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TOXICOLOGICAL PROFILE FOR HEPTACHLOR and HEPTACHLOR EPOXIDE

Prepared by:

Syracuse Research Corporation
Under Contract No. 200-2004-09793

Prepared for:

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

November 2007

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UPDATE STATEMENT

A Toxicological Profile for Heptachlor/Heptachlor Epoxide, Draft for Public Comment was released in September 2005. 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 and Environmental Medicine/Applied Toxicology Branch
1600 Clifton Road NE
Mailstop F-32
Atlanta, Georgia 30333

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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 is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Howard Frumkin, M.D., Dr. P.H.
Director
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Agency for Toxic Substances and
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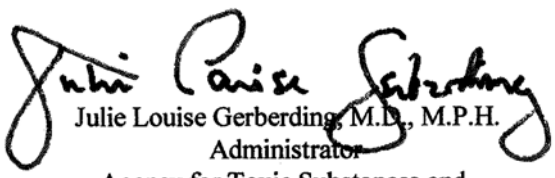

Julie Louise Gerberding, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

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 December 7, 2005 (70 FR 72840). 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); October 25, 2001 (66 FR 54014); and November 7, 2003 (68 FR 63098). 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: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY) ***Fax:*** (770) 488-4178
E-mail: cdcinfo@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 Applied Toxicology 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.

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PEER REVIEW

A peer review panel was assembled for heptachlor and heptachlor epoxide. The panel consisted of the following members:

1. Richard Dickerson, Ph.D., DABT, Department of Pharmacology and Neuroscience and Department of Environmental Toxicology, Texas Tech University Health Sciences Center, Lubbock, TX;

2. Sam Kacew, Ph.D., Department of Cellular and Molecular Medicine, University of Ottawa, Ottawa, Ontario, Canada; and

3. James Klaunig, Ph.D., Department of Pharmacology and Toxicology, Indiana University School of Medicine, Indianapolis, IN.

These experts collectively have knowledge of heptachlor and heptachlor epoxide'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 heptachlor and heptachlor epoxide and the effects of exposure to them.

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. Heptachlor has been found in at least 210 of the 1,684 current or former NPL sites. Heptachlor epoxide has been found in at least 200 NPL sites. Although the total number of NPL sites evaluated for these substances is not known, the possibility exists that heptachlor and heptachlor epoxide may be found 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 heptachlor or heptachlor epoxide, 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 them. 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 ARE HEPTACHLOR AND HEPTACHLOR EPOXIDE?

Heptachlor is a manufactured chemical that was used in the past for killing insects in homes, in buildings, and on food crops. It has not been used for these purposes since 1988. There are no natural sources of heptachlor or heptachlor epoxide. Trade names for heptachlor include Heptagran®, Heptamul®, Heptagranox®, Heptamak®, Basaklor®, Drinox®, Soleptax®, Gold Crest H-60®, Termide®, and Velsicol 104®. Heptachlor is both a breakdown product and a component of the pesticide chlordane (approximately 10% by weight). Pure heptachlor is a white powder.

Technical-grade heptachlor is a tan powder and has a lower level of purity than pure heptachlor. Technical-grade heptachlor was the form of heptachlor used most often as a pesticide. Heptachlor smells somewhat like camphor. Heptachlor does not burn easily and does not explode. It does not dissolve easily in water.

Like pure heptachlor, heptachlor epoxide is a white powder that does not explode easily. It was not manufactured and was not used as an insecticide like heptachlor. Bacteria and animals break down heptachlor to form heptachlor epoxide. This profile describes these two chemicals together because about 20% of heptachlor is changed within hours into heptachlor epoxide in the environment and in your body.

You might find heptachlor or heptachlor epoxide in the soil or air of homes treated for termites, dissolved in surface water or groundwater, or in the air near hazardous waste sites. You might also find heptachlor or its byproduct, heptachlor epoxide, in plants and animals near hazardous waste sites. Heptachlor can no longer be used to kill insects on crops or in homes and buildings. However, heptachlor is still approved by EPA for killing fire ants in buried power transformers, although it is unclear whether or not it is still being used for this purpose in the United States. More information on the chemical and physical properties of heptachlor and heptachlor epoxide is found in Chapter 4 of this document. More information on the production and use of heptachlor is found in Chapter 5.

1.2 WHAT HAPPENS TO HEPTACHLOR AND HEPTACHLOR EPOXIDE WHEN THEY ENTER THE ENVIRONMENT?

From 1953 to 1974, heptachlor entered the soil and surface water when farmers used it to kill insects in seed grains and on crops. It also entered the air and soil when homeowners and professional insect exterminators used it to kill termites. Today, heptachlor is no longer used by homeowners to kill termites or other insects. However, exterminators can still use existing stocks of heptachlor to kill fire ants in underground power transformers.

Heptachlor and heptachlor epoxide can enter the air, soil, groundwater, and surface water from leaks at hazardous waste sites or landfills. Heptachlor sticks to soil very strongly and evaporates

slowly into the air. Heptachlor does not dissolve easily in water. Heptachlor epoxide dissolves more easily in water than heptachlor does and evaporates slowly from water. Like heptachlor, heptachlor epoxide sticks to soil.

Both heptachlor and heptachlor epoxide can travel long distances in the wind from places where they are released, such as treated fields or manufacturing sites. In soil and water, heptachlor is changed by bacteria into the more harmful substance, heptachlor epoxide, or into other less harmful substances. Plants can absorb heptachlor through their roots from the soil. Heptachlor in the air can be deposited on plant leaves and enter the plant from contaminated soil.

Animals that eat plants containing heptachlor can also absorb it. Animals can also change heptachlor to heptachlor epoxide in their bodies. Heptachlor epoxide breaks down very slowly in the environment. It can stay in soil and water for many years. Both heptachlor and heptachlor epoxide build up in fish and in cattle. People store heptachlor epoxide in their fatty tissue. Some studies show that heptachlor epoxide can still be measured in fatty tissue 3 years after a person is exposed to it.

Most of the breakdown products of heptachlor are thought to be less harmful than heptachlor itself. However, in laboratory animals, heptachlor epoxide is more harmful than heptachlor. For more information on heptachlor and heptachlor epoxide in the environment, see Chapters 5 and 6.

1.3 HOW MIGHT I BE EXPOSED TO HEPTACHLOR AND HEPTACHLOR EPOXIDE?

Exposure to heptachlor and heptachlor epoxide most commonly occurs when you eat food contaminated with those chemicals. Contaminated foods might include fish, shellfish (such as clams), dairy products, meat, and poultry. Children and toddlers drink large amounts of milk and may have greater exposure if the milk is contaminated with heptachlor or heptachlor epoxide. Infants can be exposed to these compounds from drinking breastmilk or cow's milk.

Exposure can also occur when you drink water, breathe air, or touch contaminated soil at hazardous waste sites that contain heptachlor or heptachlor epoxide. People whose homes have been treated with heptachlor to kill termites can be exposed by breathing heptachlor in the air. After heptachlor is changed to heptachlor epoxide in the soil, it can get into the air. People who breathe this air will be exposed to heptachlor epoxide. Workers who use heptachlor to kill fire ants are exposed if they breathe in the heptachlor or get it on their skin.

Background levels of a substance are levels found in the environment that cannot be traced to a specific source. Information on background levels of heptachlor and heptachlor epoxide in the air was not found. In one survey, the background levels of heptachlor in drinking water and groundwater in the United States ranged from 20 to 800 parts of heptachlor in one trillion parts of water (ppt). Heptachlor was found in less than 2% of U.S. groundwater samples that are known to be contaminated from pesticide application. The average level of heptachlor in the contaminated groundwater samples was 800 ppt. No information was found for levels of heptachlor epoxide in groundwater or drinking water. Heptachlor epoxide has been found in surface water (river, lakes) at levels between 0.1 and 10 parts of heptachlor epoxide in one billion parts of water (ppb, 1 ppb is 1 thousand times more than 1 ppt).

Heptachlor and heptachlor epoxide stick to sediment and soil. Sediment in stream beds is likely to contain a lot of the heptachlor that enters the water. Heptachlor and heptachlor epoxide were found in less than 0.7 and 1.8% of river bed sediments that were tested from 2003 to 2005. Contaminated fish and shellfish have been found to contain 2–750 ppb heptachlor and 0.1–480 ppb heptachlor epoxide. Heptachlor epoxide has been found in human milk samples at levels ranging from 0.13 to 128 ppb. See Chapter 6 for more information on how you might be exposed to heptachlor and heptachlor epoxide.

1.4 HOW CAN HEPTACHLOR AND HEPTACHLOR EPOXIDE ENTER AND LEAVE MY BODY?

When you breathe air containing heptachlor or heptachlor epoxide, both can enter your bloodstream through your lungs. It is not known how fast these compounds enter and remain in the bloodstream. Both heptachlor and heptachlor epoxide can also enter your body through your

stomach after you eat food or drink water or milk containing them. Most of the heptachlor that is swallowed passes through your stomach into your blood. It can also enter your body through your skin. Heptachlor and heptachlor epoxide can pass directly from a mother's blood to an unborn baby through the placenta. It can also pass from the mother to an infant through breast milk.

Once inside your body, heptachlor is changed to heptachlor epoxide and other related chemicals. Most of the heptachlor, heptachlor epoxide, and other breakdown products leave your body in the feces within a few days after exposure. Some breakdown products can also leave in the urine. Some heptachlor and heptachlor epoxide are stored in your body fat for long periods after exposure has occurred. The heptachlor and heptachlor epoxide that have been stored in fat leave your body much more slowly. Chapter 3 contains more information on how heptachlor and heptachlor epoxide can enter and leave the body.

1.5 HOW CAN HEPTACHLOR AND HEPTACHLOR EPOXIDE 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.

People can begin to smell heptachlor or heptachlor epoxide at around 0.3 milligrams in a cubic meter of air (0.3 mg/m^3). No reliable studies in humans were found that show whether harmful health effects occur as a result of breathing heptachlor or heptachlor epoxide. No animal studies

examining the harmful effects resulting from breathing air that contains heptachlor or heptachlor epoxide were found.

In addition, no reliable human studies were found that show whether harmful effects occur from eating contaminated foods or by drinking liquids contaminated with heptachlor or heptachlor epoxide. Studies have shown a number of harmful health effects when animals were fed heptachlor or heptachlor epoxide. These effects were more harmful when the exposure levels were high or when exposure lasted many weeks. The effects observed in animals include damage to the liver, excitability, and decreases in fertility.

Animals fed heptachlor throughout their lifetime had more liver tumors than animals that ate food without heptachlor. EPA and the International Agency for Research on Cancer have classified heptachlor as a possible human carcinogen. EPA also considers heptachlor epoxide as a possible human carcinogen.

Chapter 3 contains more information on the adverse health effects of heptachlor and heptachlor epoxide.

1.6 HOW CAN HEPTACHLOR AND HEPTACHLOR EPOXIDE AFFECT CHILDREN?

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

Some studies in animals suggest that young animals exposed during gestation and infancy may be very sensitive to heptachlor and heptachlor epoxide. Changes in nervous system and immune function were found in these animals. There is some evidence that similar effects may occur in humans, but a study that found some changes in performance on some tests that measure nervous system function is not conclusive and exposure to other chemicals cannot be ruled out. Exposure to higher doses of heptachlor in animals can also result in decreases in body weight and death in animal newborn babies.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO HEPTACHLOR AND HEPTACHLOR EPOXIDE?

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

Heptachlor is no longer used in the United States except to control fire ants; therefore, exposure should be limited. Before the use of heptachlor was cancelled in 1988, it was used on various agricultural crops, in homes for the treatment of termites, and in power lines for fire ant control. However, because of the persistence of both heptachlor and heptachlor epoxide, exposure to the general population can occur from contaminated water, soil, and air. People who live in homes where heptachlor was used for termite control or on farms where heptachlor was used on crops may have a higher risk of exposure through contaminated crops, soil, water, and air. To avoid exposure from contaminated soil, you should discourage your children from eating or playing with dirt near home or barn foundations. Make sure they wash their hands frequently and before eating. Discourage children from putting their hands in their mouths or other hand-to-mouth activities.

Heptachlor and heptachlor epoxide are also persistent in food and milk. Eating fish from contaminated water can increase exposure to heptachlor. Avoid eating fish from contaminated water. Local fishing advisories can tell you if the water is contaminated.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO HEPTACHLOR AND HEPTACHLOR EPOXIDE?

Laboratory tests can detect heptachlor and heptachlor epoxide in blood, fat, breast milk, and body tissues after exposure to high levels of these chemicals. These tests are not commonly available at your doctor's office. Most often, the test for heptachlor epoxide is used because heptachlor is quickly changed into heptachlor epoxide in your body. Blood samples are used most often because they are easy to collect. These tests are specific for heptachlor and heptachlor epoxide. However, heptachlor is both a breakdown product and a component of

chlordane, another pesticide. So if heptachlor and heptachlor epoxide are measured in the blood, the actual exposure could have been to chlordane. Methods for measuring heptachlor and heptachlor epoxide in body fat are more precise and can detect lower levels than tests that measure levels in blood. If heptachlor or heptachlor epoxide is found in your blood or fat, it is not possible to tell when you were exposed to these chemicals or if harmful health effects will occur. See Chapters 3 and 7 for more information on detecting these chemicals in the environment or in human 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 heptachlor and heptachlor epoxide include the following:

For exposures of up to 10 days, EPA recommends that a child weighing 22 pounds or less not drink water containing more than 0.01 mg heptachlor or heptachlor epoxide per liter of water (0.01 mg/L or 0.01 ppm). EPA requires that drinking water should not contain more than 0.0004 mg/L (0.0004 ppm) heptachlor and 0.0002 mg/L (0.0002 ppm) of heptachlor epoxide.

FDA controls the amount of heptachlor and heptachlor epoxide on raw food crops and on edible seafood. The limit for most food crops is 0.01 parts heptachlor per million parts food (0.01 ppm). The limit in milk is 0.1 parts heptachlor per million parts of milk fat. The limit on edible seafood is 0.3 ppm.

OSHA has set a limit of 0.5 mg/m^3 for heptachlor in workplace air over an 8-hour workday for a 40-hour workweek. For more information on standards and guidelines for heptachlor and heptachlor epoxide, see Chapter 8.

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 ToxProfilesTM CD-ROM by calling the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636), by e-mail at cdcinfo@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
1600 Clifton Road NE
Mailstop F-32
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 HEPTACHLOR AND HEPTACHLOR EPOXIDE IN THE UNITED STATES

Heptachlor is a polychlorinated cyclodiene insecticide that was extensively used prior to 1970 to kill termites, ants, and soil insects in seed grains and on crops. In 1983, the manufacturers voluntarily cancelled its registered uses, with the exception of termite and fire ant control. Currently, the only permitted use of heptachlor is for fire ant control in buried power transformers; however, there are no actively registered pesticides containing heptachlor as an active ingredient. Heptachlor epoxide is the primary degradation product of heptachlor. Heptachlor epoxide is more persistent in the environment than heptachlor and biomagnifies in the terrestrial food chain. Although the use of heptachlor is restricted, exposure to the general population can occur through the ingestion of contaminated food, inhalation of vapors from contaminated soil and water, and dermal contact with contaminated soil and water. The food classes most likely to contain residues are milk and other dairy products, vegetables, meat, fish, and poultry.

2.2 SUMMARY OF HEALTH EFFECTS

There are limited data on the toxicity of heptachlor or heptachlor epoxide following inhalation or dermal exposure. Most of the available information on the toxicity of heptachlor comes from oral exposure studies in laboratory animals, although some human data have been identified. Oral exposure of laboratory animals to heptachlor results in a variety of adverse effects including liver effects, neurological effects, reproductive system dysfunction, and developmental effects. Although there are very few studies involving exposure to heptachlor epoxide, it is likely that the effects resulting from heptachlor exposure are due to its metabolism to heptachlor epoxide. Several human studies have examined the possible relationship between increased serum levels of heptachlor or heptachlor epoxide and adverse health outcomes. Most of these studies involved exposure to a variety of organochlorine pesticides and the observed effects cannot be ascribed to heptachlor. Additionally, a small number of studies have examined populations consuming milk products from cows fed heptachlor-contaminated feed. In these types of studies, there is a greater degree of certainty in attributing the observed effects to heptachlor exposure.

In mature animals, liver and neurological effects appear to have similar thresholds of toxicity. Acute- or intermediate-duration exposure of rats or mice to 5–10 mg/kg/day has resulted in a variety of liver effects

including increases in serum alanine aminotransferase activity, necrosis, hepatocytomegaly, hepatitis, and increased liver weights. These studies suggest that the severity of the hepatic lesions is related to the duration of exposure. No alterations in serum liver enzyme activity levels or hepatocytomegaly incidence were observed in individuals exposed to heptachlor and heptachlor metabolites in contaminated milk products. Neurological alterations indicative of excitability and increased arousal were observed in rats exposed to 7 mg/kg/day for an acute duration and mink exposed to 1.7 or 6.2 mg/kg/day for an intermediate duration. At higher doses (17 mg/kg/day), mice exhibited difficult standing, walking, and righting. Seizures have also been observed in mink prior to death.

The reproductive system may be a more sensitive target of heptachlor toxicity than the liver or nervous system. A decrease in fertility and an increase in resorptions were observed in female rats acutely exposed to 1.8 mg/kg/day. Exposure of males to 0.65 mg/kg/day for 70 days resulted in decreased epididymal sperm count and increased resorptions when the males were mated with untreated females. In contrast, two acute studies involving exposure to 10 mg/kg/day heptachlor, 8 mg/kg/day heptachlor epoxide, or 15 mg/kg heptachlor/ heptachlor epoxide mixture did not find dominant lethal effects. Reduced fertility has also been observed in mice exposed to 8.4 mg/kg/day.

