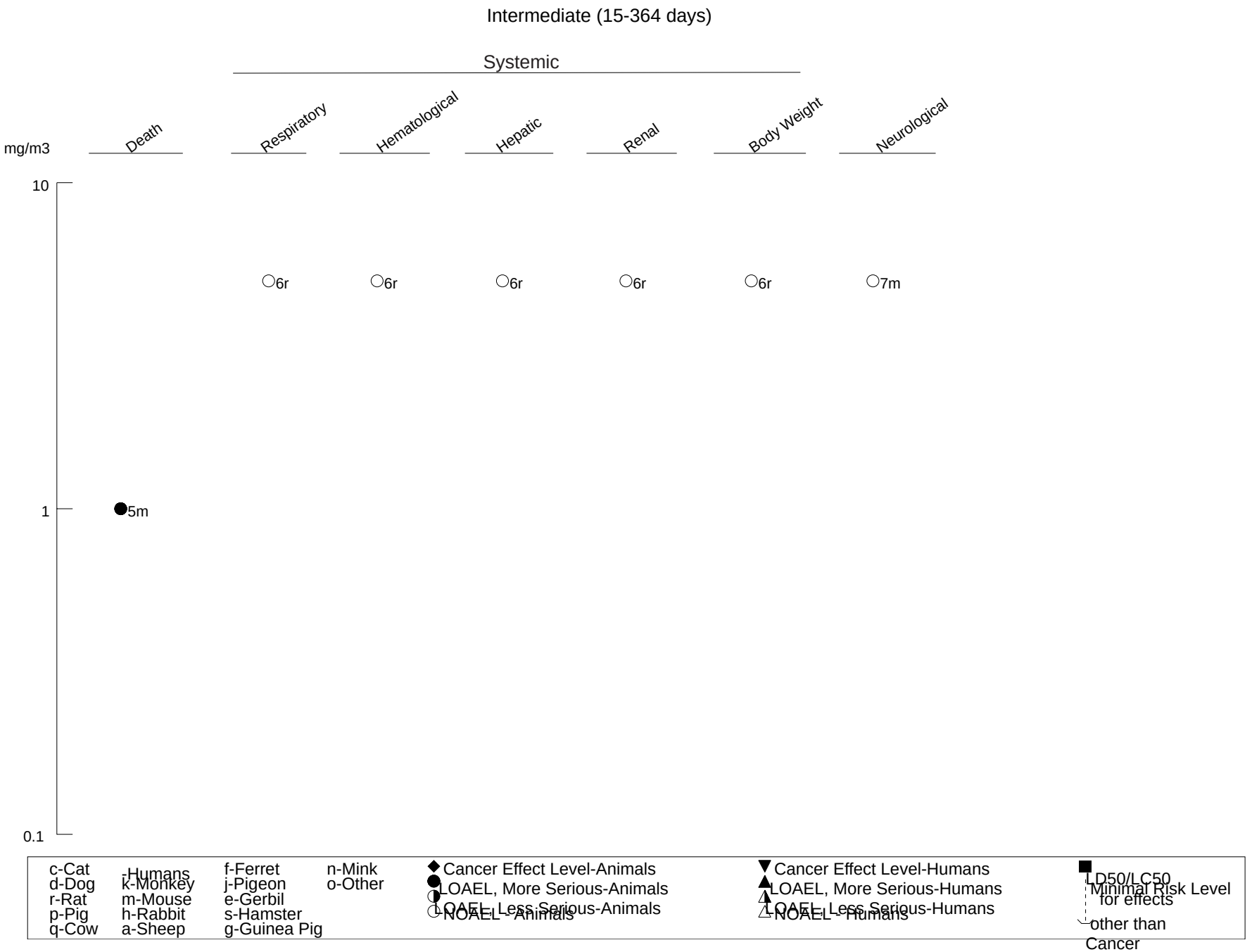


Figure 3-1 Levels of Significant Exposure to Gamma-Hexachlorocyclohexane (Lindane) - Inhalation (*Continued*)



Respiratory Effects. 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.

No respiratory effects were observed in rats exposed to up to 603 mg/m^3 γ-HCH aerosol for 4 hours (Oldiges et al. 1980). No respiratory effects 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).

Cardiovascular Effects. Cardiovascular effects of HCH have been reported in humans exposed to 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.

No studies were located regarding cardiovascular effects in animals following inhalation exposure to HCH.

Hematological Effects. Hematological effects have been reported in humans following acute or chronic inhalation exposure to γ-HCH; however, a causal relationship between exposure to γ-HCH and hematological effects in humans has not been established. 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. Other hematological abnormalities, including isolated instances of leukopenia, leukocytosis, granulocytopenia, granulocytosis, eosinophilia, monocytosis, and thrombocytopenia, have been reported following chronic human occupational exposure to γ-HCH (Brassow et al. 1981; Jedlicka et al. 1958). Exposure concentrations were not specified in these studies and concomitant dermal exposure probably occurred. Although Brassow et al. (1981) reported slight changes in clinical chemistry tests in 60 human workers exposed to

γ-HCH, there were no cases of severe impairment of health. 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; therefore, determination of a causal relationship between exposure and hematological effects cannot be made.

No hematological effects were seen in rats exposed to γ-HCH aerosol (up to 5 mg/m^3) for 90 days (Oldiges et al. 1983).

Hepatic Effects. In humans, statistically significant increases in the blood levels of the enzymes lactate dehydrogenase (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); the HCH isomer concentrations in serum showed a 10-fold increase compared to the control group of workers. Both inhalation and dermal exposure probably occurred. The large standard deviation (SD) from the mean reported for γ-glutamyl transpeptidase in exposed workers (mean±SD =22.2±40.31 IU/mL) suggests the increased activity of this enzyme may not be related to HCH exposure or that individual responses may vary.

No hepatic effects were observed in rats after acute exposure to 603 mg/m^3 γ-HCH (Oldiges et al. 1980). Rats exposed to γ-HCH aerosol (5 mg/m^3, 6 hours/day) exhibited increased hepatic cytochrome P-450 concentration after 90 days, but this level returned to control values after a 4-week recovery period (Oldiges et al. 1983).

Renal Effects. No studies were located regarding renal effects in humans following inhalation exposure to HCH.

No renal effects were seen in rats exposed to up to 603 mg/m^3 γ-HCH aerosol for 4 hours (Oldiges et al. 1980) or up to 5 mg/m^3 γ-HCH aerosol 6 hours/day for 90 days (Oldiges et al. 1983).

Endocrine Effects. Serum luteinizing hormone levels were significantly increased in 54 men occupationally exposed to γ-HCH for approximately 8 years in a γ-HCH producing factory compared to a group of 20 control individuals (Tomczak et al. 1981). The mean serum concentration of follicle

stimulating hormone was increased and testosterone was decreased, but the differences relative to controls were not statistically significant (Tomczak et al. 1981).

No studies were located regarding endocrine effects in animals following inhalation exposure to HCH.

Ocular Effects. No studies were located regarding ocular effects in humans following inhalation exposure to HCH.

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).

Body Weight Effects. No studies were located regarding body weight effects in humans following inhalation exposure to HCH.

No body weight effects were seen in rats exposed to up to 5 mg/m^3 γ-HCH aerosol 6 hours/day for 90 days (Oldiges et al. 1983).

3.2.1.3 Immunological and Lymphoreticular Effects

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.

No studies were located regarding immunological or lymphoreticular effects in animals following inhalation exposure to HCH.

3.2.1.4 Neurological Effects

Paresthesia of the face and extremities, headache, and vertigo have been 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

exposure probably occurred. Abnormal electroencephalographic (EEG) patterns (increased variation in the frequency and amplitude of wave pattern or more serious changes without specific EEG signs) have been reported in 16 of 37 workers following exposure to γ-HCH for 0.5–2 years in a fertilizer plant (Czegledi-Janko and Avar 1970). Exposure concentrations were not reported; however, these EEG changes were found to correlate with blood levels of γ-HCH. 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).

Rats exposed to various concentrations of 99.6% γ-HCH aerosol via nose-only inhalation for 4 hours exhibited concentration-related neurological effects when observed for up to 22 days after exposure (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 642 and 2,104 mg/m^3; and spasms were also noted at the highest concentration (2,104 mg/m^3). Rats exposed to 0.02–5 mg/m^3 γ-HCH aerosol for 90 days exhibited a "slightly disturbed general condition" beginning at day 15 (Oldiges et al. 1983). Mice were similarly exposed for 14 weeks and exhibited no clinical signs of neurotoxicity (Klonne and Kintigh 1988).

NOAELs and LOAELs for neurological effects in animals following inhalation exposure are listed in Table 3-1 and plotted in Figure 3-1.

3.2.1.5 Reproductive Effects

Statistically significant increases in the levels of serum luteinizing hormone 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 follicle stimulating hormone was increased and testosterone was decreased, these differences were not statistically significant compared to mean values determined in a control group. These hormonal changes may have resulted in diminished reproductive capability.

No studies were located regarding reproductive effects in animals following inhalation exposure to HCH.

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals following inhalation exposure to HCH.

3.2.1.7 Cancer

There is no clear evidence of increased risk of non-Hodgkin's lymphoma among farmers from Kansas, Nebraska, Iowa, and Minnesota who used γ-HCH (Blair et al. 1998). Results of four case control studies conducted in the 1980s were pooled for analysis of a combined data set of 987 men with non-Hodgkin's lymphoma and 2,895 population-based controls. Odds ratios (ORs) indicated that reported use of γ-HCH significantly increased the odds of developing non-Hodgkin's lymphoma by 50% (OR=1.5, 95% confidence interval (CI) 1.1–2.0). Some use characteristics suggested a dose-response relationship, although differences between cases and controls were not statistically significant. For example, ORs were greater among individuals who first used γ-HCH ≥20 years before diagnosis (OR=1.7, 95% CI 1.1–2.5) compared to those with <20 years of use (OR=1.3, 95% CI 0.7–2.3), and among persons who reported ≥5 days per year of γ-HCH use (OR=2.0, 95% CI 0.6–6.4) compared with those with <5 days per year of use (OR=1.6, 95% CI 0.6–4.0). Other factors reduced apparent risk, including adjustment for potential confounding by use of other pesticides such as 2,4-D and diazinon, which reduced the OR associated with γ-HCH use from 1.5 (95% CI 1.1–2.0) to 1.2 (95% CI 0.5–2.2) and 1.3 (95% CI 0.9–1.9), respectively. The authors concluded that γ-HCH is not a major factor in the development of non-Hodgkin's lymphoma but may play some role. There was also no clear evidence of an increased risk of non-Hodgkin's lymphoma in a population-based study of Canadian men of varying occupations. There was a significantly increased risk of non-Hodgkin's lymphoma with exposure to γ-HCH; however, after additional multivariate analysis to factor in exposure to other chemicals, history of cancer among first-degree relatives, and personal history of measles and allergy sensitization, γ-HCH was not considered a significant independent predictor (McDuffie et al. 2001).

No studies were located regarding carcinogenic effects in animals following inhalation exposure to HCH.

3.2.2 Oral Exposure

The Levels of Significant Exposure for oral exposure to γ-HCH are presented in Table 3-2 and Figure 3-2. Levels of Significant Exposure for α-, β-, δ-, and technical-grade HCH are presented in Table 3-3 and Figure 3-3.

3.2.2.1 Death

Case reports have described deaths in humans (usually children, some suicidal adults) following ingestion of γ-HCH, often from the tablets intended for γ-HCH vaporizers (Storen 1955; Sunder Ram Rao et al. 1988). The amounts of γ-HCH associated with these deaths are not known.

γ-HCH has been shown to be lethal to animals following single gavage administration (Gaines 1960; Liu and Morgan 1986; Tusell et al. 1987). The LD_{50} value for female rats is 91 mg/kg, and the LD_{50} value for male rats is 88 mg/kg (Gaines 1960). One of seven male Wistar rats died following a single oral administration of 60 mg/kg γ-HCH (Martinez et al. 1991). DBA/2 strain mice, recognized as being "unresponsive" to microsomal enzyme induction, are more sensitive to the acute lethal effects of γ-HCH than C57BL/6 strain mice when exposed to 20 mg/kg/day for 10 days (Liu and Morgan 1986). In a 15-week study, 2 of 12 F-344 rats treated with 20 mg/kg/day died (Chadwick et al. 1988). A 2-year study in rats fed γ-HCH in their diets (32 mg/kg/day) also found a significantly increased mortality rate compared with controls (Amyes 1990). The oral LD_{50} for technical-grade HCH in CFT-Wistar rats treated once by gavage was 2,428 mg/kg (Joseph et al. 1992a). Exposure to 5 mg/kg/day of technical-grade HCH for 90 days resulted in the deaths of 6/12 male rats and 4/12 female rats (Dikshith et al. 1991b). 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). However, the deaths occurred late in the study and were accompanied by other changes, indicating that they were due to pathogenic infection rather than HCH exposure. The LD_{50} for rats and the LOAEL values from the intermediate-duration studies are recorded in Tables 3-2 and 3-3 and plotted in Figures 3-2 and 3-3.

Table 3-2 Levels of Significant Exposure to Gamma-hexachlorocyclohexane (lindane) - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
ACUTE EXPOSURE							
Death							
1	Rat (Sherman)	once (GO)				88 M (LD50) 91 F (LD50)	Gaines 1960 lindane
2	Rat (Wistar)	once (GO)				60 M (1/7 deaths)	Martinez et al. 1991 lindane
Systemic							
3	Rat (Wistar)	1 x/d 5-21 d (G)	Hepatic	2.5 M	5 M (increased EROD, PROD, and NDMA-d enzyme levels)		Parmar et al. 2003 lindane
4	Rat (Sprague-Dawley)	48h 1x/d (F)	Hepatic		30 (Reduced number of cells per field; increased cell, nucleus, and nucleolus size; slight cellular disorganization)		Shahid Ali and Rauf Shakoori 1998 lindane
5	Rat	2wks (F)	Hepatic		72 (Altered activities of serum aminotransferases, alkaline phosphatase, altered soluble enzymes and altered carbohydrate metabolism)		Srinivasan and Radhakrishnamurty 1988 lindane

Table 3-2 Levels of Significant Exposure to Gamma-hexachlorocyclohexane (lindane) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
6	Rat (Wistar)	14 d ad libitum (F)	Renal			72 M (10% increase in kidney weight, altered excretion patterns, distention of glomeruli, swelling of tubular epithelia)	Srinivasan et al. 1984 lindane
7	Mouse (B6C3F1)	10 d 1 x/d (GO)	Resp	20 M			Hong and Boorman 1993 lindane
			Cardio	20 M			
			Gastro	20 M			
			Hemato		10 M (Transient decrease in marrow progenitor cell numbers)		
			Hepatic	20 M			
			Renal	20 M			
			Bd Wt	20 M			

Table 3-2 Levels of Significant Exposure to Gamma-hexachlorocyclohexane (lindane) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
8	Mouse (B6C3F1)	3 d 1x/d (GO)	Resp	40 M			Hong and Boorman 1993 lindane
			Cardio	40 M			
			Gastro	40 M			
			Hemato		20 M (Transient reduction in marrow progenitor cell number)		
			Hepatic	40 M			
			Renal	40 M			
			Endocr	40 M			
			Bd Wt	40 M			
Immuno/ Lymphoret							
9	Mouse (B6C3F1)	3 d 1x/d (GO)		10 M	20 M (decreased thymus weights)	40 M (Atrophy of thymus cortex)	Hong and Boorman 1993 lindane
10	Mouse (B6C3F1)	10 d 1x/d (GO)			10 M (Dose-related decrease in relative thymus and spleen weights)		Hong and Boorman 1993 lindane
Neurological							
11	Rat (Sprague-Dawley)	6 d 1x/d (GO)			3 M (increased pineal N-acetyltransferase, decreased serotonin levels)		Attia et al. 1991 lindane

Table 3-2 Levels of Significant Exposure to Gamma-hexachlorocyclohexane (lindane) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
12	Rat (Long- Evans)	once (GO)			5 M (myoclonic jerks and single clonic seizure in kindled animals)	10 M (myoclonic jerks and single clonic seizures in naive animals)	Gilbert and Mack 1995 lindane
13	Rat	once (G)		6	20 (Decreased motor activity and grooming behavior, increased forelimb grip strength)	60 (Clinical signs of neurotoxicity including tremors and convulsions)	Hughes 1999a lindane
14	Rat (Sprague-Dawley)	4 d 1x/d (GO)			3 M (increased kindling acquisition)	10 M (seizures)	Joy et al. 1982 lindane
15	Rat (Wistar)	once (GO)				60 (convulsions)	Martinez and Martinez-Conde 1995 lindane
16	Rat (Wistar)	once (GO)				60 M (tonic-clonic seizures)	Martinez et al. 1991 lindane
17	Rat (Wistar)	1 x/d 5 d (G)		5 M	10 M (increased EROD, PROD, and NDMA-d enzyme levels in the brain)		Parmar et al. 2003 lindane

Table 3-2 Levels of Significant Exposure to Gamma-hexachlorocyclohexane (lindane) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
18	Rat (Wistar)	1 d (G)				35 M (convulsions in 4/10 animals)	Parmar et al. 2003 lindane
19	Rat	once (G)			20 (altered acquisition of a passive avoidance task in 15-day-old pups)		Rivera et al. 1998 lindane
20	Rat (Wistar)	3 d 1x/d (GO)			5 (decreased myelin and 2',3'-cyclic nucleotide 3'-phosphodiesterase activity in brains)		Serrano et al. 1990a lindane
21	Rat (Wistar)	once (GO)		15 M		20 M (convulsions)	Vendrell et al. 1992a lindane
22	Rat (Sprague-Dawley)	once (GO)				30 M (seizures)	Wooley and Griffith 1989 lindane

Table 3-2 Levels of Significant Exposure to Gamma-hexachlorocyclohexane (lindane) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg)	LOAEL Less Serious (mg/kg)	LOAEL Serious (mg/kg)	Reference Chemical Form
Reproductive							
23	Rat	Ld 9-14 1x/d (GO)			1 M[b] (Reduced relative testicular and epididymis weight (~10%), spermatid and sperm counts (~10%), and testosterone levels (30-50%) at maturity with no effect on fertility)		Dalsenter et al. 1997b lindane
24	Rat	Ld 9 or 14 once (GO)			6 M (Reduced relative testical and epidymis weight (~10%), spermatid and sperm counts (~8-10%), testosterone levels (~30-50%), Leydig cell numbers and spermatogenisis at maturity with no effect on fertility)		Dalsenter et al. 1997b lindane
25	Rat (Long- Evans)	7 d 1x/d (GO)		40 F			Laws et al. 1994 lindane
26	Rat (CDF-F344)	once			25 (increased length of estrous cycle)		Uphouse and Williams 1989 lindane

Table 3-2 Levels of Significant Exposure to Gamma-hexachlorocyclohexane (lindane) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
27	Mouse (CD-1)	3 d 1 x/d (GO)		15 F	25 F (increase in degenerating two-cell embryos following preovulatory exposure)		Scascitelli and Pacchierotti 2003 lindane
28	Mouse (CD-1)	7 d Gd 9-16 1 x/d (GO)			15 M (Reduced testicular sperm head count and concentration and other effects on spermatogenesis in adult F1 males exposed during gestation)		Traina et al. 2003 lindane
Developmental							
29	Rat (Wistar)	Pc 15 1x (GO)			30 (reduction of serum testosterone concentration in adult offspring)		Dalsenter et al. 1997a lindane
30	Rat (Wistar)	Gd 6-15 1x/d (GO)		25 F			Khera et al. 1979 lindane
31	Rat (CFY)	Gd 6-15 1x/d (GW)		20 F			Palmer et al. 1978a lindane

Table 3-2 Levels of Significant Exposure to Gamma-hexachlorocyclohexane (lindane) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
32	Rat (Wistar)	once (GO)			20 (regional changes in brain noradrenaline and serotonin levels in suckling rats)		Rivera et al. 1991 lindane
33	Mouse C57BL/6J	Single oral dose on day 12 of gestation (GI)			30 (decrease in fetal weight, fetal thymus weight)		Hassoun and Stohs 1996a lindane
34	Mouse DBA/2J	Single oral dose on day 12 of gestation (GI)			45 (decrease in fetal and placental weight)		Hassoun and Stohs 1996a lindane
35	Rabbit (New Zealand)	Gd 6-18 1x/d (GW)		20 F			Palmer et al. 1978a lindane
INTERMEDIATE EXPOSURE							
Death							
36	Rat (Fischer- 344)	15 wk 1x/d (GO)				20 F (2/12 deaths)	Chadwick et al. 1988 lindane

Table 3-2 Levels of Significant Exposure to Gamma-hexachlorocyclohexane (lindane) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
Systemic							
37	Rat (albino)	1x d 6 wks (G)	Cardio		3 M (tachycardia, increase in blood pressure, plasma calcium levels, myocardial calcium influx. Decreased Ca,K-ATPase activity. ECG changes: increase in ST segment, T-wave amplitude; reduced R-R interval, P-wave		Anand et al. 1995 gamma
38	Rat (Wistar)	15 d ad libitum (F)	Hepatic		1.8 M (Increases in lipid peroxidation, level of cytochrome P-450, and activities of superoxide dismutase)		Barros et al. 1991 lindane
39	Rat (Wistar)	30 d ad libitum (F)	Hepatic		1.8 M (Increases in lipid peroxidation, level of cytochrome P-450, and activities of superoxide dismutase)		Barros et al. 1991 lindane
40	Rat (Wistar)	40d (F)	Hepatic	50			Desi 1974 lindane
			Renal		5 (increased kidney weight)		

Table 3-2 Levels of Significant Exposure to Gamma-hexachlorocyclohexane (lindane) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
41	Rat (Wistar)	1 x/d 5-21 d (G)	Hepatic		2.5 M (increased liver weight;increased P-450 content and P-450 dependent enzymes)		Parmar et al. 2003 lindane
42	Rat (Sprague-Dawley)	15d 1x/d (F)	Hepatic		18 (Reduced number of cells per field; incresed cell, nucleus, and nucleolus size; vacuoles in the cytoplasm and granulation; apparent fatty degeneration)		Shahid Ali and Rauf Shakoori 1998 lindane
43	Rat (Wistar)	12 wk ad libitum (F)	Hemato	10			Suter 1983 lindane
			Hepatic	0.4	2 (centrilobular hypertrophy)		
			Renal	0.4	2 (tubular distension, basophilic tubules)		
44	Mouse (dd)	24 wk ad libitum (F)	Hepatic		90 M (centrilobular hypertrophy)		Ito et al. 1973 lindane

Table 3-2 Levels of Significant Exposure to Gamma-hexachlorocyclohexane (lindane) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
Immuno/ Lymphoret							
45	Rat	8 wk ad libitum (F)			3.6 (reduced serum antibody response to SRBC)		Koner et al. 1998 lindane
46	Mouse (Swiss albino)	24 wk ad libitum (F)			0.012[c] F (changes in cell- and humoral-mediated immune system)	1.2 F (necrosis of thymus)	Meera et al. 1992 lindane
Neurological							
47	Rat (Wistar)	90 d ad libitum (F)				90 M (tonic convulsions)	Arisi et al. 1994 lindane
48	Rat (Long- Evans)	30 d 1x/d (GO)				10 M (myoclonic jerks and clonic seizures)	Gilbert 1995 lindane
49	Rat (Long- Evans)	10 wk 3 d/wk (GO)				10 M (myoclonic jerks and clonic seizures)	Gilbert 1995 lindane
50	Rat (CD)	13 wk ad libitum (F)		7.9 F	30.2 F		Hughes 1999b lindane
51	Rat (Wistar)	30 d (GO)			2 (decreased dopamine levels)		Martinez and Martinez-Conde 1995 lindane

Table 3-2 Levels of Significant Exposure to Gamma-hexachlorocyclohexane (lindane) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
52	Rat (Wistar)	30 d ad libitum (F)		12.3 M	25.4 M (reduced tail nerve conduction velocity)		Muller et al. 1981 lindane
53	Rat (Wistar)	25 d GD 6 - LD 10 ad libitum (F)		1.2 F	5.6 F (increased motor activity and decreased motor activity habituation in pups at postnatal days 11 and 65)		Myers 1999 lindane
54	Rat (Wistar)	1 x/d 15 d (G)			2.5 M (increased EROD, PROD, and NDMA-d enzyme levels in the brain)		Parmar et al. 2003 lindane
Reproductive							
55	Rat (Fischer- 344)	15 wk 1x/d (GO)		5 F	10 F (disrupted ovarian cycling, antiestrogenic effects)		Chadwick et al. 1988 lindane
56	Rabbit (hybrid)	12 wk 3 d/wk (GO)			0.8 F (reduced ovulation rate)		Lindenau et al. 1994 lindane
57	Rabbit (New Zealand)	12-15 wk 3 d/wk (GO)		0.8 F			Seiler et al. 1994 lindane

Table 3-2 Levels of Significant Exposure to Gamma-hexachlorocyclohexane (lindane) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
58	Mink (NS)	3 generations (F)			1 (reduced litter size in F2 females, reduced testis size in F3 males)		Beard and Rawlings 1998 lindane
59	Mink (NS)	12 wk 3 wk premating 8 wk postpartum (F)			1 F (reduced mating receptivity and whelping rate)		Beard et al. 1997 lindane
60	Mink (NS)	17 wk 6 wk premating 10 wk postpartum (F)			1 F (reduced whelping rate and increased post-implantation embryo loss)		Beard et al. 1997 lindane
Developmental							
61	Rat (Wistar)	Gd 0-21 Ld 1-28 (F)			25 (Increased liver weight and decreased kidney weight in pups exposed during gestatino and lactation)		Srinivasan et al. 1991a lindane
62	Rabbit (New Zealand)	12-15 wk 3 d/wk (GO)		0.8 F			Seiler et al. 1994 lindane
CHRONIC EXPOSURE							
Death							
63	Rat (Wistar)	up to 52 weeks ad libitum (F)				32 F (increased mortality rate)	Amyes 1990 lindane

Table 3-2 Levels of Significant Exposure to Gamma-hexachlorocyclohexane (lindane) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
Systemic							
64	Rat (Wistar)	up to 2 yr ad libitum (F)	Hepatic		7 M (periacinar hepatocytic hypertrophy)		Amyes 1990 lindane
			Renal	32 F			
65	Rat (Wistar)	107 weeks (F)	Hepatic	4 F	7 M (Very slight microscopic liver damage in the absence of gross liver damage)	112 M (Moderate microscopic damage [hepatic cell atrophy, fatty degeneration, and focal necrosis] in the presence of slight-to-moderate gross liver damage)	Fitzhugh et al. 1950 lindane
			Renal	4 F	7 M (focal nephritis)		
			Bd Wt	64 F	112 M (17% decrease in body weight gain)		
66	Rat (Sprague-Dawley)	18mo 1x/d (F)	Hepatic		9 (Increased cell, nucleus, and nucleolus size; extensive cytoplasmolysis; slight cytoplasmic degeneration; incresing nuclear distortion)		Shahid Ali and Rauf Shakoori 1998 lindane
Cancer							
67	Mouse (B6C3F1)	80 wk ad libitum (F)				13.6 M (CEL: hepatocellular carcinoma)	NCI 1977 lindane

Table 3-2 Levels of Significant Exposure to Gamma-hexachlorocyclohexane (lindane) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
68	Mouse (F-1 hybrid)	24 mo ad libitum (F)				27.2 F (CEL: hepatocellular carcinoma, lung tumors)	Wolff et al. 1987 lindane

a The number corresponds to entries in Figure 3-2.

b Used to derive an acute-duration oral minimal risk level (MRL) of 0.003 mg/kg/day for gamma-HCH; based on a minimal LOAEL of 1 mg/kg/day divided by an uncertainty factor of 300 (3 for use of a LOAEL, 10 for extrapolation from animals to humans, 10 for human variability)

c Used to derive an intermediate-duration minimal risk level (MRL) of 0.00001 mg/kg/day for gamma-HCH; 0.012 mg/kg/day divided by an uncertainty factor of 1000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, 10 for human variability)

Bd Wt = body weight; cardio = cardiovascular; CEL = cancer effect level; d = day(s); endocr = endocrine; EROD = 7-ethoxyresorufin-O-deethylase; F = female; (F) = food; (G) = gavage; (GO) = gavage in oil; (GW) = gavage in water; Gd = gestation day(s); GI = gastric intubation; gastro = gastrointestinal; Hemato = hematological; hr = hour(s); Ld = lactation day; LD50, lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); NDMA-d = N-nitrosodimethylamine demethylase; NOAEL = no-observed-adverse-effect level; Pc = post conception; PROD = 7-pentoxyresorufin-O-dealkylase; Resp = respiratory; wk = week(s); x = time(s); yr = year(s)

Figure 3-2 Levels of Significant Exposure to Gamma-hexachlorocyclohexane (lindane) - Oral

Acute (≤14 days)

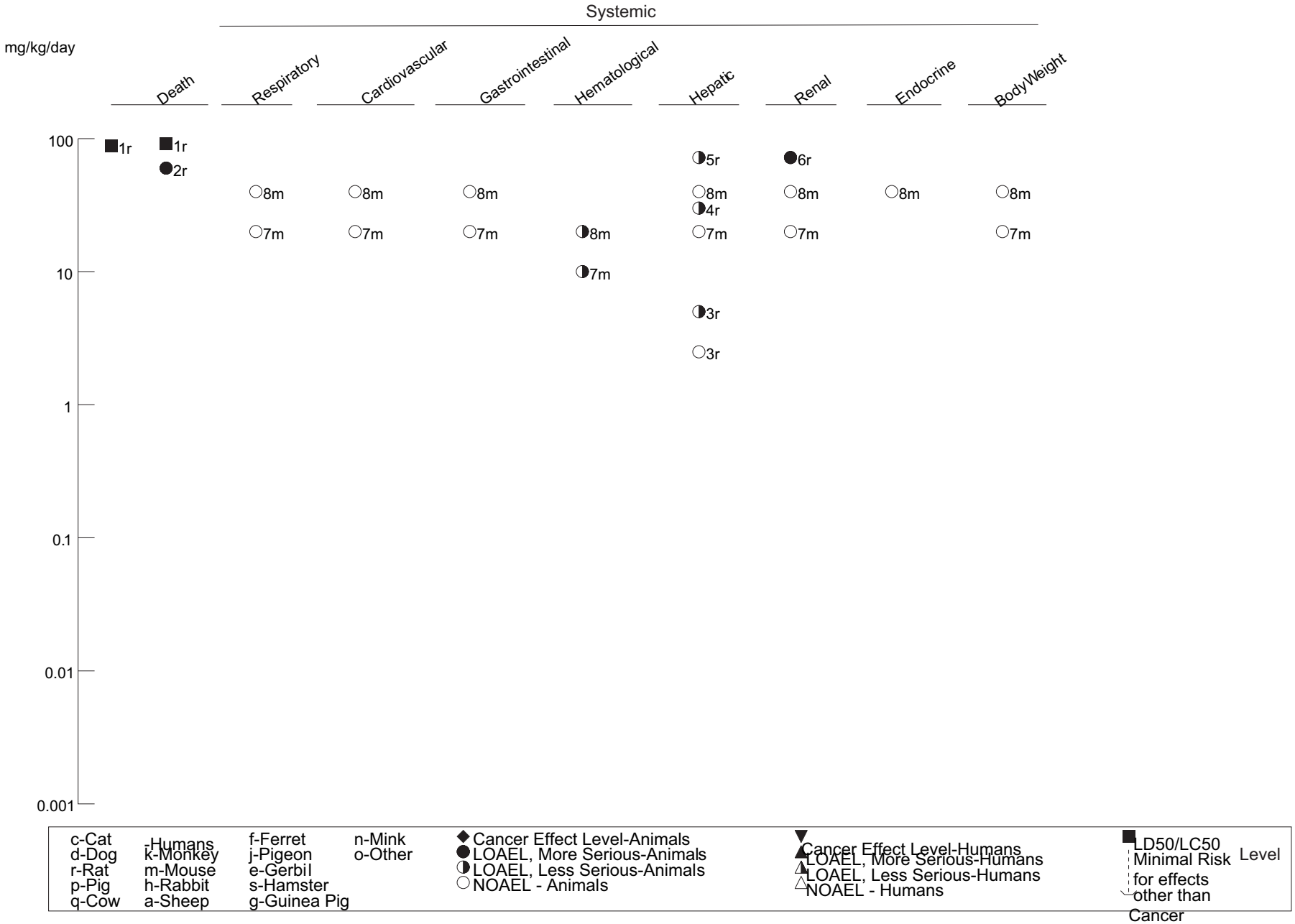


Figure 3-2 Levels of Significant Exposure to Gamma-hexachlorocyclohexane (lindane) - Oral (Continued)

Acute (≤14 days)

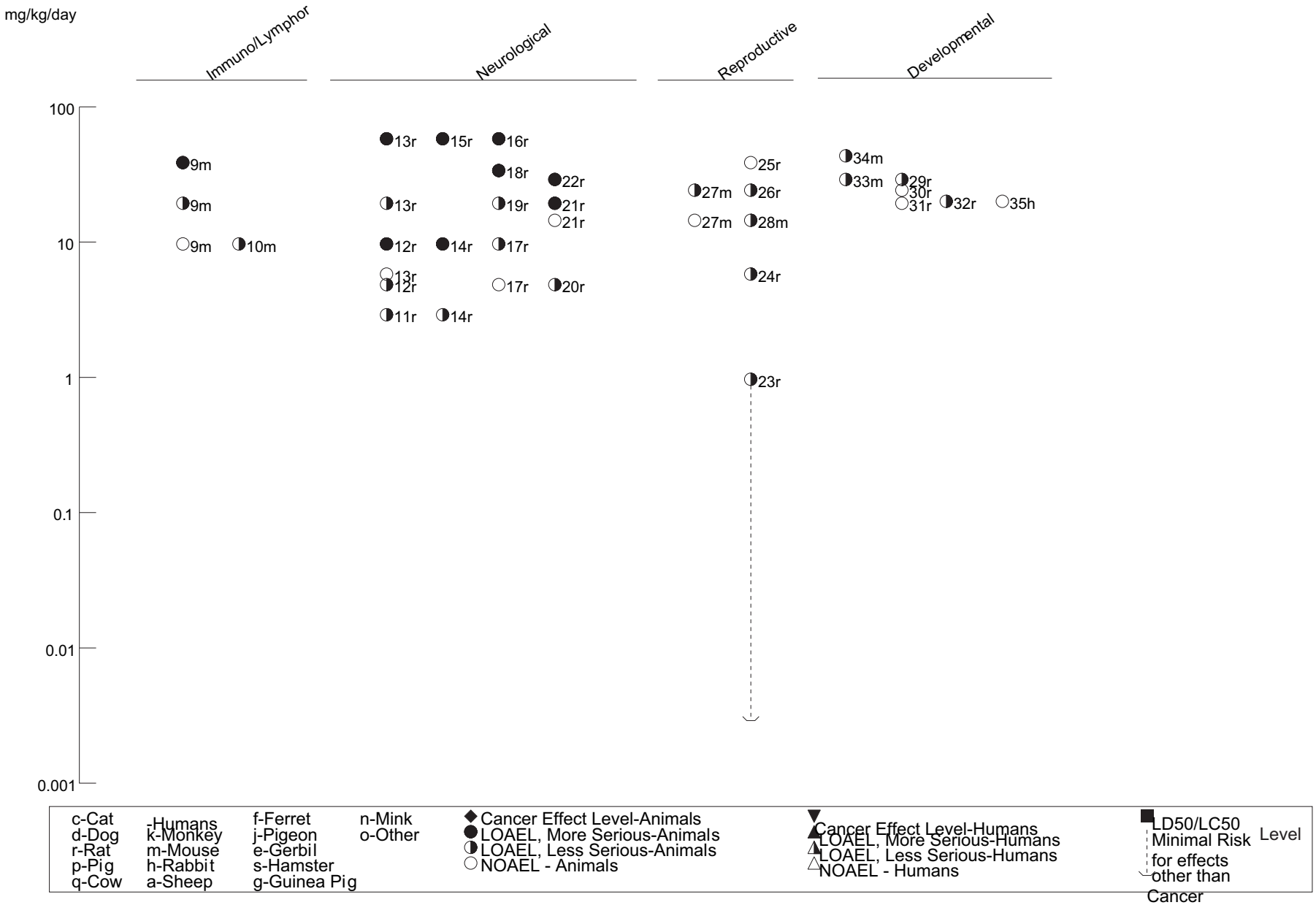


Figure 3-2 Levels of Significant Exposure to Gamma-hexachlorocyclohexane (lindane) - Oral (Continued)

Intermediate (15-364 days)

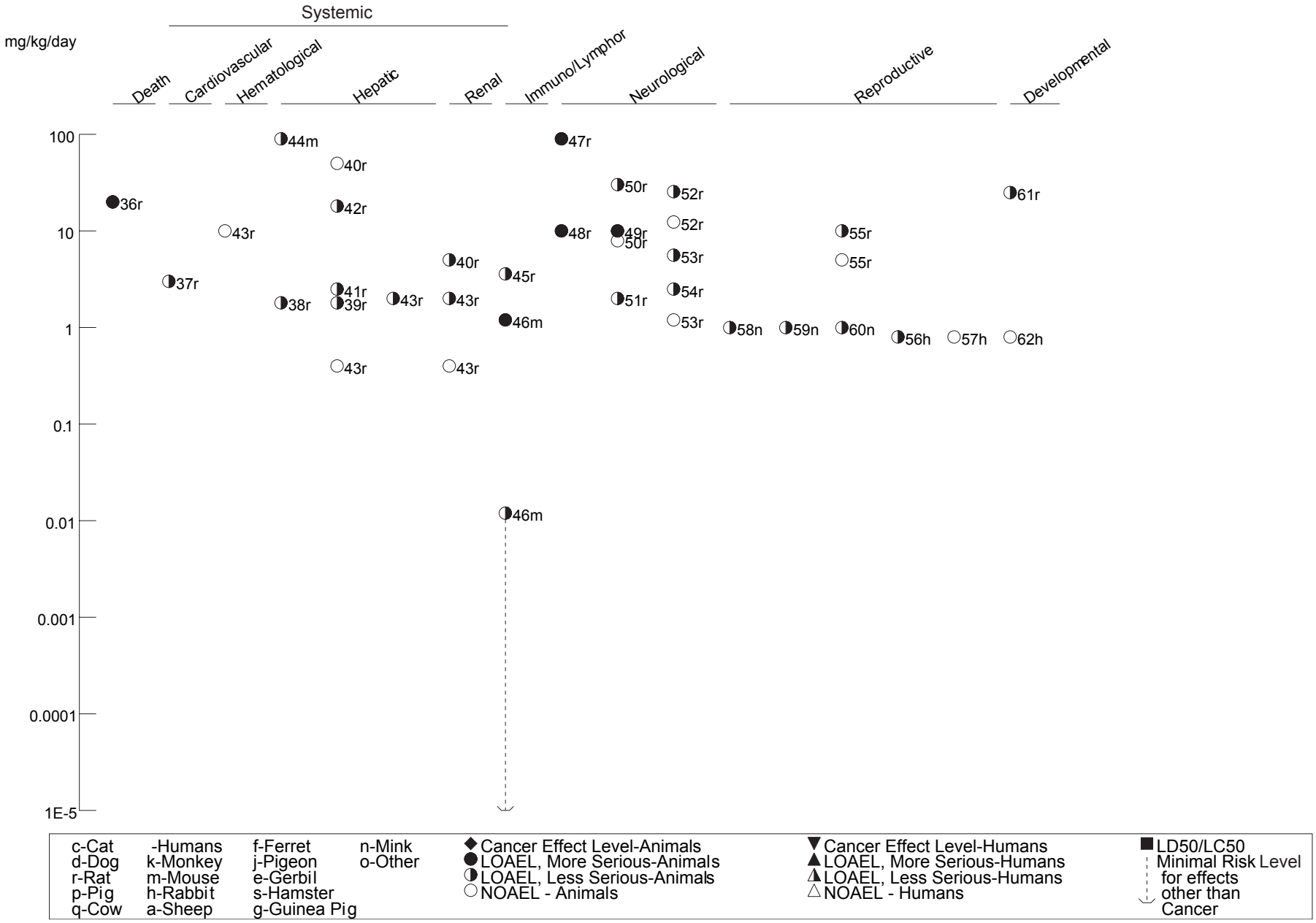


Figure 3-2 Levels of Significant Exposure to Gamma-hexachlorocyclohexane (lindane) - Oral (*Continued*)

Chronic (≥365 days)

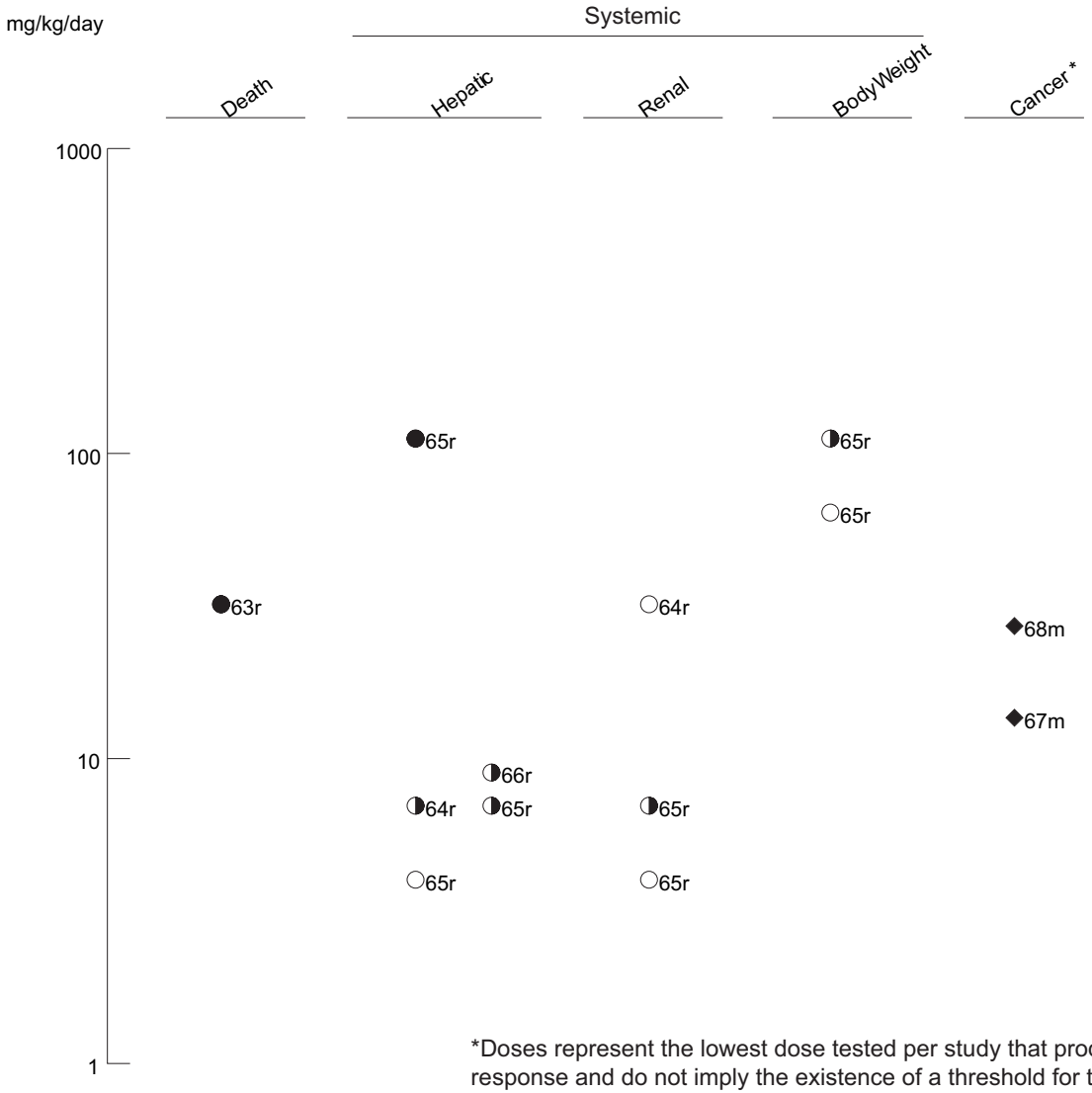


Table 3-3 Levels of Significant Exposure to Alpha-, Beta-, Delta-, And Tech-grade HCH - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
ACUTE EXPOSURE							
Death							
1	Rat (CFT-Wistar)	once (GO)				2428 M (LD50)	Joseph et al. 1992a technical
Systemic							
2	Rat (NS)	once (GO)	Metab		100 F (increased phosphoinositide turnover in erythrocyte membranes)		Agrawal et al. 1995 technical
3	Rat (Sprague-Dawley)	2 wk ad libitum (F)	Hepatic		90 M (increased triglycerides, phospholipids and cholesterol, increased cytochrome C reductase and decreased glutathione peroxidase)		Ikegami et al. 1991a beta
4	Rat (Sprague-Dawley)	2 wk ad libitum (F)	Hepatic		90 M (increased relative liver weight and cytochrome P-450 levels and decreased hepatic vitamin A levels)		Ikegami et al. 1991b beta
5	Rat (Wistar)	14 d ad libitum (F)	Renal			72 M (tubular degeneration, distention of glomeruli, swelling of tubular epithelia, 22% increase in kidney weight, altered excretion patterns)	Srinivasan et al. 1984 beta

Table 3-3 Levels of Significant Exposure to Alpha-, Beta-, Delta-, And Tech-grade HCH - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
6	Mouse (Swiss albino)	Gd 9 once (GO)	Hepatic		5 F (significantly decreased GOT and lactate dehydrogenase (LD) activities)		Dikshith et al. 1990 technical
7	Mouse (NS)	1, 5, 15 d 1x/d (GO)	Hepatic			50 (congestion of portal vessels and central vein, fatty changes, granular degeneration)	Philip et al. 1989 technical
			Renal			50 (congestion of blood vessels and glomeruli, fatty changes, interstitial hemorrhaging)	
8	Mouse (Swiss albino)	2 wk ad libitum (F)	Hepatic		72 M (127% increase in relative liver weight, increased serum alanine and aspartate aminotransferases and ALP, increased hepatic phosphatases and acid cathepsin)		Ravinder et al. 1989 technical
9	Mouse (Swiss albino)	2 wk ad libitum (F)	Hepatic		72 M (cellular hypertrophy, centrilobular degeneration, focal necrosis)		Ravinder et al. 1990 technical

Table 3-3 Levels of Significant Exposure to Alpha-, Beta-, Delta-, And Tech-grade HCH - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
Neurological							
10	Rat (Wistar)	2 wk ad libitum (F)		5 M 4.5[b] F		22.5 M (ataxia, inactivity) 25 F (ataxia, inactivity)	Van Velsen et al. 1986 beta
11	Mouse (B6C3F1)	1 wk ad libitum (F)		19 F	57 F (ataxia)	190 F (lateral recumbancy)	Cornacoff et al. 1988 beta
Reproductive							
12	Mouse (Swiss albino)	Gd 9 once (GO)		5 F		25 F (increased fetal resorptions)	Dikshith et al. 1990 technical
INTERMEDIATE EXPOSURE							
Death							
13	Rat (NS)	360 d ad libitum (F)				0.4 M (4/20 deaths)	Dikshith et al. 1991a technical
14	Rat (NS)	90 d 1x/d (GO)				5 (6/12 M, 4/12 F died)	Dikshith et al. 1991b technical
Systemic							
15	Rat (NS)	3-6 mo 5 d/wk (GO)	Metab		5 F (significant reductions in phosphoinositide levels in erythocyte membranes and cerebrum)		Agrawal et al. 1995 technical

Table 3-3 Levels of Significant Exposure to Alpha-, Beta-, Delta-, And Tech-grade HCH - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
16	Rat (Wistar)	15 d ad libitum (F)	Hepatic		1.8 M (increased cytochrome P-450 level, superoxide dismutase, catalase, and lipid peroxidation activities)		Barros et al. 1991 alpha
17	Rat (Wistar)	30 d ad libitum (F)	Hepatic		1.8 M (increased cytochrome P-450 level, superoxide dismutase, catalase, NADPH-cytochrome P-450 reductase activities, and lipid peroxidation)		Barros et al. 1991 alpha
18	Rat (NS)	30 d 1x/d (GO)	Hemato	60 M			Dikshith et al. 1989a technical
			Hepatic		60 M (decreased GOT and LDH activities, increased ALP activity, 65% increase in liver weight)		
			Renal	60 M			

Table 3-3 Levels of Significant Exposure to Alpha-, Beta-, Delta-, And Tech-grade HCH - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
19	Rat (NS)	360 d ad libitum (F)	Hepatic	0.4 M	2 M (increased liver weight)	20 M (focal necrosis, enlargement of hepatocytes, nuclear pyknosis, vacuolation, margination)	Dikshith et al. 1991a technical
			Renal	2 M		20 M (tubular necrosis, glomerular degeneration)	
20	Rat (NS)	90 d 1x/d (GO)	Hepatic		5 M (decreased liver and serum GOT and alkaline phosphatase activities)		Dikshith et al. 1991b technical
21	Rat (Charles Foster)	180 d 1x/d (G)	Bd Wt		3 M (17% decrease in body weight gain)		Gautam et al. 1989 technical
22	Rat (CFT-Wistar)	7 wk ad libitum (F)	Hepatic		90 M (Decreased hepatic vitamin A content, increased GPT and beta-GLR activities, 56% increase in liver weight)		Joseph et al. 1992b technical
23	Rat (CFT-Wistar)	7 wk ad libitum (F)	Hemato		90 M (decreased white blood cell counts)		Joseph et al. 1992c technical

Table 3-3 Levels of Significant Exposure to Alpha-, Beta-, Delta-, And Tech-grade HCH - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
24	Rat (NS)	30 d 1x/d (GO)	Hepatic	50 M			Khanna et al. 1990 technical
			Renal	50 M			
25	Rat (Wistar)	90 d ad libitum (F)	Bd Wt		20 F (significantly decreased body weight gain)		Nagaraja and Desiraju 1994 technical
26	Rat (Wistar)	13 wk ad libitum (F)	Hemato	5 F	22.5 M (decreased red blood cells, leukocyte and hemoglobin concentrations)		Van Velsen et al. 1986 beta
			Hepatic		0.18[c] M (hyalinization of centrilobular cells)	4.5 M (hyalinization of centrilobular cells, focal cell necrosis, increased mitoses)	
			Renal	4.5 M	22.5 M (calcinosis in males)		
			Bd Wt	5 F	22.5 M (15% decrease in body weight)		
27	Mouse (dd)	32 wk ad libitum (F)	Hepatic	20 F	54 M (nuclear irregularities in foci of enlarged hepatocytes)		Hanada et al. 1973 beta

Table 3-3 Levels of Significant Exposure to Alpha-, Beta-, Delta-, And Tech-grade HCH - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
28	Mouse (dd)	24 wk ad libitum (F)	Hepatic		45 M (centrilobular hypertrophy)		Ito et al. 1973 beta
29	Mouse (dd)	24 wk ad libitum (F)	Hepatic		90 M (centrilobular hypertrophy)		Ito et al. 1973 delta
30	Mouse (dd)	24 wk ad libitum (F)	Hepatic		18 M (centrilobular hypertrophy)		Ito et al. 1973 alpha
31	Mouse (Swiss)	2-8 mo ad libitum (F)	Hepatic		90 (100% increase in liver weight, decreased G6P and FDP activity, glycogen accumulation, smooth endoplasmic reticulum proliferation)		Karnik et al. 1981 technical
32	Mouse (HPB)	50 wk ad libitum (F)	Hepatic		90 M (hyperplastic nodules)		Tryphonas and Iverson 1983 alpha
Immuno/ Lymphoret							
33	Rat (Wistar)	13 wk ad libitum (F)		5 F		22.5 M (cortical atrophy in thymus)	Van Velsen et al. 1986 beta

Table 3-3 Levels of Significant Exposure to Alpha-, Beta-, Delta-, And Tech-grade HCH - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
34	Mouse (B6C3F1)	30 d ad libitum (F)		20 F	60 F (decreased lymphoproliferative responses to T-cell mitogens, decreased natural killer cytolytic activity)		Cornacoff et al. 1988 beta
Neurological							
35	Rat (NS)	90 d 6 d/wk 1x/d (GO)			50 M (increased dopamine and decreased serotonin and norepinephrine. Behavioral changes, increased brain wave frequency)		Anand et al. 1991 technical
36	Rat (NS)	360 d 1x/d (F)		0.04 M		0.4 M (convulsions, tremors, hindlimb paralysis, salivation)	Dikshith et al. 1991a technical
37	Rat (NS)	120 d 1x/d (GO)			50 M (increased motor activity, decreased resting stereotypic time)		Gopal et al. 1992 technical
38	Rat (Wistar)	30 d ad libitum (F)		106.2 M			Muller et al. 1981 alpha

Table 3-3 Levels of Significant Exposure to Alpha-, Beta-, Delta-, And Tech-grade HCH - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
39	Rat (Wistar)	30 d ad libitum (F)			66.3 M (reduced tail nerve conduction velocity)		Muller et al. 1981 beta
40	Rat (Wistar)	90 d ad libitum (F)			20 F (increased GABA levels, increased GAD activity, decreased glutamate levels)		Nagaraja and Desiraju 1994 technical
41	Rat (Wistar)	13 wk ad libitum (F)		5 F		22.5 M (ataxia, coma)	Van Velsen et al. 1986 beta
Reproductive							
42	Rat (NS)	360 d 1x/d (F)		2 M		20 M (testicular degeneration)	Dikshith et al. 1991a technical
43	Rat (Charles Foster)	180 d 1x/d (GO)			3 M (6% decrease in vas deferens weight, degeneration of inner muscle and cell layers)		Gautam et al. 1989 technical

Table 3-3 Levels of Significant Exposure to Alpha-, Beta-, Delta-, And Tech-grade HCH - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
44	Rat (Charles Foster)	180 d 1x/d (G)			3 M (decreased seminiferous tubular diameter and Leydig cell nuclear population)	6 M (seminiferous tubular degeneration)	Roy Chowdhury and Gautam 1990 technical
45	Rat (Wistar)	13 wk ad libitum (F)		0.9 M 0.2 F[d]	4.5 M (decreased testes weight) 1 F[d] (increased absolute ovary and uterus weights)	22.5 M[d] (atrophy of testes) 25 F (atrophy of ovary; hyperplastic and vacuolized endometrium epithelium in uterus)	Van Velsen et al. 1986 beta
46	Mouse (B6C3F1)	30 d ad libitum (F)		60 F			Cornacoff et al. 1988 beta
47	Mouse (Swiss)	3 mo ad libitum (F)				90 M (increased testis weight, degeneration of seminiferous tubules, decreased spermatocytes)	Nigam et al. 1979 technical
Developmental							
48	Rat (Wistar)	60 d ad libitum			10 F (alterations in levels of dopamine, serotonin, and noradrenaline in pup brains)		Nagaraja and Desiraju 1994 technical

Table 3-3 Levels of Significant Exposure to Alpha-, Beta-, Delta-, And Tech-grade HCH - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
49	Rat (Wistar)	Gd 0-21 Ld 1-28 (F)			5 (increased liver weight in pups exposed during gestation and lactation)	20 (increased pup mortaility)	Srinivasan et al. 1991a beta
Cancer							
50	Rat (Wistar)	20 wk ad libitum (F)				2 F (CEL: increase in preneoplastic hepatic foci)	Schroter et al. 1987 alpha
51	Rat (Wistar)	20 wk ad libitum (F)				3 F (CEL: increase in preneoplastic hepatic foci)	Schroter et al. 1987 beta
52	Mouse (dd)	32 wk ad libitum (F)				18 M (CEL: hepatoma)	Hanada et al. 1973 alpha
53	Mouse (dd)	24 wk ad libitum (F)				45 M (CEL: hepatocellular carcinoma)	Ito et al. 1973 alpha
54	Mouse (DDY)	16-36 wk ad libitum (F)				90 M (CEL: hepatocellular carcinoma)	Ito et al. 1976 alpha

Table 3-3 Levels of Significant Exposure to Alpha-, Beta-, Delta-, And Tech-grade HCH - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
55	Mouse (Swiss)	2-4 mo ad libitum (F)				90 F (CEL: hepatocellular carcinoma)	Karnik et al. 1981 technical
56	Mouse (DDY, ICR, DBA/2, C57BL/6, C3H/He)	24 wk ad libitum (F)				90 M (CEL: hepatocellular carcinoma)	Nagasaki et al. 1975 alpha
57	Mouse (Swiss)	2-8 mo ad libitum (F)				90 (CEL: hepatocellular carcinoma)	Thakore et al. 1981 technical
58	Mouse (HPB)	50 wk ad libitum (F)				90 M (CEL: hyperplastic nodules and adenomas in liver)	Tryphonas and Iverson 1983 alpha
59	Mouse (DD)	16-36 wk ad libitum (F)				90 M (CEL: hepatoma)	Tsukada et al. 1979 alpha

Table 3-3 Levels of Significant Exposure to Alpha-, Beta-, Delta-, And Tech-grade HCH - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
CHRONIC EXPOSURE							
Systemic							
60	Rat (Wistar)	107 weeks ad libitum (F)	Hepatic		0.8 F (Very slight microscopic damage in the absence of gross liver damage, 33% increase in liver weight)	56 M[d] (Moderate microscopic damage [hepatic cell atrophy, fatty degeneration, and focal necrosis] in the presence of marked gross liver damage)	Fitzhugh et al. 1950 beta
						64 F	
			Renal	8 F	56 M (focal nephritis)		
			Bd Wt	56 M 0.8 F[d]	8 F (12% decrease in body weight gain)		
61	Rat (Wistar)	107 weeks ad libitum (F)	Hepatic	0.8 F	3.5 M (very slight to slight microscopic damage in the absence of gross liver damage)	56 M (Moderate microscopic damage [hepatic cell atrophy, fatty degeneration, and focal necrosis] in the presence of moderate gross liver damage. 36% increase in liver weight)	Fitzhugh et al. 1950 technical
			Renal	8 F	56 M (focal nephritis)		
			Bd Wt	8 F	56 M (decreased body weight gain)		

Table 3-3 Levels of Significant Exposure to Alpha-, Beta-, Delta-, And Tech-grade HCH - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
62	Rat (Wistar)	107 weeks ad libitum (F)	Hepatic	0.8[e] F	3.5 M (very slight to slight microscopic damage in the absence of gross liver damage; 32% increased liver weight)	56 M (Moderate microscopic damage [hepatic cell atrophy, fatty degeneration, and focal necrosis] in the presence of moderate gross liver damage)	Fitzhugh et al. 1950 alpha
			Renal	8 F	56 M (focal nephritis)		
			Bd Wt	8 F	56 M (18% decrease in body weight gain)		
Neurological							
63	Mouse (Swiss)	80 wk ad libitum (F)				17 (convulsions)	Kashyap et al. 1979 technical
64	Mouse (Swiss)	80 wk 1x/d (GO)				10 (convulsions)	Kashyap et al. 1979 technical
Cancer							
65	Rat (NS)	72 wk ad libitum (F)				75 M (CEL: hepatocellular carcinoma)	Ito et al. 1975 alpha
66	Mouse (Swiss)	80 wk 1x/d (GO)				10 (CEL: hepatocellular carcinoma)	Kashyap et al. 1979 technical

Table 3-3 Levels of Significant Exposure to Alpha-, Beta-, Delta-, And Tech-grade HCH - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form
67	Mouse (Swiss)	80 wk ad libitum (F)				17	(CEL: hepatocellular carcinoma)	Kashyap et al. 1979 technical
68	Mouse (Swiss)	20 mo ad libitum (F)				21.3 M	(CEL: hepatocellular carcinoma)	Munir et al. 1983 technical
69	Mouse (CF1)	104 wk ad libitum (F)				34	(CEL:hepatocellular carcinoma)	Thorpe and Walker 1973 beta

a The number corresponds to entries in Figure 3-3.

b Used to derive an acute-duration oral minimal risk level (MRL) of 0.05 mg/kg/day for beta-HCH; 19 mg/kg/day divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, 10 for human variability).

c Used to derive an intermediate-duration oral minimal risk level (MRL) of 0.0006 mg/kg/day for beta-HCH; 0.18 mg/kg/day divided by an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for extrapolation from animals to humans, 10 for human variability).

d Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-3. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

e Used to derive a chronic-duration oral minimal risk level (MRL) of 0.008 mg/kg/day for alpha-HCH; 0.8 mg/kg/day divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, 10 for human variability).

ALP = alkaline phosphatase; Bd Wt = body weight; CEL = cancer effect level; d = day(s); (F)= feed; F = female; FDP = fructose-1,6-diphosphatase; (G) = gavage; (GO) = gavage in oil; Gd = gestation day; GABA = gamma-aminobutyric acid; GAD = glutamate decarboxylase; GLR = glucorinidase; GOT = glutamate oxaloacetate transaminase; G6P = glucose-6-phosphatase; GPT = glutamate pyruvate transaminase; Hemato = hematological; Ld = lactation day; LD50, lethal dose, 50% kill; LDH = lactate dehydrogenase; LOAEL = lowest-observed-adverse-effect level; M = male; metab = metabolism; mo = month(s); NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); x = time(s)

Figure 3-3 Levels of Significant Exposure to Alpha-, Beta-, Delta-, and Tech-grade HCH - Oral

Acute (≤14 days)

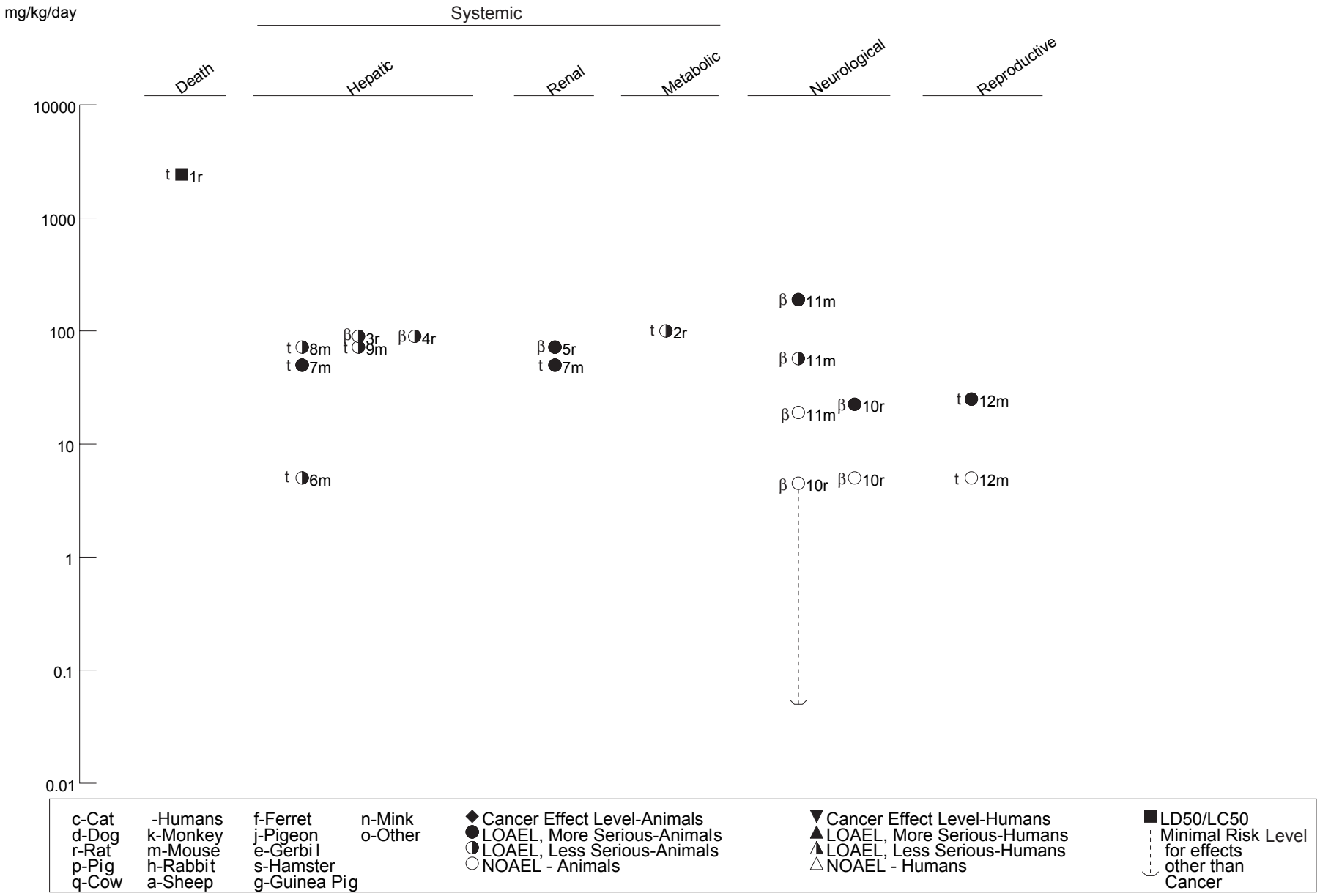


Figure 3-3 Levels of Significant Exposure to Alpha-, Beta-, Delta-, and Tech-grade HCH - Oral (*Continued*)

Intermediate (15-364 days)

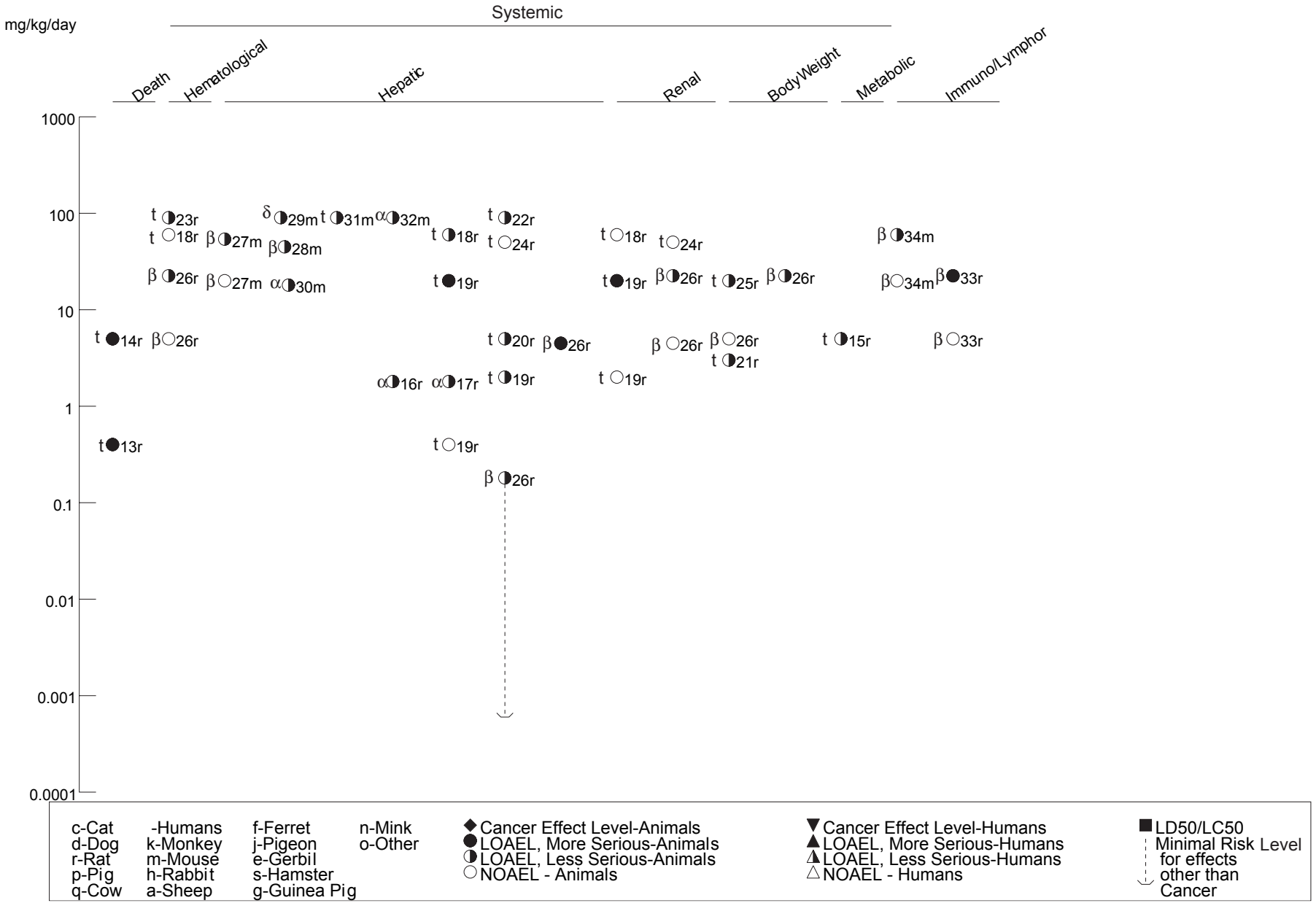


Figure 3-3 Levels of Significant Exposure to Alpha-, Beta-, Delta-, and Tech-grade HCH - Oral (*Continued*)

Intermediate (15-364 days)

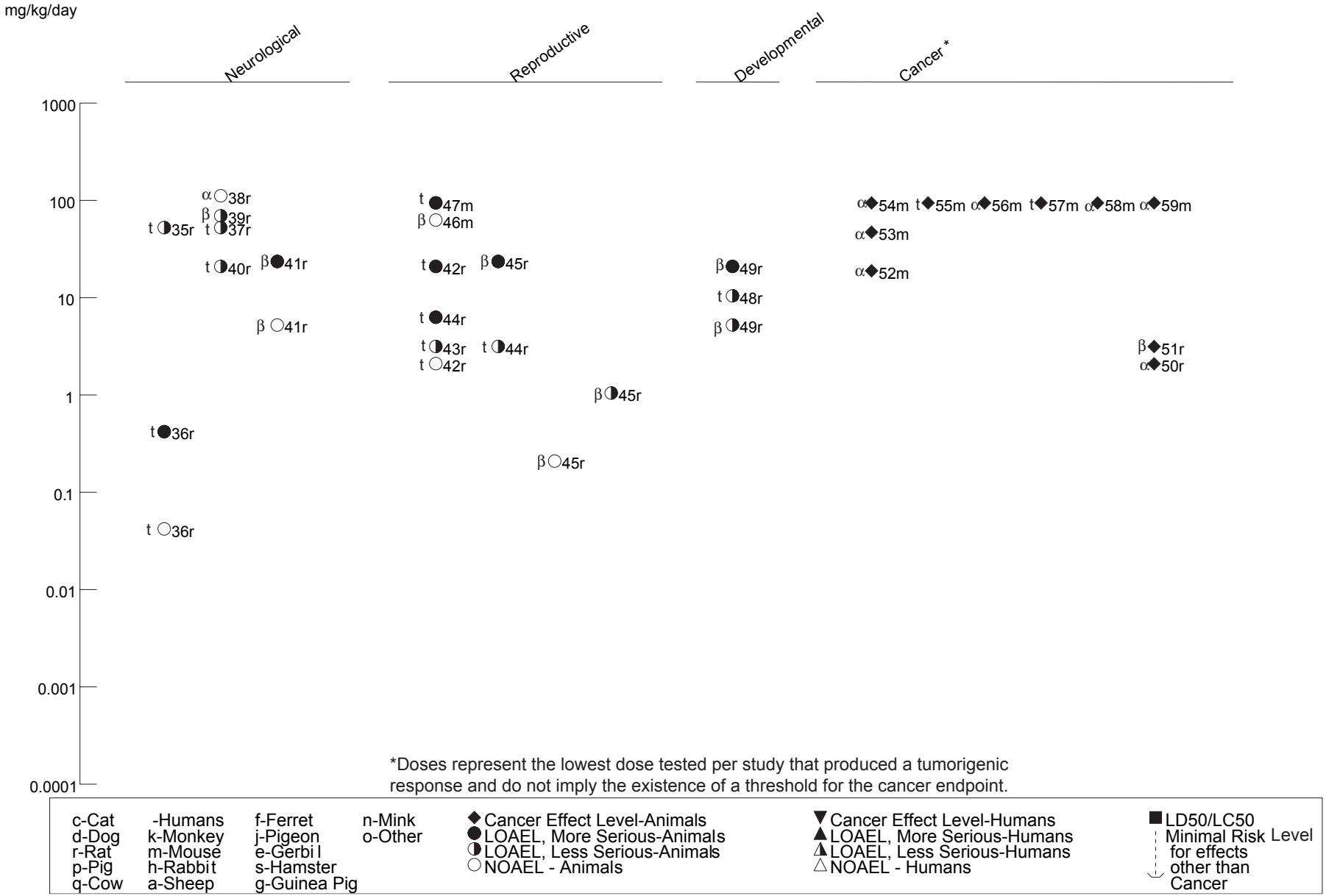
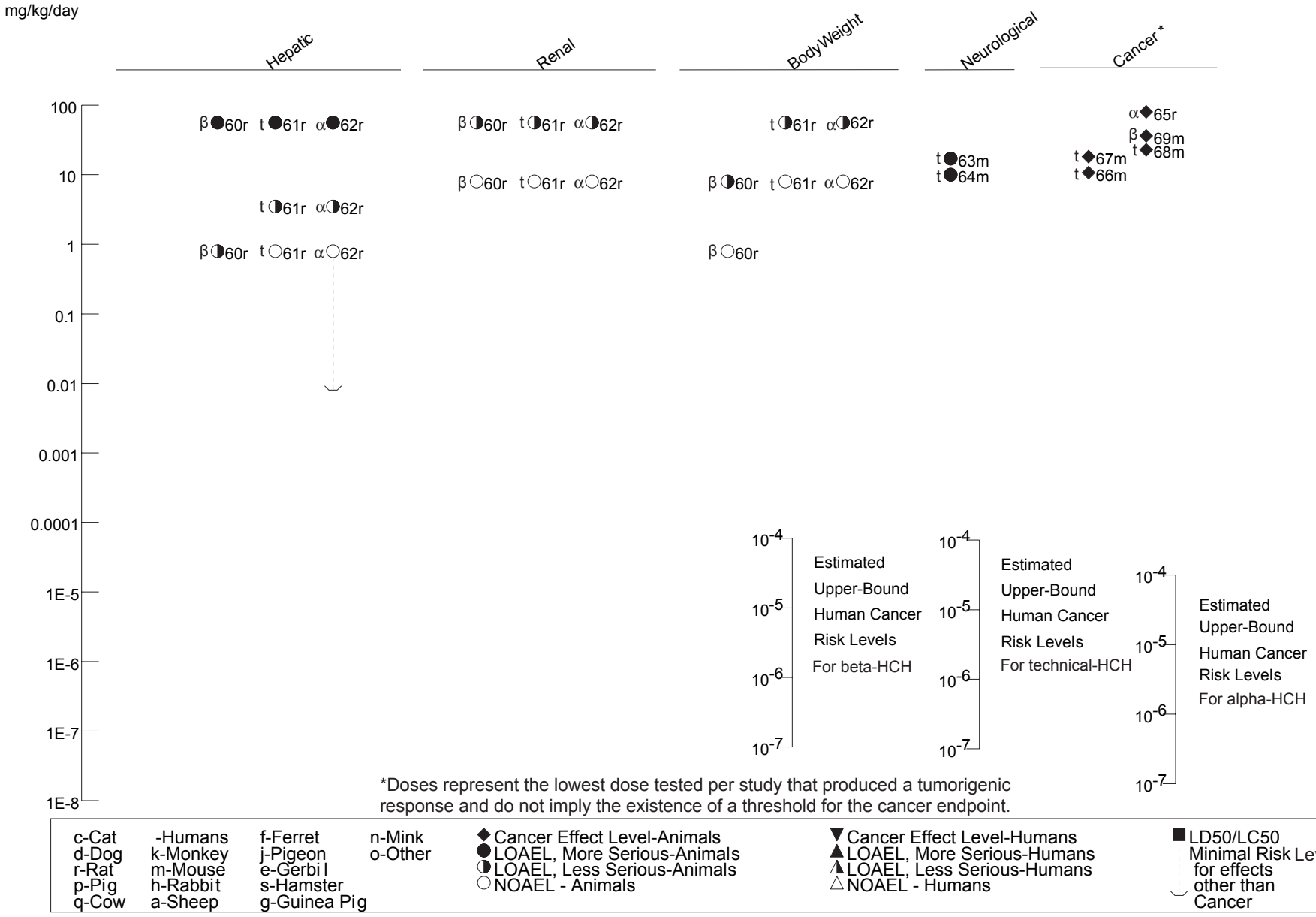


Figure 3-3 Levels of Significant Exposure to Alpha-, Beta-, Delta-, and Tech-grade HCH - Oral (*Continued*)

Chronic (≥365 days)



3.2.2.2 Systemic Effects

No studies were located regarding respiratory, dermal, or ocular effects in humans or animals following oral exposure to HCH. The animal studies in which systemic effects of HCH were examined, in most cases, used isomers of >99% purity.

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Tables 3-2 and 3-3 and plotted in Figures 3-2 and 3-3.

Gastrointestinal Effects. Decreased appetite, vomiting, nausea, and diarrhea have been observed in humans following ingestion of food contaminated with unknown amounts of γ-HCH; exposure was inferred from levels of γ-HCH measured in urine (Nantel et al. 1977). Vomiting and nausea are usual manifestations of γ-HCH ingestion (Sunder Ram Rao et al. 1988).

γ-HCH has been shown to affect the absorption of substances such as glucose, glycine, and calcium in the gastrointestinal tract of rats (Labana et al. 1997), and the effect depends on the nutritional status of the animals. Additional reports of gastrointestinal effects after oral administration of γ-HCH were not located; however, γ-HCH administered subcutaneously at 20 mg/kg/day to rats for 15 days reduced (Na^+-K^+)-ATPase activity in the rat jejunum (Moreno et al. 1996).

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans following inhalation exposure to HCH.

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 Ca,K-ATPase activity. Electrocardiographic changes included increased ST segment and T-wave amplitude and reduced R-R interval and P-wave (Anand et al. 1995).

Hematological Effects. A woman who committed suicide by drinking γ-HCH was found to have disseminated (dispersed) intravascular coagulation during the period when serum γ-HCH levels were elevated (Sunder Ram Rao et al. 1988). No other reports were found on the possible effect of γ-HCH on blood-clotting factors in humans.

No hematological effects were noted in beagle dogs exposed to 12.5 mg γ-HCH/kg/day in the diet for 32 weeks or to 2.9 mg γ-HCH/kg/day in the diet for 104 weeks (Rivett et al. 1978). A 12-week study in rats using 10 mg γ-HCH/kg/day, support this finding (Suter 1983). However, exposure to 22.5 mg β-HCH/kg/day in the diet for 13 weeks in rats was found to be more toxic, resulting in a statistically significant decrease in numbers of red blood cells and white blood cells and reduced hemoglobin and packed cell volume values (Van Velsen et al. 1986). Significant decreases in total white blood cell counts and clotting time were reported in rats fed vitamin A-free diets containing technical-grade HCH at a dose level of 90 mg/kg/day for 7 weeks (Joseph et al. 1992c). In rats fed a vitamin A-supplemented diet containing the same dose level of technical-grade HCH, a significant reduction in total white blood cell count, but not red blood cell count, was observed (Joseph et al. 1992c). Significant suppression in bone marrow cellularity, erythrocyte precursors, and granulocyte-macrophage progenitor cells, and residual progenitor cell damage were reported in male $B6C3F_1$ mice given 20 or 40 mg γ-HCH/kg/day by gavage in corn oil for 3 days (Hong and Boorman 1993). Following 10 days of exposure to 10 or 20 mg γ-HCH/kg/day, dose-dependent decreases in bone marrow cellularity, granulocyte-macrophage progenitor cells, and pluripotent bone marrow stem cells were noted (Hong and Boorman 1993).

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).

Musculoskeletal Effects. In humans, ingestion of a single dose of approximately 15–30 mL γ-HCH powder (amount not reported by weight) 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).

Decreased cross-sectional bone area was found in young rats treated with 20 mg/kg/day of γ-HCH by gavage for 10 weeks (Andrews and Gray 1990). Myelotoxicity, manifested as significant, dose-dependent decrease in marrow progenitor numbers, was seen in mice exposed to 10 or 20 mg/kg/day γ-HCH for 10 days (Hong and Boorman 1993).

Hepatic Effects. No studies were located regarding hepatic effects in humans following oral exposure to HCH.

Significantly increased liver microsomal 7-ethoxycoumarin-O-dealkylase activity was found in Osborne-Mendel rats exposed to 11.2 mg γ-HCH/kg/day and in CF_1 and $B6C3F_1$ strain mice exposed to 23.6 and 50.5 mg/kg/day in the diet for 3 days (Oesch et al. 1982). Although no histopathological examinations were performed to confirm the presence or absence of toxicity, no significant increase in liver weight or other adverse effects were noted in rats exposed to 10 mg γ-HCH/kg/day for a minimum of 4 days (Joy et al. 1982). Rats exposed to 15 mg γ-HCH/kg/day for 5 days, and 2.5 mg γ-HCH/kg/day for 21 days, showed a significant increase in absolute liver weight (Parmar et al. 2003). A dose- and time-dependent increase of P-450 and P-450-dependent enzyme levels was observed in the liver of rats exposed to γ-HCH (Parmar et al. 2003). P-450 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 P-450 content in rats exposed to <10 mg γ-HCH/kg/day for 5 days. Several P-450- dependent enzymes, 7-ethoxyresorufin-O-deethylase (EROD), 7-pentoxyresorufin-O-dealkylase (PROD), and N-nitrosodimethylamine demethylase (NDMA-d), significantly increased in rats exposed to 5 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 (Parmar et al. 2003). Hepatocellular damage as indicated by elevation in serum aminotransferases and decrease in hepatic soluble enzymes was found in rats given 72 mg/kg/day γ-HCH for 2 weeks (Srinivasan and Radhakrishnamurty 1988). Significant increases in hepatic microsomal cytochrome P-450 levels and increases in hepatic microsomal superoxide anion production and cytoplasmic superoxide dismutase activity and lipid peroxidation were found in Wistar rats fed diets containing 1.8 mg/kg/day γ-HCH for 15 or 30 days (Barros et al. 1991). Male Wistar rats fed 13.5 mg γ-HCH/kg/day in their diet for 12 days exhibited decreased activities of liver lipogenic enzymes and increased levels of serum triglycerides (Boll et al. 1995).

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). Rabbits treated with 4.21 mg γ-HCH/kg/day by gavage for 28 days exhibited a significant increase of plasma alkaline phosphatase and alanine aminotransferase (ALT) activities immediately following initiation of dosing; these activities returned to control levels by day 14 (Cerón et al. 1995). Activity of aspartate aminotransferase (AST) also increased immediately following dosing and remained elevated up to 7 days postexposure (day 35). γ-HCH residues were detected in the fat 28 days after dosing.

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 increases in liver microsomal mixed-function oxidase activity and in

significant increases in absolute and relative liver weights; histopathological examinations were not performed (Oesch et al. 1982). 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). Liver cell lipospheres were reported in rats fed 2.5 mg γ-HCH/kg/day in the diet for 32 weeks (Ortega et al. 1957). In mice, administration of 90 mg γ-HCH/kg/day in the diet for 24 weeks was reported to result in centrilobular hypertrophy (Ito et al. 1973). Other studies of intermediate-duration exposure (3–48 weeks) have reported slight liver effects or increased liver weight in mice exposed to 18 mg/kg/day of α-HCH, 45 mg/kg/day of β-HCH, and 90 mg/kg/day for δ-HCH and γ-HCH (Ito et al. 1973). These studies were limited by either a small sample size or lack of statistical analysis.

Chronic exposure of rats to 112–128 mg/kg/day γ-HCH in the diet for 107 weeks resulted in liver necrosis and fatty degeneration (Fitzhugh et al. 1950). A dose-related increase in periacinal hepatocytic hypertrophy was seen in Wistar rats given 7–8 mg γ-HCH/kg/day in the diet for 104 weeks (Amyes 1990). No liver effects were reported in dogs exposed to 2.9 mg/kg/day for 104 weeks (Rivett et al. 1978). In mice, chronic administration of 13.6–27.2 mg γ-HCH/kg/day in the diet was associated with an increased incidence of liver cancer (NCI 1977; Wolff et al. 1987) (see Section 3.2.2.8).

Similar liver effects were reported in animals following intermediate- or chronic-duration exposure to α-HCH in the diet. Administration of 1.8 mg/kg/day α-HCH in the diet to rats for 15 or 30 days resulted in increases in hepatic cytochrome P-450 content, hepatic lipid peroxidation, and hepatic microsomal superoxide production (Barros et al. 1991). Ito et al. (1975) reported liver cell hypertrophy and hyperplasia in rats exposed to 45 mg/kg/day α-HCH for 24–48 weeks. Hypertrophied liver cells were reported in mice fed 18 mg/kg/day α-HCH and 45 mg/kg/day β-HCH for 24 weeks (Ito et al. 1973), and hepatomegaly was reported in mice exposed to 90 mg/kg/day in the diet for 50 weeks (Tryphonas and Iverson 1983). Liver cancer has also been reported 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; Tsukada et al. 1979) (see Section 3.2.2.8). Long-term exposure to lower doses of α-HCH was reported to result in fatty degeneration and focal necrosis in rats exposed to 56–64 mg/kg/day for 107 weeks (Fitzhugh et al. 1950), and liver cancer was reported in rats administered 50 mg/kg/day in the diet for 72 weeks (Ito et al. 1975).

Significant increases in liver weight and in the levels of hepatic cytochrome P-450, triglycerides, phospholipids, and cholesterol were observed in rats administered 90 mg/kg/day β-HCH in the diet for 2 weeks (Ikegami et al. 1991a, 1991b); decreases in cytochrome c reductase activity were also reported. Intermediate and chronic exposure to β-HCH in the diet is also associated with liver effects in animals. A

dose-dependent increase in liver weight was noted in rats exposed for 13 weeks to 0.18–4.5 mg β-HCH/kg/day; the increase was significant at doses of >1 mg/kg/day (Van Velsen et al. 1986). Liver cell hypertrophy was reported in rats fed 25 or 50 mg/kg/day in the diet for 24 or 48 weeks (Ito et al. 1975). In mice, exposure to 45 mg/kg/day for 24 weeks resulted in liver cell hypertrophy (Ito et al. 1973), and exposure to 54–57 mg/kg/day for 32 weeks resulted in hepatic foci of degeneration (Hanada et al. 1973). β-HCH was not found to be carcinogenic in rats or mice exposed for 24–48 weeks (Hanada et al. 1973; Ito et al. 1975). Chronic exposure to lower doses of β-HCH resulted in fatty degeneration and necrosis in the liver of mice fed 56–64 mg/kg/day for 107 weeks (Fitzhugh et al. 1950), and Thorpe and Walker (1973) reported liver cancer in mice fed 34 mg/kg/day for 26 months.

Liver hypertrophy was observed in rats fed with 45 mg/kg/day of α-, β-, or δ-HCH in the diet for 24 or 48 weeks (Ito et al. 1975) and in mice fed 18 mg/kg/day α-HCH in the diet for 24 weeks (Ito et al. 1973). The toxicity of ingested δ-HCH has not been investigated following chronic exposure.

Technical-grade HCH was reported to cause increases in liver weight and enzymatic activity (e.g., alkaline phosphatase, aminotransferases) in male Swiss mice given 72 mg/kg in the diet for 2 weeks (Ravinder et al. 1989). The same dosing regime also caused 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 activity of glutamic oxaloacetate transaminase (GOT), also known as aspartate aminotransferease (AST), and lactate dehydrogenase (LD) were observed in pregnant mice administered a single dose of technical-grade HCH (5 mg/kg) on gestation day 9 (Dikshith et al. 1990). Pregnant mice dosed with 25 mg/kg technical-grade HCH experienced a statistically significant decrease in glutamic pyruvic transaminase (GPT), also known as alanine aminotransferase (ALT), and alkaline phosphatase (AP) activity. 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. Statistically significant increases in liver AP activity were observed in the virgin mice administered 25–200 mg/kg technical-grade HCH. However, with the exception of AST activity in pregnant mice, the dose response relationships were questionable (Dikshith et al. 1990). There were also no corresponding pathological changes in the liver. Similar effects were seen in male, but not female, rats given 5 or 25 mg/kg/day by gavage for 90 days (Dikshith et al. 1991b). A 65% decrease in liver weight, decreased liver aspartate aminotransferase and lactate dehydrogenase activities, and increased alkaline phosphatase 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). However, 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). No adverse hepatic effects were seen in rats treated with 50 mg/kg/day technical-grade HCH for 30 days (Khanna et al. 1990).

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). Pronounced fatty degeneration and necrosis of the liver were found in rats exposed to 56–64 mg/kg/day of technical-grade HCH for 107 weeks (Fitzhugh et al. 1950). Mice treated daily with 50 mg/kg/day technical-grade HCH for 1, 5, or 15 days by oil gavage exhibited congestion of hepatic portal vessels and central vein, swollen hepatic cells with vacuolar or parenchymatous degeneration, and fatty changes in periportal and centrilobular cells (Philip et al. 1989). 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). Technical-grade HCH was also reported to cause liver cancer in mice following exposure to 90 mg/kg/day in the diet for 2–8 months (Karnik et al. 1981; Thakore et al. 1981) or exposure to 10–50 mg/kg/day for 80–88 weeks (Kashyap et al. 1979; Munir et al. 1983) (see Section 3.2.2.8).

Based on the occurrence of hepatic effects in rats and mice exposed to β-HCH, an intermediate MRL of 0.0006 mg/kg/day has been calculated from the LOAEL of 0.18 mg β-HCH/kg/day (Van Velsen et al. 1986), as described in the footnote in Table 3-3.

An MRL of 0.008 mg/kg/day has been derived for chronic-duration oral exposure to α-HCH, based on a NOAEL of 0.08 mg/kg/day for hepatic effects in female rats (Fitzhugh et al. 1950).

Renal Effects. 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). The myoglobin release resulting from muscle lysis in this case led to kidney shutdown, which was the ultimate cause of death.

Male Fischer-344 rats receiving gavage doses of 10 mg/kg/day of γ-HCH for 4 days showed α-2μ-globulin staining in the kidney cortex. Histopathological changes in the proximal tubule epithelial cells included accumulation of protein droplets, hypertrophy and necrosis, pyknotic nuclei, cellular exfoliation, and regenerative epithelium (Dietrich and Swenberg 1990, 1991). These effects did not occur or were seen to a very slight extent in Fischer-344 male controls, Fischer-344 female exposed rats, or exposed NBR rats (a strain that does not synthesize α-2μ-globulin). These results indicate that damage to

male rat kidneys by γ-HCH may be caused by α-2μ-globulin, a protein that is not present in humans. Thus, it is unlikely that humans are at risk for developing this type of pathology from γ-HCH (EPA 1991a). Other biochemical changes indicative of kidney injury, such as significantly increased excretion of glucose in urine, and histological changes, such as hypertrophy and degeneration of the renal tubular epithelia, were observed in Wistar rats exposed to 72 mg/kg/day of γ-HCH for up to 2 weeks (Srinivasan and Radhakrishnamurty 1988; Srinivasan et al. 1984).

However, no renal effects other than significantly increased kidney weight were observed in rats exposed to up to 5–50 mg γ-HCH/kg/day in the diet for up to 40 days (Desi 1974); histological examination of the kidney did not reveal any changes. Slight kidney damage (calcified tubular casts) was reported in rats exposed to 9–10 mg γ-HCH/kg/day for an average of 39.7 weeks (Fitzhugh et al. 1950); the results of this study are limited by poor survival in control and treated animals at all doses. Male rats exposed for 2 years to γ-HCH in their diet exhibited hyaline droplets in the renal proximal tubules at 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). Hyaline droplet formation also occurred in a dose-dependent manner in rats treated with 0.02–10 mg γ-HCH/kg/day in their diets for 12 weeks (Suter 1983). Dose-dependent incidents of renal tubular distension and degeneration were seen in this study beginning at a dose of 2 mg γ-HCH/kg/day.

Fitzhugh et al. (1950) reported kidney damage (nephritis and basal vacuolation) in rats fed 72–80 mg α-HCH/kg/day for an average of 35.9 weeks; no such effects were observed in rats fed 5 mg/kg/day. Poor survival was noted in both control and treated animals.

Renal effects have also been noted in rats exposed to β-HCH in the diet. 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 β-HCH/kg/day for up to 2 weeks. Van Velsen et al. (1986) reported significantly increased kidney weights in female rats exposed to 0.18 mg β-HCH/kg/day for 13 weeks; males did not show a significant increase until they were exposed to a dose of 4.5 mg/kg/day. At 22.5 mg/kg/day, both males and females exhibited renal calcinosis in the outer medulla; however, the female controls also exhibited calcinosis. The study authors noted that renal calcinosis is common in female rats but that this finding was of significance in males (Van Velsen et al. 1986). Fitzhugh et al. (1950) also examined the renal effects of exposure to β-HCH in rats that died after an average of 4.4 weeks and found nephritis and basal vacuolation similar to that

described in rats exposed to α-HCH; poor survival due to unspecified causes was reported in both control and treated animals.

Nephritis, pigmentation, and basal vacuolation were also observed in rats fed 56–64 mg technical-grade HCH/kg/day (64% α-HCH, 10% β-HCH, 13% γ-HCH, 9% δ-HCH, and 1.3% ε-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 was seen in animals exposed for 360 days to 20 mg/kg/day of technical-grade HCH (Dikshith et al. 1991a), but no renal effects were seen in rats exposed to 60 mg/kg/day technical-grade HCH for 30 days by oil gavage (Dikshith et al. 1989a). Mice treated daily with 50 mg/kg/day technical-grade HCH for 1, 5, or 15 days by oil gavage exhibited 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 rats treated with 50 mg/kg/day technical-grade HCH for 30 days (Khanna et al. 1990).

Endocrine Effects. No studies were located regarding endocrine effects in humans following oral exposure to HCH.

The endocrine effects of γ-HCH were reported in ewe lambs (Beard and Rawlings 1999) and young rams (Beard et al. 1999a) given 1 mg/kg/day in treated feed from conception to sexual maturity. In ewes, effects included increased pulse frequency of serum luteinizing hormone, slower increase and earlier decrease of progesterone levels, and lower T4 levels. In young rams, observed endocrine effects included lower serum luteinizing hormone and estrodiol concentrations. While serum testosterone levels were similar across treatment groups, the γ-HCH treated rams showed attenuated testosterone response to stimulation with gonadotropin releasing hormone.