The available data provide suggestive evidence that the developing organism is the most sensitive target of heptachlor toxicity. Increases in pup mortality have been observed at doses of 5.0 mg/kg/day and higher in rats and at 1.7 mg/kg/day in mink; these doses were also associated with serious maternal toxicity. Decreases in pup body weight have also been observed at 4.5 mg/kg/day and higher. Heptachlor does not appear to increase the occurrence of anomalies or malformations. Perinatal and postnatal exposure adversely affected the development of the nervous and immune systems; the lowest-observed-adverse-effect level (LOAEL) for these effects is 0.03 mg/kg/day. No adverse effects were observed in the developing reproductive system. Studies of a population exposed to heptachlor-contaminated milk products found similar effects to those reported in animals. The risk of fetal or neonatal deaths, low birth weight infants, or major congenital malformations was not significantly altered. However, alterations in neurobehavioral performance were found when the children of women exposed to contaminated milk products reached high school. In particular, abstract concept formation, visual perception, and motor planning were adversely affected.

The carcinogenicity of heptachlor and heptachlor epoxide has been evaluated in a number of human studies. In general, these studies have examined possible associations between heptachlor and/or heptachlor epoxide tissue levels or a surrogate of heptachlor exposure and the prevalence of cancer.

Mixed results have been reported across tumor types and within tumor types. Interpretation of the studies is limited by the lack of information on heptachlor exposure, variables that may affect organochlorine levels (including diet and body mass index), and possible concomitant exposure to other chemicals. Increases in the incidence of hepatocellular carcinoma were observed in mice exposed to 2.4 mg/kg/day heptachlor and higher for 2 years, but not in rats exposed to 2.6 mg/kg/day and higher. The EPA has classified heptachlor and heptachlor epoxide in group B2 (probable human carcinogen) and the International Agency for Research on Cancer (IARC) considers heptachlor as possibly carcinogenic to humans (Group 2b). EPA has derived an oral slope factor of 4.5 per (mg/kg)/day for heptachlor and 9.1 per (mg/kg)/day for heptachlor epoxide. These slope factors correspond to drinking water unit risk levels of $1.3x10^{-4}$ and $2.6x10^{-4}$ per (µg/L), respectively.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for heptachlor. 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 1990b), 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.

Inhalation MRLs

Data on the toxicity of heptachlor or heptachlor epoxide following inhalation exposure are limited to several mortality studies of pesticide applicators or manufacturers (Blair et al. 1983; MacMahon et al.

1988; Shindell and Associates 1981; Wang and MacMahon 1979a) and a case control study examining the possible association between organochlorine pesticide exposure and aplastic anemia (Wang and Grufferman 1981). No significant associations were found. Interpretation of the results are limited by co-exposure to other organochlorine pesticides and lack of monitoring data. No inhalation exposure animal studies were identified.

The available inhalation data are considered inadequate for the development of MRLs for heptachlor and heptachlor epoxide.

Oral MRLs

Heptachlor.

- An MRL of 0.0006 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to heptachlor.

A number of studies have examined the toxicity of heptachlor following acute-duration oral exposure; many of the toxicity studies are limited by the lack of statistical analysis and poor reporting of the observed effects, including incidence data. Despite the limitations in the studies, the acute database does identify several targets of toxicity including the liver, nervous system, reproductive capacity, and the developing offspring. Although some other adverse health effects have been reported, they have not been replicated in other studies or were observed at lethal doses. The most sensitive effect following acute-duration exposure appears to be a decrease in fertility and an increase in resorptions observed in female rats administered via gavage 1.8 mg/kg/day heptachlor in groundnut oil for 14 days prior to mating (Amita Rani and Krishnakumari 1995). Gestational exposure to 4.5 or 6.8 mg/kg/day resulted in decreases in pup body weight (Narotsky and Kavlock 1995; Narotsky et al. 1995); a decrease in pup righting reflex was also observed at 4.2 mg/kg/day (Purkerson-Parker et al. 2001b). At twice these dose levels, an increase in pup mortality was observed (Narotsky et al. 1995; Purkerson-Parker et al. 2001b). Liver effects were observed at doses similar to those resulting in developmental effects. Increases in serum alanine aminotransferase and aldolase activity levels, hepatocytomegaly, and minimal monocellular necrosis were observed in rats administered 7 mg/kg/day heptachlor in oil for 14 days (Berman et al. 1995; Krampl 1971). Exposure to 7 mg/kg/day also resulted in excitability and increased arousal in rats administered heptachlor in oil via gavage for 1 or 14 days (Moser et al. 1995).

The lowest LOAEL identified in the acute-duration oral database is 1.8 mg/kg/day for reduced fertility and an increase in resorptions in female rats (Amita Rani and Krishnakumari 1995). In this study, groups of 30 female CFT-Wistar rats received gavage doses of heptachlor in groundnut oil for 14 days (presumably 7 days/week). The total administered doses were 25 and 50 mg/kg body weight and the daily doses were 1.8 and 3.6 mg/kg/day. A vehicle control group was also used. After 14 days of exposure, the animals were mated with unexposed male rats. A significant decrease in the number of pregnant females (56.3 and 44.4%) and increase in the number of resorptions (18.90 and 11.40%) were observed in both groups of heptachlor-exposed rats. Significant decreases in estradiol-17beta and progesterone levels were also observed in the 1.8 mg/kg/day group. No alterations in the number of implantations were observed. The investigators noted that focal necrosis was observed in the liver; however, they did not note at which dose level and no incidence data were provided. This LOAEL of 1.8 mg/kg/day was divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from rats to humans, and 10 for human variability) and a modifying factor of 3 to account for the use of a serious end point, resulting in an acute-duration oral MRL of 0.0006 mg/kg/day.

- An MRL of 0.0001 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to heptachlor.

Intermediate-duration oral exposure studies have identified a number of targets of heptachlor toxicity including the liver, nervous system, reproductive system, and the developing offspring. Other less documented effects have also been observed. In the absence of maternal toxicity, heptachlor is not associated with alterations in pup mortality or body weight gain (Lawson and Luderer 2004; Purkerson-Parker et al. 2001b; Smialowicz et al. 2001). Additionally, gestational exposure does not appear to result in significant alterations in the occurrence of anomalies or abnormalities (Narotsky et al. 1995; Smialowicz et al. 2001) or the development of the reproductive system (Lawson and Luderer 2004; Smialowicz et al. 2001). *In utero* exposure followed by postnatal exposure (until postnatal day 42) did not alter reproductive function (Smialowicz et al. 2001), but did adversely affect neurobehavioral performance (Moser et al. 2001) and immune function (Smialowicz et al. 2001). The neurological effects included impaired spatial memory at 0.03 mg/kg/day and higher, impaired spatial learning at 0.3 or 3 mg/kg/day, and decreased righting reflex (Moser et al. 2001; Purkerson-Parker et al. 2001b) and increased open field activity (Moser et al. 2001) at 3 mg/kg/day. When the exposure was terminated at postnatal day 21, rather than postnatal day 42, spatial memory and learning were not adversely affected (Moser et al. 2001). The difference in results may have been due to higher heptachlor epoxide body burden in rats exposed to postnatal day 42, testing at different ages, or exposure may have occurred during a critical window of vulnerability. The effects observed in rats are consistent with those observed

in humans. Impaired performance on several neurobehavioral tests, including abstract concept formation, visual perception, and motor planning, was observed in high school students presumably prenatally exposed to heptachlor from contaminated milk products (Baker et al. 2004b). Alterations in immune function were also observed in the rats exposed until postnatal day 42. At 0.03 mg/kg/day and higher, suppression of the immune response to sheep red blood cells was observed (Smialowicz et al. 2001). A reduction in the percentage of B lymphocytes was also observed in the spleen of rats exposed to 3 mg/kg/day. Other tests of immune function were not significantly altered.

The liver effects observed in rats or mice exposed to heptachlor in the diet include increased liver weights (Izushi and Ogata 1990; Pelikan 1971), increased serum alanine aminotransferase activity levels (Izushi and Ogata 1990), steatosis (Pelikan 1971), and hepatitis and necrosis (Akay and Alp 1981). The lowest LOAEL values for these effects range from 5 to 8.4 mg/kg/day. Neurological signs such as hyperexcitability, seizures, and difficulty standing, walking, and righting were observed at similar dose levels; LOAELs ranged from 1.7 to 17 mg/kg/day (Akay and Alp 1981; Aulerich et al. 1990; Crum et al. 1993). Decreases in epididymal sperm count were observed in rats administered 0.65 mg/kg/day heptachlor in groundnut oil for 70 days (Amita Rani and Krishnakumari 1995). This dose also resulted in increased resorptions when the exposed males were mated with unexposed females. Reduced fertility was observed in all mice exposed to 8.4 mg/kg/day heptachlor for 10 weeks (Akay and Alp 1981).

The intermediate-duration oral MRL for heptachlor is based on the results of the study reported by Moser et al. (2001) and Smialowicz et al. (2001), which found alterations in development of the nervous and immune systems. In this study, groups of 15–20 pregnant Sprague Dawley rats were administered via gavage 0, 0.03, 0.3, or 3 mg/kg/day heptachlor in corn oil on gestational day 12 through postnatal day 7; pups were also exposed from postnatal day 7 to 21 or 42. The liver, kidneys, adrenals, thymus, spleen, ovaries, uterus/vagina, testes, epididymides, seminal vesicles/coagulating glands, and ventral and dorsolateral prostate were histologically examined in the offspring on postnatal day 46. Neurological (functional observational battery tests, motor activity, passive avoidance tests learning and memory, and Morris water maze test to assess spatial and working memory) and immunological (splenic lymphoproliferative responses to T cell mitogens, and to allogeneic cells in a mixed lymphocyte reaction, primary immunoglobulin M (IgM) antibody response to sheep red blood cells, examination of splenic lymphocytes subpopulations, and delayed-type and contact hypersensitivity) function tests were performed on the offspring exposed until postnatal day 42; neurological function tests were also performed on offspring exposed until postnatal day 21. Reproductive assessment included evaluation of vaginal opening (index of female puberty) and prepuce separation (index of male puberty) beginning at

postnatal days 25 and 35, respectively. The offspring were mated with an untreated mate and the dams were allowed to rear the first litter to postnatal day 10. The results of the neurobehavioral assessment were reported by Moser et al. (2001); the remaining results were reported by Smialowicz et al. (2001).

No significant alterations in maternal body weight, number of dams delivering litters, litter size, or pup survival were observed. Additionally, no alterations in pup growth rates, age at eye opening, anogenital distance, or age at vaginal opening or preputial separation were observed. A significant decrease in pup body weight at postnatal day 1 was observed at 3 mg/kg/day; this effect was not observed at postnatal days 7, 14, or 21. No consistent, statistically significant alterations in offspring body weights were observed at post natal days 21, 28, 35, or 42. Significant alterations in absolute and relative liver weights were observed in males and females exposed to 3 mg/kg/day; increases in absolute and relative ovary weights were also observed at 3 mg/kg/day. No histological alterations were observed in the examined tissues. No alterations in fertility were observed in the adult males and females mated to untreated partners, and no effects on soft tissue or gross body structure of the offspring (F_2 generation) were observed. No alterations in sperm count or sperm motility were observed.

A dose-related, statistically significant suppression of primary IgM antibody response to sheep red blood cells (sRBC) was found in male offspring, but not females. The primary IgM response to sRBCs was reduced in 21-week-old males exposed to 0.3 mg/kg/day. A second immunization with sRBCs administered 4 weeks later resulted in a significant reduction in IgG antibody response in males administered 0.03, 0.3, or 3 mg/kg/day heptachlor; no response was seen in females. A decrease in the $OX12^{+}OX19^{-}$ (i.e., B/plasma cells) population was also found in the spleen of males exposed to 3 mg/kg/day. No alterations in the following immunological parameters assessed at 8 weeks of age were found: lymphoid organ weights, splenic NK cell activity, splenic cellularity or cell viability, and lymphoproliferative responses of splenic lymphocytes to T-cell mitogens ConA and phytohemagglutinin (PHA) or to allogenic cells in the mixed lymphocyte reaction. The results of this portion of the study suggest that exposure to heptachlor adversely affects the development of the immune system.

Righting was significantly delayed in the female offspring of rats exposed to 3 mg/kg/day heptachlor; no significant alterations were observed in the male offspring. The investigators suggested that this was due to a delay in the ontogeny of righting rather than an inability to perform the task. The following significant alterations in the functional observation battery (FOB) and motor activity tests were found in the offspring dosed until postnatal day 21: increased open field activity in 3 mg/kg/day males, non-dose-related increased activity in figure-eight chambers in females (significant only in 0.03 mg/kg/day group),

and faster decline in habituation of activity in 3 mg/kg/day males. Alterations in the offspring dosed until postnatal day 42 included: increased levels of urination in males in the 0.03 and 0.3 mg/kg/day groups, increased landing foot splay in males in the 0.03 mg/kg/day group, and removal reactivity in males and females in the 0.03 mg/kg/day group. No alterations in the passive avoidance test were observed in the offspring exposed until postnatal day 21; in those exposed until postnatal day 42, an increase in the number of nose pokes was observed in all groups of females. No significant alterations in performance on the water maze test were found in the offspring exposed until postnatal day 21. In those exposed until postnatal day 42, increases in latency to find the platform were observed in males and females exposed to 3 mg/kg/day and increases in the time spent in the outer zone were found in males exposed to 0.3 or 3 mg/kg/day. In the water maze memory trial, no differences in performance were found between controls and animals exposed until postnatal day 21. Alterations in significant quadrant bias were observed in 0.03, 0.3, and 3 mg/kg/day males during the first probe test and in 0.3 and 3 mg/kg/day males and 3 mg/kg/day females in the second probe test. The study investigators noted that the heptachlor-exposed rats did not develop an efficient search strategy for locating the platform; they spent more time circling the outer zone of the tank. By the second week of the test, control rats had learned to venture into the zone where the platform was located.

The Smialowicz et al. (2001) and Moser et al. (2001) study identified a LOAEL of 0.03 mg/kg/day for developmental immunological and neurological effects. These alterations were considered to be minimally adverse and suggestive of immunotoxicity and neurotoxicity. An intermediate-duration oral MRL was calculated by dividing the minimal LOAEL of 0.03 mg/kg/day by 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 resulting MRL is 0.0001 mg/kg/day.

There is a limited publicly available database on the chronic oral toxicity of heptachlor. In a multigeneration study conducted by Mestitzova (1967), decreases in litter size, increased postnatal mortality, and increased occurrence of lens cataracts (observed in F_0, F_1, and F_2 generations) were observed at a heptachlor dose of 6 mg/kg/day. Because the only reliable chronic-duration study identified a serious LOAEL at the lowest dose tested, a chronic-duration MRL was not derived for heptachlor.

Heptachlor Epoxide. Publicly available data on the toxicity of heptachlor epoxide are limited to an LD_{50} study (Podowski et al. 1979), and a dominant lethal study (Epstein et al. 1972). Neither of these studies is suitable for derivation of MRLs for heptachlor epoxide.

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 heptachlor and heptachlor epoxide. 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 heptachlor and heptachlor epoxide are indicated in Table 3-1 and Figure 3-1.

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.

3.2.1 Inhalation Exposure

3.2.1.1 Death

Limited information exists regarding exposure to heptachlor or heptachlor epoxide and mortality. One of the four reports available studied pesticide manufacturers (Wang and MacMahon 1979b), whereas the other three examined pesticide applicators (Blair et al. 1983; MacMahon et al. 1988; Shindell and Associates 1981; Wang and MacMahon 1979a). Exposure data were not available in any of these studies and none of them provided specific information for heptachlor or heptachlor epoxide. An occupational mortality study on workers employed in the manufacture of heptachlor and other chlorinated hydrocarbon pesticides for at least 3 months between 1952 and 1979 revealed no pattern of disease or medical condition that indicated that persons were at greater risk of adverse outcome than the general population (Shindell and Associates 1981). The only significant finding observed in workers employed at two facilities manufacturing chlordane or heptachlor and endrin was an excess of deaths from cerebrovascular disease, which was unrelated to duration of exposure or latency, and occurred exclusively after termination of employment (Wang and MacMahon 1979b). In professional pesticide applicators at three U.S. companies who were employed for 3 months or longer between 1967 and 1976, only deaths due to bladder cancer were significantly elevated in the applicators as a whole (Wang and MacMahon 1979a). In a separate analysis conducted for persons ever holding jobs as “termite control operators,” a group

more likely to be exposed to chlordane and heptachlor, bladder cancer was elevated in both the termite control operators and the group comprising the rest of the applicators. However, since confidence intervals were not provided, it is unknown whether this increase was statistically significant. A follow-up analysis of the same cohort extending to the end of 1984 reported that deaths due to cancer of the lung was the only outcome significantly elevated in the group as a whole (MacMahon et al. 1988). Separate analyses, as done in the earlier study, revealed that deaths due to lung cancer were not significantly elevated in the group with the highest likelihood of exposure to chlordane and heptachlor. In the last study of licensed male pesticide applicators in Florida, the standardized mortality ratio (SMR) for all causes of death was 103, but increased SMRs, although not statistically significant, were seen for leukemia, cancers of the brain, and lung cancer (Blair et al. 1983). The increased SMRs for brain and leukemia were based on small numbers. Mortality from lung cancer was related to years licensed, but could not be attributed to any specific pesticide due to lack of information on frequency and intensity of exposures. Furthermore, information on smoking was not available. In conclusion, the information available is insufficient to determine whether there is an association between exposure of workers to heptachlor or heptachlor epoxide and mortality.