Body Weight Effects. No studies were located regarding body weight effects in humans following oral exposure to HCH.

Significantly decreased body weight gain has been seen in rats treated orally with 800 ppm α-HCH (Fitzhugh et al. 1950), 250 mg/kg β-HCH (Fitzhugh et al. 1950; Van Velsen et al. 1986), 40 mg/kg/day γ-HCH (Fitzhugh et al. 1950; Laws et al. 1994), and 3 or 20 mg/kg/day technical-grade HCH (Gautam et al. 1989; Nagaraja and Desiraju 1994).

Metabolic Effects. No studies were located regarding metabolic effects in humans following oral exposure to HCH.

Increased phosphoinositide turnover and generation of second messengers from phosphoinositides were seen in erythrocyte membranes from female rats treated by gavage with a single dose of 100 mg/kg technical-grade HCH, or with doses of 5 mg/kg/day technical-grade HCH for 3–6 months, 5 days/week (Agrawal et al. 1995). The latter exposure regime also resulted in a significant decrease in phosphatidylinositol, phosphatidylinositol 4-phosphate, and phosphatidylinositol 4,5-bisphosphate in erythrocyte membrane and cerebrum; the levels decreased with increased time of treatment (3–6 months).

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological or lymphoreticular effects in humans following oral exposure to HCH.

Some evidence of possible immunotoxic effects of γ-HCH is available from acute- and intermediate-duration studies in animals. Dose-related decreases in thymus and spleen weights were observed in mice gavaged with 10–20 mg/kg/day γ-HCH for 10 days and decreased thymus weight was observed in mice gavaged with 20–40 mg/kg/day γ-HCH for 3 days (Hong and Boorman 1993). Immunosuppression, as measured by decreased agglutinin titers against typhoid vaccine and *Salmonella* vaccine, was reported in rats exposed by gavage to 6.25 and 25 mg γ-HCH/kg/day 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 injected 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 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. 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. Cortical atrophy of the thymus was observed in rats fed 22.5–25 mg/kg/day β-HCH (Van Velsen et al. 1986). A biphasic dose-dependent immunological effect of γ-HCH on components of cell- and humoral-mediated immunity, characterized by initial stimulation followed by immunosuppression, was reported in mice fed 0.012, 0.12, or 1.2 mg

γ-HCH/kg/day for 24 weeks (Meera et al. 1992). In addition, histological examinations revealed decreased lymphocyte populations in the thymus and lymph nodes and 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 dinitroflurobenzene antigen, was suppressed in sheep that were exposed to 1.25 ppm γ-HCH in the diet for 6 months (Khurana et al. 1999). The LOAEL values for immunological effects are recorded in Tables 3-2 and 3-3 and plotted in Figures 3-2 and 3-3.

Based on immunological effects of γ-HCH on components of cell- and humoral-mediated immunity in mice, an intermediate MRL of $1x10^{-5}$ mg/kg/day has been calculated from the LOAEL of 0.012 mg γ-HCH/kg/day (Meera et al. 1992), as described in the footnote in Table 3-2.

3.2.2.4 Neurological Effects

In humans, the most commonly reported effects associated with oral exposure to γ-HCH are neurological. Most of the information is from case reports of acute γ-HCH poisoning. No studies were located regarding neurological effects in humans following long-term ingestion of α-, β-, γ-, or δ-HCH. Seizures and convulsions have been observed in individuals who have accidentally or intentionally ingested γ-HCH in insecticide pellets, liquid scabicide, or contaminated food (Davies et al. 1983; Harris et al. 1969; Munk and Nantel 1977; Nordt and Chew 2000; Powell 1980; Starr and Clifford 1972; Storen 1955). Several case studies of acute γ-HCH exposure to children ingesting liquid scabicide report similar neurological effects, including vomiting, tremors, and tonic/clonic seizures (Aks 1995; Lifshitz et al. 2002; Wheeler 1977). In these cases, the affected children returned to normal health in 6–48 hours following exposure. In most cases, exposure to γ-HCH was inferred from the presence of γ-HCH in the urine or blood. Also, the actual amount of γ-HCH ingested could not be determined because the γ-HCH was present in solution or in pellets in which other substances were present. Liquid scabicide has been reported to contain approximately 1% γ-HCH (Davies et al. 1983; Powell 1980).

Neurotoxic effects have been reported in several species of animals exposed to γ-HCH. The most serious effects were seizures following a single intragastric administration of approximately 15–60 mg/kg in rats (Martinez and Martinez-Conde 1995; Martinez et al. 1991; Tilson et al. 1987; Tusell et al. 1987; Vendrell et al. 1992a, 1992b; Woolley and Griffith 1989). Less-serious effects in rats included increased anxiety following a single gavage dose of 20 mg/kg (Llorens et al. 1990b) and increased spontaneous motor behavior observed at 10 mg/kg (Llorens et al. 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 HCH poisoning. A single oral dose of 5–20 mg γ-HCH/kg to rats previously kindled by electrical stimulus produced incidences of myoclonic jerks and clonic seizures, which increased in a dose-dependent manner (Gilbert and Mack 1995). Nonkindled animals displayed these symptoms at a dose of 10 mg γ-HCH/kg. Enhanced susceptibility to kindled seizures brought on by electrical stimulation was seen in rats exposed for 10 weeks to 10 mg γ-HCH/kg/day, 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).

Epileptiform seizures have been reported in male rats fed milk, from dams that were gavaged with 20 mg γ-HCH/kg, on postnatal days 3–15 (Albertson et al. 1985). These data suggest that γ-HCH can be transferred in the dam's milk and can elicit neurological effects in offspring. It is not possible to determine the doses received by the pups. Avoidance response latency was statistically increased in rats administered a single dose of 15 mg/kg by gavage (Tilson et al. 1987). Acquisition of a passive avoidance task was improved in 15-day-old rat pups that were treated with non-convulsant levels of γ-HCH by gavage as either a single 20 mg/kg dose or 7-day repeated 10 mg/kg/day doses, although changes in motor activity and brain monoaminergic levels (e.g., ratios of 5-HIAA/serotonin and DOPAC/dopamine) depended on the treatment schedule (Rivera et al. 1998). No clinical signs of behavioral effects were seen in suckling Wistar rats treated once with 20 mg/kg γ-HCH by gavage at postnatal days 8, 15, 22, or 29, although regional changes in brain noradrenaline and serotonin were seen, with differential effects depending on age at the time of exposure (Rivera et al. 1991).

Changes in levels of brain norepinephrine (Rivera et al. 1991) and serotonin (Attia et al. 1991; Rivera et al. 1991) have also been reported in rats administered acute oral doses of γ-HCH. Decreased dopamine levels were seen in rats treated by gavage with 10 doses totaling 60 mg γ-HCH/kg (half the LC_{50}) over a period of 30 days (Martinez and Martinez-Conde 1995). Increase in the levels of brain catecholamines, particularly norepinephrine and dopamine, and associated signs of toxicity such as mild tremor, lacrimation, salivation, and dysnea 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) in the cerebrum showed a marginal decrease, while the cerebellum and spinal cord indicated a significant increase and decrease in MAO, respectively. 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).

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, indicating that the tonic convulsions observed throughout the exposure period were probably not brought on by oxidative stress in the brain (Arisi et al. 1994). Decreased myelin basic protein was observed in rats exposed to 5 mg/kg/day by gavage for 3 days (Serrano et al. 1990a).

The neurotoxicity of γ-HCH has also been assessed in acute, subchronic, and developmental exposure screening batteries in rats (Hughes 1999a, 1999b; Myers 1999). In the acute study, a single 0, 6, 20, or 60 mg/kg dose of γ-HCH was administered to Crl:CDBR rats (Hughes 1999a). End points included functional observational battery (FOB) and motor activity (MA) tests performed prior to treatment, within 3 hours of dosing (time of peak effect), and on post-exposure days 7 and 14, as well as histopathology of nervous system tissues at study termination. No clinical signs or other effects were observed at 6 mg/kg. Exposure to 20 mg/kg caused decreased motor activity 3 hours post-treatment in females at ≥20 mg/kg and in males at 60 mg/kg. 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. 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). Compared with the liver, the magnitude of the induction of the P-450 enzymes in the brain was much smaller. 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 P-4501A1/1A2, had no significant effect in the incidence of convulsions induced by γ-HCH. However, pretreatment with phenobarbitol (PB), an inducer of P-4502B1/2B2, or ethanol, an inducer of P-4502E1, or blocking P-450-mediated metabolism with cobalt chloride, significantly increased the incidence of convulsions caused by γ-HCH. Taken together, the results suggest that the convulsive activity is due to γ-HCH *per se* and/or to metabolites formed by PB- or ethanol-inducible P-450 isoenzymes.

In the subchronic neurotoxicity screening battery, Crl:CDBR rats were exposed to 0, 20, 100, or 500 ppm γ-HCH in the diet for 13 weeks (Hughes 1999b). Due to severe toxicity, the high concentration was reduced to 400 ppm on day 11. Reported average daily intake levels of γ-HCH for the entire study were 0, 1.4, 7.1, and 28.1 mg/kg/day for the males and 0, 1.6, 7.9, and 30.2 mg/kg/day for the females. End points included FOB and MA tests performed prior to administration and after 4, 8, and 13 weeks of treatment, and histopathology of nervous system tissues at study termination. No clinical signs or other changes were observed in females at 1.6 mg/kg/day or males at ≤7.1 mg/kg/day. Effects in females at

7.9 mg/kg/day included decreased body weight gain and food consumption (40 and 16% lower than controls, respectively, during the first week). Both systemic and neurotoxic effects occurred in both sexes at the high dose, including clinical signs (e.g., staining of urogenital region, piloerection, abnormal grooming behavior), increased rearing, walking on tiptoes, hypersensitivity to touch, hunched posture, weight loss, and several deaths.

In the developmental neurotoxicity study, Han Wistar rats were exposed to 0, 10, 50 or 120 ppm γ-HCH in the diet from gestation day 6 through lactation day 10 (Myers 1999). 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 F_1 offspring were evaluated for FOB, motor activity, auditory startle response, learning and memory, developmental landmarks (e.g., vaginal perforation and balanopreputial separation), and brain end points (weight, histology, and morphometrics) on postpartum days 11 and 65. Maternal toxicity occurred at 13.7 mg/kg/day as shown by effects that included decreased body weight gain (64–79% less than controls on gestation days 6–20), decreased food consumption, and increased reactivity to handling. The offspring showed effects at the two highest dose levels, including increased motor activity (both sexes), decreased habituation of motor activity (females), decreased body weights (12–20% less than controls), and decreased body weight gains (60–84% less than controls) during lactation days 1–11 (both sexes) at ≥5.6 mg/kg/day. Effects observed at 13.7 mg/kg/day included reduced auditory startle response habitation in both sexes, increased stillbirths (live birth index of 77% compared to 99% in controls), and increased neonatal mortality (postnatal day 4 viability index of 71% compared to 89% in controls). This study was classified as an unacceptable developmental neurotoxicity study by EPA (2000) because there was no laboratory validation of the neurobehavioral tests and the number of animals (six per dose level) was insufficient.

There is evidence that γ-HCH exposure causes functional impairment of the developing blood brain barrier (BBB) in young rats (Gupta et al. 1999). The integrity (permeability) of the BBB 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).

Longer exposures to lower doses of γ-HCH were reported to result in significantly altered Skinner box behavior (operant conditioning) in a small number of rats exposed to 2.5 mg/kg/day for 40 days (Desi 1974), and significantly decreased nerve conduction velocity in rats exposed to 25.4 mg/kg/day for 30 days (Muller et al. 1981). The latter study did not examine any behavioral parameters.

Similar neurological effects have not been reported in animals treated with 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. However, neurological effects have been reported in rats exposed to β-HCH. Mice treated with 57 or 190 mg/kg/day β-HCH for 30 days developed ataxia within 1 week of treatment (Cornacoff et al. 1988). 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. An acute-duration oral MRL of 0.05 mg/kg/day was derived based on a NOAEL of 4.5 mg/kg/day for ataxia, progressive inactivity, and coma in male rats exposed to 25 mg β-HCH/kg/day for 2 weeks (Van Velsen et al. 1986).

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. Increase 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. 1991b). 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 or 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).

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following oral exposure to HCH.

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). 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). 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. Mouse dams treated with γ-HCH (6.2 mg/kg) during gestation period days 6–12 had increased numbers of resorbed fetuses (Sircar and Lahiri 1989). A lack of implantation sites and pups death were observed following treatment with 10.8 mg/kg/day on gestation days 1–4 and 3.6 mg/kg/day on gestation days 14–19, respectively. 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 oral 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.

Acute preovulatory exposure to γ-HCH caused embryonic effects in mice (Scascetelli 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-fertilization treatment. 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). However, rabbits given the same treatment regime followed by artificial insemination exhibited no effects on the fertilization rate or on pre- or postimplantation losses (Seiler et al. 1994).

Gavage administration of 15 mg γ-HCH/kg/day (only dose tested) in corn oil to pregnant CD-1 mice on gestational days 9–16 did not affect the relative or absolute weights of the uterus, ovaries, or mammary gland, monitored on postnatal day 23 (Maranghi et al. 2003). Microscopic examination of sections from these organs showed no significant treatment-related alterations. Female offspring from treated mice exhibited a slight increase (4.3%) in relative uterus weight when sacrificed on postnatal day 60. In addition, earlier vaginal opening (2 days) and increased branching of villi and oedema in the endometrial stroma was observed in the offspring from treated mice when compared to controls. Neither the ovary nor mammary glands from female offspring showed significant alterations (Maranghi et al. 2003).

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. Similarly, Shivanandappa and Krishnakumari (1983) reported testicular atrophy, degeneration of seminiferous tubules, and disruption of spermatogenesis in male rats fed 75 mg γ-HCH/kg/day for 90 days. Significant reductions in the relative weight of testicles and epididymis, spermatid and sperm counts, and testosterone levels were observed in pubescent or adult rats fed milk as neonates from dams gavaged with 6 mg/kg γ-HCH on lactation day 9 or 14 or 1 mg/kg γ-HCH on lactation days 9–14 (Dalsenter 1997b). Histopathological observations included a reduction in Leydig cell numbers and spermatogenesis, but fertility, as measured by impregnation of female rats, was unaffected. 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 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, although the rate decreased and 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.

Effects of prenatal exposure on spermatogenesis were evaluated in adult offspring of mice that were administered 15 or 25 mg/kg/day doses of γ-HCH in olive oil by gavage on gestation days 9–16 (Traina et al. 2003). F_1 offspring were assessed on postnatal day (pnd) 60 (both dose levels) and pnd 100 (25 mg/kg/day); end points included litter size, growth and sexual maturation indices, and male reproductive indices (e.g., sperm number and concentration, testicular biochemistry and histology, and testicular cytotoxicity and germ cell damage). Statistically significant effects included testicular histological alterations at ≥15 mg/kg/day on pnd 60 (increased number and size of Leydig cells), reduced sperm head count (sperm/testis) at ≥15 mg/kg/day on pnd 60, reduced sperm head concentration (sperm/g testis) at 25 mg/kg/day on pnds 60 and 100, reduced activities of testicular serum sorbitol dehydrogenase (SDH) at ≥ 15 mg/kg/day and lactate dehydrogenase (LDH) at 25 mg/kg/day (only evaluated on pnd 60), altered testicular germ cell distribution at 25 mg/kg/day on pnds 60 and 100, and increased number of epididymal sperm with chromatin abnormalities at ≥15 mg/kg/day on pnd 60.

Multigeneration reproduction studies were conducted in rats exposed to technical HCH or γ-HCH (King 1991; Srivastava and Raizada 2000). In the study with technical HCH, 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 throughout three generations (Srivastava and Raizada 2000). Toxicity occurred in the P_0 parental animals, as shown by effects that included reduced body weight gain in both sexes at ≥16 mg/kg/day, and hepatic histopathological changes and some deaths at 32 mg/kg/day. There were no signs of toxicity in the subsequent parental generations (F_{1b} or F_{2b}), no exposure-related effects on reproduction in any of the three parental generations, and no morphological or teratological changes in any of the offspring generations (F_{1b}, F_{2b}, or F_{3b}). In the 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 two generations during the mating periods only (King 1991). No treatment-related clinical signs of toxicity, effects on body weight or food consumption were observed in the F_0 or F_1 males or females during premating. Body weight gain decreased in the high-dose F_0 parental females during gestation, however, indicating that systemic toxicity occurred at 13.1 mg/kg/day. Other indications of systemic toxicity included renal histopathological changes characteristic of alpha 2μ globulin accumulation in F_0 and F_1 males at ≥1.7 mg/kg/day; however, this syndrome is specific to male rats and not relevant to humans. No gross or histopathological changes were observed in females in either generation. There were no effects on mating, fertility, gestation survival,

liveborn indices, or mean litter sizes in either generation, although offspring 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 F_2 pups. Body weights of the high-dose pups of both generations were significantly lower than controls on lactation days 1 and 25. Viability indices (survival on lactation day 4) for the high dose F_1 and F_2 pups were 81 and 85%, respectively, compared with ≥96% for the controls. The onset and completion of tooth eruption and completion of hair growth were 10.5, 11.6, and 24% delayed in the high dose F_2 pups, respectively, compared to controls.

A two-generation reproduction study of γ-HCH was also conducted in mink that were exposed to dietary doses of 0 or 1 mg/kg/day (Beard and Rawlings 1998). The parental (P_0) generation was exposed from 3 weeks before breeding until weaning of the offspring. Following weaning, the F_1 females were exposed throughout growth and mating (to untreated males), and subsequently throughout pregnancy and lactation until 3 months post-lactation. The F_2 females were exposed until they reached full adult body size at 30 weeks of age. The F_1 and F_2 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, thyroxine, cortisol, testosterone) and histology, including male and female reproductive and endocrine tissues (e.g., thyroid, parathyroid, adrenal, pituitary, and pancreas), 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 and serum thyroxine concentration in F_2 males.

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 β-HCH/kg/day in the diet for 13 weeks (Van Velsen et al. 1986). Technical-grade HCH caused transient changes in testes' weights and decreased sperm counts in a 7-week study (Pius et al. 1990), degeneration of seminiferous tubules and Leydig cells (Roy Chowdhury and Gautam 1990), and changes in the muscle layer of the vas deferens (Gautam et al. 1989). None of these studies provide adequate evidence for the effects of technical-grade HCH on sperm function in animals or humans.

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). End points 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), weights of testis and accessory sex organs, and testicular histology including epididymal sperm counts and sperm anomalies. 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. 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. 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). 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). 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 the ninth gestation day (Dikshith et al. 1990).

The reproductive effects of γ-HCH were reported in ewe lambs (Beard and Rawlings 1999) and young rams (Beard et al. 1999a) given 1 mg/kg/day in treated feed from conception to sexual maturity. In estrus synchronized ewes, treated animals had significantly shorter estrous cycle length and lower number and less total volume of corpus lutea. No other detrimental fertility effects were observed. The subjectively-scored sexual behavior in young rams was significantly reduced in treated animals presented with estrous ewes.

3.2.2.6 Developmental Effects

In a study of women from India, 30 pregnant women diagnosed with intra-uterine fetal growth retardation (IUGR) had higher mean serum levels of γ-HCH (OR=1.38, 95% CI 1.05–1.80), α-HCH (OR=1.22, 95% CI 1.02–1.46), δ-HCH (OR=1.61, 95% CI 1.01–2.54), and total HCH (OR=1.07, 95% CI 1.01–1.13) than 24 mothers of non-IUGR babies after adjusting for potential confounders (Siddiqui et al. 2003). Similarly, γ-HCH, δ-HCH, and total HCH cord blood levels of IUGR babies were higher than the cord blood levels in the normal-weight babies (OR=1.14, 95% CI 1.00–1.31; OR=1.31, 95% CI 1.00–1.75; and OR=1.07, 95% CI 1.00–1.14, respectively) (Siddiqui et al. 2003). Since other organochlorine pestides, including DDT and its metabolites, were also present in the blood, the role of HCH, if any, cannot be ascertained. In this study, exposure is likely due to consumption of the pesticides in food; however, other

environmental contamination pathways, including inhalation and dermal exposure, may be possible routes of exposure as well.

A single oral dose of 25 mg/kg technical-grade HCH caused increased resorptions of the fetus in female mice, but fetal development was normal (Dikshith et al. 1990). Srivastava and Raizada (1993) further studied the prenatal effect of orally administered technical-grade HCH. While mice exposed to HCH during the preimplantation period (days 2–6 of gestation) did not show fetolethality, exposure during the postimplantation period (days 6–12 of gestation) 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 days 6–15 of gestation failed to produce teratogenic effects in rats (Khera et al. 1979). 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. 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).

Another study of γ-HCH was conducted in which the compound was administered to pregnant mice by gastric intubation on day 12 of gestation (Hassoun and Stohs 1996a). At doses of 30 and 45 mg/kg body weight in C57BL/6J mice, significant decreases in fetal weight, fetal thymic weight, and placental weight were observed. When given to DBA/2J mice at a dose of 45 mg/kg body weight, γ-HCH caused significant reductions in fetal and placental weight. No malformations in the fetuses of both strains of mice were observed, even though the administered doses caused maternal deaths. Increases in the production of lipid metabolites in maternal sera and the amniotic fluids were found to parallel the observed fetotoxicities (Hassoun et al. 1996). Superoxide production, lipid peroxidation and DNA-single strand breaks were increased in fetal and placental tissues 48 hours after administration of single dose of 30 mg/kg γ-HCH to pregnant mice on day 12 of gestation (Hassoun and Stohs 1996b). Significant increases in lipid peroxidation also occurred in fetal livers collected on day 18 of gestation. 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 the fetal and placental tissues of mice.

Developmental/reproductive effects of γ-HCH were studied in male offspring of rats that were exposed during lactation (Dalsenter et al. 1997b). Females were treated with 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. Male offspring were evaluated on pnd 65 (puberty) or 140 (adulthood) and evaluated for testis and epididymis weights, spermatid and sperm numbers, serum testosterone level, sexual behavior at 130 days of age during mating with unexposed females, reproductive indices (mating, pregnancy and fertility), pregnancy end points (numbers of litters, implantations/litters, fetuses/litter, resorptions), and testicular histology (6 mg/kg offspring). The 1 mg/kg/day offspring had statistically significant reductions in relative testicular weight at pnd 140, relative epididymis weight at pnd 65, spermatid number at pnds 65 and 140, sperm number at pnd 140, and serum testosterone at pnd 65. Effects were generally similar in type and magnitude in the 6 mg/kg offspring exposed on lactation day 9 or 14. There were no significant effects on sexual behavior or fertility in the 1 mg/kg/day or 6 mg/kg offspring. 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, including necrotic changes and reductions in Leydig cell numbers and spermatogenesis. An acute oral MRL of 0.003 mg/kg/day has been derived for γ-HCH based on the 1 mg/kg/day minimal LOAEL for reproductive effects in rats (Dalsenter et al. 1997b).

An isomer comparison study in rats found that dietary exposure to 25 mg/kg/day of γ-HCH during gestation and lactation did not cause developmental effects in pups, whereas 20 mg/kg/day of β-HCH during gestation caused increased fetal deaths within 5 days of birth and 5 mg/kg/day of β-HCH during gestation and lactation resulted in increased liver weights of pups (Srinivasan et al. 1991a). 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 gestation days 6–15; statistical significance was attained only at 20 mg/kg (Palmer et al. 1978a). The incidence of fetuses with an extra 13^{th} rib was statistically increased in rabbits exposed to 20 mg/kg γ-HCH by gavage during gestation days 6–18 (Palmer et al. 1978a). 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). No effects on embryonic development were seen in rabbits treated by oral gavage with 0.8 mg γ-HCH/kg, 3 times/week for 12–15 weeks before artificial insemination and throughout gestation (Seiler et al. 1994). A two-generation study of γ-HCH was conducted in rats exposed to estimated dietary doses of 0, 0.09, 1.7, or 13.1 mg/kg/day (King 1991). As detailed in Section 3.2.2.5 (Reproductive Effects), 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 F_2 pups.

Regional changes in brain noradrenaline, serotonin and the dopamine metabolite 3,4-dihydroxyphenyl-acetic acid (DOPAC) levels were noted in suckling rats treated with 20 mg/kg/day γ-HCH, as a single dose (Rivera et al. 1991). Alterations in levels of brain dopamine, serotonin, gamma-aminobutyric acid ($GABA_B$), 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 (Nagaraja and Desiraju 1994).

3.2.2.7 Cancer

In a study of women from India, blood levels of HCH, and its isomers (α, β, and γ), were found to be higher in women with breast cancer when compared to healthy women without the disease (Mathur et al. 2002). In this study, 135 breast cancer patients and 50 females without cancer filled out questionnaires and were evaluated for their body burden of pesticides through blood testing. α- and γ-HCH blood levels were significantly higher in breast cancer patients, 41–50 years of age, compared to women of the same age without the disease. β-HCH blood levels were significantly higher in breast cancer patients, 31–50 years of age, compared to those without the disease (Mathur et al. 2002). Other organochlorine pesticides, including DDT and its metabolites, were also present in the blood and could have contributed to the incidence of breast cancer. In contrast to the Mathur et al. (2002) findings, there were no positive associations between serum levels of β-HCH and incidence of breast cancer in studies of 95 Mexican women (Lopez-Carrillo et al. 2002), 150 Norwegian women (Ward et al. 2000), or 240 women from Denmark (Hoyer et al. 1998). In addition, Hoyer et al. (1998) did not find an association between serum levels of γ-HCH and the incidence of breast cancer. The risk for endometrial cancer was also not associated with β-HCH serum concentrations in a study of 90 women from the United States (Sturgeon et al. 1998). Levels of β- and γ-HCH in surgically removed breast tissue samples from 65 women in Germany were not indicative of malignant breast disease; there was no significant difference between the levels of β- and γ-HCH in the breast tissue surrounding malignant and benign breast disease (Guttes et al. 1998). Exposure to HCH, and other organochlorine pesticides, to the populations of these studies is mainly through food where the pesticides are primarily used for agricultural applications; however, other possible environmental contamination pathways include inhalation and dermal routes of exposure.

α-HCH, β-HCH, γ-HCH, and technical-grade HCH have been shown to be liver carcinogens in rats and mice; however, in some studies, the liver was the only organ examined. Ito et al. (1973) examined the carcinogenicity of HCH isomers in dd mice exposed to 45 mg/kg/day of each isomer (total dosage was 90 mg/kg/day) for 24 weeks. Exposure to β-, γ-, or δ-HCH alone did not result in hepatocellular

carcinoma. However, when these isomers were mixed with α-HCH, hepatocellular carcinoma was observed. These results suggest that α-HCH is itself a hepatocellular carcinogen or acts synergistically with the other isomers.

In Wistar rats, exposure to 25 mg γ-HCH/kg/day in the diet for 24 or 48 weeks did not result in any identifiable carcinogenic effect (Ito et al. 1975); however, high mortality in the control and treatment groups precludes determination that γ-HCH is not carcinogenic to rats 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 carcinogenic effects (Ito et al. 1973). Although 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), this dose level may have exceeded the maximum tolerated dose (MTD), based on effects of γ-HCH on survival. Liver nodules developed following doses of 39 mg/kg/day. The study was limited by the lack of statistical analysis (Hanada et al. 1973).

Information concerning the cancer effects of γ-HCH following chronic-feeding exposure is equivocal. 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) and 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. On the other hand, hepatocellular carcinomas have been reported in F_1 and B6C3F_1 mice exposed to 13.6–27.2 mg/kg/day in the diet for 80 or 104 weeks, respectively (NCI 1977; Wolff et al. 1987). Hepatocellular carcinomas were also increased in yellow (YS/UY)F-1 mice exposed to 27.2 mg/kg/day in the diet for 96 weeks (Wolff et al. 1987); this strain of mouse has a dominant mutation at the agouti locus (A^{vy}) that results in an increased susceptibility to formation of strain-specific neoplasms. Chronic dietary studies of γ-HCH additionally showed that incidences of benign lung adenomas were increased in female Agouti and Pseudoagouti mice exposed to 27.2 mg/kg/day for 24 months (Wolff et al. 1987) and in female CD-1 mice exposed to ≥26.8 mg/kg/day for 78 weeks (Chase 2000; Huntington Life Sciences Ltd. 2001). The EPA has classified γ-HCH (lindane) into the category “suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential” (EPA 2001a, 2002b). No cancer potency factors have been estimated for γ-HCH or γ-HCH (EPA 2001a, 2002b; IRIS 2005).

No evidence of liver carcinogenicity was reported in Wistar rats exposed to 45 or 90 mg α-HCH/kg/day in the diet for 24 or 48 weeks (Ito et al. 1975; Nagasaki et al. 1975); high mortality was observed in both the treated and control groups. However, α-HCH appears to be carcinogenic in mice following intermediate-

duration exposure. Hepatomas and hepatocellular carcinomas have been reported in a number of strains of mice exposed to 13–95 mg/kg/day for 16–36 weeks (Hanada et al. 1973; Ito et al. 1973, 1976; Nagasaki et al. 1975; Tsukada et al. 1979). Tryphonas and Iverson (1983), however, reported no evidence of a carcinogenic effect in male mice exposed to 90 mg α-HCH/kg/day in the diet for 50 weeks. Ito et al. (1975) reported an increased incidence of hepatocellular carcinoma in male rats exposed to 50 and 75 mg α-HCH/kg/day in the diet for 72 weeks, suggesting that α-HCH may be carcinogenic in rats after long-term exposure. A study of enzyme-altered liver foci in rats treated first with the tumor initiator *N*-nitrosomorpholine, and then 20 mg α-HCH/kg/day in food for 49 weeks, found that the tumor promoter activity of HCH is apparently due to increased cell proliferation caused by a lowering of the cell death (apoptosis) rate (Luebeck et al. 1995). In another study in rats, additional 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). IRIS (2005) lists α-HCH as a probable human carcinogen and estimated an oral cancer potency factor for α-HCH of 6.3 $(mg/kg/day)^{-1}$ based on the incidence of hepatic nodules and hepatocellular carcinomas observed in male mice administered α-HCH in the diet (Ito et al. 1973). The doses corresponding to cancer risk levels ranging from 10^{-4} to 10^{-7} are $1.6x10^{-5}$–$1.6x10^{-8}$ mg/kg/day, respectively, as indicated in Figure 3-3. The oral cancer potency factor is a plausible upper-bound estimate of the lifetime probability of an individual developing cancer as a result of oral exposure per unit intake of the chemical.

β-HCH has not been found to be carcinogenic in Wistar rats exposed to 25 or 50 mg/kg/day in the diet for 24 or 48 weeks (Ito et al. 1975) or 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, Thorpe and Walker (1973) reported an increased incidence of hepatocellular carcinomas in CF1 mice exposed to 26 mg/kg/day in the diet for 104 weeks. The studies with negative results were, in general, of short duration, used a small number of animals, or failed to examine all of the animals. IRIS (2005) lists β-HCH as a possible human carcinogen and estimated an oral cancer potency factor for ingested β-HCH of 1.8 $(mg/kg/day)^{-1}$ based on the incidence of hepatic nodules and hepatocellular carcinomas observed in male mice administered β-HCH at a single dose level in the diet (Thorpe and Walker 1973). The doses corresponding to cancer risk levels ranging from 10^{-4} to 10^{-7} are $5.6x10^{-5}$–$5.6x10^{-8}$ mg/kg/day, respectively, as indicated in Figure 3-3. This is the only chronic study from which to estimate cancer risk from exposure to β-HCH. The study is limited by the use of only one nonzero dose group. Also, the use of incidence of liver tumors alone in mice to predict a compound's carcinogenicity in humans may be equivocal (Vesselinovitch and Negri 1988). Diversity of factors has been shown to influence the development of liver cell tumors in mice, such as the

strain of the mice (Nagasaki et al. 1975), the protein or calorific value of the diet (Tannenbaum and Silverstone 1949), and the microbial flora of the animals (Roe and Grant 1970).

δ-HCH has not been found to be carcinogenic in male Wistar rats exposed to 45 or 90 mg/kg/day in the diet for 24 or 48 weeks (Ito et al. 1975) or in male dd mice exposed to 18–90 mg/kg/day in the diet for 24 weeks (Ito et al. 1973). However, these studies were of relatively short-exposure duration. δ-HCH is structurally related to carcinogenic HCH isomers, but it is currently listed as not classifiable for human carcinogenicity (IRIS 2005).

Increased incidence of carcinoma was reported in Swiss mice following exposure to 90 mg technical-grade HCH/kg/day in the diet for 8–32 weeks (Thakore et al. 1981). Increased incidences of hepatocellular carcinoma were also reported in Swiss mice exposed to 21.3–85 mg/kg/day in the diet for 20 months (Munir et al. 1983) and in Swiss mice exposed to 10 or 17 mg/kg/day through gavage or the diet, respectively, for 80 weeks (Kashyap et al. 1979). The EPA has derived a cancer potency estimate for oral exposure to technical HCH (IRIS 2005). The oral slope factor is 1.8 per (mg/kg)/day and the doses corresponding to risk levels ranging from 10^{-4} to 10^{-7} are $5.6x10^{-5}$–$5.6x10^{-8}$ mg/kg/day, respectively, as indicated in Figure 3-3.

The DHHS has determined that γ-HCH and other HCH isomers may reasonably be anticipated to cause cancer in humans (NTP 2002). IARC has determined that HCH is possibly carcinogenic to humans (IARC 2003). As previously mentioned, the EPA has classified technical HCH and α-HCH as probable human carcinogens, β-HCH as a possible human carcinogen, and δ- and ε-HCH as not classifiable as to human carcinogenicity (IRIS 2005). The EPA has additionally classified γ-HCH into the category "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential" (EPA 2001a, 2002b).

3.2.3 Dermal Exposure

Studies examining the dermal toxicity of HCH in humans are limited. Most of the available information is derived from cases in which γ-HCH was dermally applied as a scabicide. γ-HCH in topical creams and lotions is efficiently absorbed through the skin (Ginsburg et al. 1977). Although it has been reported that these lotions contain 1% γ-HCH, it is not possible to quantify the amount of γ-HCH to which these individuals were exposed, because of the different areas of skin treated.

3.2.3.1 Death

No studies were located regarding lethal effects in humans following dermal exposure to α-, β-, or δ-HCH. An acute whole-body dermal application of 1% γ-HCH lotion to a 2-month-old infant for the treatment of scabies was reported to result in death (Davies et al. 1983), and a concentration of 110 ppb γ-HCH was identified in the brain. 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. The causal association between HCH exposure and death is difficult to establish since the women had numerous pre-existing health problems. In general, most humans dermally poisoned with γ-HCH have recovered with no apparent adverse effects (Fagan 1981).

In animals, acute dermal exposures to high doses of γ-HCH were reported to result in death. The dermal LD_{50} values for γ-HCH are 900 mg/kg in female rats and 1,000 mg/kg in male rats (Gaines 1960). Rats exposed to moistened γ-HCH for 24 hours exhibited no mortality at 250 mg/kg, 20% mortality at 600 mg/kg, 40% mortality at 1,000 mg/kg, and 30% mortality at 2,000 mg/kg (Ullmann 1986a). Significant lethality (47%) was seen in female rats, but not male rats, exposed dermally to 400 mg γ-HCH/kg/day for 6 hours/day, 5 days/week, for 13 weeks (Brown 1988). Calves dermally exposed to 33.3 mg/kg γ-HCH died within 5 months (Venant and Sery 1991). 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 exposure to technical-grade HCH at 100 mg/kg/day for 15–30 days (Dikshith et al. 1991c). 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 γ-HCH/kg (Hanig et al. 1976). This suggests that children might be at a greater risk than adults for toxic responses to dermal absorption of HCH. 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). These and other values are in Tables 3-4 and 3-5.

3.2.3.2 Systemic Effects

No studies were located regarding musculoskeletal, endocrine, ocular, or body weight effects in humans or animals after inhalation exposure to inorganic tin or organotin compounds. Reliable LOAELs for

Table 3-4 Levels of Significant Exposure to Gamma-hexachlorocyclohexane (lindane) - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL Less Serious		LOAEL Serious		Reference Chemical Form
ACUTE EXPOSURE								
Death								
Rat (Sherman)	10 d (GOC)					1000 M mg/kg/day	(LD50)	Gaines 1960 lindane
						900 F mg/kg/day	(LD50)	
Rat (Wistar)	24 hr once					1000 mg/kg/day	(LD50)	Ullmann 1986a lindane
Systemic								
Rat (Wistar)	24 hr once	Resp	600 mg/kg/day	1000 mg/kg/day	(dyspnea)			Ullmann 1986a lindane
Rabbit (New Zealand)	once	Ocular		40 mg/kg/day	(mild eye irratation)			Ullmann 1986c lindane
Rabbit (New Zealand)	4 hr once	Dermal	200 mg/cm²/kg					Ullmann 1986d lindane
Neurological								
Rat (Wistar)	24 hr once		600 mg/kg/day	1000 mg/kg/day	(slight sedation)	2000 F mg/kg/day	(severe spasms)	Ullmann 1986a lindane

Table 3-4 Levels of Significant Exposure to Gamma-hexachlorocyclohexane (lindane) - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL Less Serious		LOAEL Serious		Reference Chemical Form
INTERMEDIATE EXPOSURE								
Death								
Rat (Crl:(WI)BR)	13 wk 5 d/wk 6 hr/d		60 F mg/kg/day			400 F mg/kg/day	(23 deaths out of 49)	Brown 1988 lindane
Systemic								
Rat (Crl:(WI)BR)	13 wk 5 d/wk 6 hr/d	Resp		10 mg/kg/day	(rapid respiration or wheezing)			Brown 1988 lindane
		Hepatic	10 mg/kg/day	60 mg/kg/day	(centrilobular hypertrophy)			
		Renal	10 F mg/kg/day	10 M mg/kg/day	(hyaline droplet formation)			
				60 F mg/kg/day	(basophilic tubules)			
Rat	once for 25 days			180 F mg/kg	(mild dermatitis)			Dikshith et al. 1973 lindane
Neurological								
Rat (Crl:(WI)BR)	13 wk 5 d/wk 6 hr/d			10 mg/kg/day	(hyperactivity)	60 F mg/kg/day	(ataxia, tremors, convulsions)	Brown 1988 lindane

d = day(s); F = female; hr = hour(s); LD50, lethal dose; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

Table 3-5 Levels of Significant Exposure to Technical - Grade Hexachlorocyclohexane - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL			Reference Chemical Form
				Less Serious		Serious	
ACUTE EXPOSURE							
Death							
Gn Pig (NS)	5-12 d 1x/d				200 M mg/kg/day	(24/24 deaths)	Dikshith et al. 1978 technical - grade
INTERMEDIATE EXPOSURE							
Death							
Rat (Wistar)	15 d 1x/d				100 F mg/kg/day	(2/10 deaths)	Dikshith et al. 1991c technical - grade
Rabbit (NS)	30 d 1x/d				25 M mg/kg/day	(6/24 deaths)	Dikshith et al. 1989b technical - grade

Table 3-5 Levels of Significant Exposure to Technical - Grade Hexachlorocyclohexane - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL				Reference Chemical Form
				Less Serious		Serious		
Systemic								
Rat (Wistar)	30 d 1x/d	Hepatic				100 F mg/kg/day	(hypertrophy, fatty degeneration, nuclear pyknosis of hepatocytes, diffuse and focal liver necrosis)	Dikshith et al. 1991c technical - grade
		Renal				100 F mg/kg/day	(tubular necrosis)	
		Dermal		100 F mg/kg/day	(hyperkeratosis, epidermal cell vacuolization, thickening of collagen fibers)			
Gn Pig (NS)	30 d 1x/d	Hepatic		100 M mg/kg/day	(38% increase in liver weight, hepatic hypertrophy, pycnotic nuclei in cytoplasm, foca fatty inclusions, increased GOT and ALF activity)			Dikshith et al. 1978 technical - grade
		Renal	100 M mg/kg/day					

Table 3-5 Levels of Significant Exposure to Technical - Grade Hexachlorocyclohexane - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL				Reference Chemical Form
				Less Serious		Serious		
Rabbit (NS)	30 d 1x/d	Hepatic		25 M mg/kg/day	(hepatocyte degeneration, pycnotic nuclei, enlarged liver, altered GOT, GPT, LDH and ALP activities)			Dikshith et al. 1989b technical - grade
		Renal				25 M mg/kg/day	(altered epithelial lining o proximal convoluted tubules, loss of brush borders of tubules, atrophy of glomerular capsules)	
		Dermal		25 M mg/kg/day	(thickened epidermis, hyperkeratinization, and infiltration of mononuclear cells)			
CHRONIC EXPOSURE								
Cancer								
Mouse (Swiss)	80 wk 2 d/wk					2.4 mg/kg/day	(CEL: liver tumors)	Kashyap et al. 1979 technical - grade

ALP = alkaline phosphatase; CEL = cancer effect level; d = day(s); F = female; Gn pig = guinea pig; GOT = glutamate oxaloacetate transaminase; GPT = glutamate pyruvate transaminase; LDH = lactate dehydrogenase; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; NS = not specified; wk = week(s); x = time(s)

respiratory, hepatic, and renal effects in animals after acute and intermediate exposure to γ-HCH are shown in Table 3-4. Reliable LOAELs for hepatic, renal, and dermal effects in animals after intermediate exposure to technical-grade HCH are shown in Table 3-5.

Respiratory Effects. 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 (tiny reddish spots that contain blood) (Davies et al. 1983). Slight dyspnea was observed in rats exposed dermally for 24 hours to 1,000 or 2,000 mg γ-HCH/kg 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 γ-HCH/kg/day for 13 weeks (Brown 1988).

Cardiovascular Effects. 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 findings were minimal but revealed epicardial petechiae (Davies et al. 1983).

No studies were located regarding cardiovascular effects in animals following dermal exposure to HCH.

Gastrointestinal Effects. Vomiting and diarrhea occurred in a child (Ramchander et al. 1991) and a woman (Hall and Hall 1999) who had 1% γ-HCH applied to the skin to treat a rash and to treat scabies.

No studies were located regarding gastrointestinal effects in animals following dermal exposure to HCH.

Hematological Effects. Aplastic anemia was documented in a man who applied γ-HCH to his skin for 3 weeks for treatment of scabies (Rauch et al. 1990). 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 in a preparation that reportedly contained 2% HCH (Woodliff et al. 1966). 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).

No studies were located regarding hematological effects in animals following dermal exposure to any of the HCH isomers.

Hepatic Effects. No studies were located regarding hepatic effects in humans following dermal exposure to HCH.

Liver pathology, 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 with 100 mg technical-grade HCH/kg/day for 30 days (Dikshith et al. 1978). The patch 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 GPT and alkaline phosphatase (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, and the number of animals affected were not reported (Dikshith et al. 1991c). Centrilobular hypertrophy was reported in male and female rats exposed dermally to 60 mg γ-HCH/kg/day for 6 hours/day, 5 days/week, for 13 weeks (Brown 1988).

Renal Effects. No studies were located regarding renal effects in humans following dermal exposure to HCH.

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 (Dikshith et al. 1989b). 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 positive scores for protein, blood, and turbidity in treated males (Brown 1988). Females in the same study exhibited a slight increase in the incidence of tubular basophilia at 60 mg/kg/day.

Dermal Effects. 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 for 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). 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).

Ocular Effects. No studies were located regarding ocular effects in humans following dermal exposure to HCH.

Mild eye irritation was seen in rabbits exposed to 40 mg/kg γ-HCH in the conjunctival sac for up to 72 hours, giving a primary irritation score of 0.6 out of a maximum possible cumulative score of 16 (Ullmann 1986c).

3.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological or lymphoreticular effects in humans or animals following dermal exposure to HCH.

3.2.3.4 Neurological Effects

There have been several reports of human intoxication involving convulsions in adults and children after excessive topical application of γ-HCH (Boffa 1995; Fischer 1994; Hall and Hall 1999; Lee and Groth 1977; Matsuoka 1981; Ramchander et al. 1991; Telch and Jarvis 1982; Tenenbein 1991); exposure levels were not reported. Heiberg and Wright (1955) reported convulsions in a woman who had treated calves with an insecticide containing 11% γ-HCH and 16% other HCH isomers. Central nervous systems symptoms of severe γ-HCH poisoning, including incontrollable 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 antiscabies 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 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 man with human immunodeficiency virus (HIV) exhibited generalized tonic-clonic seizure activity after a single topical application of a 1% γ-HCH lotion to treat scabies (Solomon et al. 1995).

Studies in animals have substantiated the neurological symptoms resulting from γ-HCH application. Manifestations such as excitability, seizures, and convulsions have been observed in rabbits following a single topical application of 60 mg γ-HCH/kg 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). Sedation was severe in one female receiving the highest dose (2,000 mg/kg). This female also showed severe spasms. 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). Aggressiveness or hyperactivity was noted in female rats exposed dermally for 13 weeks to 10 mg γ-HCH/kg/day, while ataxia and tremors were seen at 60 mg/kg/day (Brown 1988).

3.2.3.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following dermal exposure to HCH. 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. In a similar study, 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-glucoronidase. 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.

3.2.3.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals following dermal exposure to HCH.

3.2.3.7 Cancer

A case-control study surveying childhood brain cancer cases among Missouri residents found that the odds ratios for the use of Kwell, a shampoo containing γ-HCH for lice control, were slightly elevated during the first 7 months of age to diagnosis (Davis et al. 1992). Thus, Kwell use was significantly associated with childhood brain cancer compared to controls. However, this study was limited by small sample sizes, potential recall bias in questionnaires, multiple comparisons, and the lack of detailed exposure information.

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). Increases that were not statistically significant were reported in the incidences of hyperplastic and preneoplastic areas in the liver and hepatic tumors in Swiss mice exposed to 2.4 mg technical-grade HCH/kg/day for 80 weeks (Kashyap et al. 1979). Limitations of these studies, including less-than-lifetime exposure and study duration, the testing of only one dose, and the potential for ingestion of some of the compound from the skin, preclude determination that dermally applied HCH is noncarcinogenic in mice.

3.3 GENOTOXICITY

The available genotoxicity data indicate that γ-HCH and other individual HCH isomers have some genotoxic potential, but the evidence for this is not conclusive.

No appreciable increase in the frequency of chromosome aberrations was observed in humans exposed primarily to γ-HCH by inhalation in a pesticide production factory (Kiraly et al. 1979). These individuals had been exposed for 8 hours/day for at least 6 months. Other studies are available regarding genotoxic effects in humans exposed to a wide variety of pesticides, including γ-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 the other exposures, are not known.

In animals, ingestion of technical-grade HCH was reported to induce dominant-lethal mutations in mice (Lakkad et al. 1982). It did not induce chromosome aberrations in bone marrow cells of Syrian hamsters (Dzwonkowska and Hubner 1986), but positive results were reported in bone marrow cells of rats exposed to β-HCH (Shimazu et al. 1972). Oral exposure to α-HCH was reported to result in mitotic disturbances including an increased mitotic rate and an increased frequency of polyploid hepatic cells in

rats (Hitachi et al. 1975). γ-HCH has also been tested *in vivo* in animals. Incidence of chromosome clastogeny 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). γ-HCH was negative in a micronucleus assay in mice (Jenssen and Ramel 1980). α-HCH produces DNA fragmentation in primary cultures of rat and human hepatocytes, but not in mouse hepatocytes (Mattioli et al. 1996). DNA repair induction was absent in hepatocytes from all three species. Both α- and γ-HCH have been observed to bind to mouse liver DNA at a low rate (Iverson et al. 1984).

γ-HCH has been tested in several *in vitro* genotoxicity studies. In bacteria, it was not observed to induce gene mutations in assays with or without a metabolic activation system (Moriya et al. 1983; Nagy et al. 1975), and it did not produce DNA damage, although a mammalian metabolic activation system was not present (Shirasu et al. 1976). γ-HCH was also not mutagenic in yeast (Shahin and von Borstel 1977) or 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 mammalian cells, γ-HCH (purity not reported) induced a marginal increase in the frequency of chromosome aberrations (including chromosomal gaps) in Chinese hamster cells, which was interpreted by the authors of the study as providing suggestive, but not conclusive, evidence of an effect (Ishidate and Odashima 1977). DNA damage was observed in cultures of rat nasal and gastric mucosa cells, and human nasal mucosa cells (Pool-Zobel et al. 1994). γ-HCH (NTP 1984) and technical-grade γ-HCH (Murli 1990) were both reported to be negative for cytogenetic effects in Chinese hamster ovary cells. α-HCH and γ-HCH were reported to bind to calf thymus DNA in the presence of metabolic activation (Iverson et al. 1984). γ-HCH was found inactive for inducing unscheduled DNA synthesis in human SV-40 fibroblasts, with and without activation (Ahmed et al. 1977), while it was found to induce unscheduled DNA synthesis in human peripheral lymphocytes (Rocchi et al. 1980). More recent studies by Kalantzi et al. (2004) with human mammary carcinoma MCF-7 and human prostate carcinoma PC-3 cell lines showed that incubation of the cells with low concentrations of γ-HCH (10-12–10-10 M) induced increases in micronuclei in both cell lines in the absence of DNA damage or cytotoxicity, suggesting a clastogenic effect for this chemical. The α- and β- stereoisomers were less active than γ-HCH. Cultured human lymphocytes taken from three healthy males showed a dose-dependent increase in chromosomal aberrations (gaps, breaks, and fragments) with significant increases at 0.1 μL/mL technical-grade HCH (6.5% γ-HCH) for 48-hour treatment and at 0.05 and 0.1 μL/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 μL/mL) producing the only significant result. These results suggest mild mutagenic activity at high

doses in humans (Rupa et al. 1989d). Technical-grade γ-HCH was also found inactive for inducing unscheduled DNA synthesis in rat primary hepatocytes *in vitro* (Cifone 1990).

Tables 3-6 and 3-7 present the results of *in vivo* and *in vitro* genotoxicity studies on HCH isomers, respectively.

3.4 TOXICOKINETICS

Absorption of the various HCH isomers following inhalation, oral, or dermal exposure has been inferred from humans who have become ill or who had increased serum levels of the various isomers following exposure by these routes. 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 (Albro and Thomas 1974). 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 (Baumann et al. 1980; Siddiqui et al. 1981a). β-HCH accumulates to a much greater extent than γ-HCH. The excretion of HCH isomer metabolites is primarily through the urine. The isomers have also been detected in breast milk (Ejobi et al. 1996; Schoula et al. 1996) and semen (Szymczynski and Waliszewski 1981). The primary urinary metabolites are chlorophenols and 1,2,4-trichlorocyclohexane-4,5-epoxide. The conversion occurs mainly by the action of hepatic enzymes.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Evidence exists that humans absorb γ-HCH vapor or dusts via inhalation. This can be inferred from occupational studies in which adverse health effects, including hematological abnormalities and neurological effects, have been reported in workers exposed to γ-HCH in workplace air (Brassow et al. 1981; Czegledi-Janko and Avar 1970; Kashyap 1986; Samuels and Milby 1971). In addition, 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 does take place (Baumann et al. 1980; Czegledi-Janko and Avar 1970; Kashyap 1986; Nigam et al. 1986; Saxena et al. 1980, 1981a, 1981b). There are no specific studies that have quantified the rate or extent of absorption of the HCH isomers following inhalation exposure. No information is available on the absorption of α-, β-, γ-, and δ-HCH following inhalation exposure in experimental animals.

Table 3-6. Genotoxicity of Hexachlorocyclohexane Isomers *In Vivo*

Species (test system)	End point	Results	Isomer	Reference
Mammalian cells:				
Human (peripheral lymphocytes)	Chromosomal aberrations	–	Gamma	Kiraly et al. 1979
Human hepatocytes	DNA fragmentation	+	Alpha	Mattioli et al. 1996
Syrian hamster (bone marrow)	Chromosomal aberrations	–	Gamma	Dzwonkowska and Hubner 1986
Rat (bone marrow)	Chromosomal aberrations	+	Beta	Shimazu et al. 1972
Rat (primary cultures)	DNA fragmentation	+	Alpha	Mattioli et al. 1996
Mouse (germ cells)	Dominant lethal	+	Technical	Lakkad et al. 1982
Mouse	Micronuclei	–	Gamma	Jenssen and Ramel 1980
Mouse (bone marrow)	Chromosomal aberrations	+	Gamma	Kumar et al. 1995
Mouse (liver)	DNA binding	(+)	Alpha/ gamma	Iverson et al. 1984
Mouse (hepatocytes)	DNA fragmentation	–	Alpha	Mattioli et al. 1996
Rat (liver)	Mitotic disturbances	+	Alpha	Hitachi et al. 1975

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

Table 3-7. Genotoxicity of Hexachlorocyclohexane Isomers *In Vitro*

Species (test system)	End point	Results		Isomer	Reference
		With activation	Without activation		
Prokaryotic organisms:					
Salmonella typhimurium (TA100, TA98, TA1535, TA1537, TA1538)	Gene mutation	–	–	Gamma	Moriya et al. 1983
Escherichia coli (WP2/spot test)	Gene mutation	NT	–	Gamma	Nagy et al. 1975
E. coli (WP2 *hcr*)	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
Nostoc muscorum	Gene mutation	NT	–	Gamma	Kar and Singh 1979a
Allium cepa	Mitotic disturbances	NT	+	Gamma	Nybom and Knutsson 1947
Mammalian cells:					
Human (SV-40 fibroblasts)	Unscheduled DNA synthesis	–	–	Gamma	Ahmed et al. 1977
Human (peripheral lymphocytes)	Unscheduled DNA synthesis	NT	+	Gamma	Rocchi et al. 1980
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 (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 (peripheral lymphocytes)	Sister chromatid exchange	NT	+	Technical	Rupa et al. 1989d
Human (peripheral lymphocytes)	Chromosomal aberrations	NT	+	Technical	Rupa et al. 1989d
Chinese hamster (CHL cells)	Chromosomal aberrations	NT	(+)	Gamma	Ishidate and Odashima 1977
Chinese hamster (CHL cells)	Chromosomal aberrations	NT	–	Gamma	NTP 1984
Chinese hamster (CHL cells)	Sister chromatid exchange	NT	–	Gamma	NTP 1984
Chinese hamster (CHL cells)	Chromosomal aberrations	–	–	Technical	Murli 1990

Table 3-7. Genotoxicity of Hexachlorocyclohexane Isomers *In Vitro*

Species (test system)	End point	Results		Isomer	Reference
		With activation	Without activation		
Rat (primary hepatocytes)	Unscheduled DNA synthesis	NT	–	Technical	Cifone 1990
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

3.4.1.2 Oral Exposure

In humans, HCH is absorbed following oral exposure. Many accidental poisonings have occurred in humans as a result of γ-HCH ingestion, and high blood concentrations have been demonstrated in a number of acute poisoning 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).

HCH is similarly absorbed following oral exposure in animals. Information concerning the rate of absorption from the gastrointestinal tract can be inferred from studies conducted in mice and rats. These studies indicated that γ-HCH is readily absorbed from the gastrointestinal tract (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 radiolabelled 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.

Absorption of technical-grade HCH following oral exposure has been quantified in rats. The extent of absorption of technical-grade HCH has been estimated to be 95.8% in rats within 4 days following the oral 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 percentage of 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).

3.4.1.3 Dermal Exposure

The ready absorption of γ-HCH across human skin, due to its lipid solubility, has been demonstrated in several studies that examined the absorption of γ-HCH from an antiscabies lotion (Feldmann and Maibach

1974; Franz and Lehman 1996; 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).

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). One with 120 mg γ-HCH/mL in acetone as the vehicle and the other, a commercial product, consisted of 3 mg γ-HCH/mL formulation, which primarily contained white spirit as the solvent base. 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. 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.

γ-HCH is similarly absorbed through the skin of animals. Toxicity was observed in guinea pigs and rabbits following dermal exposure to γ-HCH and following dermal exposure to technical-grade HCH (Dikshith et al. 1978; Hanig et al. 1976). Male rats treated dermally with radiolabelled 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 radiolabelled 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).

The absorption of γ-HCH in infants and children who had received dermal treatment with 1% γ-HCH lotion was investigated in one study (Ginsburg et al. 1977). Maximum blood concentrations of γ-HCH were observed in 6 hours, and averaged at 0.028 μg/mL for the group infected with scabies and 0.024 μg/mL for the noninfected group.

3.4.2 Distribution

Placental transfer of HCH in humans has been well documented (Saxena et al. 1981a). The levels of HCH and other organochlorine insecticides were found to be higher in the maternal blood, placenta, and umbilical-cord blood of stillborn cases than those of live-born cases (Saxena et al. 1983). Similarly, γ-, α-, δ-, and total HCH maternal blood and umbilical-cord blood levels were higher in mothers who gave birth to IUGR babies than in women who gave birth to normal weight babies (Siddiqui et al. 2003). HCH has been shown to accumulate in amniotic fluid, placenta, and fetal tissues after oral treatment of pregnant mice (Srivastava and Raizada 1993) and can be related to fetolethality. HCH isomers have been detected in human breast-milk, particularly in developing countries that still use HCH as a pesticide. Detected concentrations in these studies are discussed in Section 6.6. In a study on rats, γ-HCH has been reported to be transferred in the breastmilk and to elicit neurological effects in neonates. Epileptiform seizures have been reported in male rats fed maternal milk for 12 days beginning on the third day after birth, from dams exposed daily to 20 mg γ-HCH/kg by gavage (Albertson et al. 1985). In another study, in which lactating females were treated orally with a single dose of 6 mg/kg of γ-HCH on days 9 or 14 of lactation, the testosterone level of the male offspring was reduced 50% when puberty was reached (day 65) when compared to the control group (Dalsenter et al. 1997b). When the offspring reached adulthood (postnatal day 140), the relative testicular weight was significantly lower (Dalsenter et al. 1997b). The number of sperm and spermatids was also significantly reduced. 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).

3.4.2.1 Inhalation Exposure

Information on the distribution of the HCH isomers, following inhalation by humans, comes from studies of humans exposed to HCH in the workplace. 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 levels of total HCH 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 the adipose tissues of workers occupationally exposed and individuals exposed via the ambient environment (Baumann et al. 1980; Siddiqui et al. 1981a). Accumulation of β-HCH has been shown to increase approximately linearly with

time of exposure (Baumann et al. 1980). Siddiqui et al. (1981a) found adipose levels of 0.1–1.5, 0.06–0.9, 0.7–3.0, and 0.97–5.8 ppm of α-, β-, γ-, and total HCH, respectively, in the tissues collected during an autopsy case study conducted in India.

In a study with 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.

3.4.2.2 Oral Exposure

Information on the distribution of the HCH isomers following ingestion by humans comes from case reports. A fatal poisoning case confirmed that γ-HCH is, in part, 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).

More detailed information on the distribution of HCH or its isomers is available from studies in which laboratory animals were exposed by ingestion (Chand and Ramachandran 1980; Eichler et al. 1983; Srinivasan and Radhakrishnamurty 1983b). These studies examined the overall distribution pattern of HCH isomers. γ- and β-HCH are primarily stored in the fat of rats acutely exposed for 5, 10, or 15 days (Srinivasan and Radhakrishnamurty 1983b). The overall distribution of γ-HCH was greatest in fat, followed by brain, kidney, muscle, lungs, heart, spleen, liver, and blood. More recently, 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 gavaged with 5 or 12 mg/kg/day began to decline after 8 days. This reduction was not observed in rats gavaged with 20 mg/kg/day (Tusell et al. 1988). In rats gavaged with γ-HCH on lactation days 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. 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 it is equally lipophilic. Differences in distribution of γ-HCH and α-HCH are most likely due to stereospecific forces.

The distribution pattern for β-HCH was found to be in the following order: fat > kidney > lungs > liver > muscle > heart > spleen > brain > blood. For γ-HCH, the distribution pattern was as follows: fat > brain > kidney > muscle > lungs > heart > spleen > liver > 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 1983b). 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 mixed-function oxygenase system, 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-duration exposure of rats to HCH (isomer unspecified) in the diet (overall distribution: fat > liver > serum) (Chand and Ramachandran 1980) or exposure to α- or γ-HCH by gavage (overall distribution: fat > kidney > liver > brain > blood) (Eichler et al. 1983).

3.4.2.3 Dermal Exposure

Information on the distribution of the HCH isomers in exposed humans comes from case reports. A fatal poisoning case indicated that γ-HCH is, in part, distributed to the brain following topical application. The isomer was 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). In another study, blood levels of γ-HCH peaked 6 hours following topical application of a 1% solution to 20 children (12 infected with scabies, 8 noninfected) (Ginsburg et al. 1977). Mean concentrations did not differ statistically between the two groups at 6 hours and were 0.024 µg/mL in healthy children and 0.028 µg/mL in infected children. The half-lives in blood were 17.9 and 21.4 hours in infected and healthy children respectively. Differences in dosage between the two groups of children were considered marginally significant ($p=0.11$). However, the infected children were younger. The mean ages for the infected and noninfected groups were 32.5 and 64.3 months, respectively.

The distribution 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 the acetone and white-spirit based applications were 0.91 and 0.47 ng/mL, respectively; although the preparation in acetone contained a 40-fold higher concentration of γ-HCH. 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.

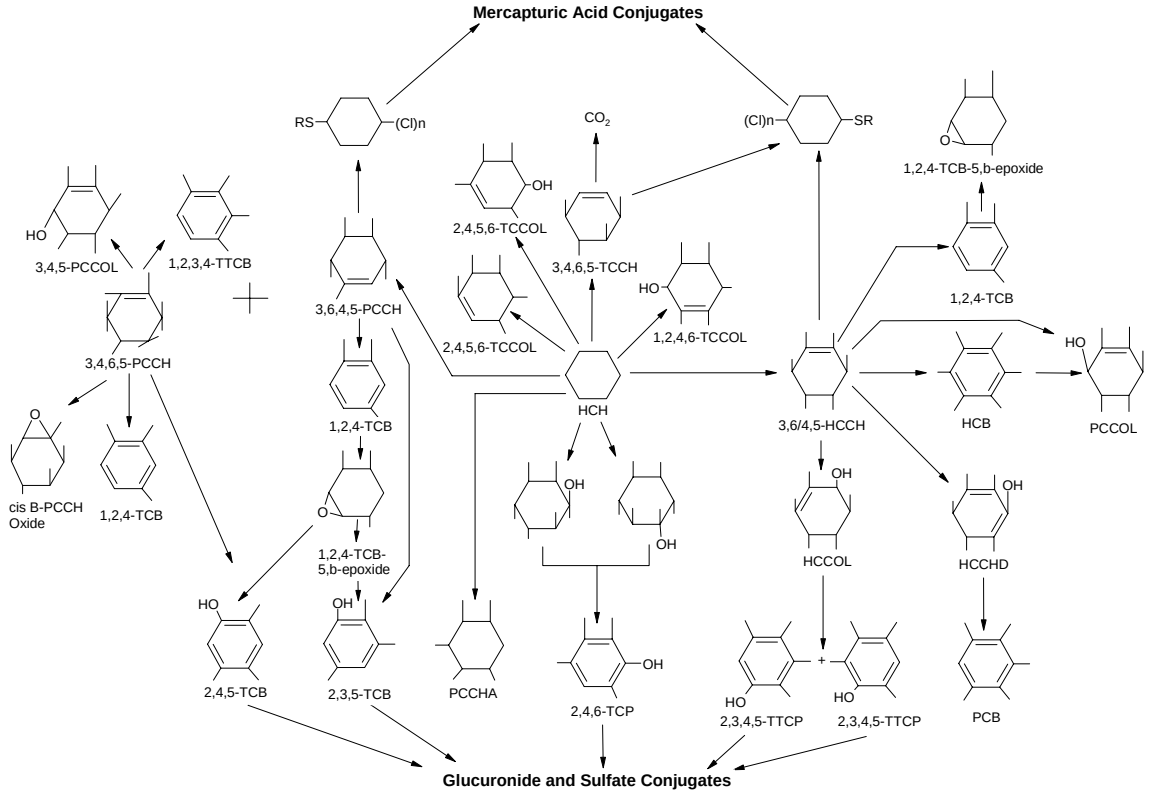
Some information on the distribution of γ-HCH is available from studies in which laboratory animals were exposed by dermal application (Bosch 1987a, 1987b; Hanig et al. 1976; Solomon et al. 1977a, 1977b). A study on the distribution of γ-HCH in guinea pigs following acute dermal exposure indicates that 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. Experiments with radiolabelled γ-HCH in dermally treated rats (Bosch 1987a) and rabbits (Bosch 1987b) found that absorption of radiolabel increased with time of exposure, with greater absorption and subsequent excretion in the urine occurring at the lower treatment doses. In weanling rabbits, which appear to be more sensitive to γ-HCH toxicity from dermal exposure than young adults, 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.

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.

3.4.3 Metabolism

The metabolism of γ-HCH is illustrated in Figure 3-4. 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*

Figure 3-4. The Proposed Metabolism of Hexachlorocyclohexane*



Abbreviations:

HCB:	Hexachlorobenzene
HCCHD:	Hexachlorocyclohexadiene
HCCOL:	Hexachlorocyclohexenol
HCH:	Hexachlorocyclohexane
PCCHA:	Pentachlorocyclohexane
PCCOL:	Pentachlorocyclohexenol
PCCH:	Pentachlorocyclohexene
PCB:	Pentachlorobenzene
TCCOL:	Tetrachlorocyclohexenol
TCCH:	Tetrachlorobenzene
TTCP:	Tetrachlorophenol
TCB:	Trichlorobenzene
TCP:	Trichlorophenol
3,6/4,5-HCCH:	3,6/4,5-Hexachlorocyclohexene

*Adapted from Chadwick et al. 1979, 1985; Fitzloff and Pan 1984; Fitzloff et al. 1982

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).

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 yet 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 the P-450 oxidative system. Intermediate exposure to γ-HCH resulted in greater toxicity in DBA/2 (D2) mice than in C57BL/6 (B6) mice; the former are unresponsive to microsomal enzyme induction by γ-HCH (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 phenobarbitol. Following pretreatment with Aroclor 1254, a 7-fold increase in expired metabolites was observed. Naphthoflavone had no effect on the excretion rate.

Metabolic transformations also affect the neurotoxicity of γ-HCH. Experiments in rats pretreated with 3-methylcholanthrene (MC), an inducer of P-4501A1/1A2, phenobarbitol (PB), an inducer of P-4502B1/2B2, or ethanol, an inducer of P-4502E1, suggested that the convulsive activity of γ-HCH is due to γ-HCH *per se* and/or to metabolites formed by PB- or ethanol-inducible P-450 isoenzymes (Parmar et al. 2003).

Metabolism of HCH has not been studied in children. However, although it is unknown whether the ability to metabolize HCH specifically differs between children and adults, some enzymes that belong to the enzyme superfamilies involved in phase II HCH metabolism are developmentally regulated in humans. The development of 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-glutamyltranspeptidase, glutathione S-transferase, cysteinyl glycinase, and N-acetyl transferase (Sipes and Gandolfi 1991). There are two superfamilies of N-acetyltransferases, and one (i.e., the N-acetyl-transferase 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 (there is a genetic polymorphism in this enzyme in adults). 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).

3.4.4 Elimination and Excretion

Excretion of hexachlorocyclohexane has not been studied in children.

3.4.4.1 Inhalation Exposure

Humans excrete γ-HCH and its metabolites in urine, milk, and semen (Angerer et al. 1981). Chromatographic 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 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. HCH is commonly detected in low concentrations (0.015 mg/kg fat) in the breastmilk of women exposed to HCH in the environment (Fytianos et al. 1985). All five of the HCH isomers discussed in this profile have been detected in human semen following environmental exposure, suggesting another route of elimination (Szymczynski and Waliszewski 1981). No animal studies using the inhalation route of exposure were located.

3.4.4.2 Oral Exposure

Excretion of γ-HCH and its metabolites in laboratory animals has been well documented. Data indicate that its 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 β-HCH seems to resist, to some extent, conversion to the glutathione derivative; γ-HCH and α-HCH are readily conjugated (Fitzloff and Pan 1984; Fitzloff et al. 1982). γ-HCH derivatives are not only excreted in the form of phenylmercapturic acids; there is ample evidence that they are also excreted in the form of glucuronides and sulfate conjugates (Chadwick et al. 1978a).

No studies were located regarding genotoxic effects in animals following oral exposure, in humans following inhalation exposure, or in humans or animals following dermal exposure to HCH.

3.4.4.3 Dermal Exposure

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 infected with scabies and their noninfected 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 infected children and 21.4 hours in noninfected children.

In male rats treated dermally with radiolabelled γ-HCH, 0.28, 0.08, and 0.02% radiolabel were excreted in urine 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 were excreted in urine from the same respective doses. In a similar study with male rabbits, 3.8, 2.6, and 1.3% radiolabel were excreted in urine 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 were excreted in urine from the same respective doses.

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

Physiologically based pharmacokinetic (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 end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-5 shows a conceptualized representation of a PBPK model.

The overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

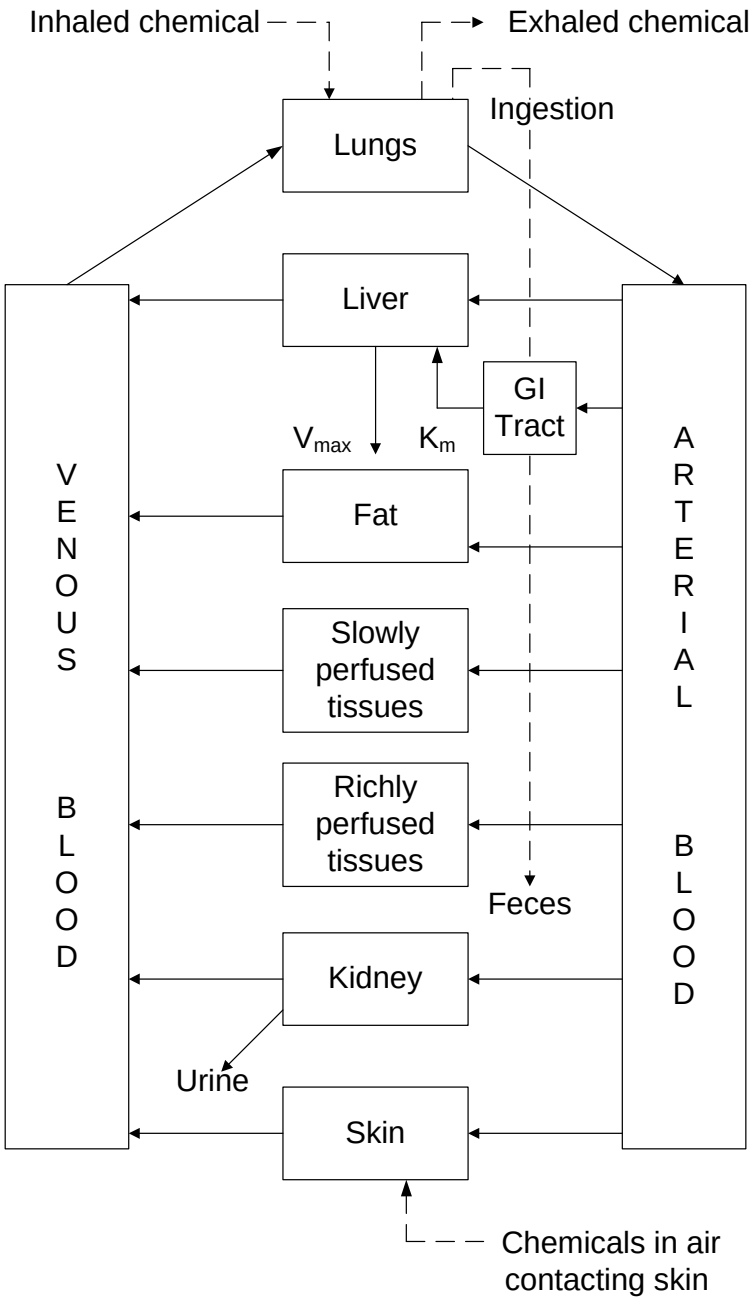
DeJongh and Blaauboer (1997) simulated the toxicokinetics of γ-HCH in rats with a PBPK model. A five-compartment model for the rat as presented in Figure 3-5 was constructed, including (1) the liver, serving as the metabolizing organ; (2) blood; (3) fat; (4) brain; and (5) a lumped compartment representing all other tissues, consisting mainly of muscle tissue. Values for the physiological parameters, tissue-blood partition coefficients, were obtained from the literature and are presented in Figure 3-6 and Table 3-8. 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 blood, brain, muscle, and fat after single intraperitoneal and chronic oral dosage compared adequately well with experimental results. However, the model is not validated via biological evaluation of kinetic parameters.

There are no PBPK models for HCH in children.

Currently, the Agency of Toxic Substances and Disease Registry is assessing the feasibility of using tools such as PBPK modeling and pharmacodynamic modeling to extrapolate data across routes or durations of exposure. Such extrapolation may be done on a substance-by-substance basis after adequate toxicokinetic information has been collected.

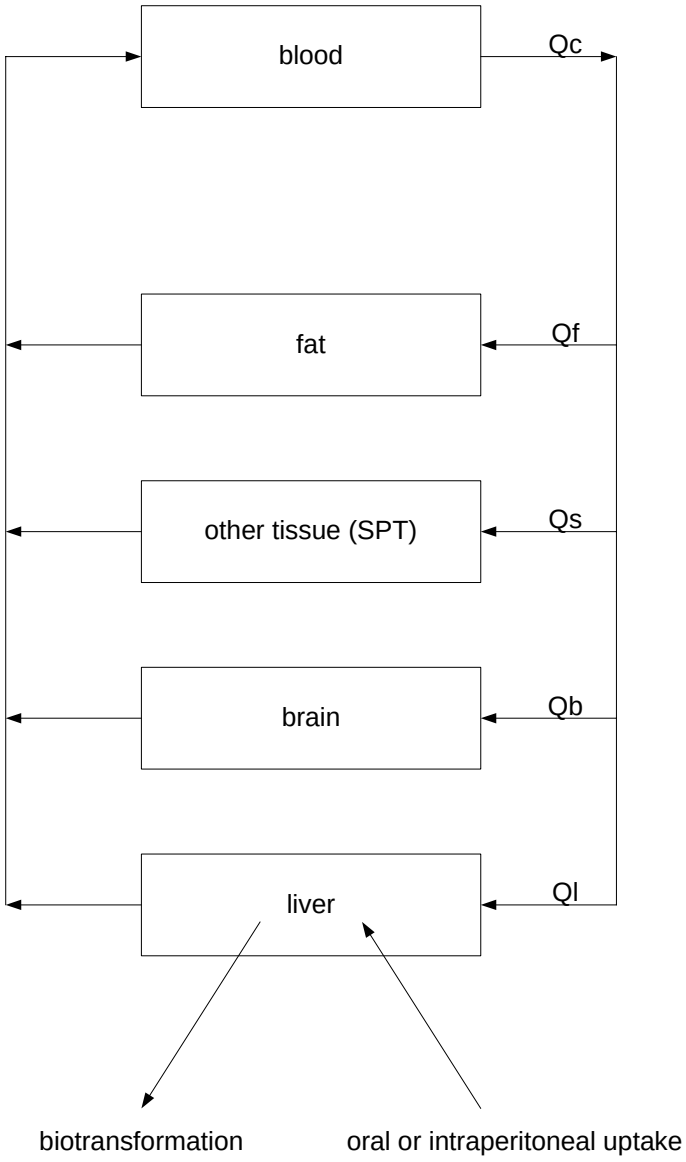
Figure 3-5. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Figure 3-6. Structure of the PBPK Model for γ-HCH*



Source: DeJongh and Blaauboer (1997)

*Model parameters are described in Table 3-8.

Table 3-8. Parameters for a PBPK Model for γ-Hexachlorocyclohexane in Rats

Parameter	Value	Scaling factor
Body weight (kg)	0.135–0.313	
Cardiac output (L/hour kg)[a] $BW^{0.74}$	14	
Blood flow fractions[a]		
Liver	0.25	–
Fat	0.09	–
Other tissues (SPT)	0.63	–
Brain	0.03	–
Tissue group volume fractions		
Blood[a]	0.06	–
Liver[a]	0.04	–
Brain[a]	0.0006	–
Fat[b]	0.2xBW+0.0166	–
Remaining tissues (SPT)	0.894-VFC	–
Partition coefficients for lindane		
Liver-blood[c]	4.2	–
Fat-blood[c]	95.3	–
SPT-blood[c]	1.6	–
Brain-blood[d]	4.1	–
Metabolic and uptake constants		
Biotransformation rate[e] ($hour^{-1}kg^{-1}$)	4.5	$BW^{-0.3}$
Oral/intraperitoneal uptake rate[e] ($hour^{-1}$)	0.035	–
Oral/intraperitoneal uptake efficiency[d]	0.8	–

Source: DeJongh and Blaauboer 1997

BW = body weight; SPT = slowly perfused tissue; VFC = relative adipose tissue mass where VFC=0.2*BW+0.0166

[a]Reference values (Arms and Travis 1988)
[b]Calculated as a function of body weight (Bailey et al. 1980)
[c]Measured *in vitro* (Jepson et al. 1994)
[d]Measured *in vivo* (Oshiba 1972)
[e]Value obtained by calibration

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Information is available to assess the extent and rate of HCH absorption following oral and dermal exposure (Ahdaya et al. 1981; Albro and Thomas 1974; Turner and Shanks 1980). However, inhalation absorption of HCH can only be inferred from toxicity studies and studies assessing the distribution and excretion of γ-HCH. No quantitative information is available to assess the rate and extent of inhalation absorption.

Following oral exposure to γ-HCH in rats, little, if any, metabolism was observed in the gut as indicated by the absence of metabolites in the feces (Kujawa et al. 1977). Rather, it is readily absorbed, where the majority is transported via the blood rather than the lymphatics (Turner and Shanks 1980). HCH, a lipophilic compound, is well distributed in adipose tissue, though whether these compounds are absorbed into tissues via active or passive mechanisms is unknown. HCH metabolism is mediated primarily in the liver by the cytochrome P-450 oxygenase system. The many metabolites of HCH, mostly polychlorophenols, are eliminated primarily in the urine.

Additional data concerning the mechanisms of inhalation and dermal absorption of HCH in animals may provide information to assist in characterizing absorption of HCH in humans.

3.5.2 Mechanisms of Toxicity

In the nervous system, γ-HCH is thought to interfere with GABA neurotransmitter function by interacting with the $GABA_A$ receptor-chloride channel complex at the picrotoxin binding site (Abalis et al. 1985; Anand et al. 1998; Casida and Lawrence 1985; Lawrence and Casida 1984; Pomès et al. 1994). Thus, the seizures caused by γ-HCH can be antagonized by $GABA_A$ mimetics. The δ-HCH isomer has also been shown to act at the picrotoxin binding site, but to a lesser extent (Fishman and Gianutsos 1988). Intraparataneal doses of γ-HCH or picrotoxin administered to rats resulted in epileptic events, but different levels of extracellular excitatory amino acids were observed in the hippocampus, suggesting a difference in mechanism of action (Nyitria et al. 2002). In rat cortical neurons, expression of the protooncogene *c-fos*, which is associated with seizure activity and is induced by elevated intracellular calcium levels, was increased by γ-HCH treatment but decreased by δ-HCH treatment (Barrón et al. 1995). Treatment-related changes in *c-fos* expression suggested that γ-HCH induces seizures through the

activation of calcium channels, while inhibition of calcium channels by δ-HCH results in anticonvulsant effects. The α-HCH isomer, another nonconvulsant, has been shown, like δ-HCH, to suppress c-*fos* induction (Vendrell et al. 1992a). In a study on the cytotoxic action of δ-HCH and γ-HCH in cultured rat cerebellar granule neurons (Rosa et al. 1997), both isomers were found to induce an increase in the free intracellular Ca^{2+} concentration. However, the γ-isomer mainly caused this increase by a release from intracellular Ca^{2+} stores. On the other hand, δ-HCH may exert its action by stimulating a large influx of Ca^{2+}. δ-HCH was found to be more potent and active as a cytotoxic agent than γ-HCH, and the differences in cytotoxicity and neurotoxic action may be related to their action on the different Ca^{2+} pools. Other suggestive data concerning mechanisms by which HCH causes neurological effects in animals include enhanced synaptic activity (Joy 1982; Joy and Albertson 1985) altered GABA functional activity (Bhatt and Panchal 1994; Cattabeni et al. 1983; Fishman and Gianutsos 1987, 1988; Hulth et al. 1978; Joy and Albertson 1985), and inhibition of (McNamara and Krop 1948a; Nakajima 1983; Uchida et al. 1974) or oxidative damage to Na^{+}-K^{+}-ATPase activity (Sahoo and Chainy 1998). In general, the mechanism of toxicity of HCH on the nervous system appears to be similar to those of other neurotoxic organochlorine insecticides.

γ-HCH interacts with cellular membranes and may produce several generalized cytotoxic effects associated with impaired membrane function. In rat renal cortical tubules, glucose uptake and cyclic AMP accumulation were altered by γ-HCH treatment (López-Aparicio et al. 1994). Transport of D-galactose and L-leucine across enterocytes was decreased in chickens injected daily with γ-HCH for 7 days (Moreno et al. 1994). Rats exposed orally to 5 mg/kg/day technical-grade HCH 5 days/week, for 3–6 months, exhibited significantly decreased levels of phosphatidylinositol, phosphatidylinositol 4-phosphate, and phosphatidylinositol 4,5-bisphosphate in the erythrocyte membrane and cerebrum (Agrawal et al. 1995). An *in vitro* study showed that γ-HCH altered the action potential and transmembrane currents in frog heart (atrial) myocytes (Sauviat et al. 2002). γ-HCH also has been shown to block gap junctional intercellular communication in Sertoli cells by inducing the aberrant endocytosis of Connexin 43 and zonula occludens-1 within Rab5 positive endosomes via the activation of the extracellular signal-regulated kinases (Defamie et al. 2001; Mograbi et al. 2003). Inhibition of intercellular communication could potentially lead to uncontrolled cell growth and tumor promotion. γ-HCH inhibited gap junction and intercellular communication in myometrial cell cultures isolated from rats on gestation day 10 by creating an oxidative stress environment (Kreiger and Loch-Caruso 2001; Loch-Caruso et al. 2003). γ-HCH also inhibited spontaneous phasic contractions in late gestation rat uterus (Loch-Caruso et al. 2003).

Oxidative stress in the liver has been suggested as a mechanism of γ-HCH-induced hepatotoxicity (Azzalis et al. 1995; Barros et al. 1988, 1991; Junqueira et al. 1997; Puri and Kohli 1995; Srinivasan and Radhakrishnamurty 1983a; Videla et al. 1991). This condition is characterized in the rat liver by a reduction in hepatic glutathione content, lipid peroxidation, the microsomal generation of superoxide radical coupled to cytochrome P-450 induction, and a decrement in superoxide dismutase and catalase activity (Junqueira et al. 1993). Dose-dependent inhibition of intercellular communication in cultured rat hepatocytes, with subsequent reversal by addition of vitamin E or superoxide dismutase, indicates oxidative stress as a hepatotoxic mechanism (Leibold and Schwarz 1993). Species differences exist in the activities of hepatic metabolizing enzymes, and it has been demonstrated that γ-HCH at a dose of 10 mg/kg/day for 6 days increased the hepatic cytochrome P-450 as well as glutathione-*S*-transferase in the rat, but not in the rabbit or monkey (Puri and Kohli 1995). Thus, oxidative stress and hepatotoxicity are produced with γ-HCH treatment in rats, but not in the rabbit and monkey (Puri and Kohli 1995). Inhibition of Mg^{2+}-ATPase activity has also been observed in rat liver tissue, suggesting an ATPase enzyme sensitivity to the action of γ-HCH (Gopalaswamy and Aiyar 1984). The researchers suggested that some toxic effects appearing in mammals as a result of γ-HCH exposure may arise from its influence on this ATPase activity (Gopalaswamy and Aiyar 1984). An *in vitro* study in mammalian CHO-K1 cells indicated that both γ-HCH and an unspecified HCH isomer mixture induced glutathione peroxidase and glutathione reductase activities as a defense mechanism against oxidative stress (Garcia-Fernandez et al. 2002).

The toxic mechanisms acting on prenatal development are poorly understood. Some studies of γ-HCH in rodents suggest that oxidative stress and depletion of GSH may be developmentally significant. Mouse fetal and placental tissues exhibited increased superoxide production, lipid peroxidation, and DNA-single strand breaks at 48 hours after administration of single dose of 30 mg/kg γ-HCH to pregnant dams on day 12 of gestation (Hassoun and Stohs 1996b). *In vitro* exposures of rat conceptuses to γ-HCH solutions of ≥50 μM on gestational day 10 resulted in significantly lower intracellular levels of GSH compared to controls (McNutt and Harris 1994). Data were not available, however, to determine whether a relationship exists in the prenatal rat between oxidative stress and GSH depletion.

3.5.3 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.

Metabolism of HCH isomers is believed to be carried out primarily by the P-450 monooxygenase system in 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 cases (Blair et al. 1998; Kashyap 1986; Tomczak et al. 1981) 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.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Colborn and Clement (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types

of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

Studies indicating that γ-HCH may act as an endocrine disruptor are summarized below. The amount of evidence is limited and further investigation is necessary to ascertain the relevance and impact to public health.

Estrogen influences the growth, differentiation, and functioning of various target tissues, including male and female reproductive systems such as mammary gland, uterus, vagina, ovary, testes, epididymis, and prostate. Findings indicative of antiestrogenic activity of oral exposure to γ-HCH include reduced embryo implantation in mice (Sircar and Lahiri 1989), reduced ovulation rate in rabbits (Lindenau et al. 1994), and delayed vaginal opening, disrupted estrous cycling, and reduced uterine weight in rats (Chadwick et al. 1988). Conversely, Raizada et al. (1980) indicated induction of estrogenic activity by γ-HCH based on increased glycogen content of the uterus, cervix, and vagina. Inconsistencies in the classification of estrogenic activity for γ-HCH may have been due to variations in experimental protocols, examination of different end points, and controversy in the interpretation of hormonal effects (Chadwick et al. 1988). 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), indicating that the antiestrogenic effects of γ-HCH in rat reproductive tissues do not appear to be due to direct action on estrogen receptors or the induction of

progesterone receptors. This is consistent with *in vitro* tests showing that γ-HCH had no significant agonistic action on the estrogen receptor (ER) in the MCF-7 human cell line (Soto et al. 1995), or activity in ER-mediated assays with luciferase reporter systems transfected to MCF-7 and HeLa human cells (Balaguer et al. 1999).

Nativelle-Serpentini et al. (2003) showed that γ-HCH can modulate the activity of human aromatase, the enzyme that catalyzes the aromatization of androgens to estrogens, thus potentially affecting sexual maturation in developing organisms. The study showed that short-term (10 minutes to 18 hours) incubation of human placental JEG-3 cells with γ-HCH increased aromatase activity, whereas longer-term (18 hours) incubation produced dose-related inhibition (Nativelle-Serpentini et al. 2003). This occurred at dose levels that were not cytotoxic. Because aromatase is an enzyme that catalyzes the aromatization of androgens to estrogens, alterations in aromatase activity can have widespread consequences, particularly in developing organisms.

Studies with β-HCH in ovariectomized mice showed that mobilization of this isomer from fat during fasting produced estrogenic effects including stimulation of uterine growth in mice (Bigsby et al. 1997), and that blood and fat levels of the isomer were correlated with the estrogenic end points uterine epithelial height and vaginal epithelial thickness (Ulrich et al. 2000). The blood concentrations of β-HCH that induced these effects in mice were within the same order of magnitude of blood levels of this isomer in some subjects in the general human population. β-HCH has estrogenic action in transfected MCF-7 cells, although there is evidence that this activity is mediated through ligand-independent activation of the ER (Hatakeyama et al. 2002).

The male gonad is a highly sensitive target organ for γ-HCH in animals as discussed in Section 3.2.2.5 (Reproductive Effects). For example, spermatogenesis was reduced in rats as shown by reductions in serum testosterone levels, testicular weight, and/or spermatid and sperm counts, following exposure as adults (6 mg/kg/day for 5 days or a single 30 mg/kg dose) or during gestation (1 mg/kg/day for 5 days or a single 6 or 30 mg/kg dose) (Dalsenter et al. 1996, 1997a, 1997b). Similarly, oral exposure of rats to 15 mg/kg/day γ-HCH for 5 days during gestation caused effects in adult male offspring that included testicular histological alterations, reduced sperm head counts, and increased chromatin abnormalities in epididymal sperm (Traina et al. 2003). Oral exposure to β- or technical-grade-HCH also caused degenerative changes in male reproductive tissues and sperm abnormalities in rats and mice (Dikshith et al. 1991a; Gautam et al. 1989; Nigam et al. 1979; Pius et al. 1990; Roy Chowdhury and Gautam 1990; Van Velsen et al. 1986), and similar effects on male reproductive tissues and spermatogenesis occurred in

rats and guinea pigs following dermal treatment with technical-grade HCH (Dikshith et al. 1978; Prasad et al. 1995).

In vitro exposure to γ-HCH caused depolarization, influx of extracellular Ca^{2+}, and other cell membrane changes in rat testis peritubular myoid cells (PMCs, the smooth muscle cell layer surrounding the seminiferous tubules), suggesting that interference with hormone-regulated PMC function might be involved in testicular toxicity of γ-HCH (Silvestroni et al. 1999). Other *in vitro* effects of γ-HCH included altered sperm responsiveness to progesterone (Silvestroni and Palleschi 1999) and inhibition of testicular steroidogenesis in rat Leydig cells (Ronco et al. 2001). Testing of HCH isomers for activity in an *in vitro* androgen receptor assay using a human PC-3 LUCAR- prostate carcinoma cell line showed that α- and β-HCH interacted with the human androgen receptor as agonists, whereas γ- and β-HCH had no agonist or antagonist activity (Schrader and Cooke 2000). Another isomer comparison study found that *in vitro* exposure to γ-, α-, and δ-HCH (only isomers tested) inhibited (Bu2) cAMP-stimulated progesterone production by mouse MA-10 Leydig tumor cells (Walsh and Stocco 2000).

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. 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. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics

and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

Limited information is available on the specific health effects resulting from HCH exposure in children. Generally, health effects observed in adults should also be of potential concern in children. Occasional deaths of children have been reported following ingestion of γ-HCH (Storen 1955). Although a causal relationship between exposure to γ-HCH and hematological effects in humans has not been established, there is one case report of hypochromic anemia and another of aplastic anemia in children exposed to γ-HCH by inhalation (Morgan et al. 1980; Rugman and Cosstick 1990). There are also sporadic reports of adverse effects of γ-HCH including convulsions in children after excessive topical application of γ-HCH (Lee and Groth 1977; Matsuoka 1981; Nordt and Chew 2000; Ramchander et al. 1991; Telch and

Jarvis 1982; Tenebien 1991). Based on animal data as discussed below, it can be inferred that children may be more susceptible than adults to some effects of HCH isomers.

Neurological effects have been observed in immature animals exposed to γ-HCH via gestation and/or lactation. A developmental neurotoxicity study found several changes, including increased motor activity and reduced auditory startle response habituation, in 11-day-old offspring of maternal rats that were exposed to ≥5.6 mg/kg/day doses of γ-HCH (γ-HCH) in the diet from gestation day 6 through lactation day 10 (Myers 1999). Epileptiform seizures occurred in rat pups that were exposed to maternal milk from dams that were exposed to 20 mg γ-HCH/kg by gavage for 12 days on postnatal days 3–15 (Albertson et al. 1985). Weanling rabbits were more sensitive to γ-HCH than young adults, as seen by increased mortality rates accompanied by excitement and convulsions after a single whole-body treatment with a 1% solution (60 mg γ-HCH/kg) that was absorbed dermally (Hanig et al. 1976). Although the data from these studies suggest that γ-HCH can be transferred via the placenta and maternal milk and elicit functional neurological effects in offspring, the actual doses received by the young animals is not known.

There is evidence that γ-HCH caused functional impairment of the developing blood brain barrier (BBB) in young rats (Gupta et al. 1999). The integrity (permeability) of the BBB 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).

Alterations in cerebral levels of noradrenaline, serotonin, and dopamine were observed in suckling rats treated intragastrically with a single dose of 20 mg/kg γ-HCH during the postnatal period (Rivera et al. 1991). Levels of noradrenalin were reduced in the mesencephalon. Concentrations of a serotonin metabolite were increased in the frontal cortex primarily on postnatal days 8 and 15, but the results were not statistically significant. Levels of a dopamine metabolite were decreased in the mesencephalon, but statistical significance was only obtained on postnatal day 15 (+44%, $p<0.05$). According to the authors, earlier experiments demonstrated that higher doses of γ-HCH were required to increase serotonin in adult rats. 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 orally with 10 mg technical-grade HCH/kg/day for 60 days (Nagaraja and Desiraju 1994). Acquisition of a passive avoidance task was improved in 15-day-old rat pups that were orally treated with γ-HCH as either a single 20 mg/kg dose or 7-day repeated 10 mg/kg/day doses, although changes in motor activity and brain monoaminergic levels (e.g., ratios of 5-HIAA/serotonin and DOPAC/dopamine) depended on the treatment schedule (Rivera et al. 1998).

No direct information is available regarding the effects of HCH on the developmental process in humans. However, developmental studies in animals indicated few effects from exposure to γ-HCH (Khera et al. 1979; Hassoun and Stohs 1996a; Srinivasan et al. 1991a); significant teratogenic effects were not observed (Khera et al. 1978). The proportion of embryos lost after implantation was increased after minks were treated with 1 mg/kg/day γ-HCH in the diet (Beard et al. 1997). An increase in the incidence of fetuses with extra ribs was reported in rats exposed to 20 mg/kg/day γ-HCH during gestation days 6–16 and in rabbits exposed during days 6–18 (Palmer et al. 1978a). However, the incidence of extra ribs were within or just greater than the ranges recorded for the control groups, and therefore, may not be significant evidence of teratogenicity caused by exposure to γ-HCH (Hassoun and Stohs 1996a). β-HCH given to rat dams at 20 mg/kg/day during gestation caused increased fetal deaths within 5 days of birth (Srinivasan et al. 1991a). In another study, cadmium interacted 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 in development (Saxena et al. 1986).