No studies were located regarding death in animals after inhalation exposure to heptachlor or heptachlor epoxide.

3.2.1.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, musculoskeletal, hepatic, renal, dermal, or ocular effects in humans or animals after inhalation exposure to heptachlor or heptachlor epoxide.

Hematological Effects. The available data on potential hematological effects following inhalation exposure to heptachlor or heptachlor epoxide are limited to a case-control study of exterminators, gardeners, and agricultural workers exposed to several organochlorine pesticides (heptachlor among them) (Wang and Grufferman 1981). No dose-dependent causal relationship between exposure to several organochlorine pesticides and deaths from aplastic anemia was found.

No studies were located regarding hematological effects in animals after inhalation exposure to heptachlor or heptachlor epoxide.

No studies were located regarding the following effects in humans or animals after inhalation exposure to heptachlor or heptachlor epoxide:

3.2.1.3 Immunological and Lymphoreticular Effects

3.2.1.4 Neurological Effects

3.2.1.5 Reproductive Effects

3.2.1.6 Developmental Effects

3.2.1.7 Cancer

Several studies have examined the possible association between cancer and environmental and/or occupational exposure to chlordane and heptachlor (Epstein and Ozonoff 1987; MacMahon et al. 1988; Shindell and Associates 1981; Wang and MacMahon 1979a, 1979b). Several occupational cohorts showed that workers who were involved in the manufacture of chlordane and heptachlor did not have a significant increase in death from any type of cancer (MacMahon et al. 1988; Shindell and Associates 1981; Wang and MacMahon 1979a, 1979b). These occupational studies are presumed to reflect primarily inhalation exposure, with some concomitant dermal exposure. Among workers at pesticide manufacturing facilities, the SMR for bladder cancer was of borderline statistical significance (Wang and MacMahon 1979a). A follow-up study identified an increase in lung cancer, but the SMR for deaths from lung cancer in the group with the highest chance of exposure was not significant (MacMahon et al. 1988). No information on cigarette smoking was obtained from the participants. A retrospective mortality study conducted on male workers engaged in chlordane, heptachlor, and endrin manufacture for at least 3 months also showed a slight excess of lung cancer compared to the general U.S. population, but the increase was not statistically significant (Wang and MacMahon 1979b). Leukemia was associated with exposure to chlordane and heptachlor following home termiticide use (Epstein and Ozonoff 1987). An increased risk of prostate cancer was found among Hispanic farm workers potentially exposed to heptachlor (Mills and Yang 2003). Among the workers employed in counties with the highest heptachlor use, the odds ratio (adjusted for age, surrogates for exposure initiation, and duration) was 2.01 (95% confidence interval of 1.12–3.60).

It is difficult to determine from these studies whether or not exposure to heptachlor or heptachlor epoxide causes cancer. Although some studies suggest an association between exposure and cancer, other studies have not found significant associations, and there were many limitations among the studies. Limitations include the lack of quantitative exposure information, concomitant exposure to other chemicals, lack of

control measures for confounding factors, lack of information on diet, smoking habits, and liver function, and lack of complete occupational history, including other potential causal factors such as genetic disposition or immunologic disorders.

No studies were located regarding cancer in animals after inhalation exposure to heptachlor or heptachlor epoxide.

3.2.2 Oral Exposure

3.2.2.1 Death

No studies were located regarding death in humans after oral exposure to heptachlor or heptachlor epoxide.

Acute oral LD_{50} values for heptachlor in rodents (rats, mice, hamsters, and guinea pigs) and rabbits range from 40 to 2,302 mg/kg (purity ranging from unspecified to 99.9%) (Ben-Dyke et al. 1970; Berman et al. 1995; Eisler 1968; Gaines 1969; Gak et al. 1976; Lehman 1951; Podowski et al. 1979; Sperling et al. 1972; Sun 1972). The differences in the purity of the administered heptachlor may have influenced lethality. Pure heptachlor appears to be more lethal than technical-grade heptachlor (Berman et al. 1995; Podowski et al. 1979). Acute oral LD_{50} values for heptachlor epoxide in rodents (rats and mice) and rabbits range from 39 to 144 mg/kg (Eisler 1968; Podowski et al. 1979; Sperling et al. 1972).

Heptachlor can be converted to its photoisomer, photoheptachlor, in the presence of sunlight or ultraviolet light. This photolysis can take place on plant leaves. Photoheptachlor was found to be more toxic to rats than heptachlor or heptachlor epoxide; the LD_{50} for photoheptachlor was 3.8 mg/kg (Podowski et al. 1979).

The results of the non-LD_{50} studies indicate that the lethal dose decreases with duration of exposure. A single gavage dose of up to 129 mg/kg technical-grade heptachlor (73% heptachlor, 26% chlordane) did not result in mortality in rats (Berman et al. 1995). However, repeated doses of 23 or 69 mg/kg/day of technical-grade heptachlor resulted in 100% mortality after 6 or 3 doses, respectively (Berman et al. 1995; Moser et al. 1995). Increases in mortality were also observed in male rats exposed to 30 mg/kg/day and female rats exposed to 15 mg/kg/day technical-grade heptachlor (73% heptachlor, 22% chlordane, 5% nonachlor) in the diet for 6 weeks, followed by a 2-week period of observation (NCI 1977). No deaths were observed at 14 mg/kg/day in males and 7.6 mg/kg/day in females.

Similar lethal doses were observed in mice and mink exposed to heptachlor in the diet for intermediate durations. The lethal doses were 14 mg/kg/day for mice fed diets containing technical-grade heptachlor (73% heptachlor, 22% chlordane, 5% nonachlor) for 6 weeks, followed by a 2-week period of observation (NCI 1977) and 6.19 mg/kg/day for mink fed technical-grade heptachlor (72% heptachlor) for 28 days (Aulerich et al. 1990) or 1.7 mg/kg/day for 181 days (Crum et al. 1993). No alterations in mortality were observed in mice exposed to doses of 5.2 mg/kg/day or in mink at doses of 5.67 mg/kg/day. In chronic-duration studies, no statistically significant alterations in survival were observed in male or female mice exposed to 2.4 or 3.0 mg/kg/day, respectively, technical-grade heptachlor in the diet for 80 weeks (NCI 1977).

All reliable LD_{50} values and all reliable LOAEL values for death in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.2 Systemic Effects

No studies were located regarding respiratory, musculoskeletal, or dermal effects in humans or animals after oral exposure to heptachlor or heptachlor epoxide.

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

Cardiovascular Effects. The information regarding cardiovascular effects in humans associated with heptachlor and heptachlor epoxide exposure is limited to a study that found statistically higher heptachlor epoxide serum levels among individuals with moderate to severe arterosclerosis (Pines et al. 1986). This report cannot be construed as showing a causal relationship between heptachlor epoxide exposure and arteriosclerosis because no adjustments for other risk factors were made.

Animal data are limited to a study that found increases in relative heart weight (statistical significance not reported) in female rats exposed to heptachlor in the diet 5 days/week for 4 weeks (Enan et al. 1982). The investigators noted that 10 mg/kg heptachlor was added to the diet; it is not known if this is a dietary concentration or dose. The biological significance of this effect is not known, particularly since no information on body weight changes or food intake were provided and a histological examination was not performed.

Table 3-1 Levels of Significant Exposure to Heptachlor and Heptachlor Epoxide - 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	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Fischer- 344)	once (GO)				230 F (LD50)	Berman et al. 1995 heptachlor	
2	Rat (Sherman)	1 d 1 x/d (GO)				100[b] M (LD50) 162 F (LD50)	Gaines 1969 heptachlor	
3	Rat (NS)	once (GO)				105 (LD50)	Gak et al. 1976 heptachlor	
4	Rat (Fischer- 344)	Gd 6-15 (GO)				12 F (38% mortality in pregnant rats)	Narotsky et al. 1995 heptachlor	
5	Rat (NS)	once				71 M (LD50)	Podowski et al. 1979 heptachlor	
6	Rat (NS)	once				60 M (LD50)	Podowski et al. 1979 heptachlor epoxide	
7	Mouse (NS)	once (GO)				70 (LD50)	Gak et al. 1976 heptachlor	
8	Hamster (NS)	once (GO)				100 (LD50)	Gak et al. 1976 heptachlor	

Table 3-1 Levels of Significant Exposure to Heptachlor and Heptachlor Epoxide - 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	Comments
Systemic								
9	Rat (Fischer- 344)	14 d 1 x/d (GO)	Hepatic	2 F	7 F (hepatocytomegaly)		Berman et al. 1995 heptachlor	
10	Rat (Wistar)	once (GO)	Hepatic		60 F (increased serum ALT and aldolase levels, decreased liver ALT and aldolase levels, vacuolated cells, pyknotic nuclei)		Krampl 1971 heptachlor	
11	Rat (Wistar)	3, 7, or 14 d (GO)	Hepatic		7 F (decreased liver ALT and aldolase levels, increased serum ALT and aldolase levels; monocellular necrosis and vacuolar dystrophy)		Krampl 1971 heptachlor	
12	Rat (Wistar)	14 d (F)	Resp	5			Pelikan 1971 heptachlor	
			Cardio	5				
			Gastro		5 (slightly hyperemic stomach and intestinal wall)			
			Hepatic	5				
			Renal	5				
			Bd Wt	5				

Table 3-1 Levels of Significant Exposure to Heptachlor and Heptachlor Epoxide - 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	Comments
13	Mouse (albino)	11 d (W)	Endocr			87 F (atrophy in adrenal cortex)	Akay et al. 1982 heptachlor	
Immuno/ Lymphoret								
14	Rat (Fischer- 344)	once (GO)		69 F	129 F (necrotic lymphocytes in spleen and thymus)		Berman et al. 1995 heptachlor	Limited to examination of spleen and thymus.
15	Rat (Fischer- 344)	14 d 1 x/d (GO)		69 F			Berman et al. 1995 heptachlor	Limited to examination of spleen and thymus.
16	Rat (Wistar)	14 d (F)		5			Pelikan 1971 heptachlor	Limited to examination of spleen.
Neurological								
17	Rat (Fischer- 344)	once (GO)			7 F (excitability)		Moser et al. 1995 heptachlor	
18	Rat (Fischer- 344)	14 d 1 x/d (GO)		2 F	7 F (increased arousal)		Moser et al. 1995 heptachlor	
Reproductive								
19	Rat (Wistar)	14 d (GO)				1.8[c] F (decreased fertility; increased resorptions)	Amita Rani and Krishnakumari 1995 heptachlor	
20	Mouse (CD-1)	1 d 1 x/d (G)		15 M			Arnold et al. 1977 heptachlor	

Table 3-1 Levels of Significant Exposure to Heptachlor and Heptachlor Epoxide - 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	Comments
21	Mouse (ICR)	5 d (G)		8 M			Epstein et al. 1972 heptachlor epoxide	
22	Mouse (ICR)	5 d (G)		10 M			Epstein et al. 1972 heptachlor	
Developmental								
23	Rat (Fischer- 344)	Gd 6-19 (GO)			4.5 (decreased pup body weight at pnd 6)		Narotsky and Kavlock 1995 heptachlor	
24	Rat (Fischer- 344)	Gd 6-15 (GO)		5.1 F	6.8 F (decreased pup body weight)	9 F (pup mortality)	Narotsky et al. 1995 heptachlor	
25	Rat (Sprague-Dawley)	Gd 10-21 (GO)			4.2 F (decreased righting reflex in pups)	8.4 F (decreased pup survival)	Purkerson-Parker et al. 2001b heptachlor	
INTERMEDIATE EXPOSURE								
Death								
26	Rat (Osborne-Mendel)	6 wk (F)				30 M (2/5 male rats died) 15 F[b] (4/5 female rats died)	NCI 1977 heptachlor	
27	Mouse (B6C3F1)	6 wk (F)				14 M (5/5 males died)	NCI 1977 heptachlor	
28	Mink (NS)	28 d (F)				6.2 M (3/8 died)	Aulerich et al. 1990 heptachlor	

Table 3-1 Levels of Significant Exposure to Heptachlor and Heptachlor Epoxide - 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	Comments
29	Mink (NS)	181 d (F)				1.7 F (67% mortality)	Crum et al. 1993 heptachlor	
Systemic								
30	Rat (albino)	21 d (G)	Endocr	1 M			Akhtar et al. 1996 heptachlor	Measured thyroid hormone levels.
			Bd Wt	1 M				
31	Rat (Wistar)	28 d (F)	Resp	5			Pelikan 1971 heptachlor	
			Cardio	5				
			Gastro		5 (thin mucous secretion covering the stomach and intestine mucosa)			
			Hepatic		5 (steatosis, 21-23% increased relative liver weight)			
			Renal	5				
			Bd Wt	5				

Table 3-1 Levels of Significant Exposure to Heptachlor and Heptachlor Epoxide - 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	Comments
32	Mouse (NS)	10 wk (F)	Hepatic		9.3 (hepatitis, necrosis, granuloma, congestion)		Akay and Alp 1981 heptachlor	No incidence data or statistical analysis reported.
			Renal		37 (granuloma)			
			Bd Wt		9.3 (unspecified decrease in body weight)			
33	Mouse (albino)	26 d (W)	Endocr			87 F (lipid accumulation and extensive degeneration and fibrosis in adrenal cortex)	Akay et al. 1982 heptachlor	
34	Mouse (DDY)	180 d ad lib (W)	Hepatic		6.9 M (increased serum ALT activity levels and liver weight)		Izushi and Ogata 1990 heptachlor	No histological examination.
			Bd Wt	6.9 M				
			Metab	6.9 M				
35	Mouse (DDY)	92 d 2 x/wk (GO)	Hepatic		10 M (increased serum ALT, alkaline phosphatase, and triglyceride levels, liver triglyceride levels, and liver weight)		Izushi and Ogata 1990 heptachlor	No histological examination.
			Bd Wt	10 M				
			Metab	10 M				

Table 3-1 Levels of Significant Exposure to Heptachlor and Heptachlor Epoxide - 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	Comments
36	Mink (NS)	28 d (F)	Bd Wt	3.1 M	5.7 M (22% decrease in body weight)		Aulerich et al. 1990 heptachlor	
Immuno/ Lymphoret								
37	Rat (Wistar)	28 d (F)		5			Pelikan 1971 heptachlor	Limited to examination of spleen.
38	Mouse (NS)	10 wk (F)		19	37 (splenic fibrosis)		Akay and Alp 1981 heptachlor	No incidence data or statistical analysis reported.
39	Mink (NS)	28 d (F)		5.7 M	6.2 M (49% decrease in spleen/brain weight)		Aulerich et al. 1990 heptachlor	
Neurological								
40	Mouse (NS)	10 wk (F)		9.3		19 F (difficulty standing, walking, and righting)	Akay and Alp 1981 heptachlor	
41	Mink (NS)	28 d (F)		5.7 M	6.2 M (clinical signs of hyperexcitability and incoordination)		Aulerich et al. 1990 heptachlor	
42	Mink (NS)	181 d (F)		1 F		1.7 F (hyperexcitability and seizures)	Crum et al. 1993 heptachlor	

Table 3-1 Levels of Significant Exposure to Heptachlor and Heptachlor Epoxide - 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	Comments
Reproductive								
43	Rat (Wistar)	70 d (GO)			0.65 M (decreased epididymal sperm count)	0.65 M (increased resorptions)	Amita Rani and Krishnakumari 1995 heptachlor	
44	Mouse (NS)	10 wk (F)				9.3 (100% infertility)	Akay and Alp 1981 heptachlor	
45	Mink (NS)	181 d (F)		1.7 F			Crum et al. 1993 heptachlor	Sperm motility or morphology.
Developmental								
46	Rat (Sprague-Dawley)	daily Gd 8-21, Ld 0-21 (GO)				5 F (increased pup mortality and decreased birth weights)	Lawson and Luderer 2004 heptachlor	
47	Rat (Sprague-Dawley)	Gd 12- pnd 7; pups exposed from pnd 7-21 or pnd 7-42 (GO)			0.03 (impaired spatial memory)		Moser et al. 2001 heptachlor	
48	Rat (Sprague-Dawley)	Gd 10- Ld 7; pups exposed on days 7-21 or 42 (GO)		0.3	3 (decrease in righting reflex)	8.4 (decreased pup survival)	Purkerson-Parker et al. 2001b heptachlor	
49	Rat (Sprague-Dawley)	Gd 12- pnd 71; pups exposed to day 42 (GO)			0.03[d] (suppression of immune response to sheep RBC in offspring)		Smialowicz et al. 2001 heptachlor	

Table 3-1 Levels of Significant Exposure to Heptachlor and Heptachlor Epoxide - 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	Comments
50	Mink (NS)	181 d (F)		1		1.7 (increased stillbirths and decreased kit survival)	Crum et al. 1993 heptachlor	
CHRONIC EXPOSURE								
Cancer								
51	Mouse (B6C3F1)	80 wk (F)				2.4 M (hepatocellular carcinoma)	NCI 1977 heptachlor	

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

b Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-1. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

c Used to derive an acute oral minimal risk level (MRL) of 0.0006 mg/kg/day; dose divided by an uncertainty factor of 1000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability) and a modifying factor of 3 for the use of a serious endpoint.

d Used to derive an intermediate oral minimal risk level (MRL) of 0.0001 mg/kg/day; dose divided by an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