β-HCH is lipophilic and accumulates in maternal adipose tissue and may be mobilized during pregnancy and lactation. HCH residues have been measured in human skin lipids (Dua et al. 1998) and in breastmilk (Czaja et al. 1997; Dua et al. 1997; Nair et al. 1996); HCH also crosses the placenta (Saxena et al. 1981b). Its levels in placenta, maternal blood, and umbilical-cord blood were higher in cases of stillbirths than in live-born cases; however, many other organochlorine pesticides were present that could have contributed to stillbirths (Saxena et al. 1983). γ-, α-, δ-, and total HCH maternal blood and umbilical-cord blood levels were also higher in mothers who gave birth to IUGR babies (Siddiqui et al. 2003). Similar to the Saxena et al. (1983) study, other organochlorine pestides were also present in the blood that could have contributed to the IUGR. In a study in rats, γ-HCH has been reported to be transferred in the maternal milk and to elicit neurological effects in neonates. Following intraperitoneal dosing of dams with γ-HCH on days 12–17 of gestation, $GABA_A$ receptors in rat fetuses were studied with radiolabelled t-butylbicyclophosphorothionate (TBPS), a ligand that binds to the $GABA_A$ 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. Also noted in the study, was reduced TBPS binding in brains of fetuses when compared to adults. In another study, lactating female rats were treated orally with a single dose of 6 mg/kg of γ-HCH on days 9 or 14, or with 1 mg/kg on days 9–14 of lactation; the testosterone level of the male offspring was reduced 50% at puberty (day 65) when compared to the control group (Dalsenter et al. 1997b). When the offspring reached adulthood (day 140 postnatal), the relative testicular weight was significantly lower (Dalsenter et al. 1997b). The number of sperm and spermatids was also significantly reduced.

Differences in oxidative effects have been observed in the testes of young versus mature rats, 15 and 90 days old respectively, following intrapertitoneal injection with 10 or 20 mg/kg technical-grade HCH (Samanta and Chainey 1997b). 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 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-glucuronosyl-transferase. 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-glutamyltranspeptidase, 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 (there is a genetic polymorphism in this enzyme in adults). 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).

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

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

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. 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 or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to HCH are discussed in Section 3.8.1.

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 effects caused by HCH are discussed in Section 3.8.2.

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 3.10 “Populations that are Unusually Susceptible.”

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Hexachlorocyclohexane

There are few quantitative data to correlate levels of any of the HCH isomers in human tissue or fluids with environmental levels. A study in which children infected with scabies and their noninfected 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 infected children and 21.4 hours in noninfected 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. 1991b). 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). The metabolites of γ-HCH have been detected in human urine (Angerer et al. 1981). However, such findings are not specific to γ-HCH exposure, and these findings could follow from exposure to both γ-HCH and a number of structurally related compounds.

3.8.2 Biomarkers Used to Characterize Effects Caused by Hexachlorocyclohexane

The individual isomers of HCH can be detected in the blood serum, urine, adipose tissue, and semen of exposed individuals. However, the concentrations measured in these biological tissues have not been exclusively correlated with the degree of adverse health effects observed. Additionally, there are no general biomarkers of effect for HCHs analogous to red blood cell or plasma cholinesterase for organophosphorous insecticides.

Adverse effects such as neurophysiological and neuropsychological disorders and gastrointestinal disturbances have been reported in workers exposed to HCH during pesticide or fertilizer formulation. Nigam et al. (1986) and Kashyap (1986) reported that nonhandlers indirectly exposed and handlers directly exposed to HCH during pesticide manufacture and formulation were found to have mean serum levels of 0.27 ppm (nonhandlers) and 0.6 ppm (handlers) total HCH. As much as 60–100% of the total HCH measured in serum was β-HCH. The ranges of serum HCH levels measured in all exposed workers were 0.07–0.72 ppm β-HCH, 0.004–0.18 ppm α-HCH, 0–0.17 ppm γ-HCH, and 0–0.16 ppm δ-HCH. Both handlers and nonhandlers complained of paresthesia of the face and extremities, headache, and giddiness; other symptoms included malaise, vomiting, tremors, apprehension, confusion, loss of sleep, impaired memory, and loss of libido. Similar but less-severe effects were noted in 19 maintenance workers who visited the plant frequently. Serum HCH levels measured in these workers were 0.004–0.1 ppm α-HCH, 0.02-0.2 ppm β-HCH, 0–0.32 ppm γ-HCH, and 0–0.04 ppm δ-HCH. Kashyap (1986) also reported higher serum enzyme levels of alkaline phosphatase, lactate dehydrogenase, ornithine carbamyl transferase, γ-glutamyl transpeptidase, and leucine aminopeptidase and increased IgM in the handlers as compared with the nonhandlers and a control population of 14 workers with no occupational contact with HCH. Czegledi-Janko and Avar (1970) reported that γ-HCH blood levels of 0.024–0.16 ppm were associated with clinical symptoms including muscle jerking and variations in EEG in 37 workers exposed to γ-HCH in a fertilizer plant.

HCH and other organochlorine pesticides have been found in the blood serum of some individuals in a population of men attending an infertility clinic in Israel. Serum levels of organochlorine pesticides, including γ-HCH, have been found in men with low sperm counts to be two times higher than that of

fertile men (Pines et al. 1987). Maternal mean serum γ-HCH levels were reported to be higher in cases of premature delivery and spontaneous abortions than in controls (Saxena et al. 1980; Wassermann et al. 1982). Saxena et al. (1980) reported HCH levels of 69.3–550.4 ppb and γ-HCH levels of 30.8–113.6 ppb in the blood of women in India who had experienced spontaneous abortions or premature labor compared with blood HCH levels of 22.2–85.5 ppb and γ-HCH levels of 7.1–32.5 ppb in women who had undergone full-term pregnancy. β-HCH levels were significantly higher in German women with a history of miscarriages (Gerhard et al. 1999). Serum levels of a number of other pesticides including aldrin, PCP, PCB, HCB, DDE, DDT, and DDD were also found to be higher in cases of premature labor and spontaneous abortions. It was, therefore, not possible to establish a quantitative, causal relationship between the serum HCH levels and these adverse effects.

Blood serum levels of 1–17 ppb β-HCH were not found to be associated with the incidence of colorectal adenocarcinoma in 10 families (Caldwell et al. 1981). Serum levels of 0–49.5 ppb γ-HCH were not found to be associated with the occurrence of hematological syndromes such as pancytopenia, thrombocytopenia, plasma cell myoma, acute leukemia, chronic lymphocytic leukemia, and anemia in 103 patients (Traczyk et al. 1977).

For more information on biomarkers for renal and hepatic effects of chemicals, see ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage (1990) and for information on biomarkers for neurological effects, see OTA (1990).

3.9 INTERACTIONS WITH OTHER CHEMICALS

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. 1972c). Vitamin A supplements decreased HCH-induced toxicity in the rat testes, while deficiencies in vitamin A potentiated the toxicity (Pius et al. 1990).

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). Liver microsomal enzymes affected by exposure were γ-HCH dehydrogenase, γ-HCH dechlorinase, and hepatic cytochrome P-450 content. This action altered the profile of metabolites excreted in the urine. 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). Cadmium also 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).

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 contents 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.

The combined application of HCH (mixed isomers) and malathion to the skin of guinea pigs for 30 days showed no significant influence of either chemical on neurological signs of toxicity before dying (e.g., tremors, dyspnea, salivation, convulsions, and paralysis of the hind limbs) or mortality induced by the other (Dikshith et al. 1987). The study suggests that HCH isomers and malathion did not elicit any potentiation effects at the doses tested (50 and 100 mg/kg HCH, 200 and 400 mg/kg malathion).

γ-HCH is a central nervous system stimulant, whereas the α-, β-, and δ-isomers of HCH are mainly depressants (McNamara and Krop 1948a; Smith 1991). Isomeric interactions can occur, such that α-, β-, and δ-HCH counteract the effects of the γ-isomer (lindane); 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 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]).

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 P-450. 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 selective effect on the oxidative degradation of γ-HCH to the tetrachlorophenols and enhances its elimination in the urine (Chadwick and Freal 1972b). In addition, since HCH is hepatotoxic, therapeutic agents, which can produce liver toxicity, such as acetaminophen, might also enhance the symptoms of HCH exposure.

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. A single dose of α-HCH significantly increased the convulsive threshold 3 and 24 hours after dosing and resulted in a significant 17% increase in brain levels of γ-aminobutyric acid (GABA) 24 hours after dosing.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to HCH than will most persons exposed to the same level of HCH in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of HCH, or compromised function of organs affected by HCH. Populations who are at greater risk due to their unusually high exposure to HCH are discussed in Section 6.7, Populations with Potentially High Exposures. Based on information from animal studies as discussed in Section 3.7, Children's Susceptibility, it can be inferred that children may be more susceptible than adults to some effects of HCH isomers. Individuals possessing genetic polymorphisms affecting HCH metabolism and elimination may be more susceptible, though supporting data do not exist.

People with excoriated (peeling) skin exhibited higher levels in blood of γ-HCH following dermal exposure to γ-HCH lotion than those with normal skin (Ginsburg et al. 1977). It was not known if there were any increased toxic effects to individuals with excoriated skin. It is also not known with certainty if children are unusually susceptible to the toxic effects of HCH, but case reports of acute neurotoxicity in children treated for scabies with γ-HCH suggest that it should not be used on infants and young children (Telch and Jarvis 1982). The potential hazards of using γ-HCH dermal preparations on infants and young children are underscored by the fact that the very young have a large surface area-to-volume ratio, possibly less efficient hepatic detoxification abilities, and are more likely to lick treated skin (Kramer et al. 1980). Therefore, the use of γ-HCH as a scabicide on infants and very young children, especially those who have very little body fat, has been discouraged (Telch and Jarvis 1982).

Evidence suggests that pregnant women should exercise extreme caution in their exposure to γ-HCH (Ginsburg et al. 1977; Kramer et al. 1980; Solomon et al. 1977a). Refer to Section 3.7 for more detailed explanation. In pregnant animals and humans, γ-HCH crosses the placenta. HCH and γ-HCH body tissue

levels have also been associated with premature labor, spontaneous abortions, and IUGR in babies (Rasmussen 1980; Saxena et al. 1980, 1981a, 1981b; Siddiqui et al. 2003; Wassermann et al. 1982). However, no causal relationship has been established between blood and tissue levels of γ-HCH and premature termination of pregnancy.

Nair et al. (1996) demonstrated that there is a significant bioconcentration of the α-, β-, and γ- isomers of HCH in the breastmilk of mothers exposed to technical-grade HCH.

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). Those individuals suffering from malnutrition (e.g., low protein, low fiber, and low vitamin intake) may be more susceptible than the general public to the toxic effects of γ-HCH (Rasmussen 1987). Individuals with liver and/or kidney disease may be at risk because of compromised detoxification mechanisms in the liver and impaired excretory mechanisms in the kidney. Additionally, individuals with existing or suspected immunodeficiencies may be at risk because HCH isomers may enhance immunosuppression.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to HCH. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to HCH. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to HCH:

Reigart JR, Roberts JR. 1999. Recognition and management of pesticide poisonings. 5th edition. Washington, DC: U.S. Environmental Protection Agency, 55-61.

Goldfrank L, Flomenbaum N, Lewin N, et al. 2002. Goldfrank's toxicologic emergencies. 7th edition. New York, NY: McGraw-Hill, 1366-1378.

Ellenhorn MJ, Barceloux DG. 1988. Medical toxicology: Diagnosis and treatment of human poisoning. New York, NY: Elsevier, 1078-1080.

3.11.1 Reducing Peak Absorption Following Exposure

When a large amount of HCH has been swallowed, emetics have been used to induce vomiting. One of the problems with inducing vomiting is that the insecticidal form of HCH is often dissolved in an organic solvent, which presents an aspiration hazard. Activated charcoal can also be used to decrease gastrointestinal absorption. To avoid skin absorption after exposure, clothing should be removed, and the skin should be washed with water and mild soap (Ellenhorn and Barceloux 1988). There are no known methods for reducing absorption following inhalation exposure.

3.11.2 Reducing Body Burden

The traditional methods of increasing elimination or decreasing distribution (e.g., dialysis, diuresis, and hemoperfusion) are not useful because of the high volume of distribution of HCH into adipose tissue (Ellenhorn and Barceloux 1988). HCH accumulates in adipose tissue following all routes of exposure. However, peritoneal dialysis may be required if rhabdomyolysis (muscle necrosis) leads to myoglobinuria and kidney shutdown (Sunder Ram Rao et al. 1988).

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Possible mechanisms of action of HCH on some of the target organs have been described. In the nervous system, γ-HCH is thought to interfere with the GABA system by interacting with the $GABA_A$ receptor-ionophore complex at the picrotoxin binding site (Portig and Schnorr 1988; Rivera et al. 1991; Sunol et al. 1988). Thus, the seizures caused by γ-HCH can be antagonized by $GABA_A$ mimetics; diazepam is the anticonvulsant of choice (Ellenhorn and Barceloux 1988). Phenobarbital and/or phenytoin or fosphenytoin may be used if seizures are uncontrollable (HSDB 1998). Use of anticonvulsants (especially in children and other susceptible individuals) should include careful monitoring of hypotension, respiratory depression, and the need for endotracheal interbation. In the liver, γ-HCH is thought to produce oxidative stress by inducing oxidative enzymes such as cytochrome P-450 and depleting hepatic glutathione content (Barros et al. 1988, 1991; Srinivasan and Radhakrishnamurty 1988; Videla et al. 1991). Another possible mechanism for hepatic toxicity is increased lipid metabolism (Ravinder et al. 1990; Srinivasan and Radhakrishnamurty 1988). It is possible that interfering with these mechanisms can decrease the toxicity of HCH.

3.12 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 the National Toxicology Program (NTP), is required to assure the iniiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of HCH.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health 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.

Most of the literature reviewed concerning the health effects of inhaled α-, β-, γ-, or δ-HCH in humans consists of case reports of individuals occupationally exposed or exposed in the home by a γ-HCH vaporizer. The predominant route of exposure in occupational studies is presumed to be inhalation, although dermal exposure is also likely. The health effects in humans associated with ingested HCH are reported primarily in case studies in which individuals ingested pesticide pellets or therapeutic lotions containing γ-HCH to control scabies, and in several epidemiological studies where exposure is likely through ingestion of pesticide residues in the diet. Information concerning the health effects of HCH in humans following dermal exposure is limited to case studies of individuals who have misused therapeutic lotions containing γ-HCH to control scabies and head and body lice. The duration and level of exposure to HCH generally cannot be quantified from the information presented in these reports. In addition, the case study reports in humans are limited because concomitant exposure to other toxic substances or other substances present in the atmosphere may have occurred.

Limited information was found regarding the health effects of γ-HCH following inhalation exposure in animals. The health effects of α-, β-, γ-, and δ-HCH following oral exposure have been well documented in a variety of species. Limited information is available concerning the health effects of technical-grade HCH and γ-HCH following dermal exposure.

γ-HCH is the isomer most thoroughly tested in intermediate- and chronic-duration studies. The carcinogenic effects of technical-grade HCH and α-, β-, and γ-HCH have been examined, but the carcinogenic potential of δ-HCH has not been as well studied. Studies on the long-term effects of dermal exposure to γ-HCH are inadequate for the determination of carcinogenicity status.

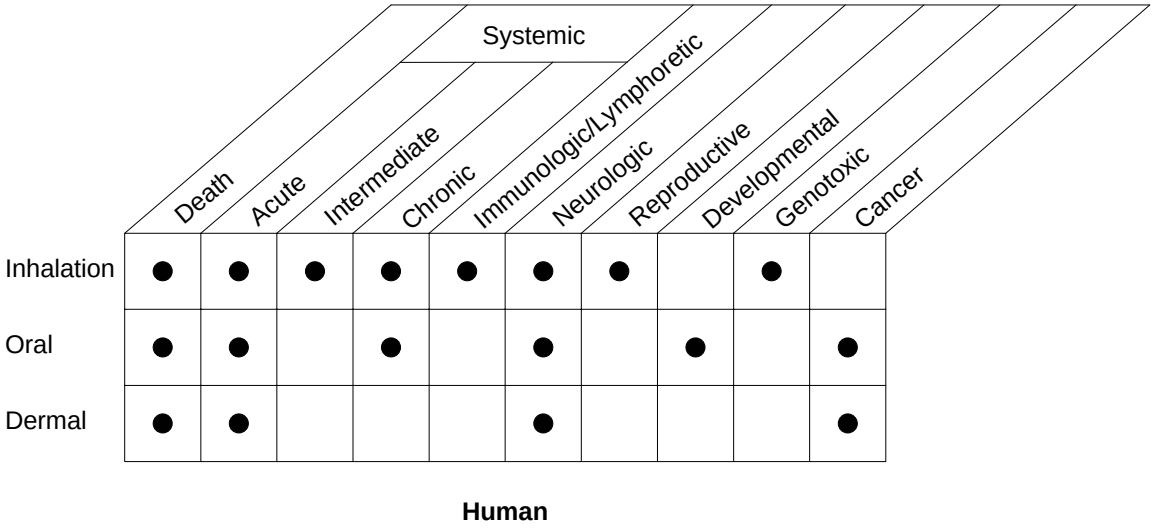
3.12.1 Existing Information on Health Effects of Hexachlorocyclohexane

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to HCH are summarized in Figure 3-7. The purpose of this figure is to illustrate the existing information concerning the health effects of HCH. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure 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 (Agency for Toxic Substances and Disease Registry 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.

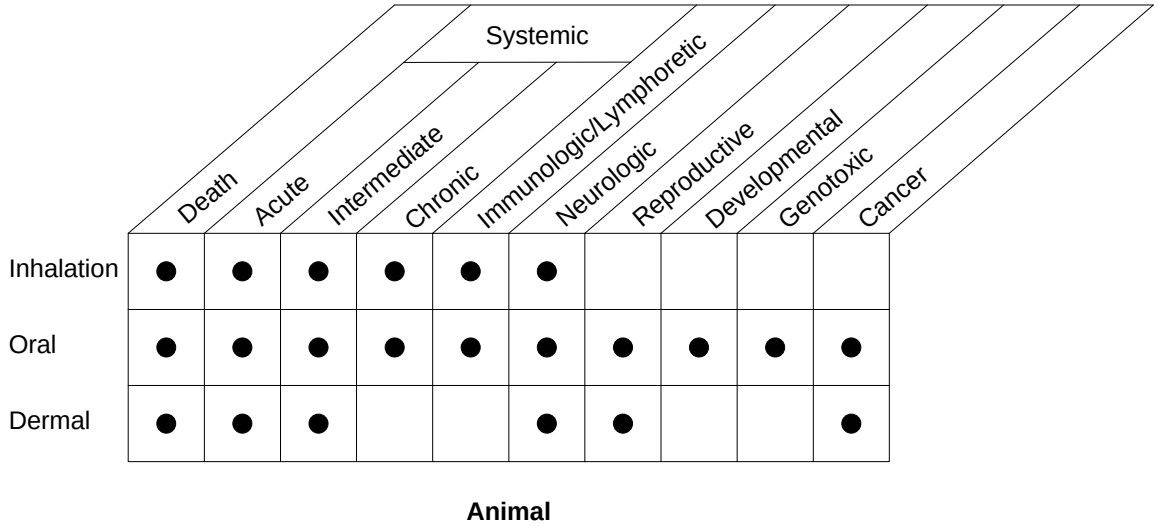
3.12.2 Identification of Data Needs

Acute-Duration Exposure. Occasional case reports are available for humans who have had adverse health effects, including irritation of the nose and throat and death, from excessive inhalation exposure from γ-HCH vaporizers (Conley 1952; Loge 1965). Oral exposure to large amounts has resulted in a few human deaths (Storen 1955; Sunder Ram Rao et al. 1988) and adverse neurological, musculoskeletal, and renal effects (Munk and Nantel 1977; Sunder Ram Rao et al. 1988). When applied dermally, γ-HCH has also been shown to have adverse effects such as pulmonary and epicardial petechiae, aplastic anemia, and rashes in a few humans (Davis et al. 1992; Fagan et al. 1981; Rauch et al. 1990). The level of exposure in the human studies generally cannot be quantified because the information is derived from anecdotal case reports. Therefore, there is little reliable information in humans associating dose with effect. Such information might allow investigators to establish thresholds for systemic toxicity due to acute exposure, although it is not necessarily a priority data need.

Figure 3-7. Existing Information on Health Effects of α-, β-, γ-, and δ-HCH



Human



Animal

● Existing Studies

Information on health effects (death and neurological) following acute inhalation of γ-HCH in animals (Klonne and Kintigh 1988; Oldiges et al. 1980; Ullmann 1986b) is limited. Neurological effects following acute inhalation exposure to γ-HCH include excitation, sedation, ataxia, and spasms (Ullmann 1986b). Acute inhalation studies for the other HCH isomers and technical-grade HCH are not available. No acute inhalation MRL was developed because of insufficient data. Additional acute inhalation data are needed for all isomers (e.g., threshold, dose-response, and target organ). This information is necessary for determining levels of significant human exposure to hexachlorocyclohexane and the associated effects following exposure.

Acute oral studies in animals exposed to γ-HCH have reported death in rats (Gaines 1960) and mice (Liu and Morgan 1986); neurological effects in rats including enhanced susceptibility to kindling (Gilbert and Mack 1995; Joy et al. 1982), reduced brain serotonin level (Attia et al. 1991), reduced brain barrier permeability in 10-day-old pups (Gupta et al. 1999), and neurobehavioral changes (Hughes 1999a); increased hepatic microsomal mixed-function oxidase activity in mice (Oesch et al. 1982); increased hepatic cytochrome P-450 and P-450-dependent enzyme levels and increased absolute liver weight (Parmar et al. 2003), and degeneration of renal tubular epithelia in rats (Srinivasan et al. 1984). Oral exposure to β-HCH has resulted in an increase in hepatic cytochrome P-450 levels, and renal tubular degeneration in rats (Ikegami et al. 1991b; Srinivasan et al. 1984). Exposure to technical-grade HCH has resulted in hepatic focal necrosis, fatty changes, and enzyme activation and renal hemorrhage (Dickshith et al. 1990; Phillip et al. 1989; Ravinder et al. 1989). An acute oral MRL of 0.5 mg/kg/day for β-HCH has been developed based on ataxia in mice (Van Velsen et al. 1986). Additional studies that examine systemic effects (e.g., cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, and renal) following acute oral exposure to all HCH isomers would be helpful. Acute dermal studies in rats are available on γ-HCH and technical-grade HCH (Dikshith et al. 1991c; Gaines 1960). Acute dermal exposure of rats to γ-HCH (Gaines 1960) or of guinea pigs to technical-grade HCH (Dikshith et al. 1978) was associated with lethality. Additional acute dermal data in animals are needed, for example, threshold, dose-response, and target organs. This information is necessary for determining levels of significant human exposure to HCH and the associated health effects following dermal exposure, and is particularly important for γ-HCH given the use of γ-HCH in shampoos and lotions for the pharmaceutical treatment of scabies and head lice.

Intermediate-Duration Exposure. Information on human health effects of repeated exposure to HCH is available from studies of occupationally exposed individuals (Kashyap 1986); no information is

available on the effects of repeated oral or dermal exposure in humans. EEG abnormalities and increased liver enzymes have been observed in factory workers involved in the production of technical-grade HCH (Kashyap 1986). The exact duration and level of exposure in the human studies are often not provided in the studies. Such information would allow investigators to determine health effects associated with known levels of exposure.

Intermediate-duration inhalation studies of γ-HCH have been performed in rats with mortality reported (Klonne and Kintigh 1988). Inhalation of 603 mg/m^3 γ-HCH for 4 hours or 5 mg/m^3 for 90 days has not resulted in adverse respiratory, hematological, hepatic, or renal effects in rats (Oldiges et al. 1983). However, the data are insufficient for developing an intermediate-inhalation MRL. Additional intermediate-inhalation data in animals are needed (e.g., threshold, dose-response, and target organs). This information is necessary for determining levels of significant human exposure to HCH and the associated health effects following inhalation.

Intermediate-duration oral studies have been performed in animals. Oral γ-HCH did not affect the hematological parameter in rats (Suter 1983) and dogs (Rivett et al. 1978). A decrease in blood cell numbers was observed in rats fed β-HCH (Van Velsen et al. 1986) and technical-grade HCH (Joseph et al. 1992c). The endocrine effects of γ-HCH exposure were reported in ewe lambs (Beard and Rawlings 1999) and young rams (Beard et al. 1999a) given 1 mg/kg/day in treated feed from conception to sexual maturity. In ewes, effects included increased pulse frequency of serum luteinizing hormone, slower increase and earlier decrease of progesterone levels, and lower T4 levels. In young rams, observed endocrine effects included lower serum luteinizing hormone and estrodiol concentrations. While serum testosterone levels were similar across treatment groups, the γ-HCH treated rams showed attenuated testosterone response to stimulation with gonadotropin releasing hormone. Hepatic effects in animals following γ-HCH exposure included an increase in P-450-dependent enzymes, hypertrophy, necrosis, and cancer (Hanada et al. 1973; Ito et al. 1973; Parmar et al. 2003; Suter 1983). Hepatic effects in animals, following exposure to β-HCH, included cellular hypertrophy and necrosis (Hanada et al. 1973; Ito et al. 1973; Van Velsen et al. 1986); α-HCH induced hepatic effects included enzyme activation, hypertrophy, necrosis, and cancer (Barros et al. 1991; Hanada et al. 1973; Ito et al. 1973). Hepatic effects from technical-grade HCH exposure in animals included changes in enzyme activities and enlargement of hepatocytes, nuclear pyknosis, and vacuolation (Dikshith et al. 1989a, 1991a; Fitzhugh et al. 1950; Karnik et al. 1981; Joseph et al. 1992b). Renal effects from γ-HCH exposure included nephritis, accumulation of protein droplets, hypertrophy, and necrosis (Suter 1983); nephritis was observed following α-HCH exposure (Fitzhugh et al. 1950). Exposure to β-HCH has resulted in calcinosis and nephritis (Fitzhugh et

al. 1950; Van Velsen et al. 1986); technical-grade HCH exposure has resulted in nephritis and tubular necrosis (Dikshith et al. 1991a; Fitzhugh et al. 1950). Two MRLs have been derived for intermediate-duration oral exposure in animals. An intermediate oral MRL of 0.0006 mg/kg/day for β-HCH has been developed based on hepatic effects in rats (Van Velsen et al. 1986). An intermediate oral MRL for γ-HCH of 0.00001 mg/kg/day has also been developed based on immunological effects in mice (Meera et al. 1992). Insufficient data are available to derive an intermediate-duration oral MRL for α-HCH; additional studies using known or possible sensitive end points, including reproductive and immunological indices, could address this data need.

Intermediate-duration dermal studies have been performed in rabbits, guinea pigs, and rats; some deaths were observed following exposure to γ-HCH (Brown 1988). There are limited data pertaining to systemic effects (e.g., increased respiratory rate and wheezing, hepatic hypertrophy, and basophilic renal tubules) and neurological effects (e.g., hyperactivity, ataxia, and convulsions) in rats following intermediate-duration dermal exposure to γ-HCH (Brown 1988). Death and systemic effects (e.g., hepatic hypertrophy and fatty degeneration and renal tubular necrosis) have been observed in rats (Dikshith et al. 1991c); hepatic hypertrophy and enzyme activation were observed in guinea pigs (Dikshith et al. 1978) following intermediate-duration dermal exposure to technical-grade HCH. Additional intermediate-dermal data in animals are needed (e.g., threshold, dose-response, and target organs). This information is necessary for determining levels of significant human exposure to HCH and the associated health effects following dermal exposure.

Chronic-Duration Exposure and Cancer. Controlled epidemiological studies have been conducted in humans exposed to HCH, but are few in number and limited in scope. Hematological effects have been observed in persons exposed to γ-HCH in the workplace via the inhalation and/or dermal route (Brassow et al. 1981; Jedlicka et al. 1958). A number of case reports are available from individuals who had exposure to γ-HCH 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). Effects that have been described in these case reports include hematological effects including granulocytopenia, aplastic anemia, paramyeloblastic leukemia, and pancytopenia. Blood levels of HCH, and its isomers (α, β, and γ), were found to be higher in women with breast cancer when compared to healthy women without the disease (Mathur et al. 2002). α- and γ-HCH blood levels were significantly higher in breast cancer patients, 41–50 years of age, compared to women of the same age without the disease. β-HCH blood levels were found significantly higher in breast cancer patients, 31–50 years of age, compared to those without the disease (Mathur et al. 2002). Other

organochlorine pesticides, including DDT and its metabolites, were also present in the blood and could have contributed to the incidence of breast cancer. Exposure to HCH, and other organochlorine pesticides, to the population is likely through food where the pesticides are primarily used for agricultural applications; however, other possible environmental contamination pathways include inhalation and dermal routes of exposure.

No chronic-duration inhalation studies in animals are available for any isomer. Altered renal excretions and hepatic hypertrophy and have been observed in chronic oral studies on rats with γ-HCH (Amyes 1990). A chronic oral MRL of 0.008 mg/kg/day for α-HCH has been developed based on hepatic effects in rats (Fitzhugh et al. 1950). Chronic dermal studies in animals are not available. Since there are insufficient data to develop inhalation and dermal chronic-duration MRLs, further data from the inhalation and dermal routes are needed (e.g., threshold, dose-response, and target organs). This information is needed for determining levels of significant human exposure to HCH and the associated health effects. However, the need for dermal studies is not a priority as data on skin absorption can be used to calculate equivalent oral doses.

Use of γ-HCH pesticides by farmers was associated with a 50% increased risk of non-Hodgkin's lymphoma (Blair et al. 1998). However, a causal relationship could not be determined due to confounding effects such as use of other pesticides. Limited chronic dermal data in humans are available (Davis et al. 1993), but chronic oral data in humans are not available. There are no inhalation studies in animals. Several chronic toxicity/carcinogenicity bioassays have been conducted in animals following oral exposure to technical-grade HCH and α-, β-, γ-, and δ-HCH (Hanada et al. 1973; Ito et al. 1975; Karnik et al. 1981; Kashyap et al. 1979; Munir et al. 1983; NCI 1977; Thorpe and Walker 1973; Wolff et al. 1987). Chronic dermal exposure to technical-grade HCH caused liver cancer in mice (Kashyap et al. 1979). However, the results were not useful in determining carcinogenic potential because of limitations of these studies, such as testing only one dose and the potential for oral ingestion. 2,4,6-Trichlorophenol, a metabolite of γ-HCH, may be responsible for some or all of the carcinogenic activity observed in mice. This metabolite has been classified by EPA as a group B2 carcinogen. Pentachlorocyclohexene epoxide, a metabolite of γ-HCH that has been identified in the liver of rats, may also be responsible for the carcinogenic effects of γ-HCH. Cancer classifications of several HCH isomers have been made by the U.S. Department of Health and Human Services (DHHS) and the EPA. EPA has classified technical-grade HCH, α-HCH, β-HCH, and δ-HCH as B2, B2, C, and D, carcinogens, respectively (EPA 1998a). γ-HCH has not been assigned a cancer classification by EPA. Additional carcinogenicity information would not be needed at this time. DHHS has classified γ-HCH and other HCH isomers as "reasonably

anticipated to be human carcinogen" in the 8th Report on Carcinogens (DHHS 1998). The International Agency for Research on Cancer (IARC) has classified HCH isomers as Group 2B, possibly carcinogenic to humans.

Genotoxicity. HCH did not produce chromosomal aberrations in humans exposed primarily by inhalation (Kiraly et al. 1979). Dominant lethal mutations occurred in mice orally exposed to technical-grade HCH (Lakkad et al. 1982). Increased frequency of polyploid cells occurred in rats exposed orally to α-HCH (Hitachi et al. 1975). Information on the genotoxic effects of γ-HCH is also obtained from *in vitro* studies. Gene mutations were observed in bacteria treated with γ-HCH (with and without metabolic activation) (Moriya et al. 1983; Nagy et al. 1975). γ-HCH was not mutagenic in yeast (Shahin and von Borstel 1977) or algae (Kar and Singh 1979a). Results of chromosomal aberration tests in γ-HCH-treated hamster cells were questionable (Ishidate and Odashima 1977). Technical-grade HCH produced chromosomal aberrations in cultured human lymphocytes (Rupa et al. 1989d) but did not produce cytogenetic effects in Chinese hamster cells (Murli 1990) or unscheduled DNA synthesis in rat hepatocytes (Cifone 1990). Human mammary carcinoma MCF-7 and human prostate carcinoma PC-3 cell lines showed that low concentrations of γ-HCH induced increases in micronuclei in both cell lines in the absence of DNA damage or cytotoxicity, suggesting a clastogenic effect for this chemical (Kalantzi et al. 2004). In general, the available information suggests that α-, β-, and γ-HCH may have some genotoxic potential; however, the evidence is not conclusive. Further testing in clastogenicity and genotoxicity tests *in vivo* would be valuable.

Reproductive Toxicity. The only available human data are from one study on hormone levels in pesticide workers in which increases in the levels of serum luteinizing hormone were noted following exposure to γ-HCH for 8 years (Tomczak et al. 1981). There are no inhalation data in animals for any HCH isomer. Anti-estrogenic properties were found in female rats given γ-HCH by the oral route (Chadwick et al. 1988), and female rabbits treated orally with γ-HCH had a reduced ovulation rate (Lindenau et al. 1994). γ-HCH exposure in female mice and their offspring on gestational days 9–16 resulted in slightly increased relative uterus weight in F1 females, and earlier vaginal opening and increased branching of villi and oedema in the endometrial stroma in treated mice (Maranghi et al. 2003). Reductions in testicular and epididymis weights, spermatid and sperm numbers, and serum testosterone level were found in male rats exposed to relatively low doses of γ-HCH during lactation and evaluated at puberty and adulthood (Dalsenter et al. 1997b). Effects on testicular histology and sperm numbers similarly occurred in adult male offspring of mice that were exposed to γ-HCH during gestation (Traina et al. 2003). Reproductive effects of γ-HCH exposure were reported in ewe lambs (Beard and Rawlings

1999) and young rams (Beard et al. 1999a) given 1 mg/kg/day in treated feed from conception to sexual maturity. In estrus synchronized ewes, treated animals had significantly shorter estrous cycle length and lower number and less total volume of corpus lutea. No other detrimental fertility effects were observed. The subjectively-scored sexual behavior in young rams was significantly reduced in treated animals presented with estrous ewes. Developmental/reproductive effects in male rats were used as the basis for an acute-duration MRL for oral exposure to γ-HCH. Results of single and multigeneration reproduction studies in rats and mink indicate that exposure to γ-HCH or technical HCH caused effects, such as decreased numbers of offspring at birth, reduced neonatal viability, and delayed maturation of pups, that were primarily results of prenatal and/or postnatal developmental toxicity (Beard and Rawlings 1998; Beard et al. 1997; King 1991; Srivastava and Raizada 2000). Oral exposure of rats and mice to β- or technical-grade-HCH has resulted in degeneration of male reproductive organs and sperm abnormalities (Dikshith et al. 1991a; Gautam et al. 1989; Nigam et al. 1979; Pius et al. 1990; Roy Chowdhury and Gautam 1990; Van Velsen et al. 1986), and ovarian atrophy was observed in rats exposed to β-HCH for 13 weeks (Van Velsen et al. 1986). Similar effects were also observed in reproductive organs of rats following dermal treatment with technical-grade HCH for 120 days (Prasad et al. 1995). The reproductive effects on guinea pigs after dermal exposure to technical-grade HCH (100–500 mg/kg/day) have also been investigated (Dikshith et al. 1978). Testicular hypertrophy and atrophy and complete inhibition of spermatogenesis were observed in the guinea pigs. Studies via the inhalation and dermal routes would provide information regarding the reproductive effects of HCH in animals for these exposure routes and could be useful in the assessment of potential reproductive effects in humans. Pharmacokinetic data suggest that HCH isomers might have the potential to affect reproduction across routes of exposure, although data are insufficient to predict effect levels.

Developmental Toxicity. Developmental effects in humans, specifically IUGR, may result from oral exposure to HCH (Siddiqui et al. 2003). The blood of mothers with IURG babies had higher levels of γ-, α-, δ-, and total HCH. Similarly, γ-, δ-, and total HCH cord blood levels of IUGR babies were higher than the cord blood levels in the normal-weight babies (Siddiqui et al. 2003). Other organochlorine pestides, including DDT and its metabolites, were also present in the blood, and could have contributed to IUGR. There are no inhalation data in animals for any isomer. No adverse prenatal developmental effects of γ-HCH from oral exposure have been found in rats or rabbits (Khera et al. 1979; Palmer et al. 1978a; Seiler et al. 1994) or from exposure to technical-grade HCH in mice (Dikshith et al. 1990). Alterations in neurotransmitter levels were noted in suckling rats treated once with γ-HCH by gavage (Rivera et al. 1991). γ-HCH exposure in F1 females of female mice treated on gestational days 9–16, resulted in slightly increased relative uterus weight (Maranghi et al. 2003). An acute oral MRL of

0.003 mg/kg/day has been developed from data on developmental/reproductive effects in mature male offspring of rats that were exposed to γ-HCH during lactation; these effects included reduced testicular and epididymis weights, reduced spermatid and sperm numbers, and alterations in mating behavior (Dalsenter et al. 1997b). Decreases in fetal weight, fetal thymic weight, and placental weight have been reported in mice exposed to a single oral dose of γ-HCH on day 12 of gestation (Hassoun and Stohs 1996a). No effects on embryonic development were seen in rabbits treated orally with γ-HCH (Seiler et al. 1994).

Alterations in neurotransmitter levels were observed in female rat pups treated orally with technical-grade HCH (Nagaraja and Desiraju 1994). No data on the developmental effects of α-, β-, or δ-HCH were located for the oral or dermal route and there is no information for dermal exposure to technical-grade HCH. Due to the lack of developmental toxicity studies in humans, as well as the lack of inhalation and dermal data in animals, insufficient information is available to indicate whether HCH affects development via all three routes of exposure. Pharmacokinetic data suggest that HCH isomers might have the potential to affect development across routes of exposure. Additional developmental studies in animals exposed to α-, β-, or δ-HCH would provide useful information concerning possible fetotoxic and teratogenic effects in animals, which might be relevant to humans.

Immunotoxicity. A statistically significant increase (approximately 18%) in IgM has been reported in individuals occupationally exposed to technical-grade HCH (Kayshap 1986). The HCH isomer concentrations in serum showed a 10-fold increase when compared to the control. There are no oral or dermal data in humans. Also, there are no inhalation or dermal data in animals. Depressed antibody response to *Salmonella* antigens was reported in rats (Dewan et al. 1980) and rabbits (Desi et al. 1978) exposed to γ-HCH via the oral route. γ-HCH exposure has been shown to result in thymus cortex atrophy, suppressed bone marrow cellularity, erythrocyte precursors, and granulocyte-macrophage progenitor cells in mice (Hong and Boorman 1993). Based on immunological effects of γ-HCH on components of cell- and humoral-mediated immunity in mice, an intermediate oral MRL has been developed (Meera et al. 1992). Decreased lymphoproliferative responses to T-cell mitogens were observed in mice treated by the oral route with β-HCH (Cornacoff et al. 1988). No immunological effects were observed in rats treated with β-HCH by the oral route for 13 weeks (Van Valsen et al. 1986). There are no immunotoxicity data for technical-grade HCH. The biological significance of increased immunoglobulin levels remains to be established. In addition, exposure to technical-grade or γ-HCH may also affect the immune system in humans (Kashyap 1986) and animals (Desi et al. 1978; Dewan et al.

1980). Further studies on all isomers using all three routes of exposure would be useful in the assessment of potential immunotoxic effects in humans.

Neurotoxicity. Exposure to γ-HCH and other isomers has been shown to be associated with neurological effects in both humans and animals, and there is no basis to suspect that these effects may be route-, species-, or age-dependent. Paresthesia has been reported in workers exposed via the inhalation or dermal routes (Fonseca et al. 1993; Kashyap 1986). Abnormal EEG patterns have also been noted in workers (Czegledi-Janko and Avar 1970). Seizures and coma have been observed in individuals who have ingested large amounts of γ-HCH (Davies et al. 1983; Harris et al. 1969; Munk and Nantel 1977; Nantel et al. 1977; Powell 1980; Starr and Clifford 1972; Storen 1955). Convulsions have been reported in children following dermal application of γ-HCH (Ramchander et al. 1991; Tenebein 1991). Neurological effects including sedation, restlessness, excitation, and ataxia were seen in rats exposed by inhalation to γ-HCH for 4 hours (Ullmann 1986b). Mice exposed via the inhalation route to γ-HCH in a chronic study did not display any neurotoxic signs (Klonne and Kintigh 1988). Convulsions have been observed in rats and mice following oral exposure to γ-HCH (Arisi et al. 1994; Attia et al. 1991; Gilbert 1995; Gilbert and Mack 1995; Joy et al. 1982; Martinez and Martinez-Conde 1995; Martinez et al. 1991; Parmar et al. 2003; Vendrell et al. 1992a; Wooley and Griffith 1989). Less serious neurological effects of oral exposure to γ-HCH in rats included reduced brain serotonin level, reduced brain barrier permeability in pups, decreased myelin and enzyme activity in brain, reduced tail nerve conduction velocity, enhanced susceptibility to kindling, motor activity changes, and other neurobehavioral alterations (Attia et al. 1991; Hughes 1999a; Joy et al. 1982; Muller et al. 1981; Serrano et al. 1990a). Oral exposure of mice and rats to β-HCH has resulted in lateral recumbency, coma, and reduced tail nerve conduction velocity (Cornacoff et al. 1988; Muller et al. 1981; Van Velsen et al. 1986). Rats and mice exposed orally to technical-grade HCH experienced convulsions, increased motor activity, and variations in neurotransmitter levels (Anand et al. 1991; Dikshith et al. 1991a; Gopal et al. 1992; Kashyap et al. 1979). Neurological effects were not observed in rats following oral exposure to α-HCH (Muller et al. 1981). Information is available on the neurotoxic effects of α-, β-, and γ-HCH in experimental animals following acute-duration oral exposure (Tilson et al. 1987; Tusell et al. 1987; Woolley and Griffith 1989) and intermediate-duration oral exposure (Desi 1974; Muller et al. 1981; Van Velsen 1986). An acute oral MRL of 0.2 mg/kg/day for β-HCH was developed based on ataxia in mice (Cornacoff et al. 1988). Studies in animals have substantiated the neurological symptoms resulting from dermal application of γ-HCH. Effects in rats included sedation, spasms (Ullmann 1986a), tremors, and convulsions (Brown 1988). Neurochemical and neurophysiological studies in animals exposed via the oral route would provide useful information regarding the mechanisms of HCH-related neurotoxic effects. Because an

MRL could not be developed for inhalation exposures and dermal data are limited, additional studies for all isomers for these two exposure routes are needed.

Epidemiological and Human Dosimetry Studies. Information on the adverse health effects of HCH in groups of humans comes from reports of occupationally exposed individuals (Brassow et al. 1981; Jedlicka et al. 1958; Kayshap 1986). Adverse health effects include EEG abnormalities, increased liver enzymes, and changes in hematological parameters. Limitations inherent in these studies include unquantified exposure concentrations and durations and concomitant exposure to HCH mixtures and other chemicals and pesticides. The few industrial surveys and studies of exposed individuals generally reported blood levels of HCH following exposure and the health effects associated with these levels (Czegledi-Janko and Avar 1970). However, the reported blood levels of HCH have not been quantitatively correlated with ambient HCH levels or health effects. Studies that provide information correlating exposure levels with body levels of HCH would allow investigators to monitor humans for exposure, including populations living near hazardous waste sites. Well-conducted studies are needed to determine and quantifying the effects of inhalation, oral, or dermal HCH exposure on human health including neurological, hematologic, and hepatic effects. However, considering the magnitude of the needed studies, possible difficulty in identifying a suitable potentially exposed subpopulation in the general populace or workplace, and lowered likelihood of exposure in present day society, the value of such studies is questionable.

Biomarkers of Exposure and Effect.

Exposure. Methods exist for the analysis of HCH in blood and urine (Angerer et al. 1981). Thus, biological monitoring for exposure to HCH is possible by measuring the levels of HCH in the blood or urine. In an occupational study, abnormal EEG changes were found to correlate with blood levels of γ-HCH (Czegledi-Janko and Avar 1970). 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 level represents long-term exposures. β-HCH has been measured in numerous human tissues and is the isomer that is consistently detected at the highest concentration (Baumann et al. 1980; Kashyap 1986; Morgan and Lin 1978; Nigam et al. 1986; Ramachandran et al. 1984). However, the reported blood levels of HCH have not been quantitatively correlated with ambient HCH levels. 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.

Effect. No biomarkers of effect, specific for HCH, have been identified in the literature. Nonspecific biomarkers of effect include EEG abnormalities, increases in liver enzymes, hematological effects, seizures and convulsions, neuropsychological, and gastrointestinal effects (Kashyup 1986; Nigam et al. 1986). Muscle spasms and EEG abnormalities have also been observed in workers exposed to γ-HCH (Czegledi-Janko and Avar 1970). High levels of HCH and other organochlorine insecticides have been detected in men with low sperm counts and in women who miscarry or deliver prematurely (Pines et al. 1987; Saxena et al. 1980; Wassermann et al. 1982). No quantitative correlation can be made between body levels of HCH and adverse health effects based on the existing data. Studies quantitatively correlating HCH exposure with body levels of HCH and the occurrence of specific adverse health effects are needed to monitor populations possibly exposed near hazardous waste sites. Studies designed to identify specific biomarkers of effect for HCH would be useful.

Absorption, Distribution, Metabolism, and Excretion. Information is available to assess the extent and rate of HCH absorption following oral exposure in animals and humans (Ahdaya et al. 1981; Albro and Thomas 1974; Turner and Shanks 1980). High blood concentrations of γ-HCH have been demonstrated in a number of acute poisoning cases in which humans were exposed to γ-HCH as the result of ingestion (Berry et al. 1987). Animal studies indicate that γ-HCH is readily absorbed from the gastrointestinal tract (Ahdaya et al. 1981). Both *in vivo* and *in vitro* studies that evaluate dermal absorption of γ-HCH in humans are available (Dick et al. 1997a, 1997b). However, absorption of HCH via inhalation can only be inferred from toxicity studies and studies assessing the distribution and excretion of γ-HCH. No quantitative information is available to assess the rate and extent of inhalation absorption in humans or animals. Additional data concerning the absorption of HCH in animals may provide information to assist in characterizing absorption of HCH in humans.

Information on the distribution of HCH isomers in humans is inferred from case studies, clinical studies, and industrial surveys (Baumann et al. 1980; Nigam et al. 1986; Siddiqui et al. 1981a). Air concentrations of α-, β-, and γ-HCH have been found to be associated with blood serum levels in workers (Baumann et al. 1980). HCH isomers have been detected in the adipose tissue of workers (Baumann et al. 1980). γ-HCH was detected in the cerebral spinal fluid of a young boy following ingestion of γ-HCH (Davies et al. 1983). γ-HCH was detected in brain tissue collected during the autopsy of an infant who was treated with a whole-body application of γ-HCH lotion (Davies et al. 1983). The distribution of HCH in animals following oral exposure has been well documented (Chand and Ramachandran 1980; Eichler et al. 1983; Srinivasan and Radhakrishnamurty 1983b). γ- and β-HCH were found to be primarily stored in

the fat of rats after acute oral exposure. Except in the brain, β-HCH accumulates in tissues to a greater degree than γ-HCH. α-HCH has been shown to accumulate preferentially in the white matter of the brain (Portig et al. 1989). Data exist on the rate and overall distribution of HCH in animals following dermal application. In guinea pigs, the accumulation of γ-HCH in the brain was greater than in the blood following acute dermal exposure (Solomon et al. 1977a, 1977b).