ALT = alanine aminotransferase; Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; (GO) = gavage in oil; Ld = lactation day; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolic; NOAEL = no-observed-adverse-effect level; NS = not specified; pnd = post-natal day; RBC = red blood cell(s); Resp = respiratory; x = time(s); (W) = drinking water; wk = week(s)

Figure 3-1 Levels of Significant Exposure to Heptachlor and Heptachlor Epoxide - Oral

Acute (≤14 days)

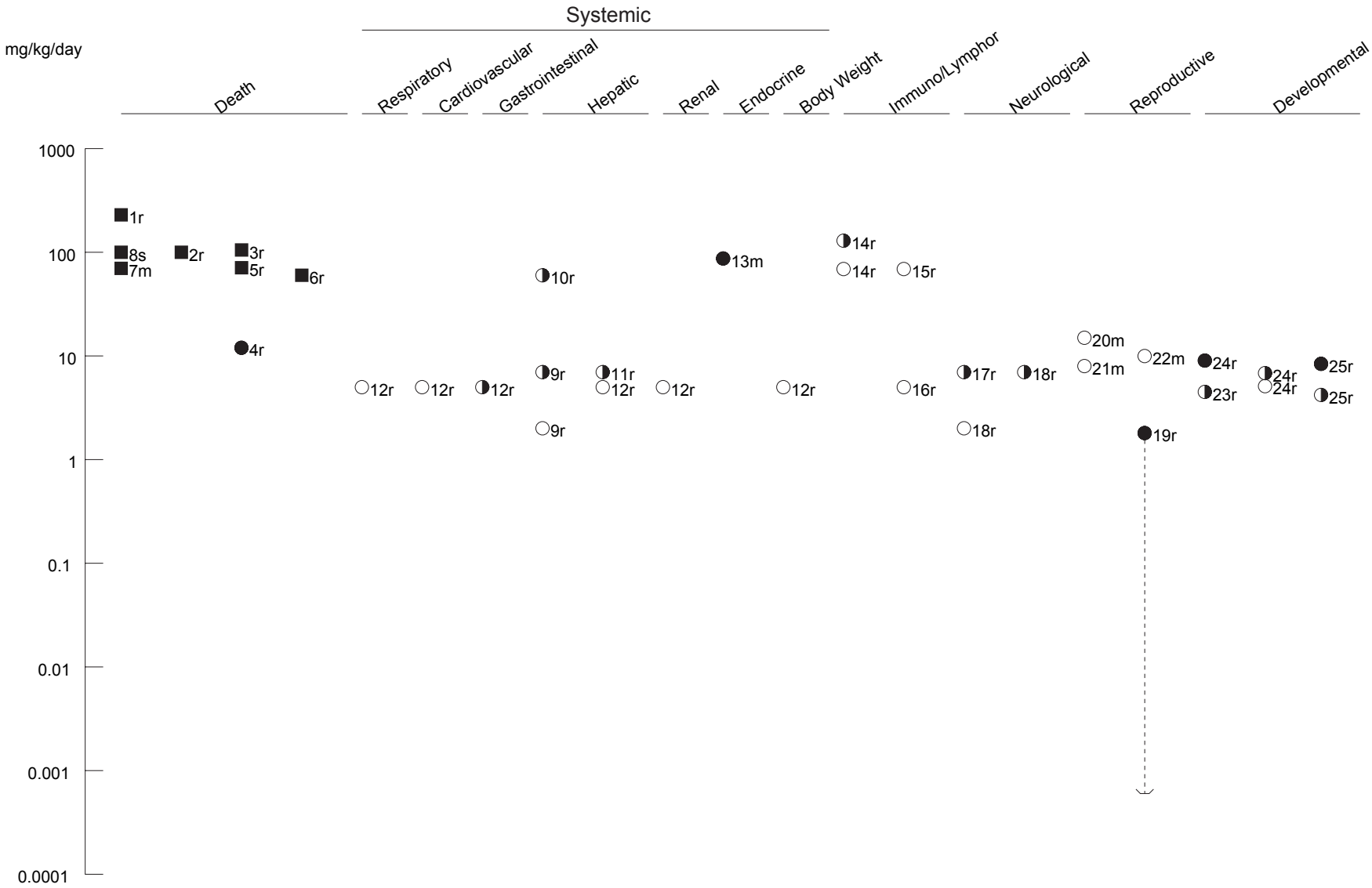


Figure 3-1 Levels of Significant Exposure to Heptachlor and Heptachlor Epoxide - Oral *(Continued)*

Intermediate (15-364 days)

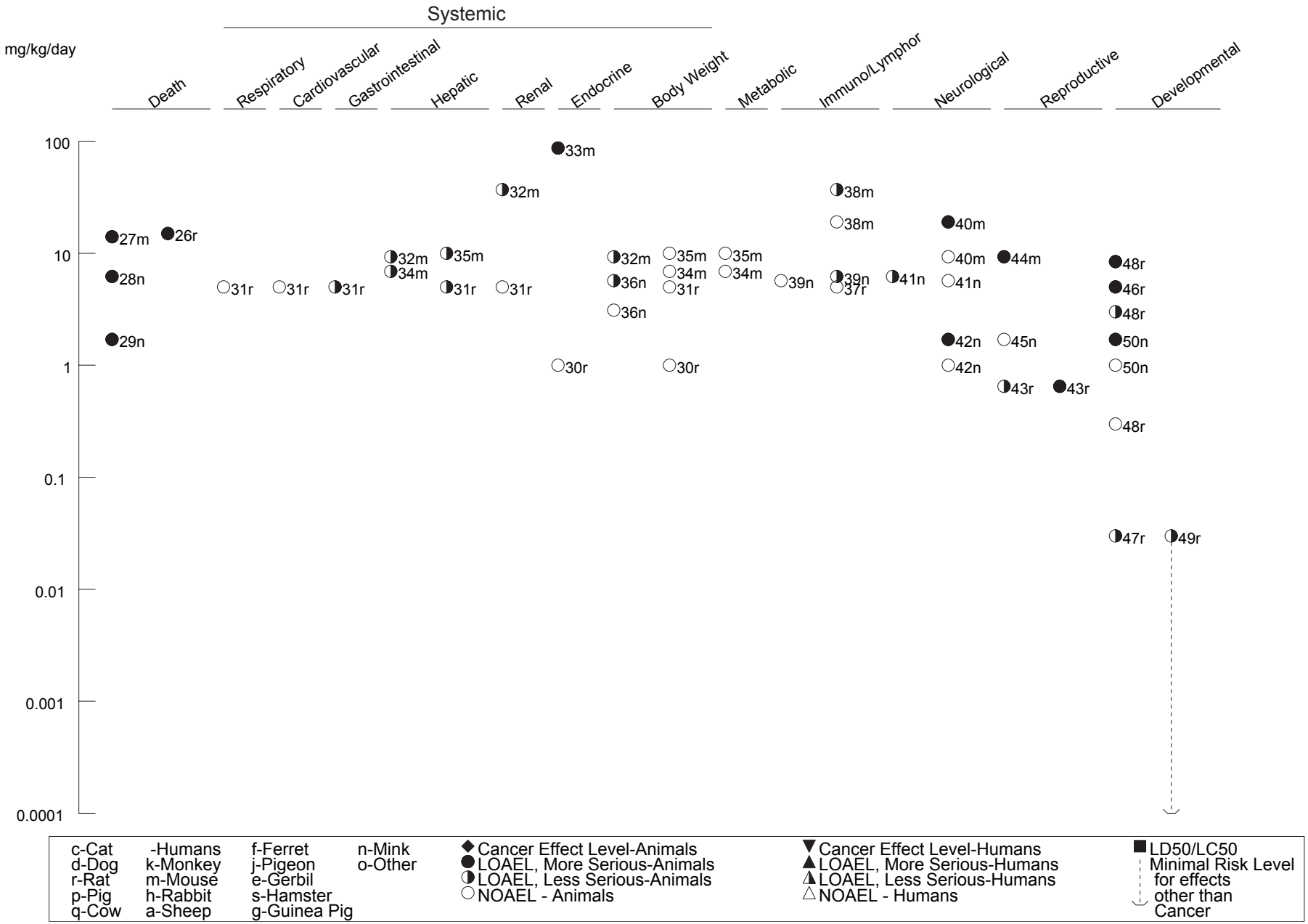
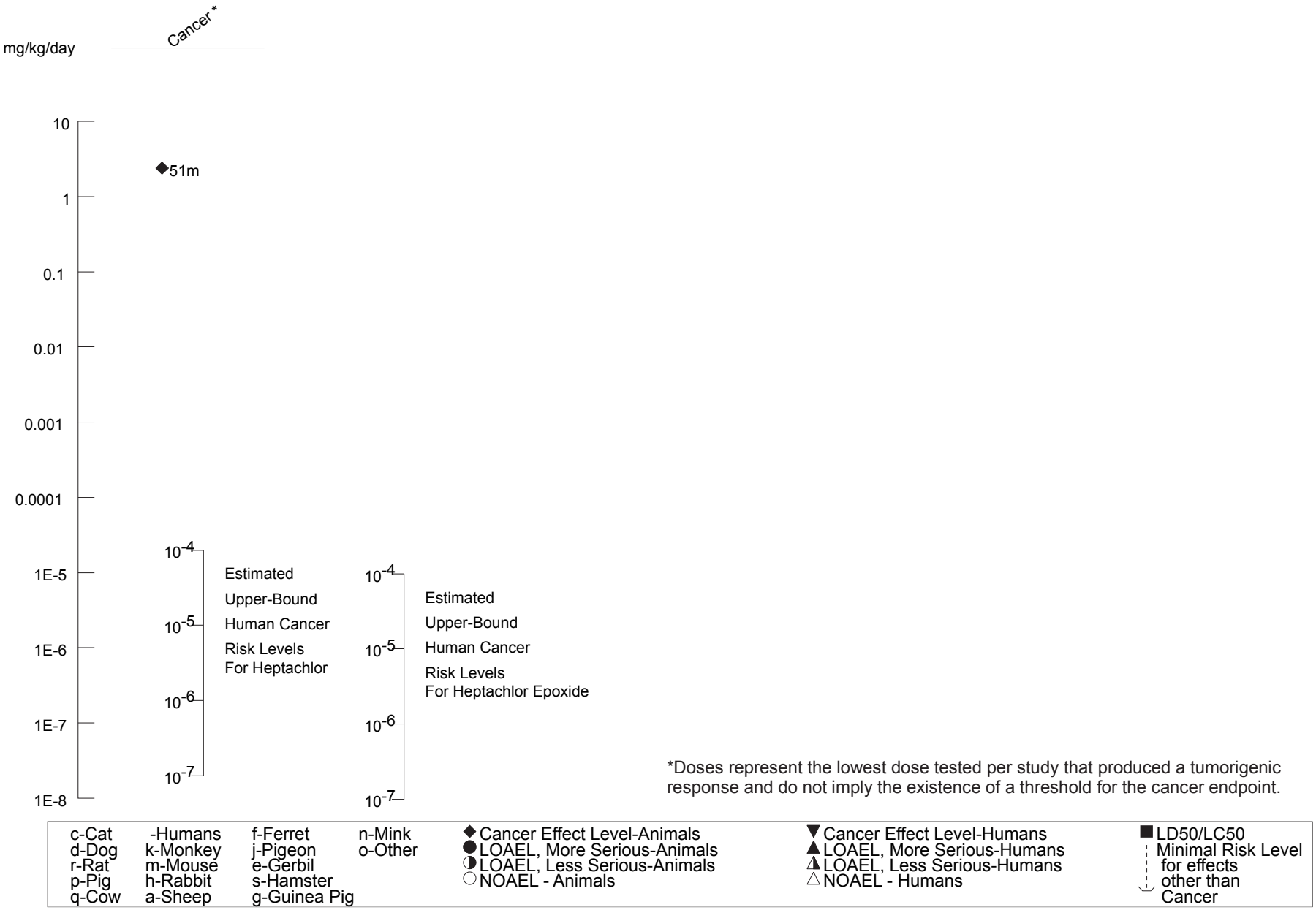


Figure 3-1 Levels of Significant Exposure to Heptachlor and Heptachlor Epoxide - Oral *(Continued)*

Chronic (≥365 days)



Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after oral exposure to heptachlor or heptachlor epoxide. Gross necropsy showed that the stomach and intestinal walls were slightly hyperemic in rats exposed to 5 mg/kg/day of heptachlor in the diet for 14 days (Pelikan 1971); after 28 days of exposure, the mucosa of the stomach and intestine was covered by a thin mucus secretion. No histological alterations were observed in gastrointestinal tissues at either duration. Ulceration and bloody mucus were observed in the stomachs of mink exposed to 1.7 or 3.1 mg/kg/day heptachlor in the diet for 181 days (Crum et al. 1993). These doses were also associated with mortality and pronounced neurological effects; the investigators also noted that the animals stopped eating 1–2 weeks prior to death.

Hematological Effects. No studies were located regarding hematological effects in humans after oral exposure to heptachlor or heptachlor epoxide; one animal study examining hematological end points was identified. A statistically significant increase in total leukocyte levels was observed in rats exposed to heptachlor in the diet for 1, 7, or 28 days (Enan et al. 1982). No alterations in erythrocyte levels were found. As noted previously, it is not known if the reported concentration of 10 mg/kg is a dietary concentration or dose.

Hepatic Effects. Very limited information is available regarding hepatic effects of heptachlor or heptachlor epoxide in humans. Evaluation of individuals exposed for an unspecified period of time to contaminated raw milk products from cattle fed heptachlor-contaminated feed revealed significantly elevated serum levels of heptachlor metabolites relative to national background levels from National Health and Nutrition Examination Survey (NHANES) II and to levels monitored in unexposed reference subjects (Stehr-Green et al. 1986, 1988). Compared to the reference subjects, no significant alterations in serum liver enzyme activity levels were found, and no hepatomegaly was detected by clinical examination. This information is insufficient to draw any meaningful conclusion regarding liver effects of heptachlor in humans.

A number of animal studies have reported liver effects following oral exposure to heptachlor. Although collectively, the studies indicate that the liver is a target of toxicity, interpretation of many of the individual studies is limited by the lack of statistical analysis and the incomplete descriptions of the observed effects (including incidence data). No histological alterations and a small increase (15–17%) in relative liver weight were observed in rats exposed to 5 mg/kg/day in the diet for 14 days (Pelikan 1971). In another acute exposure study, hepatocytomegaly was observed at 7 mg/kg/day in rats administered

heptachlor in corn oil via gavage for 14 days (Berman et al. 1995). Monocellular necrosis and vacuolar dystrophy (statistical significance not reported) were observed in rats administered 7 mg/kg/day heptachlor in corn oil for 3, 7, or 14 days (Krampl 1971); decreases in liver alanine aminotransferase and aldolase activity levels and increases in serum alanine aminotransferase and aldolase activity levels were also observed at this dose level. A single dose of 60 mg/kg heptachlor resulted in similar enzyme activity changes (Krampl 1971); minimal evidence of single monocellular necrosis with inflammatory reaction, vacuolated cells, and pyknotic nuclei were observed 72 hours after dosing. The investigator noted that the histological alterations paralleled the time course for the enzyme changes.

At longer durations, the severity of the liver effects appeared to increase. Steatosis was observed in rats exposed to 5 mg/kg/day in the diet for 28 days (Pelikan 1971) and hepatitis, necrosis, granuloma, and congestion were observed in mice fed diets containing 9.3 mg/kg/day heptachlor for 10 weeks (Akay and Alp 1981). As with acute exposure, intermediate exposure to heptachlor also resulted in alterations in serum enzyme levels; increases in serum aldolase, alanine aminotransferase, and alkaline phosphatase activity levels were observed at 6.9 mg/kg/day and higher (Izushi and Ogata 1990; Krampl 1971). Additionally, increases in serum and hepatic triglyceride levels were observed in mice administered 10 mg/kg heptachlor in olive oil twice weekly (2.9 mg/kg/day) for 92 days (Izushi and Ogata 1990), but not in mice fed 6.9 mg/kg/day in the diet for 180 days (Izushi and Ogata 1990). Liver effects have also been observed in non-rodent experimental animals. Ultrastructural changes indicative of liver cell damage were observed in a small number of pigs administered 2 mg/kg/day “heptachlorine” in the diet for 78 days (Dvorak and Halacka 1975; Halacka et al. 1974); no histological alterations were observed. Fatty liver was reported in mink exposed to 6.2 mg/kg/day heptachlor in the diet for 28 days (Aulerich et al. 1990) or 1.7 mg/kg/day in the diet for 181 days (Crum et al. 1993). In both studies, these doses were associated with increased mortality. One chronic exposure study reported no clear effects on liver function (BSP clearance) in rats exposed to 6 mg/kg/day for 18 months (Mestitzova 1967).

Renal Effects. No studies were located regarding renal effects in humans after oral exposure to heptachlor or heptachlor epoxide. Several studies have examined the potential of heptachlor to induce renal effects in animals. No histological alterations were observed in the kidneys from rats exposed to 5 mg/kg/day heptachlor in the diet for 14 or 28 days (Pelikan 1971) or from rats exposed to 6 mg/kg/day for 18 months (Mestitzova 1967). Increased blood urea levels were observed after 7 or 28 days in rats exposed to 10 mg/kg heptachlor in the diet (Enan et al. 1982); an increase and decrease in relative kidney weight were observed after 7 or 28 days, respectively. As noted previously, interpretation of the results of this study is limited by the poor reporting of the dose. Granulomas were observed in the kidneys of mice

that received 37 mg heptachlor/day for 10 weeks (Akay and Alp 1981); however, no incidence data or statistical analysis was reported, limiting the interpretation of the results. A significant decrease in kidney-to-brain-weight ratio and granulation and discoloration of kidneys were reported in minks fed 6.2 mg/kg/day of heptachlor daily for 28 days (Aulerich et al. 1990); the incidence of kidney damage was not reported.

Endocrine Effects. There is limited information on the potential of heptachlor to induce endocrine effects. Cortical atrophy and slight hypertrophy in the zona glomerulosa of the adrenal gland was observed in mice exposed to 87 mg/kg/day for 11 days (Akay et al. 1982). When the exposure was continued for 26 days, heavy lipid accumulation, congestion, cell degeneration, and extensive fibrosis were observed in the adrenal cortex (Akay et al. 1982). The interpretation of these findings is limited by the poor reporting of the study and the lack of incidence data. One other study examined endocrine end points; no alterations in thyroxine, triiodothyronine, or thyroid stimulating hormone levels were observed in rats administered 1 mg/kg/day via gavage for 21 days (Akhtar et al. 1996).

Ocular Effects. No studies were located regarding ocular effects in humans after oral exposure to heptachlor or heptachlor epoxide. Lens cataracts were observed in 22% of adult rats exposed to 6 mg/kg/day heptachlor in the diet for 4.5–9.5 months; cataracts were not observed in the controls (Mestitzova 1967). As discussed in the developmental toxicity section, cataracts were also observed in the F_1 and F_2 offspring. Other studies have not reported this finding among adults, although no studies were specifically designed to assess this end point. Additionally, Narotsky and Kavlock (1995) did not find increases in cataracts in the offspring of rats administered up to 6 mg/kg/day heptachlor via gavage on gestational days 6–19.

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to heptachlor or heptachlor epoxide. The available animal data do not suggest that oral exposure to heptachlor adversely affects body weight gain in the absence of decreases in food consumption. No alterations in body weight were observed in rats or mice exposed daily to doses as high as 1 and 6.9 mg/kg/day, respectively, for intermediate durations (Akhtar et al. 1996; Izushi and Ogata 1990) or mice administered 10 mg/kg 2 times/week for 92 days (Izushi and Ogata 1990). Decreases in body weight gain were observed in mink exposed to heptachlor in the diet at doses of 5.7 mg/kg/day for 28 days (Aulerich et al. 1990) or 1.7 mg/kg/day for 181 days, which included pregnancy and lactation periods (Crum et al. 1993); significant decreases in food consumption were observed in both studies.

Metabolic Effects. No studies were located regarding metabolic effects in humans after oral exposure to heptachlor or heptachlor epoxide. Studies in animals suggest that exposure to heptachlor may disrupt carbohydrate metabolism. Significant decreases in liver glycogen levels, increases in liver and kidney gluconeogenic enzymes, and increases in blood glucose levels were observed in rats administered a single dose of 200 mg/kg heptachlor (Kacew and Singhal 1973). Decreases in liver glycogen levels and increases in blood glucose were also observed in rats exposed to 10 mg/kg for 1, 7, or 28 days (Enan et al. 1982). The investigators noted that 10 mg/kg was added to the diet; it is not known if this is the dietary concentration (dose would be approximately 0.9 mg/kg/day) or dose. No alterations in blood glucose levels were observed in mice administered 6.9 mg/kg/day heptachlor in the diet for 180 days or 10 mg/kg via gavage 2 times/week (Izushi and Ogata 1990).

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological or lymphoreticular effects in humans after oral exposure to heptachlor or heptachlor epoxide.

No studies were located that specifically investigated the effects on the immune system of oral exposure to heptachlor or heptachlor epoxide in adult animals. However, several studies have found alterations in the lymphoreticular system. Necrotic lymphocytes were observed in the spleen and thymus of rats administered a single dose of 129 mg/kg heptachlor via gavage (Berman et al. 1995); the investigators noted that the effect may have been secondary to generalized toxicity. Fibrosis was observed in the spleens of mice exposed to 37 mg/kg/day heptachlor in the diet for 10 weeks (Akay and Alp 1981). Enlarged and hyperemic spleens were observed in rats exposed to 5 mg/kg/day heptachlor in the diet for 14 or 28 days (Pelikan 1971); however, no apparent alterations in relative spleen weight or histological alterations were observed and the gross changes were not considered to be biologically significant. A decrease in spleen-to-brain-weight ratio was reported in minks receiving 6.2 mg/kg/day heptachlor in the diet for 28 days (Aulerich et al. 1990); this dose was also associated with mortality, weight loss, and decreased food consumption.

The highest LOAEL values for lymphoreticular effects in each species following intermediate exposure are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to heptachlor or heptachlor epoxide.

Several studies in animals have reported adverse neurological effects shortly after exposure to heptachlor. At lethal doses, tremors and convulsions were observed in rats (Lehman 1951). Hyperexcitability, incoordination, and seizures were also observed in mink exposed to lethal doses (1.7 or 6.2 mg/kg/day) for intermediate durations (Aulerich et al. 1990; Crum et al. 1993). At nonlethal doses, alterations in a number of functional observational battery tests indicative of excitability were observed in rats following a single dose or 14 doses of 7 mg/kg (Moser et al. 1995); the excitability changes included increased arousal and reactivity to removal from the home cage and handling. The persistence of the effect was directly related to dose level. Decreases in motor activity and hunched posture in the home cage was observed 4 hours after a single dose of 129 mg/kg (Moser et al. 1995). Another study conducted by this group (Moser et al. 2003) found decreases in motor activity, increases in forelimb and hindlimb grip strength, handling reactivity and arousal, gait abnormalities, tremors, and piloerection in rats receiving gavage doses of 1–14 mg/kg/day for 10 days; a LOAEL cannot be identified from this study because the investigators did not provide data for individual end points or dose levels. Similar to the effects noted in the Moser studies, Akay and Alp (1981) reported difficulty in standing, walking, and righting in mice exposed to 19 mg/kg/day heptachlor in the diet for 10 weeks. In addition to these effects observed in mature animals, adverse neurological effects have been observed in the offspring of rats exposed to heptachlor during gestation, lactation, and postnatally; these studies are discussed in Section 3.2.2.6.

Statistically significant changes in electroencephalogram (EEG) patterns were reported in mature female rats administered heptachlor in the diet at levels of 1 and 5 mg/kg/day for three generations (Formanek et al. 1976). Interpretation of these findings is difficult because details of the dosing, the procedures used, and conditions of the rats were not described.

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species following intermediate exposure are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.5 Reproductive Effects

Significantly higher levels of heptachlor epoxide were detected in the sera of a group of women identified through hospital records with premature delivery than in the sera of a control group with normal delivery

(Wassermann et al. 1982). However, sera levels of 8 of the 10 organochlorine pesticides for which analytical data were obtained were all significantly higher in the premature delivery group. In addition, route, duration, and level of exposure information was not reported. Heptachlor epoxide has been detected in stillborn infant brain, adrenal, lung, heart, liver, kidneys, spleen, and adipose tissue, indicating transplacental transfer of heptachlor or heptachlor epoxide (Curley et al. 1969). These studies also reported the presence of polychlorinated biphenyls (PCBs), lindane, and dieldrin in the samples. It is difficult to assess the causal relationship between adverse reproductive outcome in humans and exposure to heptachlor and heptachlor epoxide due to lack of control for confounding factors such as smoking and concomitant exposure to other pesticides and lack of completeness of report data. No adverse effects on reproduction (no decrease in fertility, no increase in fetal or neonatal deaths) were reported by Le Marchand et al. (1986) among women of child-bearing age following ingestion of heptachlor-containing milk in excess of 0.1 ppm for 27–29 months.

A number of animal studies have demonstrated that exposure to heptachlor can result in decreased fertility and increased pregnancy losses. Impaired fertility was reported in female rats administered via gavage 0.65 mg/kg/day heptachlor in groundnut oil for 14 days prior to mating (Amita Rani and Krishnakumari 1995) and male and female rats fed 0.25 mg/kg/day heptachlor for 60 days (Green 1970); 100% infertility was observed in mice fed 9.3 mg/kg/day heptachlor for 10 weeks (Akay and Alp 1981). No effect on fertility was observed in male mice administered via gavage 10 mg/kg/day heptachlor or 8 mg/kg/day heptachlor epoxide for 5 days (Epstein et al. 1972) or a single dose of 15 mg/kg heptachlor:heptachlor epoxide (25%:75%) (Arnold et al. 1977).

Significant increases in resorptions were observed in male and female rats receiving gavage doses of 0.65 or 1.8 mg/kg/day, respectively, heptachlor for 70 or 14 days, respectively, prior to mating to control animals (Amita Rani and Krishnakumari 1995) and male and female rats fed 0.25 mg/kg/day heptachlor for 60 days prior to mating and throughout gestation (Green 1970). An increase in the incidence of stillbirths was observed in mink fed a diet containing 1.7 mg/kg/day heptachlor for 42 days prior to mating and throughout gestation (Crum et al. 1993). Similarly, a decrease in litter size was observed in rats exposed to 6 mg/kg/day heptachlor in the diet for an unspecified portion of an 18-month study (Mestitzova 1967). No alterations in preimplantation losses or early fetal deaths were observed in control females mated to males administered via gavage 10 mg/kg/day heptachlor or 8 mg/kg/day heptachlor epoxide for 5 days (Epstein et al. 1972) or a single dose of 15 mg/kg/day heptachlor:heptachlor epoxide mixture (Arnold et al. 1977).

Other reproductive alterations include a decrease in epididymal sperm count in rats administered gavage doses of 0.65 mg/kg/day heptachlor for 70 days (Amita Rani and Krishnakumari 1995) and decreases in estradiol-17β and progesterone levels in rats gavaged with 1.8 mg/kg/day for 14 days (Amita Rani and Krishnakumari 1995). Vaginal bleeding was reported in some rats exposed to 2.0 or 4.0 mg/kg/day technical-grade heptachlor for 80 weeks (NCI 1977); however, the incidence and statistical significance were not reported.

All reliable LOAEL values for reproductive effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.6 Developmental Effects

Several studies have examined potential developmental effects in the children of women exposed to elevated levels of heptachlor or heptachlor epoxide. Between 1980 and 1982, the commercial supply of cow's milk for the Hawaiian island of Oahu was contaminated with heptachlor epoxide; the source of exposure was treated pineapple plants that were used as cattle feed. Cow milk fat levels of heptachlor measured in Hawaii during this time ranged from 0.12 to 5.00 ppm (EPA's action level is 0.1 ppm); in a prior analysis (1978–1980), the levels were comparable to the rest of the United States. Using hospital records, Le Marchand et al. (1986) examined a possible association between heptachlor epoxide exposure and birth defects. No increase in fetal or neonatal deaths or incidence of low birth weight infants were found in this study cohort. Of the 23 categories of major congenital malformations evaluated, 22 were found to be decreased in the study population when compared with cohorts from the other Hawaiian islands and from the U.S. general population for the same time period. One type of malformation (anomalies of the abdominal wall) was found to be slightly increased in the study cohort during the period of known exposure compared with the control cohorts. However, the baseline data for this type of malformation were not available prior to study initiation, and birth defects may be underreported. It was, therefore, not possible to document the temporal change in the incidence of this type of malformation. Since women who might not have consumed the contaminated milk were included in the study group, positive findings may have been diluted as a result of misclassification bias. A subsequent study of high school students born on Oahu and likely prenatally exposed to heptachlor epoxide was conducted by Baker et al. (2004b; available as an abstract). As compared to high school students living on Oahu since first grade (but not born on Oahu), an association between gestational exposure to heptachlor epoxide and lower neurobehavioral performance was found. In particular, impaired performance was found on tests of abstract concept formation, visual perception, and motor planning; this group also had more reported

behavioral problems. No significant associations between school-based performance measures, such as grade point average, and gestational heptachlor epoxide exposure were found.

Two studies examined possible associations between maternal heptachlor epoxide levels and early childhood development (Hertz-Picciotto et al. 2004) or birth weight (Gladen et al. 2003). An association between maternal serum heptachlor epoxide levels and their children's performance on a test of nonverbal perceptual reasoning was found in San Francisco residents. However, inclusion of PCBs in the model severely reduced the magnitude of the association (Hertz-Picciotto et al. 2004; only available as an abstract). The investigators concluded that the cognitive deficits were probably due to co-exposure to other compounds. Gladen et al. (2003) found no significant association between breast milk levels of heptachlor epoxide (taken 4–5 days after birth) and birth weight among residents of two cities in Ukraine.

Several animal studies have examined the potential developmental toxicity of heptachlor. *In utero* exposure to heptachlor doses of 5.0 mg/kg and higher has resulted in pup mortality (Lawson and Luderer 2004; Narotsky et al. 1995; Purkerson-Parker et al. 2001b). These doses are also associated with significant maternal toxicity such as mortality, convulsions, and/or weight loss; however, at 5.0 mg/kg/day, increased pup mortality was also observed in dams without overt signs of toxicity (Lawson and Luderer 2004).

Gestational exposure to lower doses results in decreases in pup body weight. The threshold for this effect appears to be around 4–5 mg/kg/day (Lawson and Luderer 2004; Narotsky and Kavlock 1995; Narotsky et al. 1995). No alterations in pup body weight were observed at 3 mg/kg/day (Moser et al. 2001; Purkerson-Parker et al. 2001b; Smialowicz et al. 2001). Exposure to heptachlor does not appear to result increased frequency of anomalies or abnormalities (Narotsky et al. 1995; Smialowicz et al. 2001). Additionally, heptachlor does not appear to impair the development of the reproductive system. No delays in vaginal opening or prepuce separation (indices of female and male puberty respectively) were observed in the offspring of rats administered via gavage to 3 mg/kg/day heptachlor on gestational day 12 through postnatal day 21 (Smialowicz et al. 2001) or 5 mg/kg/day on gestational days 8–21 and lactational days 1–21 (Lawson and Luderer 2004). Additionally, continued exposure of the offspring until postnatal day 42 and subsequent mating with untreated animals did not result in adverse reproductive or developmental outcomes (Smialowicz et al. 2001).

Developmental studies have found neurological and immunological effects in offspring. Gestational, lactational, and offspring exposure until postnatal day 21 or 42 to 3 mg/kg/day heptachlor resulted in

significant delays in righting reflex, likely due to a delay in the ontogeny of righting rather than an inability to perform the task (Moser et al. 2001; Purkerson-Parker et al. 2001b). No alterations in motor activity ontogeny were observed (Moser et al. 2001; Purkerson-Parker et al. 2001b). Some alterations in functional observation battery tests were observed in rats exposed to heptachlor during gestation, lactation, and postnatally until day 21 or 42 (Moser et al. 2001). Many of these alterations were only significant at the lowest dose tested (0.03 mg/kg/day). In water maze tests, exposure to 0.03 mg/kg/day heptachlor and higher resulted in slowed acquisition of a spatial task and impaired recall (Moser et al. 2001). This was observed in rats exposed *in utero*, during lactation, and until postnatal day 42, but not in rats exposed until postnatal day 21.

Smialowicz et al. (2001) found a significant suppression of the immune response to sheep red blood cells in rats exposed to 0.03 mg/kg/day *in utero*, during lactation, and postnatally until day 42 of age. No significant alterations in the response to T-cell mitogens or in delayed-type and contact hypersensitivity were observed. A decrease in $OX12^{+}OX19^{-}$ splenic populations was observed at 3.0 mg/kg/day.

The reliable LOAEL values for developmental effects in rats following intermediate and chronic exposure are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.7 Cancer

There is limited information on the carcinogenicity of heptachlor or heptachlor epoxide in humans following oral exposure; several studies have examined the possible association between heptachlor epoxide tissue levels and cancer risk. Interpretation of the studies is limited by the lack of information on heptachlor exposure (including the route of exposure), variables that may affect organochlorine levels (including diet and body mass index), and possible concomitant exposure to other chemicals. No significant associations were found for endometrial cancer in women in the United States (Sturgeon et al. 1998) or breast cancer in Norwegian women (Ward et al. 2000). Another study found a significant association between heptachlor epoxide levels in breast tissue and the prevalence of breast cancer (Cassidy et al. 2005). Two case control studies examined the possible association between heptachlor epoxide levels and non-Hodgkin's lymphoma. One study found a significant association among individuals with the highest heptachlor epoxide adipose levels (odds ratio of 3.41, 95% confidence interval of 1.89–6.16) (Quintana et al. 2004), whereas the other study did not found a significant association between serum heptachlor epoxide levels and non-Hodgkin's lymphoma (Cantor et al. 2003).

Animal studies provide some evidence for the carcinogenicity of heptachlor. Significant increases in the incidence of hepatocellular carcinoma were observed in male and female mice exposed to time-weighted average (TWA) doses of 2.4 or 3.0 mg/kg/day, respectively, technical-grade heptachlor (72% heptachlor, 20% chlordane) in the diet for 80 weeks. Although increases in liver tumors were also observed at a lower dose (0.8 mg/kg/day for males and 1.2 mg/kg/day for females), the incidence was not significantly different than controls (NCI 1977). No significant increases in neoplastic tumor incidence were observed in male or female rats similarly exposed to technical-grade heptachlor TWA doses of 3.9 or 2.6 mg/kg/day, respectively (NCI 1977). Although a statistically significant increase in the incidence of follicular cell neoplasms (adenomas and carcinomas) was observed in the thyroid of female rats fed a TWA dose of 2.0 mg/kg/day technical-grade heptachlor for 80 weeks, the study investigators did not judge the alterations to be sufficient to clearly indicate a carcinogenic effect in the thyroid gland (NCI 1977). No other significant alterations were observed in the rats (NCI 1977). The Cancer Effect Level (CEL) in mice from chronic exposure to heptachlor is recorded in Table 3-1 and plotted in Figure 3-1.