The metabolism of γ-HCH has been studied in mice and rats (Chadwick and Freal 1972a; Chadwick et al. 1978a; Engst et al. 1979; Kujawa et al. 1977). Researchers have identified the primary metabolites (di-, tri-, and tetrachlorophenols) in humans, rats, and mice. In humans, this information is obtained from urinary excretion studies in which individuals were occupationally exposed to γ-HCH (Angerer et al. 1983; Engst et al. 1979). *In vitro* studies using rat liver microsomes have helped to delineate the major metabolic processes and have demonstrated the formation of a reactive epoxide that may be indicative of similar processes in other mammals and humans (Fitzloff and Pan 1984). Investigations have not been conducted to examine the epoxide formation *in vivo* or its role in inducing mutagenic and carcinogenic effects. Extensive metabolic studies have been conducted in animals, and adequate studies exist identifying major metabolites in the tissues and urine (Chadwick and Freal 1972a; Kujawa et al. 1977; Macholz et al. 1982a, 1982b). Multiple detoxification pathways have been delineated (Chadwick et al. 1978a, 1981; Kujawa et al. 1977). 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.

Information from occupational studies and studies in which γ-HCH was used as a therapeutic lotion is available to conclude that humans excrete HCH, principally as metabolites, in urine, breast milk, and semen (Angerer et al. 1981). Urinary excretion of γ-HCH metabolites by humans has been documented (Angerer et al. 1983). The primary urinary metabolites of γ-HCH are chlorophenols. Quantitative information also exists to conclude that the primary route of HCH excretion in animals, following oral exposure, is urine (Chadwick et al. 1985). There are no inhalation studies that have examined the excretion of HCH. In male rats treated dermally with radiolabelled γ-HCH, radiolabel was detected in the urine (Bosch 1987a).

Comparative Toxicokinetics. Evidence is available to suggest that rats and humans absorb HCH and store the isomers primarily in the fat and other body tissues (Chand and Ramachandran 1980; Eichler et al. 1983; Srinivasan and Radhakrishnamurty 1983b). Similar metabolites have been identified in the urine of exposed individuals and treated rodents, and in both, the primary route of excretion is the urine (Angerer et al. 1981; Chadwick et al. 1985).

Exposure to γ-HCH has been shown to be associated with neurological effects in both humans and animals (Czegledi-Janko and Avar 1970; Kashyap 1986; Van Velsen et al. 1986). The available human and animal data also suggest that HCH isomers may affect the blood system. In addition, HCH isomers may also affect the immune system in humans (Kashyap 1986) and animals (Desi et al. 1978; Dewan et al. 1980). Further studies are not needed at this time.

Methods for Reducing Toxic Effects. Seizures caused by γ-HCH can be antagonized by $GABA_A$ mimetics; diazepam is the anticonvulsant of choice (Ellenhorn and Barceloux 1988). Information is available to assess the extent and rate of absorption of HCH following oral and dermal exposure (Ahdaya et al. 1981; Albro and Thomas 1974; Turner and Shanks 1980), although the mechanism(s) of absorption is inadequately characterized. The available data indicate some ways in which peak absorption of HCH might be reduced following oral or dermal exposure (Ellenhorn and Barceloux 1988). Intestinal absorption can be reduced with activated charcoal, while washing with soap and water can decrease skin absorption. There are no known methods for reducing absorption following inhalation exposure.

Because of the high volume of distribution of HCH into adipose tissue, traditional methods of increasing elimination or decreasing distribution are not useful. Development of methods to enhance the excretion of HCH from adipose tissue, while minimizing toxicity, is needed for reducing the body burden.

There is some information on the mechanism (see Section 3.4) for the toxic effects of HCH on the brain (e.g., interference with the GABA system) (Abalis et al. 1985; Casida and Lawrence 1985; Lawrence and Casida 1984) and liver (e.g., disruption of oxidative defense mechanisms) (Barros et al. 1988, 1991; Srinivasan and Radhakrishnamurty 1988; Videla et al. 1991). Further studies in these areas might be helpful for developing methods for reducing toxic effects.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

Limited data are available on the health effects of HCH on exposed children.

It has been demonstrated that weanling rabbits were more sensitive to γ-HCH than young adults, as seen by increased mortality rate and associated excitement and convulsions after treatment (Hanig et al. 1976).

There is, however, no actual evidence that children are more sensitive to the neurotoxicity of γ-HCH. It would be useful to follow up on the weanling rabbits study and conduct additional studies on immature postnatal animals as an experimental model. Data needs relating to developmental effects are discussed above in developmental toxicity section. Replicating the Dalsenter et al. (1997b) study on lactational exposure and adult testosterone levels should be a priority. There is inadequate experimental evidence to determine if pharmacokinetics of HCH in children are different from adults. There is no experimental evidence to indicate whether metabolism of HCH or its mechanism of action is different in children compared with adults. Generally, it would be difficult to have data on the metabolism and mechanism of action of HCH in children (except in accidentally exposed children) to determine whether children are more vulnerable than adults to adverse health effects from exposure to HCH. There are no biomarkers of exposure or effect that have been validated in children or adults exposed as children. There are no data to determine whether there are any interactions with other chemicals that are unique to children or whether interactions observed in adults also occur in children. Although HCH is shown to have some genotoxic potential, it is not known whether parental exposure to HCH may affect children via parental germ cells, or whether HCH may indirectly affect the fetus during maternal exposure. Additional data are needed to determine the potential for genotoxicity in germ cells and adverse developmental effects.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

Federally sponsored research regarding health effects of HCH that was reported in the CRIS/USDA (2003), CRISP (2003), and FEDRIP (2004) databases is summarized in Table 3-9.

Table 3-9. Ongoing Studies on Hexachlorocyclohexane Health Effects

Investigator	Affiliation	Research area	Reference
Adler, SR	Washington University	Examination of the regulatory potential of insecticides, plasticizers, and dioxins in estrogenic and non-estrogenic pathways	CRISP 2004
Alavanja, M	Not available	Epidemiologic investigations to identify and clarify cancer risks from pesticide exposure	FEDRIP 2004
Bloomquist, JR	Virginia Polytechnic Institute	Assessment of the ability of insecticide exposure to cause biomarkers indicating Parkinsonism	CRIS/USDA 2003; FEDRIP 2004
Casida, JE	University of California at Berkeley	Modes of toxic action, biochemical targets, mechanisms of selective toxicity, and health implications of exposure of selected insecticides	CRIS/USDA 2003
Clark, JM	University of Massachusetts Amherst	Detection of pyrethroid and γ-HCH resistance in head lice	FEDRIP 2004
Dietert, RR	Cornell University, Center for the Environment	Expansion of the database of Critical Evaluations on the current evidence of carcinogenicity for selected agricultural chemicals	FEDRIP 2004
MacDonald, JF	Cornell University, Center for the Environment	Establishment of a database of critical evaluations on evidence of breast carcinogenicity of selected pesticides	FEDRIP 2003
Misra, HP	Virginia Polytechnic Institute, College of Veterinary Medicine	Assessment of the role of pesticide mixtures in potentiating the genotoxicity in immune cells *in vitro*	FEDRIP 2004
Naeher, LP	University of Georgia, Environmental Health Sciences	Environmental and dietary monitoring for organophosphate and pyrethroid pesticides in children	CRIS/USDA 2003; FEDRIP 2004
Narahashi, T	Northwestern University	Determination of the mechanism by which neuroactive insecticides exert their toxic actions on mammals	CRIS 2003; CRISP 2004
Oman, GM	Department of Veteran Affairs, Medical Center	Assessment of the impacts of metal and organochlorine contaminants indigenous to Saginaw Bay, Lake Huron, on human and fish immune systems	FEDRIP 2003
Ostrea, EM	Wayne State University	Meconium analysis of fetal exposure to environmental toxins and infant outcome	CRISP 2003; FEDRIP 2004
Schwartz, SM	Fred Hutchinson Cancer Research Center	Determination of risk of testicular germ cell carcinoma in relation to serum levels of persistent organochlorines	CRISP 2004
Wong, PS	University of California at Davis	Establishment of the existence of "ligand independent" activation mechanism for various chlorinated pesticides in human cell systems (BG-1 ovarian cancer cells, and Ishikawa endometrial cells)	FEDRIP 2004

Table 3-9. Ongoing Studies on Hexachlorocyclohexane Health Effects

Investigator	Affiliation	Research area	Reference
Woolley, DE	University of California at Davis, Neurology, Physiology, and Behavior	Investigation of the neurotoxic effects and mechanisms of action produced by acute and chronic exposure to heptachlor and γ-HCH	CRIS/USDA 2003; FEDRIP 2004
Matsumura, F	University of California at Davis, Environmental Toxicology	Identification of the action of mechanism of selected pesticides and study of the basis of their differential toxicities against mammalian, insect, and acerine large proteins	FEDRIP 2004
Matsumura, F	University of California at Davis, Environmental Toxicology	Determination of whether c-Neu plays a pivotal role in mediating the estrogenic action of OC in MCF-7 cell transformation	FEDRIP 2004
Molony, D	University of Texas, Health and Science Center, Houston	Explanation of some of the cellular events and molecular mechanisms that participate in the induction of apoptosis of renal tubular epithelial cell in response to the inhibition of specific ion channels by toxicants	FEDRIP 2004

CRIS = Current Research Information System; CRISP = Computer Retrieval of Information on Science Projects; FEDRIP = Federal Research in Progress; OC = Organochlorine; USDA = U.S. Department of Agriculture

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 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 γ-HCH, α-HCH, β-HCH, and δ-HCH is located in Table 4-1.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

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

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

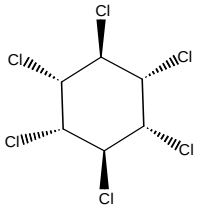
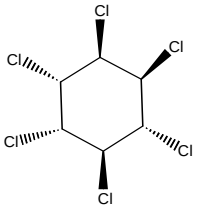
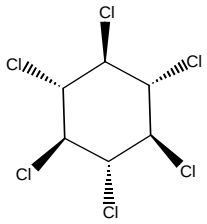
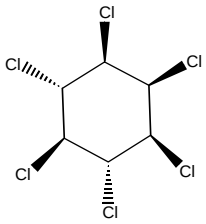
Characteristic	γ-hexachlorocyclohexane	α-hexachlorocyclohexane
Synonym(s)	Lindane; 1-alpha, 2-alpha, 3-beta, 4-alpha, 5-alpha, 6-beta-hexachlorocyclohexane; benzene hexachloride-gamma-isomer; BHC; cyclohexane 1,2,3,4,5,6-hexachloro-gamma-isomer; ENT 7796; gamma-benzene hexachloride; gamma-BHC; gamma-hexachlorocyclohexane; 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[b]	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[b]
Registered trade name(s)	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[c]; Kwell (pharmaceutical shampoo/lotion)[d]	No data
Chemical formula	$C_6H_6Cl_6$	$C_6H_6Cl_6$[b]
Chemical structure		
Identification numbers:		
CAS registry	58-89-9	319-84-6
NIOSH RTECS	GV4900000	GV3500000
EPA hazardous waste	U129; D013	No data
OHM/TADS	7216531	810002
DOT/UN/NA/IMCO shipping	NA 2761 lindane; IMCO 6.1 lindane; UN 2761, organochlorine pesticides, solid toxic, not otherwise specified	No data
HSDB	646	6029
NCI	C00204	No data

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

Characteristic	β-hexachlorocyclohexane	δ-hexachlorocyclohexane
Synonym(s)	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[b]	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[b]
Registered trade name(s)	No data	No data
Chemical formula	$C_6H_6Cl_6$	$C_6H_6Cl_6$
Chemical structure		
Identification numbers:		
CAS registry	319-85-7	319-86-8
NIOSH RTECS	GV4375000	GV4550000
EPA hazardous waste	No data	No data
OHM/TADS	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data
HSDB	6183	6184
NCI	No data	No data

[a]All information obtained from HSDB 1997 except where noted.
[b]RTECS 1993
[c]Farm Chemicals Handbook 1993
[d]Budavari et al. 1989

CAS = Chemical Abstracts Service; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

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

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

[a]Lide 1991
[b]Kirk-Othmer 1985
[c]HSDB 2003
[d]IARC 1979
[e]Budavari et al. 1989
[f]Weiss 1986
[g]Verschueren 1983
[h]Fazzalari 1978
[i]Hollifield 1979
[j]Clayton and Clayton 1981
[k]Kuihara et al. 1973
[l]Hansch and Leo 1995
[m]Ripping 1972
[n]Veith et al. 1979
[o]Pankow et al. 1984
[p]EPA 1982
[q]Same for all isomers

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

Table 5-1 lists the facilities in each state that process hexachlorocyclohexane, the intended use, and the range of maximum amounts of hexachlorocyclohexane that are stored on site. These data only pertain to γ-HCH (lindane) and reflect the amounts that are formulated into various pesticide products, pharmaceuticals (shampoos or lotions to treat lice), or seed treatments. The data listed in Table 5-1 are derived from the Toxics Release Inventory (TRI02 2004). Only certain types of facilities were required to report. Therefore, this is not an exhaustive list.

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-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 (SRI 1987). None of the isomers or technical-grade HCH are currently produced in the United States. The production of γ-HCH exceeded 2.27×10^6 g in 1976 (HSDB 2003); commercial γ-HCH production in the United States reportedly ended in that year (EPA 1989b). However, the *Directory of Chemical Producers for 1987 and 1988* lists one producer of γ-HCH, Drexel Chemical Company (SRI 1987, 1988); subsequent volumes (1989–1991) give no listings of γ-HCH producers.

γ-HCH is 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, granules, and as a smoke generator (Berg 1988; EPA 1985a). γ-HCH is sold separately or in combination with fungicides, fertilizers, other insecticides, or wood preservatives (Hayes 1982).

5.2 IMPORT/EXPORT

γ-HCH is not produced in the United States. It is imported from France, Germany, Spain, Japan, and China (EPA 1985a). Once in the United States, it can be formulated in various pesticide products and exported. The U.S. imports of γ-HCH declined from 1.52×10^5 kg in 1977 to 8.53×10^4 kg in 1982 (HSDB

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	1	10,000	99,999	2, 4
AR	2	1,000	99,999	12
CO	1	10,000	99,999	7
FL	2	No data	99,999	2, 4, 7
GA	9	1,000	999,999	2, 3, 4, 7, 9
ID	5	10,000	999,999	2, 3, 7
IL	2	1,000	99,999	7, 12
IN	1	100,000	999,999	12
KS	1	1,000	9,999	7
KY	2	10,000	99,999	7, 12
MO	3	10,000	999,999	2, 3, 7
MS	2	No data	999,999	2, 3, 7, 12
ND	7	10,000	999,999	1, 2, 3, 4, 7, 9, 10, 11
NE	4	1,000	999,999	7, 12
NJ	3	100	99,999	9, 12
OH	2	100	9,999	12
OR	1	100	999	12
SC	1	10,000	99,999	12
TX	6	1,000	999,999	2, 5, 7, 8, 12

Source: TRI02 2004 (Data are from 2002)

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

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

2003). 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). Facilities that import γ-HCH for use as a formulation component are shown in Table 5-1. 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 is expected to decline significantly as the use of γ-HCH decreases in other countries.

5.3 USE

γ-HCH was initially registered by the USDA (U.S. Department of Agriculture) 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 most recent Registration Eligibility Decision (RED), the only current food/feed use of γ-HCH that is being supported for re-registration is seed treatment on barley, corn, oats, rye, sorghum, and wheat (EPA 2002b). Since the 1998 and 1999 use deletions, the registrants are no longer interested in supporting the seed treatment use on broccoli, Brussel sprouts, celery, cabbage, cauliflower, collards, kale, kohlrabi, mustard greens, lettuce, radishes, spinach, and Swiss Chard (EPA 2002b).

γ-HCH is also available, and regulated by the U.S. Food and Drug Administration (FDA), for the pharmaceutical treatment of scabies and head lice (EPA 2002b). 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 uses have been

on the market since 1947, but were labeled as a second line therapy in 1995 after a review by the FDA. The FDA is revising the label for the treatment of scabies, which would effectively prohibit its use on infants and children weighing less than 60 kg (EPA 2002b). 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). Based on EPA estimates from 1996 to 2001, about 233,000 pounds of γ-HCH are used annually as a seed treatment (EPA 2002b).

5.4 DISPOSAL

Hexachlorocyclohexane 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 1995). Disposal of wastes containing hexachlorocyclohexane is controlled by a number of federal regulations (see Chapter 8).

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 waste waters 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 II, 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).

Disposal methods are currently subject to significant revision by EPA (HSDB 1997).

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

α-, β-, γ-, and δ-HCH have been identified in at least 146, 159, 189, and 126, respectively of the 1,662 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2005). However, the number of sites evaluated for these substances is not known. The frequency of these sites can be seen in Figures 6-1, 6-2, 6-3, and 6-4. Of these sites, all are located within the United States with the exception of three sites located in the Virgin Islands, two sites in the Commonwealth of Puerto Rico, and one site in Guam (not shown).

HCH has been released to the environment during its formulation process and through its use. Although technical-grade HCH and none of the isomers are manufactured in the United States any longer, γ-HCH (lindane) is still imported into the United States and formulated into various products. Most of these formulated products are pesticides that can still be used as a seed treatment for barley, corn, oats, rye, sorghum, and wheat. However, γ-HCH is also used in very small quantities as a prescription medication for the treatment of scabies and head lice. According to the EPA, approximately 233,000 pounds of γ-HCH were used annually from 1996 to 2001 as a seed treatment, which accounts for nearly all γ-HCH used in the United States (EPA 2002b). By contrast, in 1977, over 900,000 pounds of γ-HCH were used in the United States, with roughly half that amount being applied as a seed treatment (EPA 2002b). Once released to the environment, HCH can partition to all environmental media. Although its atmospheric lifetime is long, HCH can be degraded by reacting with photochemically produced hydroxyl radicals or can be removed from the air by wet and dry deposition. Biodegradation is believed to be the dominant decomposition process for HCH in soil and water, although hydrolysis and photolysis may also occur to a lesser extent. The rates of degradation depend on the ambient environmental conditions. Although technical-grade HCH has essentially been banned in the United States for many years, α-, β-, and δ-HCH continue to be detected in environmental media because of the long environmental persistence of these compounds. HCH has been detected in air, surface water, groundwater, sediment, soil, fish and other aquatic organisms, wildlife, food, and humans. Human exposure results primarily from medicinal use and from ingestion of contaminated plants, animals, and animal products. HCH has not been found to be a major contaminant of drinking water supplies.

Figure 6-1. Frequency of NPL Sites with α-Hexachlorocyclohexane Contamination

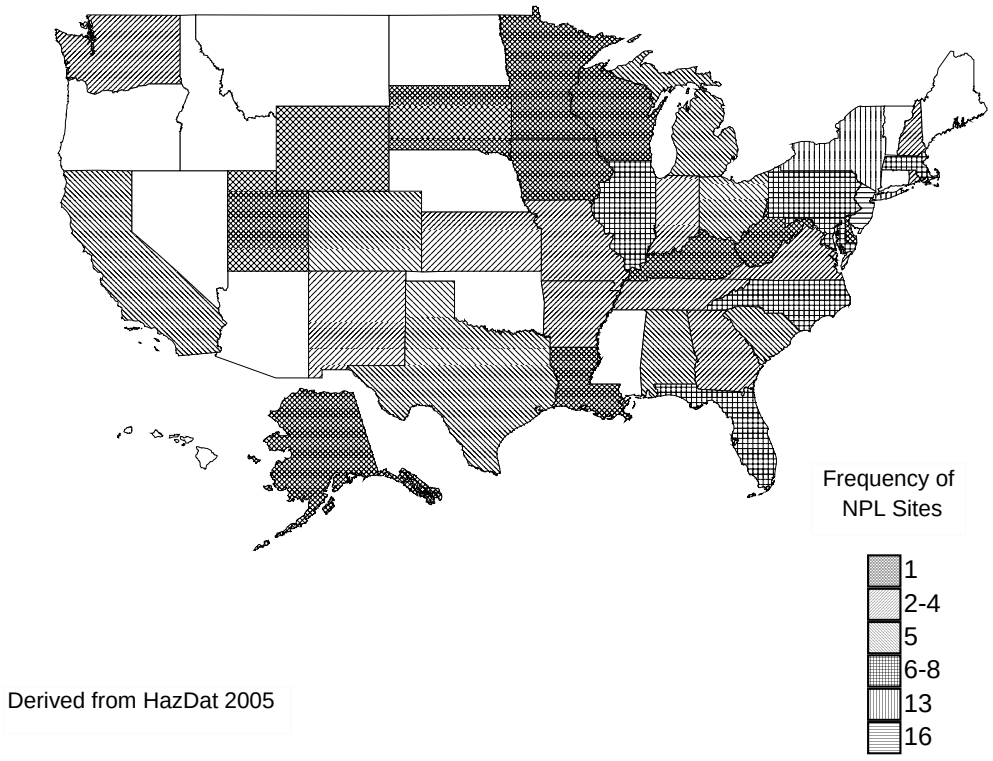


Figure 6-2. Frequency of NPL Sites with β-Hexachlorocyclohexane Contamination

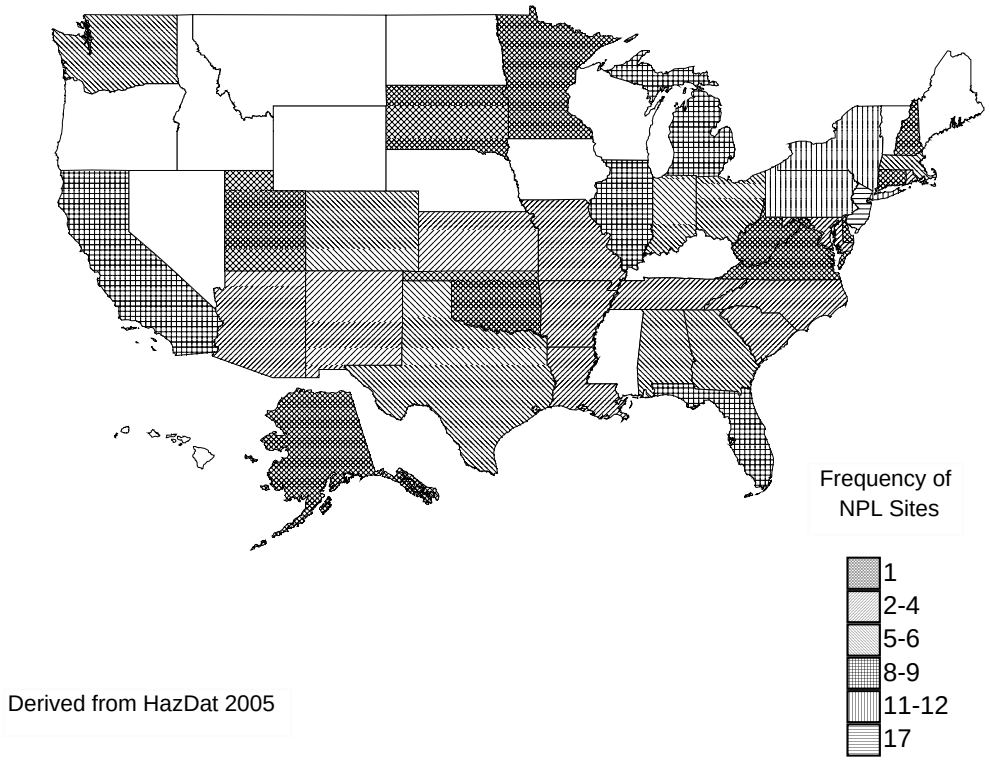


Figure 6-3. Frequency of NPL Sites with γ-Hexachlorocyclohexane Contamination

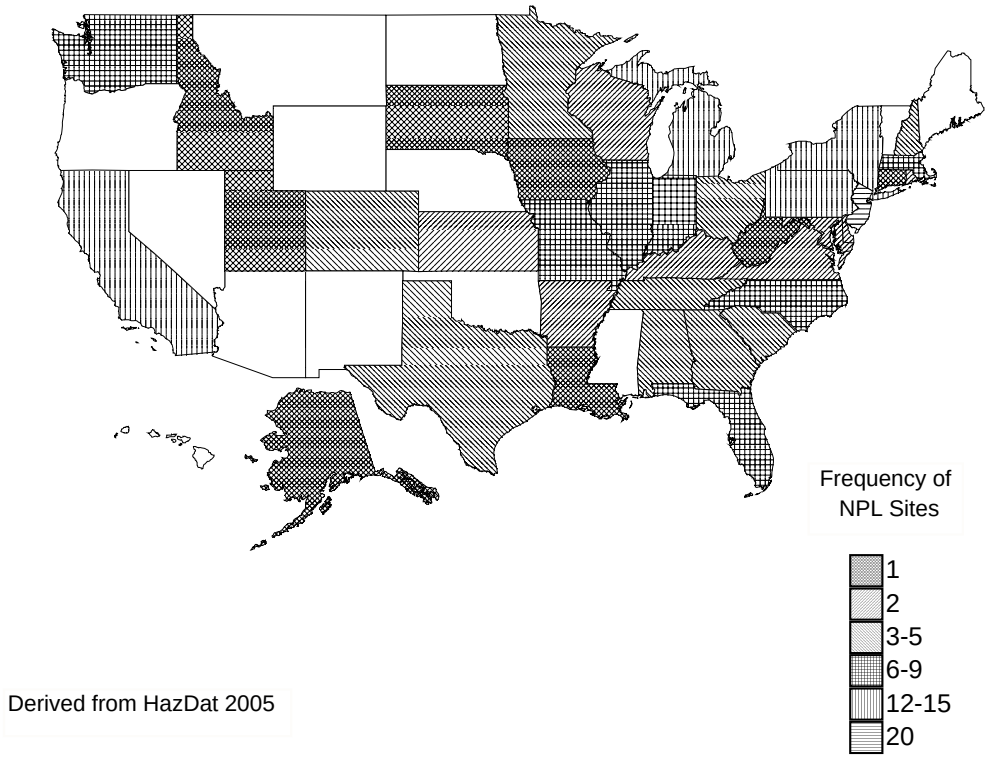
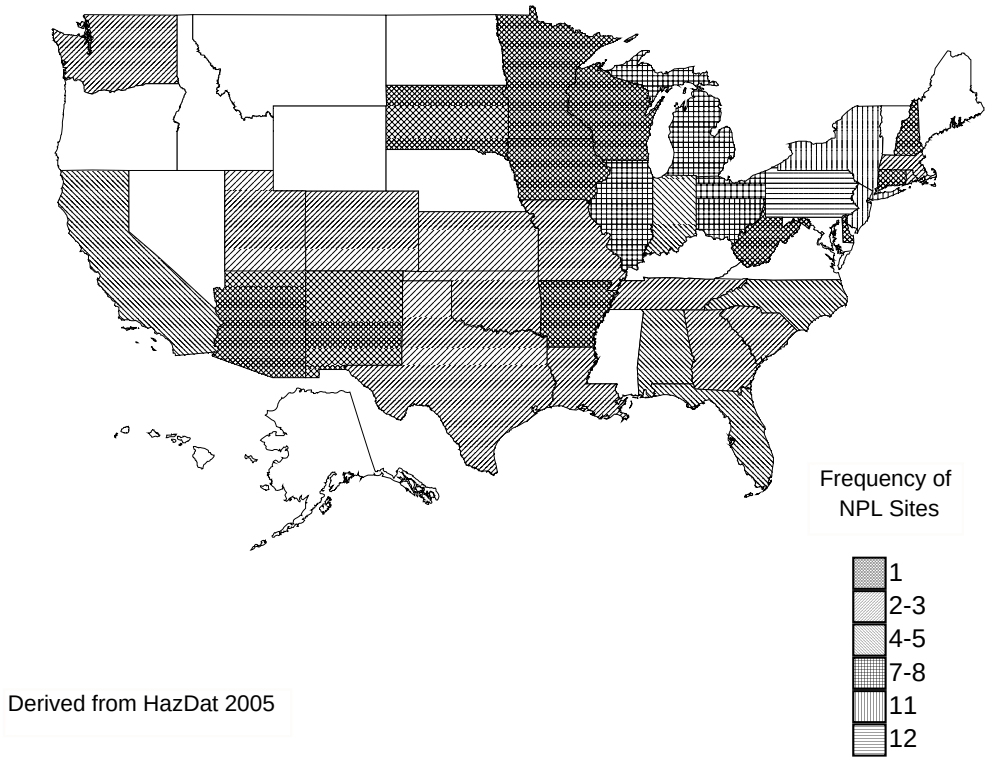


Figure 6-4. Frequency of NPL Sites with δ-Hexachlorocyclohexane Contamination



6.2 RELEASES TO THE ENVIRONMENT

This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the Toxics Release Inventory only if they employ 10 or more full-time employees; if their facility is classified under Standard Industrial Classification (SIC) codes 20–39; 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 1997).

According to the Toxic Chemical Release Inventory, in 2002, total on-site and off-site releases of γ-HCH to the environment from 10 processing facilities were 231 pounds (TRI02 2004). Table 6-1 lists amounts released from these facilities. The TRI data should be used with caution because only certain types of facilities are required to report (EPA 1997).

γ-HCH and other isomers of HCH do not occur naturally in the environment. Most current releases of γ-HCH in the United States are related to its formulation and its use as an insecticide/acaricide.

6.2.1 Air

Estimated releases of 11 pounds of γ-HCH to the atmosphere from four domestic manufacturing and processing facilities in 2002, accounted for about 5% of the estimated total environmental releases from facilities required to report to the TRI (TRI02 2004). These releases are summarized in Table 6-1.

Historically, the largest source of γ-HCH releases to the air resulted from agricultural application of the pesticide γ-HCH. Other air releases occurred during the manufacture of the pesticide. Aerial applications of γ-HCH are now prohibited in the United States as its use as a pesticide was restricted (EPA 1985b), and atmospheric releases from these sources are not expected. α-HCH and γ-HCH were detected in 60–90% of the air samples collected in the vicinity of formulation plants in Arkansas and Tennessee in 1971 at mean levels of 1.0 and 1.3 mg/m^3, respectively (Lewis and Lee 1976). Quantitative estimates of the total quantities of γ-HCH released to the air from these sources were not located.

In addition to releases from industrial facilities, γ-HCH is present in the environment as a result of its use or disposal. For example, wind erosion of contaminated soil may distribute pesticides into the

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Hexachlorocyclohexane[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
AR	1	2	0	0	0	0	2	0	2
ID	1	0	0	0	0	0	0	0	0
IL	2	2	0	0	55	43	2	98	100
ND	2	0	0	0	0	0	0	0	0
NE	1	5	0	0	0	0	5	0	5
OH	1	0	0	0	5	0	0	5	5
OR	1	0	0	0	117	0	117	0	117
TX	1	2	0	0	0	0	2	0	2
Total	10	11	0	0	177	43	128	103	231

Source: TRI02 2004 (Data are from 2002)

[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 on-site 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

atmosphere. γ-HCH can also be 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 source of atmospheric γ-HCH because of its relatively high water solubility (Mackay and Leinonen 1975). Quantitative estimates of the amount of γ-HCH released from these sources were not located in the literature.

Atmospheric release of γ-HCH from disposal sites or hazardous waste sites has not been documented but is likely, considering the physical and chemical properties of γ-HCH.

α-, β-, γ-, and δ-HCH have been detected in air at 7, 4, 9, and 4 of the 1,662 current or former EPA NPL hazardous waste sites, respectively (HazDat 2005).

6.2.2 Water

There were no estimated releases of γ-HCH to water from facilities that formulated γ-HCH (TRI02 2004).

γ-HCH can 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). For example, Lake Ontario received 7 kg/year of α-HCH and <2 kg/year of γ-HCH because of suspended sediment loading from the Niagara River between 1979 and 1981 (Kuntz and Warry 1983). The Great Lakes in general receive from 0.77 to 3.3 metric tons/year of α-HCH and from 3.7 to 15.9 metric tons/year of γ-HCH because of atmospheric deposition of these contaminants (Eisenreich et al. 1981). In 1982, α-HCH and γ-HCH were detected in samples of urban stormwater runoff from Denver, Colorado, and Washington, DC, 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, DC, in 5% of the samples at a concentration of 0.1 μg/L (Cole et al. 1984).

γ-HCH can be released to groundwater via soil leachate. Although available adsorption data indicate that γ-HCH has a low mobility in soils, the results of monitoring studies suggest that γ-HCH does migrate to groundwater (Page 1981; Sandhu et al. 1978). In water tested from 1,076 wells throughout New Jersey, γ-HCH was not detected in at least half of the samples, but a maximum concentration of 0.9 ppb γ-HCH was detected (Page 1981).

α-, β-, γ-, and δ-HCH have been detected in groundwater at 72, 69, 91, and 65 of the 1,662 current or former EPA NPL sites, respectively (HazDat 2005). α-, β-, γ-, and δ-HCH have been detected in surface water at 34, 18, 33, and 12 of the 1,662 current or former EPA NPL sites, respectively (HazDat 2005).

6.2.3 Soil

Estimated releases of 177 pounds of γ-HCH to soils from three domestic manufacturing and processing facilities in 2002, accounted for about 77% of the estimated total environmental releases from facilities required to report to the TRI (TRI02 2004). According to the TRI database, there were no underground injections in 2002 (TRI02 2004). These releases are summarized in Table 6-1.

γ-HCH can be released to the soil by direct application of the pesticide to soil or 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).

α-, β-, γ-, and δ-HCH have been detected in sediment at 17, 19, 36, and 28 of the 1,662 current or former EPA NPL sites, respectively (HazDat 2005). α-, β-, γ-, and δ-HCH have been detected in soil at 63, 78, 90, and 58 of the 1,662 current or former EPA NPL sites, respectively (HazDat 2005).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

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. The K_{oc} of γ-HCH in a mineral soil containing 1.26% organic carbon content was measured as 832 (Chiou et al. 1998). 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 mobility in soils (Hollifield 1979; Melancon et al. 1986; Rao and Davidson 1982; 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, are not sufficient to adsorb γ-HCH to the extent that groundwater contamination is prevented (Nordmeyer et al. 1992). In a study involving a laboratory sediment/water system (pH=7.42; 2.18% organic carbon), α- and γ-HCH isomers were highly adsorbed on sediments under both aerobic and anaerobic conditions and few differences were noted in the adsorption behavior of each isomer (Wu et al. 1997). 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. Using sediment obtained from a sugar-cane growing region of Australia, the K_{oc} of γ-HCH was measured as 2,164 (Just et al. 1990).

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 the warmer temperature 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). 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). 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).

An analysis of the concentrations of α-HCH to γ-HCH in air over southern Ontario suggested that high levels of γ-HCH were indicative of recent γ-HCH usage (Hoff et al. 1992a). The levels of α-HCH were less variable throughout the year, ranging from 77 to 260 pg/m^3. During the winter, higher ratios of α-HCH to γ-HCH reflect 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 reflect both increased γ-HCH usage in the region and the lack of movement of Arctic air (Hoff et al. 1992a). γ-HCH is 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 cannot 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.

γ-HCH in the atmosphere is likely to be subject to rain-out and dry deposition. γ-HCH removal rates by rainfall and dry deposition were 2.5%/week and 3.3%/week, respectively, and the estimated residence time of γ-HCH in the atmosphere was 17 weeks in a study by Atkins and Eggleton (1971). Rain-out and dry deposition of atmospheric γ-HCH results in the contamination of surface soil and water in areas not directly exposed via pesticide application. γ-HCH concentrations were positively correlated with ambient air temperature, although concentrations of α-HCH were not. 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).

In surface waters, γ-HCH has a tendency to dissolve and remain in the water column. 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 1992c). 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 the sorption of γ-HCH from water.

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 is estimated that 85% of the γ-HCH associated with the sediment gas bubbles will 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).

γ-HCH is bioconcentrated to high levels following uptake from surface waters by a number of aquatic organisms. However, uptake from soils and bioconcentration by plants and terrestrial organisms appear to be limited. For example, bioconcentration factors (BCFs) for γ-HCH from surface waters include 183 in brine shrimp (Matsumura and Benezet 1973), 319 in rainbow trout fry (Ramamoorthy 1985), 84 in pink shrimp, 218 in pinfish, 63 in grass shrimp, and 490 in sheepshead minnows (Schimmel et al. 1977). Introduction of γ-HCH onto sand resulted in a BCF of 95 in brine shrimp and 1,613 in northern brook silverside fish (Matsumura and Benezet 1973). 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 although aquatic organisms may accumulate γ-HCH from the water column, 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). 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).

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 postapplication, while at 19 weeks postapplication, 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 postapplication; 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 postapplication; 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 posttreatment, 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).

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).

Uptake of γ-HCH by earthworms from a treated humus soil has also been reported. Following exposure to 5 ppm of the compound for up to 8 weeks, the test organisms 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.

The effect of soil loading (the amount of soil deposited per unit area of skin) on the dermal bioavailability of γ-HCH from contaminated soils has been examined (Duff and Kissel 1996). A static *in vitro* diffusion apparatus and abdominal skin from human cadavers were used. It was shown that the dermal absorption of γ-HCH from soil is dependent on soil loading and was estimated to be 0.45–2.35%. Dermal absorption of γ-HCH increased significantly with decreases in soil loading, provided that monolayer or greater coverage of the skin was maintained.

6.3.2 Transformation and Degradation

6.3.2.1 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 γ-HCH and α-HCH with hydroxyl radicals were measured as $1.9x10^{-13}$ and $1.4x10^{-13}$ cm^3/molecule-second, respectively (Brubaker and Hites 1998). Using an average hydroxyl radical concentration of $5x10^5$ molecule/cm^3, the corresponding half-lives are about 84 and 115 days for γ-HCH and α-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 γ-HCH and α-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.

6.3.2.2 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 to the results. Zoetemann 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.

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 (Machholz and Kujawa 1985) and in algal cultures (Sweeney 1969).

Hydrolysis is not considered an important degradation process for γ-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 (1989d) reported a hydrolysis half-life of 207 days at pH 7 and 25 °C using distilled water.

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-HCH 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 ultraviolet 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).

6.3.2.3 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-HCH 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). However, the concentrations and persistence of γ-HCH in soil are 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).

Most available information suggests that γ-HCH transformation is favored in biologically rich, anaerobic environments (EPA 1979b; 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 tetra cyclohexanes; other isomers of HCH; and other related chemicals. The products varied depending on what organisms were present, what products were sought, and when the sample was analyzed (EPA 1979b). 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. An inability to control all environmental conditions in the laboratory was discussed as a possible reason for differences in results between laboratory and field studies.

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.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to hexachlorocyclohexane depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of hexachlorocyclohexane 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 hexachlorocyclohexane 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. The analytical methods available for monitoring hexachlorocyclohexane in a variety of environmental media are detailed in Chapter 7.

6.4.1 Air

γ-HCH was detected in ground level ambient air samples collected in College Station, Texas, in 1979–1980 at a mean concentration of 0.23 ng/m^3 (range, 0.01–1.60 ng/m^3) (Atlas and Giam 1988). The compound has also been detected in troposphere air samples collected over the Adirondack Mountains in New York State in 1985 at a mean concentration of 0.509 ng/m^3 and over Newport News, Virginia, in 1988 at a mean concentration of 0.021 ng/m^3 (Knap and Binkley 1991). α-HCH and γ-HCH were detected in the air of Alabama during an air monitoring program (January–October 1996 and May 1997) at mean concentrations of 0.092 and 0.050 ng/m^3, respectively (Jantunen et al. 2000). The average level of α-HCH at Eagle Harbor, Michigan; Sleeping Bear Dunes State Park, Michigan; and Sturgeon Point, New York ranged from 0.110 to 0.140 ng/m^3 for samples collected between 1990 and 1997 and the average levels of γ-HCH were 0.024–0.062 ng/m^3 at the same sites (Cortes and Hites 2000). Air monitoring over southern Ontario, Canada, from July 1988 to July 1989 showed annual mean air concentrations of α-, β-, and γ-isomers to be 0.145, 0.0018, and 0.06 ng/m^3, respectively with a total HCH annual mean concentration of 0.21 ng/m^3 and with the greatest total HCH concentrations during the summer months (Hoff et al. 1992a). The maximum concentration of γ-HCH measured at a site 2 km away from a canola field in south central Saskatchewan, Canada where γ-HCH had been applied as a seed treatment was 2.9 ng/m^3 in 1997, and 2.7 ng/m^3 in 1998 (Waite et al. 2001).

In a study of global distribution and atmospheric transport of chlorinated hydrocarbons in the West Pacific, Eastern Indian, and Antarctic Oceans, Tanabe et al. (1982) confirmed the widespread distribution of HCH isomers. HCH residues were detected in all 79 air and water samples collected. The concentrations ranged from 1.1 to 2.0 ng/m^3 in air and from 3.1 to 7.3 ng/L in water. Other monitoring studies include the detection of γ-HCH in the lower troposphere over the Southern Indian Ocean in 1986 at a mean concentration of 0.406 ng/m^3 (Wittinger and Ballschmiter 1990), in the lower troposphere over Bermuda in 1988 at a mean concentration of 0.012 ng/m^3 (Knap and Binkley 1991), and in ambient air samples collected at Axel Hieberg Island in the Canadian arctic at 0.017–0.07 ng/m^3 (Hargrave et al. 1988).

γ-HCH has also been detected in rainfall samples collected in College Station, Texas, in 1979–1980 at a weighted mean concentration of 2.81 ng/L (range, 0.30–7.8 ng/L) (Atlas and Giam 1988) and in Bermuda in 1983–1984 at a mean concentration of 0.126 ng/L (range, 0.001–0.936 ng/L) (Knap et al. 1988). In rainfall samples collected at four sites in Canada in 1984, γ-HCH concentrations ranged from 0.46 to 34 ng/L (Strachan 1988). The mean concentration in rainfall samples collected at Lake Superior during

the 1984 wetfall season was 3.0 ng/L, with an annual loading of 2.0 μg/m^2/year (Strachan 1988). These values were less than those determined in the years 1977, 1981, and 1983 (Strachan 1988). γ-HCH has been detected in rain and snow water in Portland, Oregon in 1982 at mean concentrations ranging from 0.45 to 11 ng/L (Pankow et al. 1984). Rainwater collected in Hawaii in 1970–1971 had a mean γ-HCH concentration of 5 ng/L, with concentrations ranging from 1 to 19 ng/L (Bevenue et al. 1972). Snow and ice samples collected at Axel Hiberg Island in the Canadian Arctic in 1986 contained γ-HCH at concentrations of 0.211–0.644 and 0.186 ng/L, respectively (Hargrave et al. 1988). Rain samples collected in Germany between June 1990 and August 1991 contained γ-HCH at a mean concentration of 208 ng/L (range, 20–833 ng/L) in 39 of 41 samples (Scharf et al. 1992).

6.4.2 Water

Surface water concentrations of γ-HCH have been measured in many areas across the United States. Concentrations of γ-HCH in the range of 0.052–0.1 μg/L were observed in Washington, DC, and Denver, CO (Cole et al. 1984). The majority of the available monitoring studies were conducted in the early to mid 1970s. A comprehensive monitoring study was conducted in 1980–1981 in the Niagara River near its entry into Lake Ontario. In that study, γ-HCH was detected in 99% of all samples at a mean concentration of 2.1 ng/L (Kuntz and Warry 1983). γ-HCH concentration in Lake Michigan tributary streams ranged from undetected to 0.15 μg/L (EPA 1974c). According to EPA's STORET (short for STOrage and RETrieval) database, γ-HCH was detected in 27% of 4,505 surface water samples collected in the United States at a median concentration of 0.020 μg/L (Staples et al. 1985). γ-HCH concentrations in groundwater samples were greatest in the West South Central region (Phillips and Birchard 1991). The compound was also found in water samples collected in Lake Ontario in 1983 at 0.806–1.85 ng/L concentration (Biberhofer and Stevens 1987). γ-HCH was detected in the Patuxent River (a tributary to the Chesapeake Bay) in 1995 at a mean concentration of 1.0 ng/L (Harmon-Fetcho et al. 1999).

γ-HCH has been detected in more than 10% of urban stormwater runoff samples in two U.S. cities at concentrations between 0.052 and 0.1 ng/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).

γ-HCH has been detected in drinking water in Chesterfield County, South Carolina, and Hampton, South Carolina at mean concentrations of 23 ng/L (0–193 ng/L, range) and 147 ng/L (0–319 ng/L, range),

respectively (Sandhu et al. 1978). γ-HCH has also been detected in drinking water from Cincinnati, Ohio (Keith et al. 1976), and Oahu, Hawaii (Bevenue et al. 1972), at mean concentrations of 0.01 ng/L, and 0.2 ng/L, respectively. In a study of α-HCH and γ-HCH in Saskatchewan, Canada, these HCH isomers were not detected frequently in surface waters that originate from ground water (Donald et al. 1997). A comprehensive groundwater monitoring study was conducted in the Ozark Plateaus Province of Arkansas, Kansas, Missouri, and Oklahoma from April to September 1993 (Adamski et al. 1996). γ-HCH was identified in two groundwater samples collected from domestic wells and springs at concentrations of 0.028 and 0.032 µg/L. γ-HCH was detected in a drinking water well in Connecticut at a concentration of 0.06 µg/L (Eitzer and Chevalier 1999). Isomers of HCH were detected in drinking water from Southern Spain between 1991 and 1994 at concentrations of 0.008–0.199 µg/L (α-HCH), 0.005–0.021 µg/L (β-HCH), and 0.002–0.228 µg/L (γ-HCH) (Garcia-Repetto and Repetto 1997).

6.4.3 Sediment and Soil

γ-HCH was detected at trace levels (<0.1 mg/kg) in surface soils from five counties in western Alabama (Albright et al. 1974). γ-HCH was detected in soil from Alabama, Arkansas, Georgia, Illinois, and Iowa at concentrations of 0.01, 0.01, 0.07, 0.02, and 0.15 mg/kg, respectively (Crockett et al. 1974). A survey of soils from six regions of Alabama showed that α-HCH was present in 24 out of 39 soils analyzed at concentrations of 0–0.269 µg/kg and γ-HCH was present in 26 out of 39 soils analyzed at concentrations of 0–1.07 µg/kg (Harner et al. 1999). γ-HCH was detected in agricultural soils from Canada at levels of 0.36–2.2 µg/kg (Webber and Wang 1995). β-HCH, γ-HCH, and δ-HCH were detected in rice growing and industrial soils in South Korea at the following concentration ranges: 0.25–0.80 µg/kg, β-HCH; 0.17–0.56 µg/kg, γ-HCH; 0.76–2.97 µg/kg, δ-HCH (Kim and Smith 2001).

According to EPA's STORET database, γ-HCH was detected in 0.5% of 596- sediment samples collected throughout the United States at a median concentration of <2.0 µg/kg (Staples et al. 1985). According to data collected in STORET between 1978 and 1987, γ-HCH was found in the greatest concentration in sediment from the West North Central census region of the United States, followed by the Mountain region and the East South Central region (Phillips and Birchard 1991). γ-HCH was detected in 33% of suspended sediment samples collected from the Niagara River; the average concentration was 2 µg/kg (Kuntz and Warry 1983). The average γ-HCH concentration in settling particulates from Lake Ontario was 2.4 ppb in 1982 (Oliver and Charlton 1984). Sediment samples from Lake St. Francis on the St. Lawrence River contained a mean total HCH concentration of 0.6 µg/kg dry weight (range, <0.1–2.0 µg/kg), suggesting that deposition of contaminated materials from Lake Ontario was of less

importance than local inputs of HCH (Sloterdijk 1991). γ-HCH concentrations in creek sediments collected in 1976 near the James River in Virginia ranged from 7.3 to 8.5 μg/kg (Saleh et al. 1978). γ-HCH was included in the analytes monitored in the National Oceanic and Atmospheric Administration's (NOAA) Status and Trends Mussel Watch Program conducted in the Gulf of Mexico. The compound was detected in 19% of the sediment samples collected in 1987 at a mean concentration of 0.07 μg/kg (median, <0.02 μg/kg; range, <0.02–1.74 μg/kg) (Sericano et al. 1990). Sediment samples collected around the Great Lakes in May 1989 contained γ-HCH concentrations ranging from below the detection limit (0.10 μg/kg) to 0.99 μg/kg (wet weight) (Verbrugge et al. 1991). Thirty-three sediment samples from 11 impoundments along the Indian River Lagoon in Florida contained γ-HCH at concentrations ranging from 34.4 μg/kg in the top layer of sediment at one impoundment to 9.4 μg/kg in the bottom layer at the same site (Wang et al. 1992). The pesticide γ-HCH had been used for mosquito control in the area from the late 1950s to the mid 1960s. Interstitial water samples from the impoundment sites did not contain detectable levels of the pesticide.

6.4.4 Other Environmental Media

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 pertinent to the isomers of HCH are summarized in Table 6-2. 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. 1990b). 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).

γ-HCH residues on tomatoes decreased by 23.9% 15 days after application of the pesticide (from 0.1956 ppm to 0.1488 ppm). Processing the tomatoes (e.g., pureeing, making tomato juice) reduced the

Table 6-2. Ten-year Study on the Occurrence of HCH in 234 Ready-to-eat Food Items in the United States

HCH isomer	N[a]	Foods[b]	Average concentration (µg/g)
α-HCH	584	88	0.0010
β-HCH	14	9	0.0027
δ-HCH	1	1	0.0030
γ-HCH	369	81	0.0012

[a]Number of samples in which residue was detected (17,050 total samples).
[b]Number of foods in which residue was detected (234 total ready-to-eat foods; 230 foods with detectable pesticide levels).

residue levels by 100% after the waiting period; however, washing the tomatoes reduced the residues by up to 55.9% (Bessar et al. 1991). 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).

As part of NOAA's Status and Trends Mussel Watch Program conducted in the Gulf of Mexico, γ-HCH was detected in 80% of the oyster samples collected in 1987 at a mean concentration of 1.74 ppb (median, 1.20 ppb; range, <0.25–9.06 ppb) (Sericano et al. 1990). Samples taken in 1992 from Mexico's Palizada River, located in a major agricultural area with substantial pesticide use, contained an average γ-HCH concentration of 0.08 ppb in shrimp but no detectable levels in oysters or mussels (Gold-Bouchot et al. 1995). Combined concentrations of other HCH isomers were found to be 1.18 ppb in shrimp, 1.04–1.97 ppb in oysters, and 1.68 ppb in mussels. Schmitt et al. (1985) reported the results of a monitoring study of fish tissues from 107 freshwater stations in the United States. A decline in tissue occurrence of detectable α- and γ-HCH residues was observed from 1976 to 1981. During 1980–1981, whole body residues of γ-HCH exceeded 0.01 ppb at only one station, where levels were 0.02–0.03 ppb. Tissue concentrations of α-HCH were higher than γ-HCH. The highest concentrations for α-HCH were 0.03–0.04 ppb and were found in fish from the southwestern and Midwestern United States. An analysis of fish from the Upper Steele Bayou in Mississippi in 1988 indicated that β-HCH concentrations ranged from undetected to 0.02 ppm wet weight in fish; no β-HCH was detected in snakes or sediments taken from the same area (Ford and Hill 1991). Atlantic cod taken from relatively isolated stock in the southern Gulf of St. Lawrence showed declining tissue concentrations of α-HCH between 1977 (1.865 ppb) and 1985 (1.792 ppb). α-, β-, δ, and γ-HCH were detected in the tissue of adult green frogs from southwestern Michigan at mean concentrations of 0.02, 0.01, 0.03, and 0.07 ppb, respectively, during a 1998 monitoring study (Gilliland et al. 2001). Only α-HCH was detected in juvenile frogs obtained from the same locations at a mean concentration of 0.04 ppb.

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).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Human exposures to γ-HCH can result from the ingestion of plants, animals, animal products, milk, and water containing the pesticide. Farm animals may be exposed to the compound through feed, air, or water or cutaneous application for protection from ectoparasites. Lipophilic pesticides such as γ-HCH accumulate in adipose tissue. 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). 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).

The most likely route of non-medicinal human exposure to γ-HCH is ingestion of food containing the pesticide. A smaller degree of exposure may result from ingestion of drinking water containing γ-HCH. For example, γ-HCH was detected in 6% of the foods collected in eight market basket surveys from different regions of the United States during the period of April 1982 to April 1984 (Gunderson 1988), in 4% of the foods surveyed from June 1984 to April 1986 (Gunderson 1995a), and in 4% of the foods surveyed from July 1986 to April 1991 (Gunderson 1995b). Foods representative of 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 in 1982–1984, 1984–1986, and 1986–1991 are shown in Table 6-3. HCH isomers have been detected in the following feed types formulated for infants and toddlers: whole milk and other dairy products; meat, fish, and poultry; oils and fats; vegetables; and sugars and adjuncts (Gartrell et al. 1986a).

HCH isomers were also detected in adult diet foodstuffs, including dairy products; meat, fish, and poultry; garden fruits; oils and fats; leafy and root vegetables; and sugar and adjuncts (Gartrell et al. 1986b). Daily intake values of HCH isomers in adult diets in 1981–1982 were reported to be 0.010 μg/kg/day for total HCH; 0.008 μg/kg/day for α-HCH; <0.001 μg/kg/day for β-HCH and δ-HCH; and 0.002 μg/kg/day for γ-HCH. In the Total Diet Study conducted by FDA in 1990 on 936 food items, γ-HCH was detected in 23 items, while α-HCH and β-HCH (combined) were detected in 11 items. Information on the amount of levels found were not provided (Yess 1991). The average concentrations of α-, β-, δ-, and γ-HCH in 234 ready-to-eat foods were 0.0010, 0.0027, 0.0030, and 0.0012 μg/g, respectively (see Table 6-2) (Rogers et al. 1995).

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

Table 6-3. Average Daily Intake (AVDI, ng/kg/day) of γ-HCH in Eight Population Groups

Date	Infants (6–11 months)	Toddlers (2 years)	14–16-year-old females	14–16-year-old males	25–30-year-old females	25–30-year-old males	60–65-year-old females	60–65-year-old males
				α-HCH				
1982–1984[a]	7.2	16.1	6.1	7.3	4.5	5.9	3.3	3.7
1984–1986[b]	3.3	7.1	2.7	3.3	2.0	2.5	1.5	1.6
1986–1991[c]	0.8	2.7	1.1	1.1	0.7	0.8	0.5	0.5
				β-HCH				
1982–1984[a]	<0.1	0.3	0.2	0.2	0.2	0.4	0.2	0.2
1984–1986[b]	No data	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
1986–1991[c]	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
				γ-HCH				
1982–1984[a]	1.9	7.9	3.1	3.4	2.0	2.5	1.6	1.8
1984–1986[b]	0.7	2.8	1.1	1.3	0.7	0.9	0.6	0.6
1986–1991[c]	0.8	3.2	1.4	1.5	0.8	1.0	0.6	0.6

[a]Gunderson 1988
[b]Gunderson 1995a
[c]Gunderson 1995b

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, the 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 <19–570 ng/g (ppb) concentrations (EPA 1986d). 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 more than 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 has decreased over time, but the compound has continued to be detected in nearly 100% of the population surveyed. Median levels are highest in the South census region and tend to increase with age but have 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).

A comparison of the levels of α-HCH 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) 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 breastmilk 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) and adipose tissue (23.4 ng/g) were lower near the Great Lakes than in other parts of Canada (0.8 and 30.8 ng/g, respectively) (Mes and Malcolm 1992). 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 (Loganathan et al. 1993). Levels have been dropping since HCHs were banned in 1971, from a maximum level of 28 μg/g to present levels of <1 μg/g. Since 1974, only the more persistent β-HCH isomer has been found (Loganathan et al. 1993).

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). The National Health and Nutrition Examination Survey (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).

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 are found in mutton, eggs, and chicken, which are common in nonvegetarian meals; therefore, there tends to be a higher level of γ-HCH in the bodies of nonvegetarians. Individuals living in rural areas are more likely to be exposed to γ-HCH because agricultural fields are the primary site of application of pesticides. In addition, studies indicate that γ-HCH is also present in breastmilk at an average level of 0.006 ppm in Alberta, Canada (Currie et al. 1979). In a study of 50 donors of breastmilk 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.

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 ppb) and his wife (5 ppb) were found to be elevated in a household in which dust levels measured 5.85 ppb (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 to 10% of the population, with mean concentrations of 0.7–5 ng/m^3 (EPA 1990c).

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).

The Centers for Disease Control and Prevention (CDC) has recently completed its Second National Report on Human Exposure to Environmental Chemicals that was derived from data obtained from the National Health and Nutrition Examination Survey (NHANES) (CDC 2003). The first report on 27 chemicals was issued in March 2001. This second report, released in January 2003, presents blood and urine levels of 116 environmental chemicals from a sample of people who represent the noninstitutionalized, civilian U.S. population during the 2-year period of 1999–2000. Lipid serum levels of β- and γ-HCH are summarized in Table 6-4.

In general, accidental or intentional ingestion 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.

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7, Children's Susceptibility.

Table 6-4. Geometric Mean and Percentiles of the Serum Concentration (ng/g) of β-HCH in the U.S. Population[a]

Age	Geometric mean	Selected percentiles						Sample size
		10th	25th	50th	75th	90th	95th	
β-HCH								
12 and older	9.68	<LOD[b]	<LOD	<LOD	19.0	42.0	68.9	1,893
12–19	NA[c]	<LOD	<LOD	<LOD	<LOD	<LOD	11.4	653
20 and older	10.9	<LOD	<LOD	<LOD	21.0	46.0	73.4	1,240
Males	NA	<LOD	<LOD	<LOD	14.5	29.8	44.6	901
Females	11.1	<LOD	<LOD	<LOD	22.0	51.3	81.1	992
Mexican Americans	16.7	<LOD	<LOD	15.5	37.5	97.9	139.0	632
Non-Hispanic Blacks	NA	<LOD	<LOD	<LOD	14.7	36.6	48.9	403
Non-Hispanic Blacks	NA	<LOD	<LOD	<LOD	17.5	34.4	51.3	702
γ-HCH								
12 and older	9.68	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	1,799
12–19	NA	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	660
20 and older	NA	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	1,139
Males	NA	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	863
Females	NA	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	936
Mexican Americans	NA	<LOD	<LOD	15.5	<LOD	<LOD	<LOD	631
Non-Hispanic Blacks	NA	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	380
Non-Hispanic Blacks	NA	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	646

[b]LOD = level of detection; 4.8 ng/g (β-HCH) and 7.5 ng/g (γ-HCH).
[c]NA = not available; proportion of results below limit of detection was too high to provide a valid result.

[a]Source: CDC 2003

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Prenatal exposure of children to HCH can occur. β-HCH and γ-HCH have been found in samples of human maternal adipose tissue, maternal blood, cord blood, and breastmilk in women who were exposed to unknown levels of various organochlorine pesticides in Kenya (Kanja et al. 1992). Placental transfer of HCH in humans has been well documented (Saxena et al. 1981b). Higher levels of total HCH and γ-HCH were found in specimens of maternal blood, placenta, and umbilical-cord blood from women experiencing premature labor, spontaneous abortions, and stillbirths when compared to matched controls (Saxena et al. 1980; Saxena et al. 1983). Saxena et al. (1980) reported HCH levels of 69.3–550.4 ppb and γ-HCH levels of 30.8–113.6 ppb in the blood of women in India who had experienced spontaneous abortions or premature labor compared with blood HCH levels of 22.2–85.5 ppb and γ-HCH levels of 7.1–32.5 ppb in women who had undergone full-term pregnancy. Serum levels of a number of other pesticides including aldrin, DDE, DDT, and DDD were also found to be higher in cases of premature labor and spontaneous abortions. It was, therefore, not possible to establish a causal relationship between the serum HCH levels and these adverse effects. However, HCH has been shown to accumulate in amniotic fluid, placenta, and fetal tissues after treatment of pregnant mice (Srivastava and Raizada 1993) and can be related to fetolethality.

HCH is commonly detected in low concentrations (0.015 mg/kg fat) in the breastmilk of women exposed to HCH in the environment (Fytianos et al. 1985). Levels of HCH isomers in breastmilk have been reported, particularly in developing countries that still use HCH as a pesticide. Studies indicate the γ-HCH is present in breastmilk at an average level of 6 ppb in Alberta, Canada (Currie et al. 1979). In a study of 50 donors of breastmilk 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 lipids. Breastmilk concentrations of α-, β-, γ-, and δ-HCH were determined from samples obtained from two areas of India that were under malaria control (Dua et al. 1997). The mean concentrations of α-, γ-,

β-, and δ-HCH in one area were 0.002, 0.002, 0.022, and 0.001 (mg/kg), while in the second area, concentrations were 0.003, 0.006, 0.078, and 0.002, respectively. Another study performed in a different region of India also demonstrated the presence of HCH isomers in breastmilk (Nair et al. 1996). Mean breastmilk concentrations of α-, β-, and γ-HCH were 0.045, 0.198, and 0.084 (mg/L), respectively. δ-HCH was not detected in the breastmilk samples. In a study designed to quantify the levels of organochlorine residues in the breastmilk of mothers in Uganda, Africa, the milk fat concentrations of α-HCH, β-HCH, and γ-HCH ranged from 0.006–0.46, 0.005–0.25, and 0.01–0.87 mg/kg, respectively (Ejobi et al. 1996). The concentration of β-HCH in breastmilk samples from three regions in the Czech Republic ranged from 71 to 80 ng/g (Schoula et al. 1996). A comparison of β-HCH levels in breastmilk and adipose tissue samples was made for populations living near the Great Lakes (Canada only) and the rest of Canada. Mean β-HCH levels in breastmilk (0.6 ng/g) and adipose tissue (23.4 ng/g) were lower near the Great Lakes than in other parts of Canada (0.8 and 30.8 ng/g, respectively) (Mes and Malcolm 1992). γ-HCH was identified in 27 out of 115 samples of breast milk obtained from mothers in Al-Kharj, Saudi Arabia at mean concentrations of 1.061 µg/L and 23.3 µg/kg milkfat (Al-Saleh et al. 1998). HCH isomers were detected in breast milk of mothers from six regions of Belarus at concentrations of 2–93 µg/L and 14–2,470 µg/kg milkfat (Barkatina et al. 1998).

As mentioned previously, exposures to HCH can result from the ingestion of plants, animals, animal products, milk, and water containing the pesticide. A smaller degree of exposure may result from ingestion of drinking water containing HCH. There is also the possibility of exposure to γ-HCH from medical usage (e.g., shampoos for control of lice and lotion for treatment of scabies). Numerous studies have documented the effects in humans overexposed to γ-HCH through misuse or accidental ingestion of products used to treat head lice (Davies et al. 1983; Jaeger et al. 1984; Lee and Groth 1977). Although some controversy exists as to whether γ-HCH is a safe therapeutic agent when used in accordance with the manufacturers' guidelines, it is clear that most exposures occur through misuse of products (Rasmussen 1980, 1981, 1987). Besides medical usage, children are likely to be exposed to HCH from the ingestion of food containing the pesticide. Based on FDA's Total Diet Analyses, γ-HCH intakes (body weight/day) are 0.8 ng/kg for 6–11-month-old infants, 3.2 ng/kg for 2-year-old toddlers, and 1.5 and 1.4 ng/kg for 14–16-year-old males and females, respectively (Gunderson 1995b). HCH isomers have been detected in the following food types formulated for infants and toddlers: whole milk and other dairy products; meat, fish, and poultry; oils and fats; vegetables; and sugars and adjuncts (Gartrell et al. 1986a).

HCH isomers have also been detected in cow's milk in those countries that still use the chemical as a pesticide. In a study performed in Uganda, Africa, the concentrations of α- HCH, β-HCH, and γ-HCH in cow's milk were 0.002–0.014, 0.003–0.018, and 0.006–0.036 mg/kg milkfat, respectively (Ejobi et al. 1996). Mean levels of HCH isomers analyzed in cow's milk samples from two separate areas in India were 0.0045 and 0.012 mg/kg α-HCH, 0.002 and 0.015 mg/kg γ-HCH, 0.0105 and 0.028 mg/kg β-HCH, and 0.002 and 0.003 mg/kg δ-HCH (Dua et al. 1997). A monitoring study of 192 samples of cow's milk from Mexico revealed 0.001–0.201 mg/kg α-HCH, 0.008–0.253 mg/kg β-HCH, and 0.002–0.187 mg/kg γ-HCH (Waliszewski 1993). HCH isomers have also been detected in buttermilk and butter prepared from cow's milk contaminated with these isomers (Sreenivas et al. 1983).

HCH is bioavailable from soil and can be absorbed both orally and dermally (Duff and Kissel 1996). 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. Some children intentionally eat dirt and most inadvertently ingest dirt by putting fingers or other objects in their mouths while playing outdoors. Thus, they are more likely than adults to be exposed to HCH via ingestion or direct contact of soil contaminated with HCH.

Children may also be exposed to a significant amount of HCH from household dust; parents' work clothes, skin, hair, tools, and other objects removed from the workplace are a likely source of exposure to children. An analysis of environmental contribution to pesticide body burden indicated household dust can be a major source of environmental HCH exposure (Starr et al. 1974), as indicated by elevated γ-HCH levels in blood sera in a pesticide formulator (16.8 ppb) and his wife (5 ppb) in a household in which dust levels measured 5.85 ppb. 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.

Children can be exposed to γ-HCH if it is used as a prescription medication for the treatment of scabies and/or head lice. A study was conducted where nine patients aged 3.5–18 years of age were prescribed a 1% γ-HCH shampoo for the treatment of head lice at label rates, but at longer than label-specified treatment durations. The maximum level of γ-HCH measured in the blood following treatment was 6.13 µg/L (EPA 2002b). This concentration is significantly lower than 320 µg/L, the blood level associated with acute accidental ingestion, which resulted in short-term adverse effects (EPA 2002b). EPA also has published a study on blood levels of γ-HCH in infants and children who had received scabies treatment with 1% topical γ-HCH lotion. In this study, serum concentrations of γ-HCH were determined in infants and children with and without scabies infection following application of the topical

preparation to the body surface area as prescribed by the label. Studies were performed on 20 infected and non-infected patients who averaged 33–64 months of age. The maximum blood level observed in the treated children was reported as 64 µg/L (EPA 2002b).

Analyses of blood samples of 186 children living in an area contaminated with HCH, which was used as an insecticide in Brazil, revealed the presence of α-, γ-, and β-, HCH isomers (Brilhante and Oliveira 1996). The authors reported that 24% of the children showed 0.89 ppb average concentrations of β-HCH in the blood. α- and γ-isomers were detected in only three and one children, respectively, at mean concentrations of 1.8 and 0.95 ppb, respectively. Lipid serum levels of β-, and γ-HCH for children 12 or older were summarized in table 6-4 (CDC 2003).

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

The populations with the most potential for chronic exposure to HCH are workers who either formulate or routinely 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.

Numerous studies have documented the effects in humans overexposed to γ-HCH through misuse or accidental ingestion of products used to treat scabies and head lice (Davies et al. 1983; Jaeger et al. 1984; Lee and Groth 1977). Although some controversy exists as to whether γ-HCH is a safe therapeutic agent when used in accordance with the manufacturers' guidelines, it is clear that most exposures occur through misuse of products (Rasmussen 1980, 1981, 1987). In addition, other studies have described cases in which patients have shown neurotoxic effects following excess exposure or ingestion of pesticides (Harris et al. 1969; Hayes 1976; West 1967).

Exposure to the other isomers of HCH (as in the technical-grade HCH) is limited in the United States as a result of regulations restricting their use. However, persons traveling or living in areas where the use of HCH is legal (e.g., South America, Eastern Europe, and Asia) should be wary of exposure to isomers of HCH through food and drinking water sources (Krauthacker et al. 1986; Radomski et al. 1971a; Saxena et al. 1980, 1981a, 1981b).

6.8 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 the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of HCH.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health 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.

6.8.1 Identification of Data Needs

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 required at this time.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2002, became available in May of 2004. This database is updated yearly and should provide a list of industrial production facilities and emissions.

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 technical-grade HCH was voluntarily canceled in 1976 (EPA 1978). Recent data suggest that the uses and import/export volumes of γ-HCH are decreasing (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 1991g). 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 (HSDB 1993). 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 [Zoetemann et al. 1980]). 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 degradation of HCH in the atmosphere occurs through the reaction with photochemically generated hydroxyl radicals, and half-lives of γ-HCH 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 a major route of exposure for the general population (Gunderson 1988, 1995a, 1995b). Additional information on the absorption of γ-HCH, following ingestion of foods 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. Besides γ-HCH, other isomers of HCH have been detected in adult diet foodstuffs (Gartrell et al. 1986b; Rogers et al. 1995). Additional information on the absorption of these other HCH isomers following ingestion of foods containing residues of these isomers

is needed. 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; Verma and Pillai 1991; Viswanathan et al. 1988). γ-HCH is bioconcentrated to high levels following uptake from surface waters by a number of aquatic organisms (Matsumura and Benezet 1973; Ramamoorthy 1985; Schimmel et al. 1977). Uptake from soils and bioconcentration by plants and terrestrial organisms appears to be limited (Verma and Pillai 1991; Wild and Jones 1992). Limited information suggests that the compound is not biomagnified in terrestrial food chains because of its metabolism by terrestrial organisms (Schmitt et al. 1985). Bioconcentration values in zebra-fish for α-HCH and β-HCH are 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. Reliable monitoring data for the levels of HCH in contaminated media at hazardous waste sites are needed so that the information obtained on levels of HCH in the environment can be used in combination with the known body burden of HCH to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Environmental monitoring data are available predominantly for γ-HCH in air (Atlas and Giam 1988; Knap and Binkley 1991), surface water (Sandhu et al. 1978; Staples et al. 1985), groundwater (Sandhu et al. 1978), soil (Carey et al. 1978; Staples et al. 1985), and foods (FDA 1989b; Gunderson 1988; Kutz et al. 1976). γ-HCH has been detected in air, surface water and groundwater, and sediment and soil. The widespread distribution of HCH isomers in air has been confirmed (Tanabe et al. 1982). Although the use of γ-HCH has been restricted and the use of technical-grade HCH was voluntarily canceled in 1976 (EPA 1978), it is not likely that new environmental measurements will show considerably lower levels of γ-HCH in these media since there are remaining impacts from importing and processing HCH. Therefore, additional information on the levels of γ-HCH and α-, β-, and δ-HCH isomers is needed to assess the current potential human exposure to the chemicals from environmental media, particularly near hazardous waste sites.

Reliable monitoring data for the levels of hexachlorocyclohexane in contaminated media at hazardous waste sites are needed so that the information obtained on levels of hexachlorocyclohexane in the environment can be used in combination with the known body burdens of hexachlorocyclohexane to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. HCH can be detected in the blood (Baumann et al. 1980; Griffith and Blanke 1975; Murphy and Harvey 1985), urine (Murphy and Harvey 1985), adipose tissue (Baumann et al. 1980; EPA 1986d), breastmilk (Takahasi et al. 1981), and semen (Stachel et al. 1989) of exposed individuals. 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., PCBs) could be tested for HCHs content. Additional information is needed on exposure to γ-HCH and 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. The different pathways for exposure of children to HCH have been discussed in Section 6.6. 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 (Nair et al. 1996; Saxena et al. 1981b) and in amniotic fluid and fetal tissues in mice (Srivastava and Raijada 1993). Infants may also be exposed via ingestion of breastmilk and cow's milk. Exposure may also occur via ingestion of water containing HCH, food and animal products, and possibly through incidental ingestion of household dust. 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 (Ginsberg et al. 1977). Adipose tissue is a major storage depot for HCH. Although data from a national human adipose tissue survey exist (EPA 1986d), 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.

Child health data needs relating to susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children's Susceptibility.

Exposure Registries. No exposure registries for HCH were located. This substance is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for sub-registries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

6.8.2 Ongoing Studies

The Federal Research Programs In Progress (FEDRIP 2004), Current Research Information System (CRIS/USDA 2003), and Computer Retrieval of Information on Scientific Projects (CRISP 2003) databases were searched for ongoing projects that may fill some existing data gaps. Carolyn Childress of the U.S. Geological Survey (USGS) is conducting a regional water-quality study for the Research Triangle area of North Carolina that contains monitoring data of chlorinated pesticides including γ-HCH (FEDRIP 2004). Dr. Rebecca Dickhut of the College of William and Mary is conducting long-range transport studies using isotopically labeled γ-HCH in order to distinguish between long-range and short-range sources of persistent organic pollutants (POPs) (FEDRIP 2004). Dr. Y.P. Chin of Ohio State University and Dr. Diane McKnight of the University of Colorado are conducting joint research to determine the level of γ-HCH in Arctic surface waters and the role that dissolved organic matter (DOM) plays in the direct and indirect photolysis of γ-HCH and other POPs in the Arctic (FEDRIP 2004). Dr. E.M. Ostrea is investigating fetal exposure to environmental toxins, including γ-HCH, through the analysis of meconium, cord blood, and neonatal hair attempting to determine the degree of agreement among these three methods (CRISP 2003). Dr. J.A. Bloomquist of Virginia Polytechnic University is investigating the links between insecticide exposure including exposure to γ-HCH (CRIS/USDA 2003).

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring α-, β-, γ-, and δ-HCH, its metabolites, and other biomarkers of exposure and effect to α-, β-, γ-, and δ-HCH. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

7.1 BIOLOGICAL MATERIALS

The α-, β-, γ-, and δ-isomers of HCH, and/or their phenolic metabolites have been measured in biological samples such as adipose tissue, serum, urine, milk, semen, and the brain by gas chromatographic methods listed in Table 7-1.

The most commonly used methods for measuring α-, β-, γ-, and δ-HCH in serum, semen, adipose tissue, and milk are gas chromatography (GC) or high-resolution gas chromatography (HRGC) combined with electron capture detection (ECD) and mass spectrometry (GC/MS) (Barquet et al. 1981; Burse et al. 1990; Butte and Fooken 1990; EPA 1980c; Gupta et al. 1978; LeBel and Williams 1986; Liao et al. 1988; Prapamontol and Stevenson 1991; Saady and Poklis 1990; Stachel et al. 1989; Waliszewski and Szymczynski 1983; Williams et al. 1988). The EPA GC/ECD method is capable of detecting γ-HCH and other HCH isomers in blood serum at the ppb level (EPA 1980c). Using HRGC, method detection limits for measuring HCH isomers in serum and milk are in the sub-ppm to low-ppb range (Butte and Fooken 1990; Prapamontol and Stevenson 1991; Saady and Poklis 1990); recovery and precision are acceptable (Butte and Fooken 1990; Prapamontol and Stevenson 1991; Saady and Poklis 1990). The use of capillary (high-resolution) GC enhances chromatographic separation of compounds with similar retention characteristics (Saady and Poklis 1990). Although GC has also been used in measuring the isomers in blood serum, recovery problems (i.e., low recoveries) have been encountered because of the volatility of the HCH isomers (Burse et al. 1990); sensitivity and precision data were not reported (Burse et al. 1990).

Table 7-1. Analytical Methods for Determining Hexachlorocyclohexane in Biological Samples

Sample matrix	Preparation method	Analytical method	Isomer	Sample detection limit	Percent recovery	Reference
Urine	Hydrolyze sample; acidify; extract with hexane; derivatize for GC/ECD or evaporate to a small volume for TLC	GC/ECD, TLC	Phenolic meta-bolites of γ-HCH	1 ppb (GC/ECD)	95%	Balikova et al. 1988
				1 ppm (TLC)	NR	
Urine	Hydrolyze acidified sample; extract with diethyl ether; concentrate phenol conjugates	GC/ECD		4.9–18.6 ppb	87–119%	Angerer et al. 1981
Serum	Extract and concentrate serum using solid-phase extraction; elute with isooctane; inject	HRGC/ ECD	α-HCH	0.18 ppm	70–75%	Saady and Poklis 1990
			γ-HCH	0.33 ppm		
Serum	Extract serum with organic solvents; sample and acid cleanup on Florisil column; sample cleanup using silica gel chromatography	GC/ECD	α-HCH	NR	57.2–58.2%	Burse et al. 1990
			γ-HCH	NR	47.7–50.4%	
Serum	Extract with hexane	GC/ECD	α-HCH	1 ppb	NR	EPA 1980a
			β-HCH	1 ppb	NR	
			γ-HCH	1 ppb	NR	
Serum	Separate plasma from blood containing anticoagulant	GC/ECD	β-HCH	0.8 ppb	85%	Barquet et al. 1981
Serum	Hexane or hexane-acetone extraction	GC/ECD	α-HCH	NR	82–83%	Gupta et al. 1978
			β-HCH		73–77%	
			γ-HCH		90–96%	
Semen	Liquid-liquid extraction; cleanup with Florisil	GC/ECD	α-HCH	0.02 ppb	72.5%	Stachel et al. 1989
		GC/MS (NCI)	β-HCH	0.32 ppb	94.7%	
Semen	Extract with acetic acid; cleanup with Florisil; elute with petroleum-diethyl ether	GC/ECD	α-HCH	NR	86.3%	Waliszewski and Szymczynski 1983
			β-HCH		101.3%	
			γ-HCH		951.0%	
			δ-HCH		101.6%	
Adipose tissue	Extract with organic solvents; reextract lipids on Florisil column; elute with hexane and concentrate	GC/MS	α-HCH	5–50 ppb	>100%	Liao et al. 1988
			β-HCH		80–100%	

Table 7-1. Analytical Methods for Determining Hexachlorocyclohexane in Biological Samples

Sample matrix	Preparation method	Analytical method	Isomer	Sample detection limit	Percent recovery	Reference
Adipose tissue	Extract fat from tissue with acetone-hexane; fractionate from fat by gel permeation chromatography with methylene chloride-cyclohexane; cleanup on Florisil column; inject	HRGC/ECD	α-HCH	1.2 ppb	>89	LeBel and Williams 1986
		GC/MS	γ-HCH	1.4 ppb	>88%	
			β-HCH	3.0 ppb	>91%	
Adipose tissue	Grind sample; isolate fat, extract residue in petroleum ether	GC/ECD	α-HCH	10 ppb	NR	EPA 1980a
			β-HCH	20 ppb	NR	
			γ-HCH	20 ppb	NR	
Adipose tissue	Grind tissue; extract with acetonitrile and acetone; evaporate; extract with hexane	GC/ECD	β-HCH	80 ppb	98%	Barquet et al. 1981
Milk	Solvent extract with ethyl-acetate-methanol-acetone; cleanup and concentrate using solid-phase extraction; elute with isooctane	HRGC/ECD	α-HCH	0.5 ppb	83–105%	Prapamontol and Stevenson 1991
			β-HCH	1 ppb	91–119%	
			γ-HCH	0.5 ppb	80–96%	
Milk	Homogenize sample; extract and cleanup using silica gel; elute with hexane/dichloromethane; concentrate; inject	HRGC/ECD	α-HCH	0.002 ppb	125%	Butte and Fooken 1990
			β-HCH	0.009 ppb	114%	
			γ-HCH	0.004 ppb	125%	
Brain	Homogenize sample in hexane; centrifuge; inject	GC/MS (NCI)	γ-HCH and metabolites	3 pg/L	NR	Artigas et al. 1988b

α-HCH = alpha-hexachlorocyclohexane; β-HCH = beta-hexachlorocyclohexane; γ-HCH = gamma-hexachlorocyclohexane; δ-HCH = delta-hexachlorocyclohexane; ECD = electron capture detection; GC = gas chromatography; HRGC = high-resolution gas chromatography; MS = mass spectrometry; NCI = negative chemical ionization; NR = not reported; TLC = thin-layer chromatography

GC/ECD combined with identification by GC/MS is a reliable method for quantitation and identification of HCH isomers in semen (Stachel et al. 1989); sensitivity of GC/ECD is in the sub-ppb range with acceptable recoveries (Stachel et al. 1989). HRGC/ECD and GC/MS have also been used for detection and identification of HCH isomers in adipose tissue (LeBel and Williams 1986; Liao et al. 1988). During sample preparation, the use of gel permeation chromatography is effective for separation of the isomers from adipose tissue (LeBel and Williams 1986). This method is sensitive (low- to sub-ppb range) and has good recoveries (>88%) and precision (≤0.12% RSD). Although sensitivity is not quite as good as that of GC/ECD, GC/MS is more specific. GC/MS is usually used as a confirmatory method, but it can be reliably used alone and produces excellent recoveries and good precision (Liao et al. 1988).

γ-HCH and its metabolites have also been detected in brain tissue using GC/MS in the chemical ionization mode (Artigas et al. 1988a). The use of GC/MS with negative ion chemical ionization (NICI) is preferred over electron impact mass spectrometry (EIMS) because the sensitivity using NICI is orders of magnitude better than with EIMS. GC/MS with NICI is also more selective than GC/MS with EI or GC/ECD (Artigas et al. 1988a). Another advantage of GC/MS with NICI is that identification and quantitation are performed without any purification or extraction procedures (Artigas et al. 1988a).

The phenolic metabolites of γ-HCH and the other HCH isomers have been measured in urine samples using GC/ECD (Angerer et al. 1981; Balikova et al. 1988). Sensitivity for this method is in the low-ppb range and recovery is excellent (95%); however, precision was not reported (Balikova et al. 1988). Thin layer chromatography (TLC) has also been used in conjunction with GC/ECD for identification of HCH isomers (Balikova et al. 1988). Although TLC does not achieve the same sensitivity (ppm range) as GC/ECD, sensitivity can be increased by extraction of a larger volume of urine. The combination of GC and TLC was reported to be a reliable confirmation tool for identifying compounds (Balikova et al. 1988). Angerer et al. (1981) developed a sensitive and specific gas chromatographic method for the simultaneous detection of 10 chlorinated phenols that appear in the urine of individuals exposed to γ-HCH. However, the study authors noted that both HCH and chlorobenzene compounds are commonly used as pesticides and that both are metabolized to chlorophenols. This suggests that detection of these metabolites does not distinguish between HCH, chlorobenzene, or pentachlorophenol (PCP) exposure. Edgerton et al. (1979) detected chlorinated phenol metabolites of HCH and PCP in the urine of experimental animals and exposed individuals by using GC/ECD. Discrimination between HCH and PCP exposure was possible through comparisons of metabolite profiles. However, detection of PCP in the urine may also be an indication of exposure to PCP or other compounds similar to HCH.

7.2 ENVIRONMENTAL SAMPLES

HCH residues are present in the environment because γ-HCH is used as an insecticide on a wide variety of vegetables, fruits, field crops, and on uncultivated land. The most commonly used methods for measuring HCH isomers in environmental samples is GC or HRGC combined with ECD or MS. Table 7-2 presents details on selected analytical methods.

HCH isomers have been measured in air using GC/ECD, HRGC/ECD, or GC with dual detection by ECD and electrolytic conductivity detection (ELCD) (Durell and Sauer 1990; Kurtz and Atlas 1990; NIOSH 1984; Stein et al. 1987; Zaranski et al. 1991). Polyurethane foam or Florisil adsorbent tubes are suitable for collecting air samples. The use of a simultaneous dual-column, dual-detector method (ECD and ELCD) was found to reduce the risk of false positive identifications without increasing the cost or time of analysis (Durell and Sauer 1990). Both columns were able to separate a large number of analytes with good reproducibility. Although ECD is more sensitive for halogenated compounds and has a lower detection limit (sub-ppb to low-ppm) than ELCD (low ppb), ELCD can greatly reduce matrix interferences. Precision and recovery were not reported for either detector (Durell and Sauer 1990; Kurtz and Atlas 1990).

The most commonly used methods for detecting HCH isomers in water (e.g., surface water, drinking water, sea water, groundwater, waste water, and rain) include GC or HRGC combined with ECD or MS (Allchin 1991; Barquet et al. 1981; Durell and Sauer 1990; EPA 1984, 1986a; Goosens et al. 1990; Kurtz and Atlas 1990; Lopez-Avila et al. 1989a, 1990b; Reding 1987; van der Hoff et al. 1991). To improve sample extraction and cleanup, the most current EPA method (Method 8120) used commercially available disposable Florisil cartridges instead of conventional Florisil cleanup (Lopez-Avila et al. 1989a). The disposable Florisil cartridges were simpler to use, shortened the analysis time, and reduced the overall cost of the analysis. The excellent precision, accuracy, and sensitivity (ppt range) of the results indicated that the revised method is reliable (Lopez-Avila et al. 1989a). Automated solid-phase extraction cartridges filled with silica and coupled on-line to GC/ECD have been effectively used to measure HCH isomers in water at low levels (ppt) (van der Hoff et al. 1991). This method is efficient and reproducible, with good recovery (>95%) and precision (<12% coefficient of variance [CV]) (van der Hoff et al. 1991). On-line liquid-liquid extraction coupled with HRGC/ECD is also a sensitive (ppb level) and reliable method (Goosens et al. 1990). A method validation study, conducted on EPA Method 508, for determining HCH isomers in finished drinking water using GC/ECD indicated the method was reliable, repeatable, and reproducible (Lopez-Avila et al. 1990b). Precision was good; recovery (>90%) was

Table 7-2. Analytical Methods for Determining Hexachlorocyclohexane in Environmental Samples

Sample matrix	Preparation method	Analytical method	Isomer	Sample detection limit	Percent recovery	Reference
Air	Collect air using filters and polyurethane foam; Soxhlet extraction; column cleanup and isolation; concentration; dual column detection	HRGC/ ECD		0.9 pg/µL	NR	Durell and Sauer 1990
		HRGC/ ELCD		15.3 pg/µL	NR	
Air	Collect sample in Florisil adsorbent tubes; elute with methylene chloride in pentane; concentrate in Kuderna-Danish evaporative concentrator; solvent exchange to hexane	HRGC/ ECD		Low pg/m^3	NR	Kurtz and Altas 1990
Air	Trap in isooctane	GC/ECD		3 µg/sample	NR	NIOSH 1984 (method 5502)
Air	Adsorb air sample on Florisil; elute with 10% 2-propanol in hexane	GC/ECD	α-HCH	0.25 pg/m^3	83%	Stein et al. 1987
			β-HCH		88%	
			γ-HCH		81%	
			δ-HCH		87%	
Surface water	Extract with hexane; concentrate; cleanup using automated solid-phase extraction technique	GC/ECD	α-HCH	7 ppt	95.6%	Van der Hoff et al. 1991
			β-HCH	10 ppt	98.2%	
			γ-HCH	7 ppt	95.6%	
			δ-HCH	6 ppt	95.9%	
Water	Extract twice with methylene chloride; dry with anhydrous sodium sulfate; concentrate; add hexane and concentrate by evaporation; cleanup on disposable Florisil cartridge and elute with hexane-acetone	GC/ECD	α-HCH	11 ppt	96%	Lopez-Avila et al. 1989a (modified EPA method 8120)
			β-HCH	31 ppt	103%	
			γ-HCH	23 ppt	96%	
			δ-HCH	20 ppt	103%	
Drinking water	Extract with methylene chloride; solvent exchange to methyl *tert*-butyl ether; concentrate	GC/ECD	α-HCH	0.025 ppb	94.6%	Lopez-Avila et al. 1989a (modified EPA method 508)
			β-HCH	0.010 ppb	93.4%	
			γ-HCH	0.010 ppb	94.2%	
			δ-HCH	0.015 ppb	92.0%	

Table 7-2. Analytical Methods for Determining Hexachlorocyclohexane in Environmental Samples

Sample matrix	Preparation method	Analytical method	Isomer	Sample detection limit	Percent recovery	Reference
Drinking water	Stripping for water with an inert gas-helium	HRGC/ ECD		0.003 ppb (method 505) 0.006 ppb (method 508)	93–130%	Reding 1987 (EPA methods 505, 508)
Drinking water	Separation with Na_2SO_4; extraction CH_3Cl_2	GC/ECD	β-HCH	0.025 ppb	88%	Barquet et al. 1981
Water and waste water	Extraction with methylene chloride	GC/ECD	α-HCH	0.003 ppb	NR	EPA 1984 (method 608)
			β-HCH	0.006 ppb	NR	
			γ-HCH	0.004 ppb	NR	
			δ-HCH	0.009 ppb	NR	
Water and waste water	Extraction with methylene chloride	GC/MS	β-HCH	4.2 ppb	NR	EPA 1984 (method 625)
			δ-HCH	3.1 ppb	NR	
Water and waste water	Extraction with methylene chloride	GC/ECD	α-HCH	0.003 ppb	NR	EPA 1986b (method 8080)
			β-HCH	0.006 ppb	NR	
			γ-HCH	0.004 ppb	NR	
			δ-HCH	0.009 ppb	NR	
Sea water	Extract twice with hexane; dry over anhydrous sodium sulfate; concnetrate; cleanup using column chormatography with 5% deactivated alumina; concentrate	GC/ECD	α-HCH γ-HCH	1 ppt	>85%	Allchin 1991
Ground-water	On-line liquid-liquid extraction of sample with isooctane and separation of aqueous and organic phases by a sandwich phase separator	HRGC/ ECD	α-HCH δ-HCH	0.1 ppb	112% 119%	Goosens et al. 1990
Sea water, rain	Liquid-liquid extraction; column cleanup and isolation; concnetration	HRGC/ ECD	Lindane	0.9 ppb	NR	Durrell and Sauer 1990
		HRGC/ ELCD		15.3 ppb	NR	
Sea water	Extract with methylene chloride; solvent exchange to hexane; cleanup on Florisil	HRGC/ ECD	α-HCH γ-HCH	Low pg/L	NR	Kurtz and Atlas 1990

Table 7-2. Analytical Methods for Determining Hexachlorocyclohexane in Environmental Samples

Sample matrix	Preparation method	Analytical method	Isomer	Sample detection limit	Percent recovery	Reference
Soil	Extract with supercritical carbon dioxide or carbon dioxide modified with 10% methanol	GC/ECD GC/MS	α-HCH β-HCH γ-HCH δ-HCH	NR	77.43–93.6% 79.28–93.6% 80.63–121% 72.4–103%	Lopez-Avila et al. 1990a
Soil	Dry sample with anhydrous sodium sulfate; extract twice with methylene chloride-acetone by sonication; filter; dry; concentrate; cleanup on disposable Florisil cartridge and elute with hexane-acetone	GC/ECD	α-HCH β-HCH γ-HCH δ-HCH	<40 ng/L	96% 103% 96% 103%	Lopez-Avila et al. 1989b (modified EPA method 8120)
Soil	Equilibrate with water; extract with acetone and hexane (1:1); wash with water and sodium chloride disiccate with anhydrous sodium sulfate; concentrate; add hexane; cleanup with SPE Florisil cartridge	GC	Lindane	5 ppm	108%	Noegrohati and Hammers 1992a
Soil, sediment, waste sludge	Extract sample with methylene chloride-acetone by sonication; cleanup using gel permeation chromato-graphy processing of extracts dissolved in 1+1 butyl chloride-methylene chloride or 100% methylene chloride	HRGC/ ECD, HRGC/MS	γ-HCH	NR	83–91%	Czuczwa and Alford-Stevens 1989
Soil	Hexane-acetone extraction	GC/ECD		NR	NR	AOAC 1984 (method 29.013)
Soil	Extraction with methylene chloride followed by cleanup on Florisil column	GC/ECD, HSD	α-HCH β-HCH δ-HCH δ-HCH	3.0 ppm 6.0 ppm 4.0 ppm 9.0 ppm	NR NR NR NR	EPA 1986b (method 8080)

Table 7-2. Analytical Methods for Determining Hexachlorocyclohexane in Environmental Samples

Sample matrix	Preparation method	Analytical method	Isomer	Sample detection limit	Percent recovery	Reference
Sediment	Extract using vapor phase distillation technique; dry isooctane extract; concentrate	GC/ECD	α-HCH γ-HCH	2.42 ppb 4.98 ppb	76% 40%	Schuphan et al. 1990
Milk	Selective extraction of HCH isomers on solid-matricx disposable column by means of acetonitrile-saturated light petroleum; concnetrate; cleanup extract on Florisil minicolumn	GC/ECD	α-HCH γ-HCH β-HCH	NR	94% 105% 113%	DiMuccio et al. 1988
Milk	Extract fortified milk samples with acetone and n-hexane; centrifuge; evaporate organic phase; dissolve residues in ether	GC/ECD	α-HCH β-HCH γ-HCH δ-HCH	NR	95.7% 99.9% 83.4% 89.7%	Kapoor et al. 1981
Soil, water, wheat, rice, beans	Extract HCH from sample by activated charchal; dechlorination of HCH to benzene; nitration of benzene to m-dinitro-benzene; reduction to m-phenylene diamine; diazotization and coupling to form azo dye	Spectro-photo-metry	γ-HCH	NR	≥89%	Raju and Gupta 1988
Mussels	Extract with acetonitrile; separate form coextractives by liquid-liquid partition between acetonitrile and water/hexane; cleanup on Sep-Pak Florisil cartridge; elute in second eluate with 15% ethyl ether in hexane	GC/ECD	Lindane	0.02 µg/kg	92–102%	Muino et al. 1991
Fish	Extract residue using one-step matrix solid phase dispersion combined with Florisil column cleanup; inject into GC	GC/ECD	Lindane	10 ng/g	82%	Long et al. 1991a

Table 7-2. Analytical Methods for Determining Hexachlorocyclohexane in Environmental Samples

Sample matrix	Preparation method	Analytical method	Isomer	Sample detection limit	Percent recovery	Reference
Fish	Petroleum ether extraction	GC/ECD		NR	NR	AOAC 1984 (method 20.029)
Fish	Combine with anhydrous Na_2SO_4; extract with petroleum ether/ethyl acetate; separate lipids with GPC; solvent exchange to isooctane; add dry N_2 gas	GC/MS (NCI)	Lindane	1.6 ppb	115%	Schmidt and Hesselberg 1992
Fruits and vegetables	Extract samples with acetonitrile; partition with sodium chloride saturated aqueous solution; concentrate	HRGC/MS	α-HCH β-HCH γ-HCH δ-HCH	0.05 µg/g (all isomers)	88% 93% 93% 112%	Liao et al. 1991
Vegetables	Extract with methanol; partition with sodium chlrodie and hexane; wash hexane layer with sodium chloride solution; disccate with anhydrous sodium sulfate; concentrate; cleanup on SPE Sil-Florisil cartridge	GC	Lindane	ppb range	87–137%	Neogrohati and Hammers 1992a
Beef fat	Extract residue using one-step matrix solid phase dispersion combined with Florisil column cleanup; inject into GC	GC/ECD	Lindane	Low ppb	85%	Long et al. 1991b
Animal fat and dairy products	For dairy products, extract fat with hexane; for animal fat, melt sample and remove fat; cleanup with gel permeation chromato-graphy; further cleanup with Florisil if necessary; inject	GC/ECD	HCH	Low to sub ppm	82%	Venant et al. 1989
Root vegetables and dairy products	Extract with CO_2 collect with *n*-hexane/dichloro-methane; evaporate; dissolve in *n*-hexane	GC/ECD	α-HCH γ-HCH	NR NR	10–100% 12–98%	Bernal et al. 1992
Beef	Extract with acetone-hexane; cleanup on Florisil column, inject	GC/ECD	β-HCH	Sub ppm	78.1–88.3%	Tonogai et al. 1989

Table 7-2. Analytical Methods for Determining Hexachlorocyclohexane in Environmental Samples

Sample matrix	Preparation method	Analytical method	Isomer	Sample detection limit	Percent recovery	Reference
Tobacco	Soak in acetonitrile water mixture, extract with petroleum ether; shake with H_2SO_4	GC/ECD	α-HCH	1.0 ppm	98.2%	Waliszewksi and Szymczynski 1986
			β-HCH	2.0 ppm	92.9%	
			γ-HCH	2.0 ppm	96.2%	
			δ-HCH	2.0 ppm	88.2%	
Wood (rasped)	Extract with toluene; sonicate and centrifuge; inject	GC/MS		10 ppb	NR	Butte and Walker 1992

α-HCH = alpha-hexachlorocyclohexane; β-HCH = beta-hexachlorocyclohexane; γ-HCH = gamma-hexachlorocyclohexane; δ-HCH = delta-hexachlorocyclohexane; CH_2Cl_2 = methylene chloride; ECD = electron capture detection; ELCD = electrolytic conductivity detector; GC = gas chromatography; GPC = gas permeation chromatography; H_2SO_4 = sulfuric acid; HRGC = high-resolution gas chromatography; HSD = halogen specific detector; MS = mass spectrometry; Na_2SO_4 = sodium sulfate; NCI = negative chemical ionization; NR = not reported; SPE = solid phase extraction

excellent. Sensitivity was in the ppb range (Lopez-Avila et al. 1990b). The EPA-established analytical test procedures to analyze water, waste water, and drinking water samples use GC coupled with MS. EPA methods 608 and 625 are recommended to detect γ-HCH and other HCH isomers in surface water and municipal and industrial discharges (EPA 1984).