The positive carcinogenicity findings of the mouse NCI (1977) study is supported by evidence that heptachlor is a tumor promoter. Dietary administration of ≥0.65 mg/kg/day heptachlor (97.6% purity) for 25 weeks promoted the development of hepatocellular foci and hepatocellular neoplasms in male mice previously initiated with 3.8 mg/kg/day diethylnitrosamine in drinking water for 14 weeks (Williams and Numoto 1984).

EPA has classified heptachlor and heptachlor epoxide in Group B2 (probable human carcinogen) (IRIS 2006). EPA has derived an oral slope factor of 4.5 per (mg/kg)/day for heptachlor and 9.1 per (mg/kg)/day for heptachlor epoxide. The doses corresponding to cancer risk levels ranging from 10^{-4} to 10^{-7} are $2.0x10^{-5}$–$2.0x10^{-8}$ mg/kg/day for heptachlor and $1.0x10^{-5}$–$1.0x10^{-8}$ mg/kg/day for heptachlor epoxide as indicated in Figure 3-1. 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. The International Agency for Research on Cancer (IARC) has classified heptachlor and heptachlor epoxide as Group 2b chemicals (possibly carcinogenic to humans) (IARC 2001).

3.2.3 Dermal Exposure

There is very little information on dermal exposures in either humans or animals. Most occupational exposures to heptachlor and heptachlor epoxide are assumed to be some combination of inhalation and

dermal exposure, but there are no data to quantify the relative contribution of each route. The occupational studies on pesticide workers are discussed in Section 3.2.1.

3.2.3.1 Death

No studies were located regarding death in humans after dermal exposure to heptachlor or heptachlor epoxide.

For heptachlor dissolved in xylene and administered once, Gaines (1969) reported dermal LD_{50} values in Sherman rats of 195 mg/kg (males) and 250 mg/kg (females).

3.2.3.2 Systemic Effects

No studies were located regarding systemic effects in humans or animals after dermal exposure to heptachlor or heptachlor epoxide.

No studies were located regarding the following health effects in humans or animals after dermal exposure to heptachlor or heptachlor epoxide:

3.2.3.3 Immunological and Lymphoreticular Effects
3.2.3.4 Neurological Effects
3.2.3.5 Reproductive Effects
3.2.3.6 Developmental Effects
3.2.3.7 Cancer

3.3 GENOTOXICITY

There are limited mammalian *in vivo* data on the genotoxicity of heptachlor or heptachlor epoxide. Heptachlor, heptachlor epoxide, and a mixture of heptachlor and heptachlor epoxide (25:75) were found to be negative in *in vivo* dominant lethal studies in the germ-line cells of male Charles River or Swiss mice (Arnold et al. 1977; Epstein et al. 1972).

Several *in vitro* studies have examined the genotoxicity of heptachlor or heptachlor epoxide (Table 3-2). The available weight of evidence suggests that neither compound alters the frequency of gene mutations in prokaryotic organisms (Glatt et al. 1983; Marshall et al. 1976; NTP 1987; Probst et al. 1981; Zeiger et

Table 3-2. Genotoxicity of Heptachlor and Heptachlor Epoxide In Vitro

Species (test system)	End point	Results		Chemical form	Reference
		With activation	Without activation		
Prokaryotic organisms:					
Salmonella typhimurium (histidine reversion)	Gene mutation	−	−	Heptachlor	Zeiger et al. 1987
S. typhimurium (Ames assay)	Gene mutation	−	−	Heptachlor	Marshall et al. 1976; NTP 1987
S. typhimurium (Ames assay)	Gene mutation	−	−	Heptachlor epoxide	Marshall et al. 1976; NTP 1987
S. typhimurium (Ames assay)	Gene mutation	+	−	Heptachlor	Gentile et al. 1982
S. typhimurium (modified Ames assay)	Gene mutation	−	−	Heptachlor	Probst et al. 1981
S. typhimurium (modified Ames assay)	Gene mutation	−	−	Heptachlor epoxide	Glatt et al. 1983
Escherichia coli (modified Ames assay)	Gene mutation	−	−	Heptachlor	Probst et al. 1981
S. typhimurium (disc assay)	DNA damage	No data	−	Heptachlor	Rashid and Mumma 1986
E. coli (DNA repair assay)	DNA damage	No data	−	Heptachlor	Rashid and Mumma 1986
Eukaryotic organisms:					
Fungi:					
Saccharomyces cerevisiae (*ade*, *trp* loci assay)	Gene conversion	−	−	Heptachlor	Gentile et al. 1982
Aspergillus nidulans (strain 35/liquid medium)	Gene mutation	No data	−	Heptachlor epoxide	Crebelli et al. 1986
A. nidulans (strain P1/liquid medium)	Chromosome malsegregation	No data	−	Heptachlor epoxide	Crebelli et al. 1986
Mammaliam cells:					
Mouse (L5178Y tk^+/tk^- lymphoma cell forward mutation assay)	Gene mutation	No data	+	Heptachlor	McGregor et al. 1988
Rat (ARL-HGPRT assay)	Gene mutation	−	NA	Heptachlor	Telang et al. 1982
Chinese hamster (ovary cells)	Chromosomal aberrations	+	−	Heptachlor	NTP 1987
Chinese hamster (ovary cells)	Sister chromatid exchange	+	+	Heptachlor	NTP 1987

Table 3-2. Genotoxicity of Heptachlor and Heptachlor Epoxide In Vitro

Species (test system)	End point	Results		Chemical form	Reference
		With activation	Without activation		
Rat (primary hepatocytes)	Unscheduled DNA synthesis	−	NA	Heptachlor	Probst et al. 1981; Maslansky and Williams 1981
Mouse (primary hepatocyte)	Unscheduled DNA synthesis	−	NA	Heptachlor	Maslansky and Williams 1981
Syrian hamster (primary hepatocytes)	Unscheduled DNA synthesis	−	NA	Heptachlor	Maslansky and Williams 1981
Human (SV-40 transformed fibroblasts)	Unscheduled DNA synthesis	+	−	Heptachlor	Ahmed et al. 1977
Human (SV-40 transformed fibroblasts)	Unscheduled DNA synthesis	+	−	Heptachlor epoxide	Ahmed et al. 1977

− = negative result; + = positive result; *ade* = adenine; ARL = adult rat liver epithelial cell line; DNA = deoxyribonucleic acid; HGPRT = hypoxanthine-guanine phosphoribosyl transferase; NA = not applicable; tk = thymidine kinase locus; *trp* = tryptophan

al. 1987). Heptachlor without metabolic activation caused gene mutations in mouse lymphoma cells but not in adult rat liver cells (McGregor et al. 1988; Telang et al. 1982). No alterations in gene conversion were observed in *Saccharomyces cerevisiae* following heptachlor exposure with and without activation (Gentile et al. 1982); heptachlor epoxide was also negative for gene mutation in *Aspergillus nidulans* (Crebelli et al. 1986).

Heptachlor did not cause DNA damage in *Salmonella typhimurium* or *Escherichia coli* in the absence of metabolic activators (Rashid and Mumma 1986). Heptachlor was negative for unscheduled DNA synthesis (UDS) in rat, mouse, and hamster (Maslansky and Williams 1981; Probst et al. 1981). In contrast, an increase in UDS was observed in human SV-40 transformed fibroblasts after exposure to heptachlor and heptachlor epoxide in the presence of metabolic activators (Ahmed et al. 1977).

Heptachlor epoxide did not alter the occurrence of chromosome malsegregration in *A. nidulans* (Crebelli et al. 1986). Chromosomal alterations were observed in mammalian cells. Chromosomal aberrations were observed in Chinese hamster ovary cells following exposure to heptachlor with metabolic activation and sister chromatid exchange was observed both with and without metabolic activation (NTP 1987). Refer to Table 3-2 for a summary of the results of these *in vitro* studies.

Several studies were located involving heptachlor genotoxicity in plants. A positive response was noted for the waxy gene mutation in maize (*Zea mays*) following exposure to heptachlor *in situ* (Gentile et al. 1982). A micronucleus test in *Tradescantia* produced a significant positive dose-related response at 1.88 ppm heptachlor, suggesting that heptachlor has clastogenic potential in plants (Sandhu et al. 1989). Early separation during metaphase, condensation, stickiness, and chromatin bridges were observed after heptachlor treatment on mitotic chromosomes in *Lens culinaris*, *Lens esculenta*, *Pisum sativum*, and *Pisum arvense* (Jain and Sarbhoy 1987a). Chromosomal abnormalities such as stickiness, non-orientation during metaphase I, fragments, multivalents, and bridges were also observed in meiotic chromosomes after heptachlor treatment (Jain and Sarbhoy 1987b). These studies by Jain and Sarbhoy report no statistical comparisons with which to interpret the results; therefore, it is difficult to evaluate the significance of their research. Even though these plant studies suggest that heptachlor is potentially genotoxic, the applicability to mammalian genotoxicity remains questionable.

3.4 TOXICOKINETICS

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

No studies were located regarding absorption in humans after inhalation exposure to heptachlor or heptachlor epoxide. One animal study provides suggestive evidence of absorption following inhalation exposure to heptachlor epoxide (Arthur et al. 1975). Elevated levels of heptachlor epoxide were found in the fat (0.039 versus 0.016 ppm in controls) of rabbits housed outdoors in an area of pesticide use; the air concentrations of DDT, dieldrin, and heptachlor epoxide were 649.6, 4.59, and 1.86 ng/m^3, respectively.

3.4.1.2 Oral Exposure

No information on the extent of oral absorption of heptachlor or heptachlor epoxide in humans was identified. Qualitative evidence of absorption was found in a study of families consuming dairy products contaminated with heptachlor epoxide (Stehr-Green et al. 1988). Higher serum heptachlor epoxide levels were detected in the family members compared to an unexposed population (0.84 versus 0.50 ppb).

Heptachlor is absorbed from the gastrointestinal tract of rats (Radomski and Davidow 1953; Tashiro and Matsumura 1978) and cattle (Harradine and McDougall 1986) as indicated by the presence of heptachlor and/or its metabolites in serum, fat, liver, kidneys, and muscle (Radomski and Davidow 1953). Based on available toxicity data (Podowski et al. 1979), it is assumed that heptachlor epoxide is also absorbed via the gastrointestinal tract. One study provides suggestive evidence that at least 50% of an orally administered dose of heptachlor is absorbed by rats (Tashiro and Matsumura 1978). Ten days after administration of a single dose, 6% of the radioactivity from radiolabeled (^{14}C) heptachlor was found in the urine and 60% was detected in the feces (primarily present as heptachlor metabolites).

3.4.1.3 Dermal Exposure

No studies were located regarding absorption in humans after dermal exposure to heptachlor or heptachlor epoxide.

Heptachlor is absorbed through the skin following topical application as indicated by its dermal toxicity in rats (Gaines 1969), but quantitative data are not available. However, the data should be interpreted

cautiously because heptachlor epoxide ingestion was not prevented by restraining the animals or removing excess heptachlor from the skin.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

No studies were located regarding distribution of heptachlor or heptachlor epoxide in humans or animals following inhalation exposure.

3.4.2.2 Oral Exposure

No human studies were located regarding the distribution of heptachlor and its metabolites after oral exposure. A number of monitoring studies found elevated levels of heptachlor epoxide in fat, serum, liver, and brain. It is not known if the elevated levels of heptachlor epoxide were the result of heptachlor or heptachlor epoxide exposure or chlordane exposure (heptachlor epoxide is a minor metabolite of chlordane) (Adeshina and Todd 1990; Barquet et al. 1981; Burns 1974; Greer et al. 1980; Klemmer et al. 1977; Polishuk et al. 1977b; Radomski et al. 1968; Stehr-Green et al. 1988; Wassermann et al. 1974).

Heptachlor epoxide was measured in a strip of skin, fat, and subcutaneous tissue from 68 children who died in the perinatal period and ranged from not detected (nondetectable) to 0.563 ppm (mean, 0.173 ppm) (Zavon et al. 1969). In 10 other stillborn infants, heptachlor epoxide levels measured in various tissues were as follows: brain (nondetectable), lung (0.17±0.07 ppm), adipose (0.32±0.10 ppm), spleen (0.35±0.08 ppm), liver (0.68±0.50 ppm), kidneys (0.70±0.28 ppm), adrenals (0.73±0.27 ppm), and heart (0.80±0.30 ppm) (Curley et al. 1969). Selby et al. (1969) reported a placenta/maternal blood concentration ratio for heptachlor epoxide of 5.8. In another study, the following heptachlor epoxide levels were measured in extracted lipids from mothers and newborn infants: maternal adipose tissue (0.28±0.31 ppm), maternal blood (0.28±0.46 ppm), uterine muscle (0.49±0.51 ppm), newborn blood (1.00±0.95 ppm), placenta (0.50±0.40 ppm), and amniotic fluid (0.67±1.16 ppm) (Polishuk et al. 1977a). These data provide evidence of transplacental transfer to the fetus.

Animal studies regarding heptachlor and heptachlor epoxide distribution in body tissues are limited. Analysis of body fat from 20 adult female rats fed heptachlor in their diet at a level of 35 ppm for 3 months revealed a high concentration of heptachlor epoxide but not heptachlor (Radomski and Davidow 1953). Further analysis showed that accumulation of heptachlor epoxide was directly related to the dose

of heptachlor given. Examination of other tissues in addition to adipose tissue showed that fat had the highest concentrations of heptachlor epoxide; markedly lower amounts were found in liver, kidneys, and muscle, and none was found in the brain. In a parallel study, three dogs were also examined. Doses of 1 mg/kg/day for 12–18 months produced the same distribution pattern as in rats, but the livers of dogs contained more heptachlor epoxide than the kidneys and muscle tissue. Levels in all tissues were higher in female dogs than in males.

The rate of heptachlor epoxide accumulation in, and elimination from, fat was determined in rats fed diets containing 30 ppm heptachlor for 12 weeks, then fed untreated diets for 12 more weeks (Radomski and Davidow 1953). Interim sacrifices at various times during treatment showed that the residue in the fat of males reached a plateau at approximately 2–8 weeks. Thereafter, the levels decreased and were below the detection limit by the end of week 6 post-dosing. In females, the heptachlor epoxide level in fat was much higher than males by the second week and throughout the remainder of the study. By the end of the 8th week post-dosing, the heptachlor epoxide level was below the detection limit in females. No estimates of elimination half-lives from fat were provided.

Heptachlor and heptachlor epoxide residues were found in the fat (≥0.16 and ≥18.25 ppm, respectively), liver (≥0.08 and ≥2.11 ppm, respectively), and muscle (0 and ≥0.03 ppm, respectively) of pigs fed 2 mg/kg/day heptachlorine (purity unspecified) for 78 days (Halacka et al. 1974). When pigs were fed 5 mg/kg/day, the levels of heptachlor and heptachlor epoxide were higher: 0.37 and 25.82 ppm, respectively, in the fat; 0.23 and 4.94 ppm, respectively, in liver; and 0 and 0.7 ppm, respectively, in muscle.

3.4.2.3 Dermal Exposure

No studies were located regarding distribution in humans or animals after dermal exposure to heptachlor or heptachlor epoxide.

3.4.3 Metabolism

No studies were located regarding metabolism of heptachlor or heptachlor epoxide in humans exposed to these pesticides. However, information is available regarding *in vivo* metabolism in rats and *in vitro* metabolism by human and rat liver microsomes.

Ten days after male rats were administered a single oral dose of ^{14}C-heptachlor by gavage in corn oil, about 72% of the radioactivity was eliminated in the feces in the form of metabolites and 26% as parent compound. The major fecal metabolites were heptachlor epoxide (13.1% of total ^{14}C compounds), 1-exo-hydroxychlordene (19.5%), 1-exo-hydroxy-2,3-exo-epoxychlordene (17.5%), and 1,2-dihydroxydihydro-chlordene (3.5%), as well as two unidentified products (Tashiro and Matsumura 1978). The proposed metabolic scheme for heptachlor is presented in Figure 3-2.

Tashiro and Matsumura (1978) also conducted experiments to compare *in vitro* metabolism of ^{14}C-heptachlor in microsomal preparations from human livers and rat livers. The primary metabolites produced by in both preparations were heptachlor epoxide, 1-exo-hydroxychlordene, 1-exo-hydroxy-2,3-exo-epoxychlordene, and 1,2-dihydroxydihydrochlordane. However, the levels of heptachlor epoxide were 4 times higher in the rat microsomal preparations than in the humans; 85.8% of the radiolabel was in the form of heptachlor epoxide in rat microsomes compared to 20.4% for human microsomes. These *in vivo* and *in vitro* data suggest that the ratio of heptachlor to heptachlor epoxide stored in adipose tissue would be higher in humans than rats (Tashiro and Matsumura 1978).

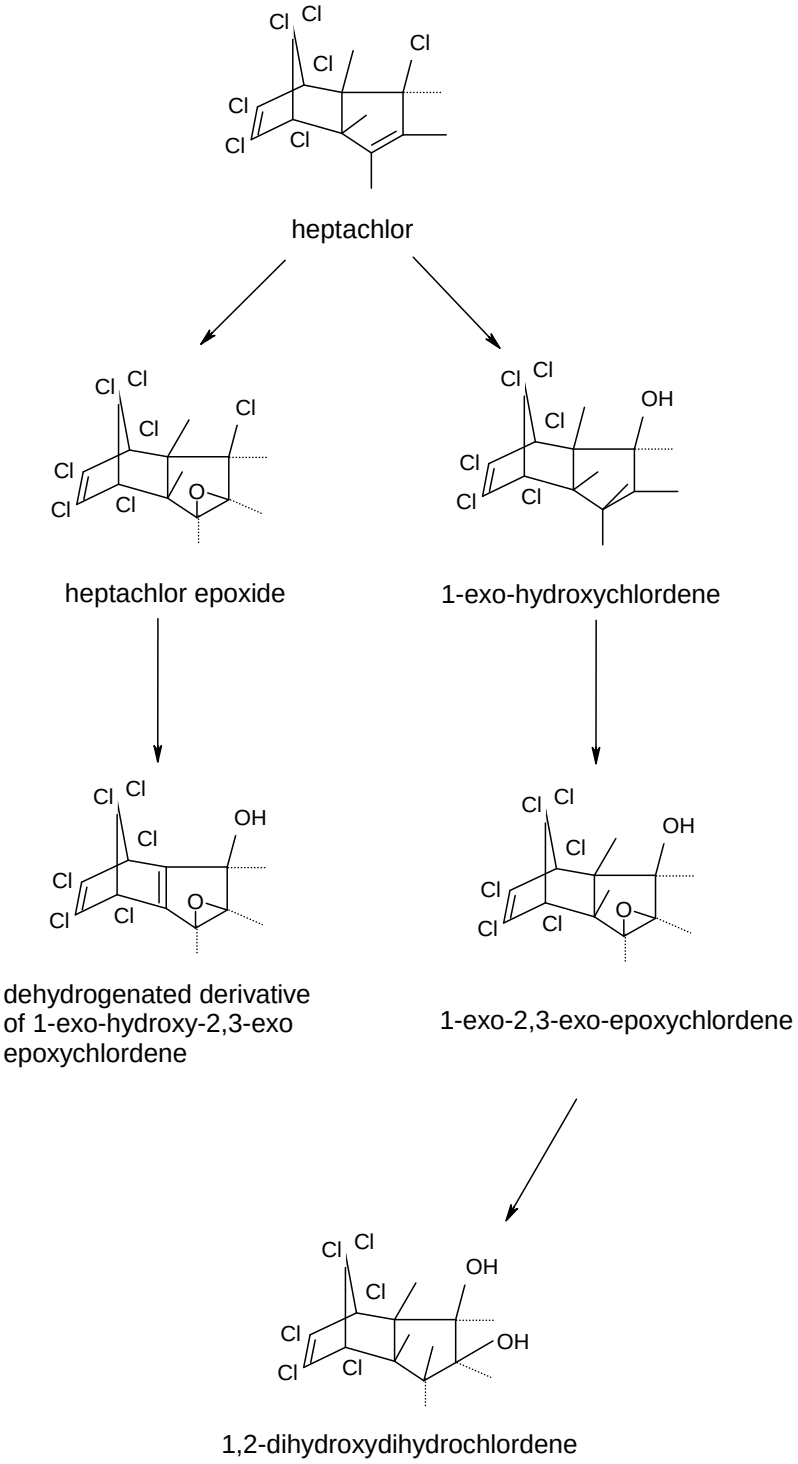
Heptachlor also is a metabolic product of chlordane. Both heptachlor and heptachlor epoxide are active inducers of microsomal epoxidation (Gillett and Chan 1968). In male Wistar rats fed a diet containing 5 ppm heptachlor or heptachlor epoxide for 10 days, the latter was much more effective in inducing epoxidation of aldrin than heptachlor (Gillett and Chan 1968). The minimally effective dietary concentration for inducing significant epoxidation was estimated to be between 1 and 5 ppm for both compounds (Gillett and Chan 1968). Heptachlor epoxide is considered more toxic than its parent compound and, like heptachlor, is primarily stored in adipose tissue (Barquet et al. 1981; Burns 1974; Greer et al. 1980; Harradine and McDougall 1986).

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

No studies were located regarding excretion in humans or animals after inhalation exposure to heptachlor or heptachlor epoxide. Based on the data from oral studies, heptachlor is expected to be excreted primarily in the form of metabolites and also as unchanged parent compound.

Figure 3-2. Metabolic Scheme for Heptachlor in Rats



Source: adapted from Tashiro and Matsumura (1978)

3.4.4.2 Oral Exposure

No studies were located regarding excretion in humans after oral exposure to heptachlor or heptachlor epoxide.

Due to their relatively high lipid solubility, heptachlor and heptachlor epoxide can accumulate in breast milk. For example, heptachlor and heptachlor epoxide were measured in 51 samples of human milk at average concentrations of 0.0027 and 0.019 ppm, respectively, from women with unknown exposure histories (Jonsson et al. 1977). Heptachlor epoxide was found in 24% of the samples, and heptachlor was found in 6%. Other investigators have reported the presence of heptachlor epoxide in human milk at concentrations ranging from not detected to 0.46 ppm (Kroger 1972; Larsen et al. 1971; Mussalo-Rauhamaa et al. 1988; Polishuk et al. 1977b; Ritcey et al. 1972; Savage et al. 1981; Takei et al. 1983). These findings suggest a potential for transfer to the nursing infant (see also Sections 3.5.1 and 6.5).

In a study in cows, the concentration of heptachlor epoxide in cow's milk reached a maximum within 3–7 days after the cows began grazing 18 hours/day on pastures immediately following treatment of the grasses with heptachlor and declined steadily thereafter. The level of heptachlor epoxide in the milk reached a concentration of 0.22 ppm (Gannon and Decker 1960).

The elimination of a single oral gavage dose of ^{14}C-heptachlor in male rats showed that most of the radioactivity was eliminated in the feces (Tashiro and Matsumura 1978). One day after dosing, 36% of the dose had been eliminated, and by day 10, approximately 62% had been eliminated in the feces. Elimination of the radioactive label in urine accounted for only 6% of the total dose in 10 days. Approximately 26.2% of the total radioactivity recovered from the feces was the parent compound and the remainder was in the form of metabolites.

3.4.4.3 Dermal Exposure

No studies were located regarding excretion in humans or animals after dermal exposure to heptachlor or heptachlor epoxide. Based on the data from oral studies, heptachlor is expected to be excreted primarily in the form of metabolites and also as unchanged parent compound.

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 parameterization, (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 3-3 shows a conceptualized representation of a PBPK model.

If PBPK models for heptachlor and heptachlor epoxide exist, 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.

No PBPK models were identified for heptachlor or heptachlor epoxide.

3.5 MECHANISMS OF ACTION

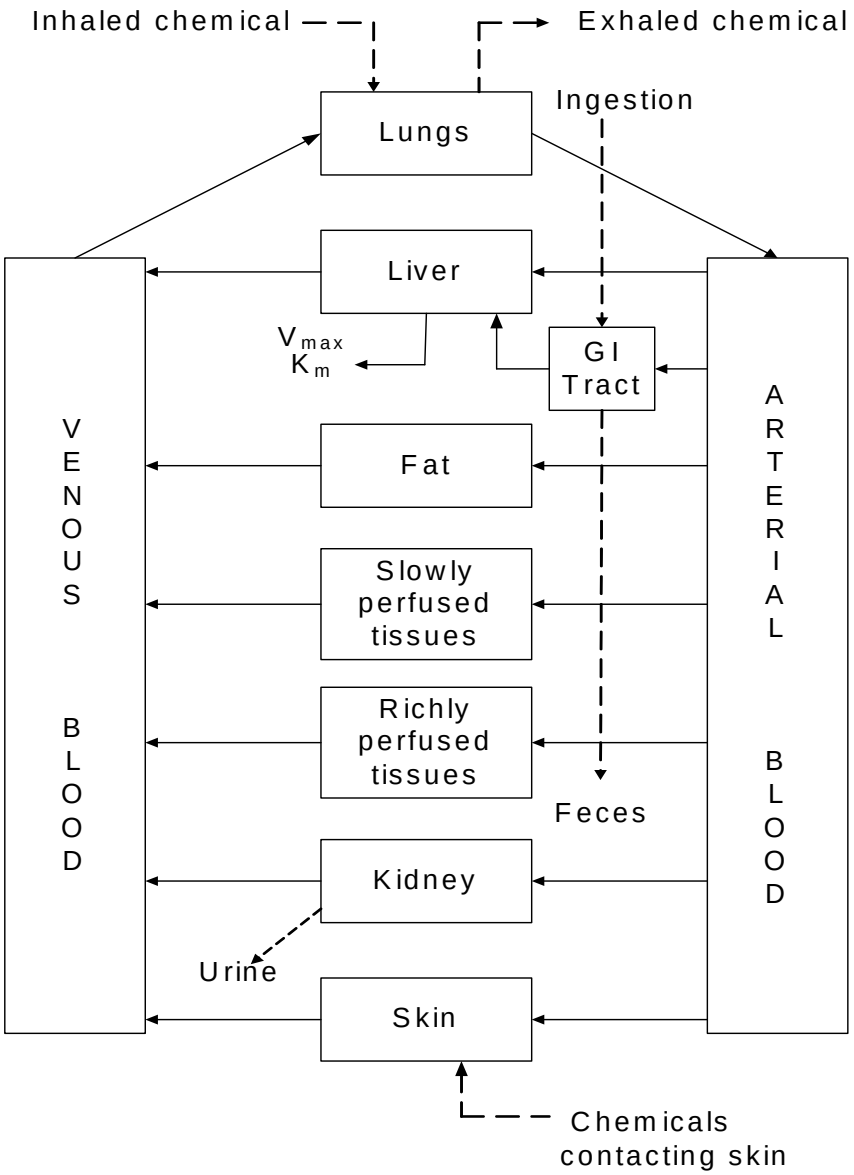
3.5.1 Pharmacokinetic Mechanisms

There is limited information on the toxicokinetics of heptachlor. No dermal toxicokinetic data were located. Heptachlor is absorbed via the lungs and digestive tract, although the site and mechanism of absorption are not known. Heptachlor is metabolized to heptachlor epoxide and is stored in the body as the parent compound and as this metabolite. Heptachlor and heptachlor epoxide are highly lipid soluble and are stored in adipose tissue; both compounds can also accumulate in breast milk. Heptachlor is primarily excreted in the feces as heptachlor epoxide.

3.5.2 Mechanisms of Toxicity

The available data suggest that the developing nervous system is the most sensitive target of heptachlor toxicity. Impaired spatial memory was observed in rats exposed to 0.03 mg/kg/day heptachlor during gestation and from postnatal day 7–42 (Moser et al. 2001). The cause of these alterions is not known. Moser et al. (2001) noted that heptachlor and other cyclodiene insecticides have a high affinity for $GABA_A$ (gamma-amino butyric acid) receptors and can alter the expression of the $GABA_A$ receptor

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



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.

Source: adapted from Krishnan and Andersen 1994

during development. In the Moser et al. (2001) study, alterations in $GABA_A$ binding sites were observed in the brainstem of female rats, but not in the cortex. However, no alterations in the functional response of the GABA receptor binding were observed. This study does not address whether the heptachlor-induced alterations in $GABA_A$ receptors and the observed neurobehavioral alterations are related.

3.5.3 Animal-to-Human Extrapolations

There are limited available data with which to compare humans and other animal species. The absorption and distribution properties of heptachlor and heptachlor epoxide appear to be the same in both humans and animals. For the most part, the human toxicity data do not allow for quantitative or qualitative comparisons with the available animal data; an exception is the neurodevelopmental toxicity data. Impaired performance on tests of abstract concept formation, visual perception, and motor planning was observed in adolescents exposed during gestation to heptachlor and/or heptachlor epoxide (Baker et al. 2004b). In rats exposed during gestation and for the first 42 postnatal days, impaired spatial memory and learning were observed (Moser et al. 2001). These data provide some qualitative support for extrapolating the rat data for human risk assessment.

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 Thomas and Colborn (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).

No studies were located regarding endocrine disruption in humans or animals after exposure to heptachlor or heptachlor epoxide. An animal study examining the impact of in utero and lactational exposure to heptachlor on the development of the reproductive system (Smialowicz et al. 2001) did not find alterations in vaginal opening, prepuce separation, or adverse reproductive or developmental outcomes when exposed offspring were mated with controls. Additionally, no *in vitro* studies were located regarding endocrine disruption of heptachlor or heptachlor epoxide.

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).

There are suggestive data indicating that children, particularly children exposed *in utero* and during infancy may be unusually susceptible to the toxicity of heptachlor. Although no studies comparing the toxicity of heptachlor in adults and children were identified, there is a possibility that very young children may exhibit particular susceptibility to hepatic effects because of the immaturity of the hepatic microsomal system. Heptachlor is bioactivated to produce heptachlor epoxide, which is more toxic than

heptachlor. Pre-adolescent children have a greater rate of glutathione turnover, and they are expected to be more susceptible to heptachlor epoxide-induced toxicity. Their susceptibility would probably depend upon their ability to detoxify heptachlor epoxide. However, Harbison (1975) observed that heptachlor was less toxic in newborn rats than in adult rats. Newborn rats pretreated with phenobarbital were more sensitive to the effects of heptachlor than those not pretreated. Thus, the ability to metabolize and bioactivate heptachlor correlates with its toxicity in the newborn.

Several developmental toxicity studies have identified the developing organisms as a sensitive subpopulation. Heptachlor exposure does not appear to increase the risk of malformations in humans (Le Marchand et al. 1986) or animals (Narotsky et al. 1995; Smialowicz et al. 2001), although increases in pup mortality (Narotsky et al. 1995; Purkerson-Parker et al. 2001b) and decreases in pup body weight (Narotsky and Kavlock 1995; Narotsky et al. 1995) have been observed in animal studies. There is some indication that the developing nervous system may be unusually susceptible to the toxicity of heptachlor. A study of high school students exposed to heptachlor epoxide *in utero* and during early childhood found impaired performance on tests of abstract concept formation, visual perception, and motor planning (Baker et al. 2004b). Delays in the righting reflex, slowed acquisition of a spatial task, and impaired recall were observed in rat offspring exposed during gestation, lactation, and postnatally (Moser et al. 2001; Purkerson-Parker et al. 2001b). The impaired learning and memory was the basis of the intermediate-duration oral MRL. In addition to the neurological effects, suppression of the immune response to sheep red blood cells was observed at the same dose level as the impaired learning and memory (Smialowicz et al. 2001).

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, 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 heptachlor and heptachlor epoxide 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 heptachlor and heptachlor epoxide 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 Heptachlor and Heptachlor Epoxide

Heptachlor and heptachlor epoxide can be measured in blood, adipose tissue, breast milk, and urine. The analytical methods available can be used to determine whether exposure has occurred, but the results cannot tell whether adverse health effects will occur. The presence of heptachlor epoxide may reflect an exposure to heptachlor or possibly chlordane since heptachlor epoxide is a metabolite of both these pesticides. However, in the absence of stable chlordane residues (e.g., nonachlor and oxychlordane), the heptachlor epoxide would most likely have been derived from heptachlor.

Detection of heptachlor or heptachlor epoxide in the body may indicate either recent or past exposure. Heptachlor epoxide has a long half-life, particularly in adipose tissue because it is very lipophilic and can remain dissolved in adipose tissue for months to years. An example of this can be found in a report in which analysis of human adipose tissue samples obtained during autopsy between 1987 and 1988 from residents of North Texas showed that tissue levels of heptachlor epoxide in subjects from the above geographical region had not significantly decreased since 1970 (Adeshina and Todd 1990). However, heptachlor epoxide is eventually mobilized into the blood and subsequently to the liver for further breakdown. Blood levels of heptachlor epoxide are often taken to indicate a more recent exposure.

As indicated in Section 3.4.4.2, due to their relatively high lipid solubility, heptachlor and heptachlor epoxide can accumulate in breast milk fat. Heptachlor and heptachlor epoxide were measured in 51 samples of human milk at average concentrations of 0.0027 and 0.019 ppm, respectively, from women with unknown exposure histories (Jonsson et al. 1977). Heptachlor epoxide was found in 24% of the samples, and heptachlor was found in 6%. Other investigators have reported the presence of heptachlor epoxide in human milk at concentrations ranging from not detected to 0.46 ppm (Kroger 1972; Polishuk et al. 1977b; Savage et al. 1981; Takei et al. 1983). These findings suggest a potential for transfer to the nursing infant (see also Sections 3.5.1 and 6.5). Other studies that have reported levels of heptachlor or heptachlor epoxide in humans' breast milk include Larsen et al. (1971), Ritcey et al. (1972), and Mussalo-Rauhamaa et al. (1988).

No studies were found correlating levels to which humans were exposed with actual body burdens.

3.8.2 Biomarkers Used to Characterize Effects Caused by Heptachlor and Heptachlor Epoxide

No clinical conditions due to specific exposure to heptachlor or heptachlor epoxide are known. The neurological and hepatic effects seen from exposure to heptachlor and heptachlor epoxide are typical of exposure to other chlorinated pesticides.

3.9 INTERACTIONS WITH OTHER CHEMICALS

Dietary administration of heptachlor (97.6% purity) at 0.65 or 1.3 mg/kg/day in diet for 25 weeks promoted the development of hepatocellular foci and hepatocellular neoplasms in male B6C3F_1 mice previously initiated with 3.8 mg/kg/day diethylnitrosamine given in the drinking water for 14 weeks (Williams and Numoto 1984).