GC/ECD, HRGC/ECD, and HRGC/MS are the most commonly used methods to measure HCH isomers in soil, sediments, and solid wastes (AOAC 1984; Czuczwa and Alford-Stevens 1989; EPA 1986b; Lopez-Avila et al. 1989b, 1990a; Noegrohati and Hammers 1992b; Schuphan et al. 1990). More efficient extraction of the isomers from soil was obtained using a disposable Florisil cartridge (modified EPA Method 8120) prior to detection by GC/ECD (Lopez-Avila et al. 1989b). The method yielded excellent recoveries (>95%), and sensitivity was in the ppt range. Sample cleanup using a disposable solid phase extraction (SPE) cartridge with detection by GC yielded a higher recovery (108%) with excellent precision (4% CV). Although sample detection limits were not reported, sensitivity was in the ppm range (Noegrohati and Hammers 1992b). Sample cleanup using gel permeation chromatography and detection and identification by HRGC/ECD and HRGC/MS resulted in good recoveries (83–91%) and good precision (≤5.1% relative standard deviation [RSD]) (Czuczwa and Alford-Stevens 1989); sensitivity was not reported (Czuczwa and Alford-Stevens 1989). A new technique, supercritical fluid extraction (SFE), has been applied to the analysis of soil samples (Lopez-Avila et al. 1990a). Recovery (>75%) and precision (<26% CV) are adequate. Because this is a relatively new method, the cost is higher than other accepted techniques. The vapor phase extraction technique has also been applied to the analysis of trace residues of HCH in sediments (Schuphan et al. 1990). The efficiency of this method was compared with conventional Soxhlet extraction and Florisil cleanup procedures. The results showed that recovery using the Soxhlet extraction method (73–81%) was better than with vapor-phase extraction (40–76%). The low recovery of γ-HCH (40%) was due to sample loss during concentration of the iso-octane extract (Schuphan et al. 1990); sensitivity was in the low-ppb range; precision was excellent (0.01–0.03% coefficient of variation).

GC/ECD and HRGC/ECD are the most commonly used methods for measuring HCH isomers in milk (DiMuccio et al. 1988; Kapoor et al. 1981), dairy products (Bernal et al. 1992; Venant et al. 1989), seafood (mussels and fish) (AOAC 1984; Long et al. 1991a; Muino et al. 1991; Schmidt and Hesselberg 1992), fruits and vegetables (Liao et al. 1991; Noegrohati and Hammers 1992), beef (Tonogai et al. 1989), and beef fat (Long et al. 1991b). Gel permeation chromatography is a suitable method for the cleanup of HCH residues in animal fats and dairy products (Venant et al. 1989); recoveries are good (82%). Although specific detection limits were not reported, sensitivity is in the low-to-sub-ppm range.

Additional cleanup with Florisil is needed when residue levels are below 0.1 ppm; precision was not reported. High-pressure soxhlet extraction coupled with Florisil column cleanup yielded recoveries up to 100% for α-HCH and γ-HCH in butter, if pressure, time, and sample volume in the extractor were optimized; detection limits and precision values were not reported. This method has also been used to detect γ-HCH residues in potatoes with similar recoveries (Bernal et al. 1992). A reliable and reproducible method has been developed to determine HCH residues in milk (DiMuccio et al. 1988). The procedure involves a single-step, selective extraction of residues from milk on a solid-matrix disposable column, clean-up with Florisil, and detection by GC/ECD. Although specific detection limits were not reported, sensitivity is in the low-ppb range. With this extraction procedure, the HCH residues are more readily extracted than milk lipids, and the addition of a small amount of acetonitrile to the milk significantly improved recoveries without increasing the amount of fat in the extracts (diMuccio et al. 1988). A reliable, rapid screening technique for extraction of residues from a complex biological matrix such as fat uses matrix solid-phase dispersion (MSPD) extraction, Florisil column cleanup, and detection by GC/ECD (Long et al. 1991a, 1991b). This method has been used to measure HCH residues in beef fat and fish. Recovery (82–85%) is good; sensitivity is in the low-ppb range. The MSPD method overcomes many of the complications associated with traditional pesticide isolation techniques because it uses small sample volumes and involves few steps (Long et al. 1991a, 1991b). GC/MS with negative ion chemical ionization (NCI) with GPC cleanup is a rapid, accurate, and simple method to quantify γ-HCH in fish. Recoveries were excellent (115%) with good precision (8.9% RSD), and a detection limit of 1.6 ppb (Schmidt and Hesselberg 1992). An HRGC/MS screening method has been developed for the determination of pesticide residues in a variety of crop samples (fruits and vegetables) (Liao et al. 1991). This technique is a useful tool because it offers simultaneous detection and confirmation, which are not provided by ECD. This method, however, lacks the sensitivity achieved by ECD. Spectrophotometry has been used to measure HCH isomers in cereals (e.g., wheat, rice, and beans) with good recoveries (≥89%) (Raju and Gupta 1988). This technique has also been used for other matrices such as soil and water (Raju and Gupta 1988). An accurate and simple extraction and cleanup method has been developed for capillary GC analysis of γ-HCH in vegetables. The sample was extracted with methanol and cleanup was executed on disposable SPE cartridges. Recoveries ranged from 87 to 137% (average 100%) with good precision (CV ≤5%). Although no specific detection limits were reported, sensitivity is expected to be in the ppb range (Noegrohati and Hammers 1992b).

HCH residues have also been detected in tobacco using GC/ECD (Waliszewski and Szymczynski 1986). Sensitivity is in the low-ppm range and recovery is excellent (88–98%) (Waliszewski and Szymczynski 1986).

GC/MS has been used to determine γ-HCH residues in wood preserving fluids on the surface of wood; the detection limit is 10 ppb. No recovery or precision values were reported (Butte and Walker 1992).

7.3 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 α-, β-, γ-, and δ-HCH is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of α-, β-, γ-, and δ-HCH.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health 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.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. Methods are available for measuring HCH residues and/or their metabolites in blood serum (Barquet et al. 1981; Burse et al. 1990; Gupta et al. 1978; EPA 1980c; Saady and Poklis 1990), urine (Angerer et al. 1981; Balikova et al. 1988), semen (Stachel et al. 1989; Waliszewski and Szymczynski 1983), adipose tissue (Barquet et al. 1981; EPA 1980c; LeBel and Williams 1986; Liao et al. 1988), breastmilk (Butte and Fooken 1990; Prapamontol and Stevenson 1991), and brain tissue (Artigas et al. 1988a). However, examination of blood and urine is most frequently conducted to determine exposure because of the ease of sample collection with these media. The available methods are accurate and reliable for most of the media. However, sensitivity and precision data for measuring HCH residues in serum are needed. Although available methods can detect and quantify background levels of HCH in the population, there is no information to quantitatively correlate levels in these fluids with exposure levels.

Additional quantitative information regarding the relationship between body and environmental levels of HCH might allow investigators to predict environmental exposure levels from measured body levels.

Methods are available to detect the chlorinated phenol metabolites present in the urine as a result of exposure to HCH (Angerer et al. 1981; Balikova et al. 1988). However, similar metabolites are detected following exposure to other pesticides. The identification of a specific urinary metabolite of HCH alone (e.g., chlorophenol) would not allow investigators to determine whether an individual has been exposed to HCH.

Effect. The individual isomers of HCH can be detected in serum, urine, adipose tissue, and semen of exposed individuals as indicated above in Section 3.8.1 Biomarkers of Exposure and Effect. Since no quantitative correlation has been made between body levels of HCH and adverse health effects based on existing data, we do not know if the methods are sensitive enough to measure levels at which biological effects occur. Further studies need to be undertaken to quantitatively correlate body levels resulting from HCH exposure and the occurrence of specific adverse health effects.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods are available to detect HCH in air (Durell and Sauer 1990; Kurtz and Atlas 1990; NIOSH 1984; Stein et al. 1987; Zaranski et al. 1991), water (Allchin 1991; Barquet et al. 1981; Durell and Sauer 1990; EPA 1984, 1986a; Goosens et al. 1990; Kurtz and Atlas 1990; Lopez-Avila et al. 1989a, 1990b; Reding 1987; van der Hoff et al. 1991), soil (AOAC 1984; Czuczwa and Alford-Stevens 1989; EPA 1986b; Lopez-Avila et al. 1989a, 1990b; Noegrohati and Hammers 1992a; Schuphan et al. 1990), food (AOAC 1984; Bernal et al. 1992; Liao et al. 1991; Long et al. 1991a, 1991b; Muino et al. 1991; Noegrohati and Hammers 1992b; Schmidt and Hesselberg 1992; Tonogai et al. 1989; Venant et al. 1989), milk (DiMuccio et al. 1988; Kapoor et al. 1981), tobacco (Waliszewski and Szymczynski 1986), and wood preserving fluid (Butte and Walker 1992). These methods are sensitive enough to measure background levels in environmental media. The precision, accuracy, reliability, and specificity of these methods are sufficiently documented. Research investigating the relationship between levels measured in air, water, soil, and food and observed health effects could increase our confidence in existing methods and/or indicate where improvements are needed.

7.3.2 Ongoing Studies

The Federal Research Programs In Progress (FEDRIP 2004), Current Research Information System (CRIS/USDA 2003), and Computer Retrieval of Information on Scientific Projects (CRISP 2003) databases were searched for ongoing projects that may fill some existing data gaps.

8. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding α-, β-, δ-, γ-, and ε-HCH in air, water, and other media are summarized in Table 8-1.

Five oral MRLs have been derived for the α-, β-, and γ-HCH isomers of HCH, as summarized below and detailed in Section 2.3 and Appendix A.

An MRL of 0.008 mg/kg/day was derived for chronic-duration (365 days and longer) oral exposure to α-HCH. The chronic oral MRL for α-HCH is based on a NOAEL of 0.8 mg/kg/day and LOAEL of 3.5 mg/kg/day for liver effects in rats (Fitzhugh et al. 1950), and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

An MRL of 0.05 mg/kg/day was derived for acute-duration (14 days or less) oral exposure to β-HCH. This MRL is based on a NOAEL of 4.5 mg/kg/day and LOAEL of 22.5 mg/kg/day for ataxia, progressive inactivity, and coma in rats exposed to β-HCH for 2 weeks (Van Velsen et al. 1986), and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

An MRL of 0.0006 mg/kg/day was derived for intermediate-duration oral exposure to β-HCH (Van Velsen et al. 1986). This MRL is based on a minimal LOAEL of 0.18 mg/kg/day for liver effects in rats (Van Velsen et al. 1986) and an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

An MRL of 0.003 mg/kg/day was derived for acute-duration oral exposure to γ-HCH (lindane). This MRL is based on a minimal LOAEL of 1 mg/kg/day for reproductive effects in male offspring of rats exposed during lactation (Dalsenter et al. 1997b), and an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

An MRL of $1x10^{-5}$ mg/kg/day was derived for intermediate-duration oral exposure to γ-HCH. This MRL is based on a LOAEL of 0.012 mg/kg/day for immunological/lymphoreticular effects in mice (Meera et al. 1992), and an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

Table 8-1. Regulations and Guidelines Applicable to Hexachlorocyclohexane and Hexachlorocyclohexane Isomers

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification		IARC 2003
	HCH (including isomers)	Group 2B[a]	
WHO	Drinking water guideline		WHO 1993
	γ-HCH	2.0 µg/L	
	Temporary ADI		WHO 1998
	γ-HCH	0–0.001 mg/kg bw	
	Proposed drinking water guideline		
	γ-HCH	0.3 µg/L	
NATIONAL			
Regulations and Guidelines:			
a. Air:			
ACGIH	TLV (8-hour TWA)		ACGIH 2003
	γ-HCH[b]	0.5 mg/m^3	
NIOSH	REL (10-hour TWA)		NIOSH 2003
	γ-HCH[c]	0.5 mg/m^3	
	IDLH	50 mg/m^3	
OSHA	PEL (8-hour TWA) for general industry		OSHA 2003a 29 CFR 1910.1000, Table Z-1
	γ-HCH[d]	0.5 mg/m^3	
	PEL (8-hour TWA) for construction industry		OSHA 2003c 29 CFR 1926.55, Appendix A
	γ-HCH[d]	0.5 mg/m^3	
	PEL (8-hour TWA) for shipyard industry		OSHA 2003b 29 CFR 1915.1000
	γ-HCH[d]	0.5 mg/m^3	
USC	Hazardous air pollutant	γ-HCH	USC 2003 42 USC 7412
b. Water			
EPA	Drinking water health advisories for γ-HCH		EPA 2002a
	1-day (10-kg child)	1.0 mg/L	
	10-day (10-kg child)	1.0 mg/L	
	DWEL[e]	0.01 mg/L	
	Lifetime[f]	2.0x10^{-4} mg/L	
	Hazardous substance designation in accordance with Section 311 (b)(2)(A) of the Clean Water Act	γ-HCH	EPA 2003p 40 CFR 116.4
	Interim primary drinking water standard		EPA 2003f 40 CFR 265, Appendix III
	γ-HCH	0.004 mg/L	

Table 8-1. Regulations and Guidelines Applicable to Hexachlorocyclohexane and Hexachlorocyclohexane Isomers

Agency	Description	Information			Reference
NATIONAL *(cont.)*					
EPA	Lifetime cancer risks (oral) in water (µg/L)	10^{-4}	10^{-5}	10^{-6}	IRIS 2005
	HCH (technical)	2.0	0.2	0.02	
	α-HCH	0.6	0.06	0.006	
	β-HCH	2.0	0.2	0.02	
	MCL for criteria for classification of solid waste disposal facilities and practices				EPA 2003a 40 CFR 257, Appendix I
	γ-HCH	0.004 mg/L			
	Pollutants of initial focus of the Great Lakes Water Quality Initiative; pollutants that are bioaccumulative chemicals of concern	HCH (technical) α-HCH β-HCH δ-HCH γ-HCH			EPA 2003q 40 CFR 132, Table 6
	Primary drinking water standards (MCL)				EPA 2003i 40 CFR 141.61
	γ-HCH	2.0×10^{-3} mg/L			
	Primary drinking water standards (MCLG)				EPA 2003h 40 CFR 141.50
	γ-HCH	2.0×10^{-3} mg/L			
	Reportable quantity of hazardous substances designated pursuant to Section 311 of the Clean Water Act				EPA 2003j 40 CFR 117.3
	γ-HCH	1 pound			
c. Food					
EPA	Residue Tolerances for γ-HCH				EPA 2003n 40 CFR 180.133
	Cattle, goat, horse, and sheep (fat of meat)	7 ppm			
	Hog (fat of meat)	4 ppm			
	Cucumber, lettuce, melon, mushroom, pumpkin, squash, summer, and tomato	3 ppm			
	Apple, apricot, asparagus, avocado, broccoli, Brussels sprouts, cabbage, cauliflower, celery, cherry, collards, eggplant, grape, guava, kale, kohlrabi, mango, mustard greens, nectarine, okra, onion (dry bulb only), peach, pear, pepper, pineapple, plum, prune, quince, spinach, strawberry, and Swiss chard	1 ppm			

Table 8-1. Regulations and Guidelines Applicable to Hexachlorocyclohexane and Hexachlorocyclohexane Isomers

Agency	Description	Information		Reference
NATIONAL *(cont.)*				
EPA	Residue Tolerances for γ-HCH			EPA 2003n
	Pecans	0.01 ppm		40 CFR 180.133
FDA	Bottled drinking water allowable level			FDA 2003 21 CFR 165.110
	γ-HCH	$2.0x10^{-3}$ mg/L		
d. Other				
ACGIH	Carcinogenicity classification			ACGIH 2003
	γ-HCH	A3[g]		
EPA	Carcinogenicity classification			IRIS 2005
	HCH-technical	B2[h]		
	α-HCH	B2[h]		
	β-HCH	C[i]		
	δ-HCH	D[j]		
	ε-HCH	D[j]		
	γ-HCH	Not available		
	γ-HCH	Suggestive evidence[k]		EPA 2002b
	RfD			IRIS 2005
	HCH-technical	Not available		
	α-HCH	Not available		
	β-HCH	Not available		
	δ-HCH	Not available		
	ε-HCH	Not available		
	γ-HCH	$3.0x10^{-4}$ mg/kg/day		
	Community right-to-know; release report; effective date of reporting			EPA 2003o 40 CFR 372.65
	α-HCH	01/01/95		
	γ-HCH	01/01/87		
	Extremely hazardous substance for (γ-HCH)			EPA 2003d 40 CFR 355, Appendix A
	Reportable quantity	1 pound		
	Threshold planning quantity	1,000/10,000 pounds		
	Identification and listing of hazardous waste; maximum concentration for the toxicity characteristic			EPA 2003e 40 CFR 261.24
	γ-HCH	0.4 mg/L		
	Land disposal restrictions; universal treatment standards	Waste water	Non-waste water	EPA 2003g 40 CFR 268.48
	α-HCH	$14x10^{-3}$ mg/L	0.066 mg/kg	
	β-HCH	$14x10^{-3}$ mg/L	0.066 mg/kg	
	δ-HCH	0.023 mg/L	0.066 mg/kg	
	γ-HCH	0.0017 mg/L	0.066 mg/kg	

Table 8-1. Regulations and Guidelines Applicable to Hexachlorocyclohexane and Hexachlorocyclohexane Isomers

Agency	Description	Information		Reference
NATIONAL *(cont.)*				
EPA	Municipal solid waste landfills; hazardous constituents	Suggested method	PQL (µg/L)	EPA 2003b 40 CFR 258, Appendix II
	α-HCH	8080	0.05	
		8270	10	
	β-HCH	8080	0.05	
		8270	20	
	δ-HCH	8080	0.1	
		8270	20	
	γ-HCH	8080	0.05	
		8270	20	
	Reportable quantity of hazardous substance in accordance with Section 307(a) of the Clean Water Act for all isomers of HCH	Not assigned to the generic or broad class		EPA 2003c 40 CFR 302.4
	Reportable quantity of hazardous substance in accordance with Section 311 (b)(2) and 307(a) of the Clean Water Act, Section 112 of RCRA, and Section 112 of the Clean Air Act for γ-HCH	1 pound		EPA 2003c 40 CFR 302.4
	Standards for owners or operators of hazardous waste TSD facilities; maximum concentration for groundwater protection	Suggested method	PQL (µg/L)	EPA 2003l 40 CFR 264, Appendix IX
	α-HCH	8080	0.05	
		8250	10	
	β-HCH	8080	0.05	
		8250	40	
	δ-HCH	8080	0.1	
		8250	30	
	γ-HCH	8080	0.05	
		8250	10	
	Standards for owners or operators of hazardous waste TSD facilities; maximum concentration for groundwater protection			EPA 2003k 40 CFR 264.94
	γ-HCH	0.004 mg/L		

Table 8-1. Regulations and Guidelines Applicable to Hexachlorocyclohexane and Hexachlorocyclohexane Isomers

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	Standards for the management of specific hazardous waste and types of hazardous waste management facilities	Risk specific doses ($\mu g/m^3$)	EPA 2003m 40 CFR 266, Appendix V
	HCH (technical)	2.0×10^{-2}	
	α-HCH	5.6×10^{-3}	
	β-HCH	1.9×10^{-2}	
	γ-HCH	2.6×10^{-2}	
NTP	Carcinogenicity classification for γ-HCH and other HCH isomers	Reasonably anticipated to be a human carcinogen	NTP 2002
STATE			
a. Air	No data		
b. Water			
Arizona	Drinking water guideline		HSDB 2003
	γ-HCH	0.2 µg/L	
California	Drinking water guideline		HSDB 2003
	α-HCH	0.7 µg/L	
	β-HCH	0.3 µg/L	
Florida	Drinking water guideline		HSDB 2003
	α-HCH	0.05 µg/L	
	β-HCH	0.1 µg/L	
	δ- HCH	0.05 µg/L	
Maine	Drinking water guideline		HSDB 2003
	γ-HCH	0.2 µg/L	
New Hampshire	Drinking water guideline		HSDB 2003
	HCH	0.02 µg/L	
	α-HCH	0.006 µg/L	
	β-HCH	0.02 µg/L	
c. Food	No data		

Table 8-1. Regulations and Guidelines Applicable to Hexachlorocyclohexane and Hexachlorocyclohexane Isomers

Agency	Description	Information	Reference
STATE *(cont.)*			
d. Other	No data		

[a]Group 2B: possibly carcinogenic to humans
[b]Skin notation: refers to the potential significant contribution to the overall exposure by the cutaneous route, including mucous membranes and the eyes, either by contact with vapors or, of probable greater significance, by direct skin contact with the substance.
[c]Skin designation: indicates the potential for dermal absorption; skin exposure should be prevented as necessary through the use of good work practices and gloves, coveralls, goggles, and other appropriate equipment.
[d]Skin designation
[e]DWEL: a lifetime exposure concentration protective of adverse, non-cancer health effects, that assumes all of the exposure to a contaminant is from drinking water.
[f]Lifetime: the concentration of a chemical in drinking water that is not expected to cause any adverse noncarcinogenic effects for a lifetime of exposure. The Lifetime HA is based on exposure of a 70-kg adult consuming 2 L water/day.
[g]A3: confirmed animal carcinogen with unknown relevance to humans
[h]B2: probable human carcinogen; sufficient evidence of carcinogenicity from animal studies and inadequate evidence from epidemiological studies.
[i]C: possible human carcinogen
[j]D: not classifiable as to human carcinogenicity
[k]Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential.

ACGIH = American Conference of Governmental Industrial Hygienists; ADI = allowable daily intake; CFR = Code of Federal Regulations; DWEL = drinking water equivalent level; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; HCH = hexachlorocyclohexane; HSDB = Hazardous Substances Data Bank; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; 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; PEL = permissible exposure limit; PQL = practical quantitation level; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfD = reference dose; TLV = threshold limit values; TSD = treatment, storage, and disposal; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

EPA derived an oral reference dose (RfD) of 0.0003 mg/kg/day for γ-HCH (IRIS 2005). The RfD is based on a NOAEL of 0.33 mg/kg/day for liver and kidney toxicity in female rats (Zoecon Corporation 1983), and uses an uncertainty factor of 1,000 (10 for use of a subchronic versus a lifetime assay, 10 to account for interspecies variation, and 10 to protect sensitive human subpopulations).

EPA has classified HCH in the following cancer weight-of-evidence classifications: technical HCH and α-HCH, Group B2 (probable human carcinogen); β-HCH, Group C (possible human carcinogen); and δ-HCH and ε-HCH, Group D (not classifiable as to human carcinogenicity) (IRIS 2005). γ-HCH is classified as having "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential" (EPA 2002b).

EPA estimates that concentrations of HCH (technical) in water of 2.0, 0.2, and 0.02 μg/L are associated in humans with excess lifetime cancer risks of 10^{-4}, 10^{-5}, and 10^{-6}, respectively. α-HCH in water at concentrations of 0.6, 0.06, and 0.006 μg/L are associated in humans with excess lifetime cancer risks of 10^{-4}, 10^{-5}, and 10^{-6}, respectively, and concentrations of β-HCH in water of 2.0, 0.2, and 0.02 μg/L are associated in humans with excess lifetime cancer risks of 10^{-4}, 10^{-5}, and 10^{-6}, respectively (IRIS 2005).

δ-HCH and γ-HCH are on the list of chemicals appearing in "Toxic Chemicals Subject to Section 313 of the Emergency Planning and Right-to-Know Act of 1986" (EPA 2003o).

Tolerances are established for γ-HCH in or on raw agricultural commodities as follows: 7 ppm in or on the fat of meat from cattle, goats, horses, and sheep; 4 ppm in or on the fat of meat from hogs; 3 ppm in or on cucumbers, lettuce, melons, mushrooms, pumpkin, squash, summer, and tomatoes; 1 ppm in or on apples, apricots, asparagus, avocado, broccoli, Brussels sprouts, cabbage, cauliflower, celery, cherry, collards, eggplant, grape, guava, kale, kohlrabi, mango, mustard greens, nectarine, okra, onion (dry bulb only), peach, pear, pepper, pineapple, plum, prune, quince, spinach, strawberry, and Swiss chard; and 0.01 ppm in or on pecans (EPA 2003n).

The use of γ-HCH has been restricted by EPA since 1977 and is to be applied only by a certified applicator following label directions (EPA 1985b).

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10. GLOSSARY

Absorption—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 or less, 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)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

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—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of 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-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

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. At least one exposed group is compared to one unexposed group.

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 one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health 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 adverse effects.

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 insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance 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.

Epidemiology—Refers to 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.

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.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

Incidence—The ratio 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.

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—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; 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. A mutation is a change 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 chemical.

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. Effects may be produced at this dose, but 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 OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Organophosphate or Organophosphorus Compound—A phosphorus-containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour 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.

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 end points. 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—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: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as air/blood 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 the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

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 reference concentration is for continuous inhalation exposures and is appropriately 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 exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL, from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater 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 chemical. 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 chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value-Time Weighted Average (TLV-TWA) may not be exceeded.

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 most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose$_{(50)}$ (TD$_{50}$)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The absorption, distribution, and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or 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 chemical that is foreign to the biological system.

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (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 duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. 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 no-observed-adverse-effect level/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 and longer) 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 chemical-induced end point 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 substance 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.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, 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 levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: α-HCH
CAS Number: 319-84-6
Date: June 2005
Profile Status: Final Post-Public Comment Draft
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 61
Species: Rat

Minimal Risk Level: 0.008 [X] mg/kg/day [ ] ppm

Reference: 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. (Table 2 of the article).

Experimental design: 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. Estimated doses were 0, 0.7, 3.5, 7, or 56 mg/kg/day in males and 0, 0.8, 4, 8, or 64 mg/kg/day in females. The mean age at death was 54.6 weeks for the 10 ppm group (NOAEL) and 58.3 weeks for the control group. The lifetime of the animals sacrificed at the end of the experiment was taken as 107 weeks. End points included clinical signs, body weight, food consumption, organ weight, gross pathology, and histopathology.

Effects noted in study and corresponding doses: No exposure-related changes occurred at the low dose in either sex, indicating that the highest NOAEL is 0.8 mg/kg/day in females. Liver effects were qualitatively described in both sexes at higher doses, progressing from very slight histological changes with increased liver weight but no gross liver pathology at 3.5–4 mg/kg/day, slight histological changes with no gross pathology at 7–8 mg/kg/day, and moderate histological damage accompanied by moderate gross pathology at 56–64 mg/kg/day. The hepatic histopathological changes classified as moderate included hepatic cell atrophy, fatty degeneration, and focal necrosis. Non-hepatic effects included decreased body weight gain (18 and 13% less than controls in males and females), slight kidney histopathology (focal nephritis), and reduced lifespan (38% less than controls) at 56–64 mg/kg/day.

Dose and end point used for MRL derivation: 0.8 mg/kg/day (10 ppm); no hepatic effects.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? Yes.
If so, explain: Food factor of 0.07 and 0.08 kg feed/kg body weight/day for male and female Wistar rats, respectively, were used to convert dose from ppm food to mg/kg body weight as follows:
10 ppm x 0.07 (male rat food factor) = 0.7 mg/kg/day; 50 ppm=3.5 mg/kg/day; 100 ppm=7 mg/kg/day; 800 ppm=56 mg/kg/day; 10 ppm x 0.08 (female rat food factor)=0.8 mg/kg/day; 50 ppm=4 mg/kg/day; 100 ppm=8 mg/kg/day; 800 ppm=64 mg/kg/day.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: NA.

Other additional studies or pertinent information which lend support to this MRL: Other studies have observed various hepatic effects after chronic-duration oral exposure to α-HCH and other HCH isomers (Amyes et al. 1990; Ito et al. 1975; Kashyap et al. 1979; Munir et al. 1983; NCI 1977; Thorpe and Walker 1973; Wolff et al. 1987). Amyes et al. 1990 observed periacinar hypertrophy in male and female Wistar rats treated with 8 mg/kg/day γ-HCH in their diet for up to 52 weeks. The NOAEL was determined to be 0.8 mg/kg/day. Hepatocellular carcinoma was observed in rats fed 50 mg/kg/day α-HCH in their diet for 72 week (Ito et al. 1975). Hepatocellular carcinoma was also reported in mice treated with 34 mg/kg/day β-HCH in their diet for 104 weeks (Thorpe and Walker 1973).

Agency Contact (Chemical Manager): Alfred Dorsey, D.V.M.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: β-HCH
CAS Number: 319-85-7
Date: June 2005
Profile Status: Final Post-Public Comment Draft
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 10
Species: Mouse

Minimal Risk Level: 0.05 [X] mg/kg/day [ ] ppm

Reference: 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.

Experimental design: Groups of 10 male and 10 female Wistar rats were exposed to diets containing 0, 2, 10, 50, or 250 ppm β-HCH in food for 13 weeks and then sacrificed. Estimated dietary doses are 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. End points that were examined included clinical signs, body weight, food consumption, hematology, blood biochemistry, organ weights, gross pathology, and histopathology.

Effects noted in study and corresponding doses: At the end of week 2, two male and two female rats receiving the highest dose (22.5 and 25 mg/kg/day, respectively) exhibited clinical signs of ataxia and became progressively inactive. Within 3 days of the first signs of ataxia, the animals became comatose and were sacrificed

Dose and end point used for MRL derivation: 4.5 mg/kg/day; no reported signs of neurotoxicity (ataxia, inactivity, coma).

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? Yes.
If so, explain: A food factor of 0.1 kg feed/kg body weight/day for female Wistar rats was used to convert from ppm in food to mg/kg as follows: 2 ppm x 0.1 (rat food factor)=0.02 mg/kg/day; 10 ppm=1.0 mg/kg/day; 50 ppm=5.0 mg/kg/day; 250 ppm=25 mg/kg/day.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: NA.

Other additional studies or pertinent information which lend support to this MRL: Support for neurotoxicity as the critical effect for acute oral exposure to β-HCH is provided by other studies of this isomer identifying the nervous system as a target of toxicity. Rats exposed to 66 mg/kg/day of β-HCH in food for 30 days (Muller et al. 1981) exhibited significantly reduced tail nerve motor conduction velocity.

Agency Contact (Chemical Manager): Alfred Dorsey, D.V.M.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: β-HCH
CAS Number: 319-85-7
Date: June 2005
Profile Status: Final Post-Public Comment Draft
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 25
Species: Rat

Minimal Risk Level: 0.0006 [X] mg/kg/day [ ] ppm

Reference: 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.

Experimental design: Groups of 10 male and 10 female Wistar rats were exposed to diets containing 0, 2, 10, 50, or 250 ppm β-HCH in food for 13 weeks and then sacrificed. Estimated dietary doses are 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. End points that were examined included body weight, food consumption, hematology, blood biochemistry, organ weights, gross pathology, and histopathology.

Effects noted in study and corresponding doses: Hepatic effects were observed that included hyalinization of centrilobular cells in males at ≥0.18 mg/kg/day and females at 25 mg/kg/day; increased absolute and relative liver weight in both sexes at ≥0.9 mg/kg/day in males and ≥1.0 mg/kg/day in females; periportal fat accumulation, increased mitosis and/or focal liver cell necrosis in males at ≥4.5 mg/kg/day and females at ≥5 mg/kg/day; and centrilobular hepatocytic hypertrophy, proliferation of smooth endoplasmic reticulum, increased microsomal activity, and/or increased glycogen content in males at 22.5 mg/kg/day and females at 25 mg/kg/day. Other systemic effects included increased absolute and/or kidney weight in females at ≥2.0 mg/kg/day and males at ≥4.5 mg/kg/day; renal medulla calcinosis in males at 22.5 mg/kg/day; and clinical signs (ataxia progressing to inactivity and coma), hematologic and splenic changes indicative of anemia (decreased red blood cells and hemoglobin, increased extramedullar hematopoiesis), and reduced body weight in males at 22.5 mg/kg/day and females at 25 mg/kg/day. Due to the dose-related nature and progression in severity of the hepatic effects, and the mild, reversible nature of the changes at the lowest dose level, 0.18 mg/kg/day is considered to be a minimal LOAEL based on hyalinization of centrilobular cells, which indicates the inititation of hepatic effects. The liver is an established target of β-HCH in other subchronic and chronic studies in rats and mice (Fitzhugh et al. 1950; Ikegami et al. 1991a, 1991b; Ito et al. 1973; Schoter et al. 1987).

Dose and end point used for MRL derivation: 0.18 mg/kg/day; hyalinization of centrilobular cells.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 3 for use of a minimal LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? Yes.
If so, explain: A food factor of 0.09 kg feed/kg body weight/day for male Wistar rats was used to convert from ppm in food to mg/kg as follows: 2 ppm x 0.09 (rat food factor)=0.18 mg/kg/day; 10 ppm=0.9 mg/kg/day; 50 ppm=4.5 mg/kg/day; 250 ppm=22.5 mg/kg/day.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: NA.

Other additional studies or pertinent information which lend support to this MRL: Significant increases in liver weight and the levels of hepatic cytochrome P-450, triglycerides, phospholipids, and cholesterol were seen in rats fed 50 mg/kg/day β-HCH for 2 weeks (Ikegami et al. 1991a, 1991b). Liver hypertrophy was seen in rats fed 25 mg/kg/day for 24 weeks (Ito et al. 1975), and in mice fed 32.5 mg/kg/day for 24 weeks (Ito et al. 1973). Fatty degeneration and necrosis were seen in liver of rats fed 0.5–40 mg/kg/day for up to 53 weeks (Fitzhugh et al. 1950). Schöter et al. (1987) also observed an increase in hepatic foci in rats exposed to 3 mg/kg/day in the diet for 20 weeks.

Agency Contact (Chemical Manager): Alfred Dorsey, D.V.M.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: γ-HCH
CAS Number: 58-89-9
Date: June 2005
Profile Status: Final Post-Public Comment Draft
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 23
Species: Rat

Minimal Risk Level: 0.003 [X] mg/kg/day [ ] ppm

Reference: 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.

Experimental design: Reproductive toxicity was evaluated in male offspring of groups of 9 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 9 controls was administered the vehicle alone on days 9-14 of lactation. Male offspring (10 or 20/group) were terminated on postnatal day (pnd) 65 (puberty) or 140 (adulthood) and evaluated for the following end points: 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 end points (numbers of litters, implantations/litters, fetuses/litter, resorptions), and testicular histology (6 mg/kg offspring only).

Effects noted in study and corresponding doses: 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 (6.4% less than controls), relative epididymis weight at pnd 65 (7.1%), spermatid number at pnd 65 and 140 (29.0 and 12.8%, respectively), sperm number at pnd 140 (13.2%), serum testosterone at pnd 65 (30.0%), 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 gestation day 9 or 14, including significantly reduced relative testicular weight at pnd 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 mg/kg/day or 6 mg/kg offspring as shown by the mating, pregnancy, and fertility indices or other pregnancy end points. Thus, the 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.

Concentration and end point used for MRL derivation: 1 mg/kg/day LOAEL for developmental/reproductive effects in male offspring exposed during lactation.

Calculations: 1 mg/kg/day x 1/300 UF = 0.003 mg/kg/day.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 3 for use of a minimal LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent concentration: NA.

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information which lend support to this MRL: Similar adverse effects on testicular histology and sperm numbers occurred in adult male offspring of mice that were orally exposed to γ-HCH in doses ≥15 mg/kg/day (lower doses not tested) on gestation days 9–16 (Traina et al. 2003). Testicular and other reproductive effects occurred in intermediate-duration studies of lindane in mink at the same dose as the acute LOAEL for developmental/reproductive toxicity in rats. 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. Reductions in litter size as well as whelping rate were observed in a three-generation study of mink exposed to 1 mg/kg/day γ-HCH in the diet (Beard and Rawlings 1998). Neurological effects of γ-HCH occurred at acute doses similar to and higher than the 1 mg/kg/day LOAEL for developmental/reproductive toxicity. Neurological responses included enhanced susceptibility to kindling (induction of seizures by repeated subthreshold electrical stimulation of the brain) following a single 5-mg/kg dose (Gilbert and Mack 1995) or 3 mg/kg/day for 4 days (Joy et al. 1982), reduced brain serotonin level following 3 mg/kg/day for 6 days (Attia et al. 1991), and reduced brain barrier permeability in 10-day-old pups exposed to 2 mg/kg as a single dose or 8 daily doses (Gupta et al. 1999). The toxicological relevance of these effects is unclear because there were no concurrent tests of neurobehavioral function (as well as the unnatural method of seizure induction).

A comprehensive neurotoxicity screening study was conducted in which groups of 10 male and 10 female Crl:CD BR rats were administered a single dose of γ-HCH by gavage at levels of 0, 6, 20, or 60 mg/kg (Hughes 1999a). This study is an unpublished CBI submission summarized by EPA (2000). End points included functional observational battery (FOB) and motor activity (MA) tests performed prior to treatment, within 3 hours of dosing, and on post-exposure days 7 and 14, as well as histopathology of nervous system tissues at study termination. No clinical signs or any other effects were observed at 6 mg/kg. Motor activity was decreased in females at ≥20 mg/kg and males at 60 mg/kg. Females also had increased forelimb grip strength and decreased grooming behavior at 20 mg/kg, as well as 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. Other acute effects of γ-HCH included hematological and immunological changes in mice at 10–20 mg/kg/day (Hong and Boorman 1993), developmental changes in rats and mice at 20–45 mg/kg/day in rats and mice (Dalsenter et al. 1997b; Hassoun and Stohs 1996a; Rivera et al. 1991), and liver and kidney changes in mice at 72 mg/kg/day (Srinivasan and Radhakrishnamurty 1988; Srinivasan et al. 1984).

Agency Contact (Chemical Manager): Alfred Dorsey, D.V.M.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: γ-HCH
CAS Number: 58-89-9
Date: June 2005
Profile Status: Final Post-Public Comment Draft
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 45
Species: Mouse

Minimal Risk Level: 0.00001 [X] mg/kg/day [ ] ppm

Reference: Meera P, Rao PR, Shanker R, et al. 1992. Immunomodulatory effects of γ-HCH (lindane) in mice. Immunopharmacol Immunotoxicol 14:261-282.

Experimental design: Groups of six female Swiss mice were exposed to γ-HCH in measured dietary doses of 0, 0.012, 0.12, or 1.2 mg/kg/day for up to 24 weeks in an immunotoxicity study. End points that were evaluated throughout the study included delayed-type hypersensitivity reaction to sheep red blood cells (SRBC), lymphoproliferative response to mitogenic stimulation by concavalin A, mixed lymphocyte reactions, response of IgM antibody forming cells in spleen (plaque formation) to SRBC or lipopolysaccharide (LPS), and peritoneal macrophage phagocytic activity in response to LPS or *Staphylococcus aureus*. Histology of the thymus, peripheral lymph nodes, and spleen was evaluated at 4, 12, and 24 weeks post-treatment.

Effects noted in study and corresponding doses: Both cell-mediated and humoral components of the immune system showed a biphasic response, characterized initially by stimulation followed by suppression in a dose-dependent manner at all dose levels, indicating that a NOAEL was not identified. Effects observed at ≥0.012 mg/kg/day included biphasic changes in delayed-type hypersensitivity reaction to SRBC (increased at 4–12 weeks and decreased at 12–24 weeks), IgM plaque formation to SRBC (increased at 4–8 weeks and decreased at 12–24 weeks), and plaque formation to LPS-SRBC (increased at 4 weeks at ≥0.12 mg/kg/day and decreased at 8–24 weeks at ≥0.012 mg/kg/day). Histological changes occurred in lymphoid organs of treated animals and were consistent with the biphasic immunomodulatory responses. Effects were observed in the spleen at ≥0.12 mg/kg/day, including no significant reaction except for active proliferation of megakaryocytes at 4 weeks post-treatment, an apparent reduction in lymphoid follicles at 12 weeks post-treatment, and considerable reduction in the overall cellularity of red pulp and white pulp areas at 24 weeks post-treatment. Histopathology at 1.2 mg/kg/day included effects in lymph nodes (reduced lymphocyte population and size of medullary cords) and thymus (necrosis in the medulla) at 12–24 weeks post-treatment at 1.2 mg/kg/day.

Dose and end point used for MRL derivation: 0.012 mg/kg/day; reduced activity of lymphoid follicles with prominent megakaryocytes and delayed hypersensitivity to immune challenge.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: NA.

Other additional studies or pertinent information which lend support to this MRL: Immunotoxic effects have been observed in other oral studies of γ-HCH. Immunosuppression in the form of reduced antibody responses to *Salmonella* and typhoid vaccines occurred in rats exposed to 6.25 mg/kg/day for up to 5 weeks (Dewan et al. 1980). Exposure to 10 mg/kg/day for 10 days caused residual bone marrow damage and suppressed granulocyte-macrophage progenitor cells in mice, and atrophy of the thymus was observed in mice following 40 mg/kg/day for 3 days (Hong and Boorman 1993). Serum antibody response to SRBC was suppressed in rats exposed to 3.6 mg/kg/day for 8 weeks (Koner et al. 1998).

Agency Contact (Chemical Manager): Alfred Dorsey, D.V.M.

APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points 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?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived 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 chemical 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. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" 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 end point 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 end point 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 (UF) 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.

Chapter 3

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, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures 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 Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(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 Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is 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) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. 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 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "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.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful 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 end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A 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.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

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.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) 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.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

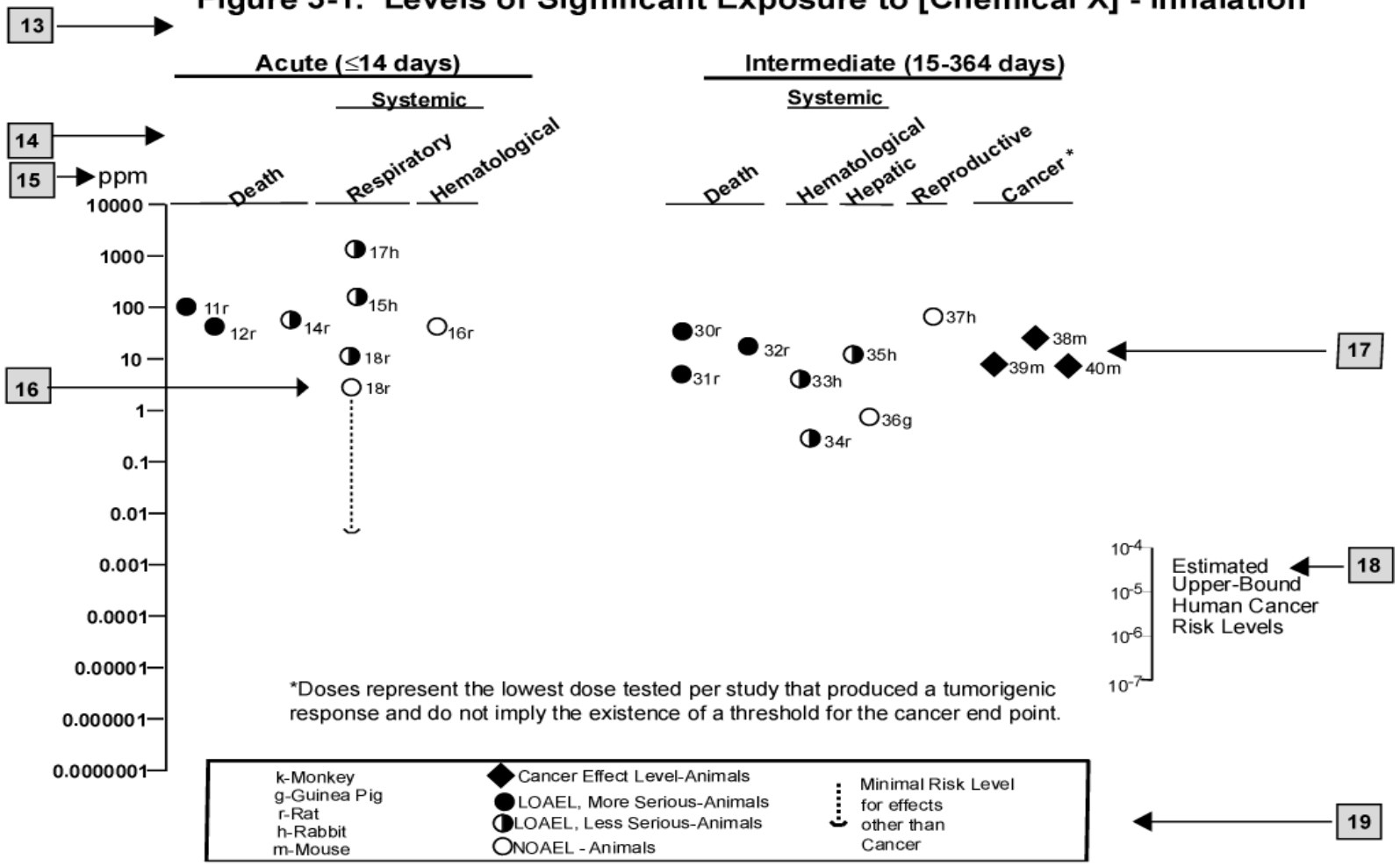
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Serious (ppm)	Reference
2 →	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
	CHRONIC EXPOSURE							
	Cancer					11		
						↓		
	38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
	39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
	40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD	benchmark dose
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation

APPENDIX C

DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	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	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans*,*trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level

MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water

OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
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
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

APPENDIX D. INDEX