Nutritional factors may influence the toxicity of pesticides. Research in this area has primarily focused on the role of dietary proteins, particularly sulfur-containing amino acids, trace minerals, and vitamins A, C, D, and E. Studies in rats show that inadequate dietary protein enhances the toxicity of most pesticides but decreases, or fails to affect, the toxicity of a few. The results of these studies have shown that at one-seventh or less normal dietary protein, the hepatic toxicity of heptachlor is diminished as evidenced by fewer enzyme changes (Boyd 1969; Shakman 1974). The lower-protein diets may decrease metabolism of heptachlor to heptachlor epoxide.

Male weanling rats were fed a 5, 20, or 40% casein diet for 10 days and then given heptachlor intraperitoneally. The animals receiving the 5% casein diet showed a 3-fold tolerance to heptachlor toxicity, but the toxicity of heptachlor epoxide was not affected (Weatherholtz et al. 1969). This was probably due to inability of weanling rats to metabolically convert heptachlor to the more toxic heptachlor epoxide. This fact is further supported by the observation that changes in protein percentage in diet did not affect the toxicity of heptachlor epoxide itself.

Walter Reed-Wistar and Charles River male adult rats were exposed to oral doses of turpentine or to turpentine vapors, which consisted of α- and β-pinene. These exposures were followed by oral administration of heptachlor epoxide or of one of three pesticides, paraoxon, heptachlor, or parathion, or by an intraperitoneal injection of hexobarbital. The studies revealed that pretreatment with turpentine reduced hexobarbital sleeping time, reduced the parathion LD_{50}, and increased the heptachlor LD_{50}. The paraoxon and heptachlor epoxide LD_{50} values were unchanged. α-Pinene and β-pinene vaporized from turpentine had no effect on either hexobarbital sleeping time or parathion, paraoxon, or heptachlor epoxide mortality but did increase the heptachlor LD_{50} (Sperling et al. 1972). The authors speculated that increases in hepatic microsomal enzyme activity are responsible for these differences.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to heptachlor and heptachlor epoxide than will most persons exposed to the same level of heptachlor and heptachlor epoxide 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 heptachlor and heptachlor epoxide, or compromised function of organs affected by heptachlor and heptachlor epoxide. Populations who are at greater risk due to their unusually high

exposure to heptachlor and heptachlor epoxide are discussed in Section 6.7, Populations with Potentially High Exposures.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to heptachlor and heptachlor epoxide. 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 heptachlor and heptachlor epoxide. 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 heptachlor and heptachlor epoxide:

Ellenhorn MJ. 1997. Ellenhorn's medical toxicology. Diagnosis and treatment of human poisoning. 2nd ed. Baltimore, MD: Williams and Wilkins, 1614-1631.

EPA. 1999. Recognition and management of pesticide poisonings. 5th. Washington, DC: U.S. Environmental Protection Agency. EPA735R98003. PB99149551.

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

3.11.1 Reducing Peak Absorption Following Exposure

Human exposure to heptachlor or heptachlor epoxide can occur by inhalation, oral, or dermal contact. Treatment of exposure to these substances is primarily supportive. Following a significant inhalation exposure, the patient is removed from the source to fresh air. Treatment may include administering oxygen and, if needed, maintaining ventilation with artificial respiration (Bronstein and Currance 1988; HSDB 2007a). General recommendations for reducing absorption of heptachlor following acute dermal exposure have included removal of contaminated clothing followed by washing the skin and hair with soap and water, (HSDB 2007a; Morgan 1989). Since leather absorbs pesticides, it has been recommended that leather not be worn while using heptachlor or heptachlor epoxide, and that any leather contaminated with these substances be discarded (HSDB 2007a). Oils have not been recommended as dermal cleansing agents because they could increase absorption (Haddad and Winchester 1990). If the eyes have been exposed, they are flushed with water (Bronstein and Currance 1988; HSDB 2007a). Treatment for ingestion of this substance may require gastric emptying by gastric lavage (Haddad and Winchester 1990) and administration of activated charcoal and cathartic (Haddad and Winchester 1990; HSDB 2007a; Morgan 1989). Heptachlor may be present with a hydrocarbon vehicle, which could result

in aspiration pneumonitis following the induction of emesis. Therefore, emesis may not be indicated. Some sources do not recommend the use of emetics (Bronstein and Currance 1988), although others do under some circumstances (HSDB 2007a; Morgan 1989). Treatments such as emesis and lavage may be most appropriate following ingestion of large quantities; it is unlikely that the types of exposure likely to occur at hazardous waste sites would require such measures. Treatment with milk, cream, or other substances containing vegetable or animal fats, which enhance absorption of chlorinated hydrocarbons, has not been recommended (Haddad and Winchester 1990; Morgan 1989). If seizures occur, diazepam administration, followed if necessary by additional anticonvulsant medicines such as phenytoin, pentobarbital, thiopental, or succinylcholine, may be recommended (Bronstein and Currance 1988; HSDB 2007a; Morgan 1989). As adrenergic amines, such as epinephrine, may further increase myocardial irritability and produce refractory ventricular arrhythmias, their use has not been recommended (Bronstein and Currance 1988; Haddad and Winchester 1990; HSDB 2007a; Morgan 1989).

3.11.2 Reducing Body Burden

Heptachlor is rapidly metabolized by the body, mostly to heptachlor epoxide. Most of the metabolites are rapidly excreted in the feces, with the adipose tissue serving as the major storage depot for the remainder. From the fat, heptachlor epoxide can be slowly released into the bloodstream for further metabolism and excretion. Cholestyramine resin may accelerate the biliary-gastrointestinal excretion of the more slowly eliminated organochlorine compounds, and its use has been suggested (Morgan 1989). Because of the lipophilicity of heptachlor and heptachlor epoxide, dialysis and exchange transfusion are thought to be ineffective (HSDB 2007a).

Because heptachlor epoxide is lipophilic, it is likely that the loss of adipose tissue, as may occur during fasting, will mobilize the stored compound and increase the rate of its elimination. However, this mobilization is also likely to temporarily increase the blood levels of heptachlor epoxide. Hence, any possible benefits due to a reduced body burden accompanying fat reduction would need to be balanced against potential harmful results due to the expected temporary increase in blood levels.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Since the metabolized form of heptachlor, heptachlor epoxide, is the most toxic, it may be possible to reduce the toxic effects of heptachlor by inhibiting the enzyme catalyzing this conversion. This is the same enzyme that catalyzes the epoxidation of aldrin to dieldrin (Gillett and Chan 1968). Further

research into the specificity of this enzyme, drugs that could inhibit the enzyme, and any side effects of these drugs could help to determine the feasibility of such a treatment strategy.

In the central nervous system, symptoms observed in animals following exposure include tremors, convulsions, ataxia, and changes in EEG patterns (Formanek et al. 1976). These central nervous system symptoms could be due either to (1) inhibition of the Na^+/K^+ ATPase or the Ca^+/Mg^+ ATPase activity, which can then interfere with nerve action or release of neurotransmitters (Yamaguchi et al. 1979) and/or (2) inhibition of the function of the receptor for GABA (Yamaguchi et al. 1980). In support of the latter possibility, another study showed that heptachlor epoxide inhibited the GABA-stimulated chloride uptake in the coxal muscle of the American cockroach and directly competed against [^{3}H]a-dihydropierotoxinin for binding in the rat brain synaptosomes. These results indicate that some of the nerve excitation symptoms that insecticides cause are probably due to their interaction with the picrotoxin binding site of the GABA receptor (Matsumura and Ghiasuddin 1983). A more detailed understanding of the mechanism of heptachlor/heptachlor epoxide action on the central nervous system may lead to new approaches for reducing the toxic effects.

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 heptachlor and heptachlor epoxide 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 heptachlor and heptachlor epoxide.

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.

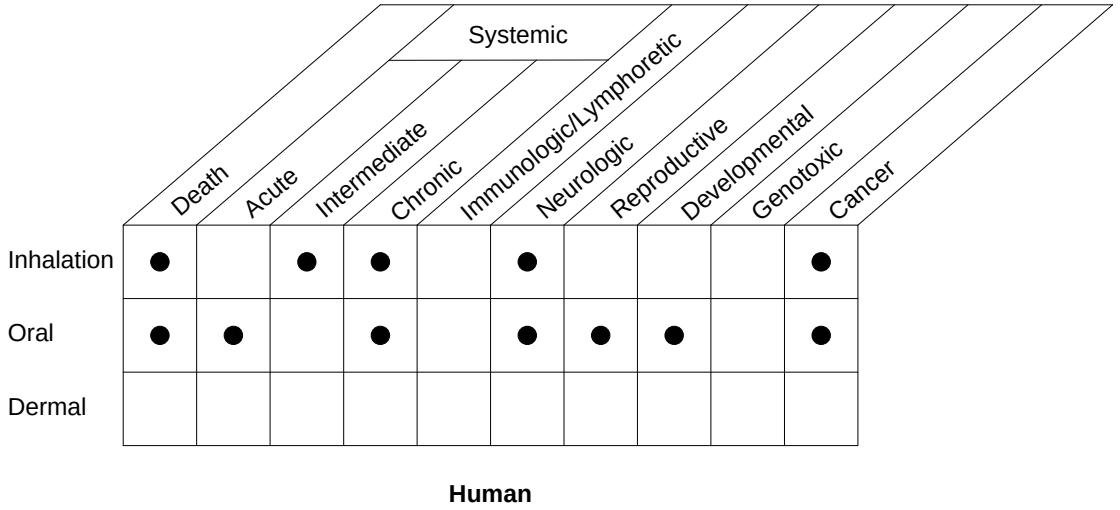
3.12.1 Existing Information on Health Effects of Heptachlor and Heptachlor Epoxide

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to heptachlor and heptachlor epoxide are summarized in Figure 3-4. The purpose of this figure is to illustrate the existing information concerning the health effects of heptachlor and heptachlor epoxide. 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.

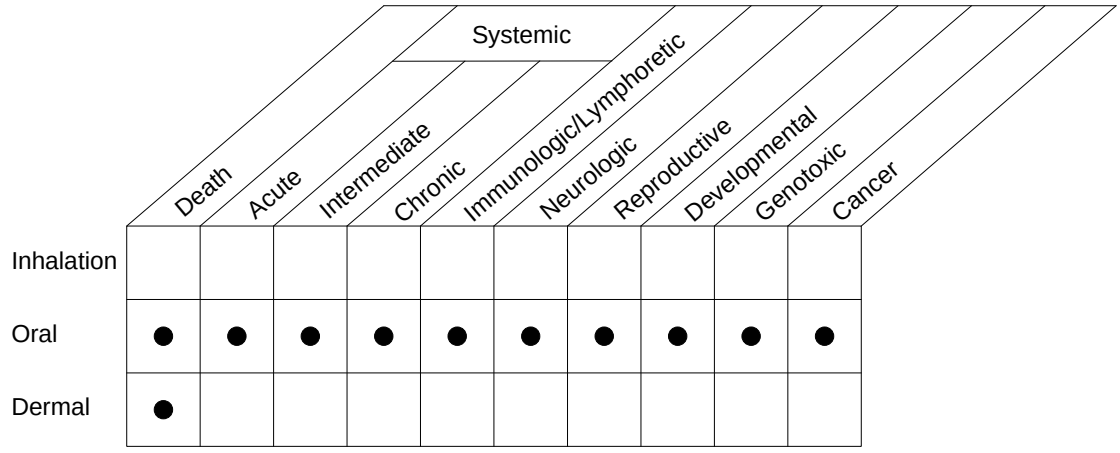
Most of the data located concerning the health effects of heptachlor and heptachlor epoxide in humans come from case reports and occupational epidemiology studies of workers engaged either in the manufacture or application of pesticides. There is some information on people who have consumed heptachlor-contaminated food or dairy products, but no adverse health effects have been related to these exposures. The occupational studies involve exposures that are predominantly inhalation with contributions from dermal exposure, whereas all the animal studies were conducted using oral or intraperitoneal exposures. The occupational and case reports provide no quantitation of dose or duration of exposure, which makes it impossible to determine with any precision the effect levels for humans. There are no data that indicate that heptachlor or heptachlor epoxide are carcinogenic to humans. However, human studies are limited by the long latency period of carcinogenesis and by ascertainment and follow-up biases.

The animal studies for oral exposure to heptachlor and heptachlor epoxide are almost all limited to some extent by the number of doses used, the lack of appropriate statistics, or the small number or lack of controls. No information was located regarding the health effects of inhalation or dermal exposure, with the exception of a dermal LD_{50} in rats. Exposure of the general population via the inhalation and dermal routes may result from contaminated soil or vapors from treated houses. Some exposures from contaminated soil or water may occur in populations located near hazardous waste sites in which these chemicals have been stored or from food grown in contaminated soil.

Figure 3-4. Existing Information on Health Effects of Heptachlor and Heptachlor Epoxide



Human



Animal

● Existing Studies

3.12.2 Identification of Data Needs

Acute-Duration Exposure. There are no studies that have evaluated the acute toxicity of heptachlor or heptachlor epoxide following inhalation exposure; thus, acute-duration inhalation MRLs were not derived. A number of studies have evaluated the toxicity of heptachlor following acute oral exposure. The results of these studies suggest several sensitive targets of toxicity including the liver, nervous system, reproductive system, and the developing organism (Amita Rani and Krishnakumari 1995; Berman et al. 1995; Krampl 1971; Narotsky and Kavlock 1995; Narotsky et al. 1995; Purkerson-Parker et al. 2001b). The available data suggest that the most sensitive effect is impaired fertility observed in female rats administered heptachlor for 14 days prior to mating (Amita Rani and Krishnakumari 1995); this end point was used to derive an acute-duration oral MRL. Additional studies that examined a variety of systemic, neurological, reproductive, and developmental end points are needed to support the identification of critical effect and to establish dose-response relationships. Although there are limited toxicokinetic and mechanistic data for heptachlor, it is likely that its toxicity is not route-specific. The identified target organs would likely be the same for oral, inhalation, and dermal exposure; however, it is not possible to predict threshold concentrations. Toxicokinetic studies, which would allow for route-to-route extrapolation, and inhalation and dermal toxicity studies would be useful for confirming whether the toxicity of heptachlor is independent of route of exposure.

The available acute-duration studies for heptachlor epoxide are limited to oral lethality and dominant lethal studies (Epstein et al. 1972; Podowski et al. 1979). The toxicity of heptachlor is likely due to heptachlor epoxide; thus, the targets of toxicity are likely to be the same as those observed following heptachlor exposure. However, the toxic thresholds are likely to be different. Studies are needed to establish dose-response relationships and to confirm whether the targets of toxicity are the same as those identified for heptachlor.

Intermediate-Duration Exposure. The targets of toxicity of heptachlor following intermediate-duration oral exposure appear to be the same as those identified following acute-duration oral exposure and include the liver, nervous system, reproductive system, and the developing organism (Akay and Alp 1981; Amita Rani and Krishnakumari 1995; Aulerich et al. 1990; Crum et al. 1993; Izushi and Ogata 1990; Moser et al. 2001; NCI 1977; Pelikan 1971; Purkerson-Parker et al. 2001b; Smialowicz et al. 2001). Of these targets, the developing organism appears to be the most sensitive (Moser et al. 2001; Smialowicz et al. 2001). Impaired development of the nervous and immune systems have been observed

in rats exposed to heptachlor *in utero*, during lactation, and from postnatal day 7 through 42; a NOAEL has not been identified for these end points. The intermediate-duration oral MRL for heptachlor was based on these developmental effects. The potential systemic toxicity of heptachlor has not been adequately assessed; although several studies have evaluated systemic end points (Akay and Alp 1981; Akay et al. 1982; Akhtar et al. 1996; Izushi and Ogata 1990; Pelikan 1971), many of these studies were poorly reported or examined a limited number of end points. Studies examining a variety of systemic end points would be useful for identifying target tissues and establishing dose-response relationships. No intermediate-duration inhalation or dermal studies were identified. As discussed in the Acute-Duration Exposure section, it is likely that the targets of toxicity would be the same for inhalation, oral, and dermal exposure; however, toxicokinetic data are not available to confirm this conjecture. Inhalation and dermal exposure studies are needed.

No publicly available studies on the intermediate-duration toxicity of heptachlor epoxide were identified. A 60-day dog study, which was submitted to EPA under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) identifies the liver as a critical target of toxicity (IRIS 2006). It is likely that the targets of heptachlor epoxide toxicity are the same as those for heptachlor. Additional studies, particularly those examining the development of the nervous and immune systems are needed to identify targets of toxicity and establish dose-response relationships.

Chronic-Duration Exposure and Cancer. There are no data on chronic oral exposures in humans. There are occupational studies of workers engaged in the manufacture of heptachlor in which the exposures are presumed to be predominantly inhalation with contributions from the dermal route. No adverse health effects have been identified in these cohorts that could be positively associated with heptachlor exposure (Infante et al. 1978; MacMahon et al. 1988; Stehr-Green et al. 1988). There is a limited publicly available database on the chronic oral toxicity of heptachlor. The database is limited to a multigeneration study (Mestitzova 1967), which reported increased postnatal mortality at the lowest dose tested, and a study examining a limited number of noncancer end points (NCI 1977); thus, the database was not considered adequate for derivation of a chronic duration oral MRL. A 2-year study submitted to EPA under FIFRA identified the liver as a critical target of toxicity (IRIS 2006). This finding is consistent with the available intermediate-duration studies. However, intermediate-duration studies have also identified the nervous system, reproductive system, and the developing organism as targets of toxicity. Additional studies are needed to identify the most sensitive target following chronic duration exposure and to establish dose-response relationships; these studies would be useful for deriving an oral

MRL. Inhalation and dermal studies are also needed; these studies in animals would be useful for determining whether the target organ is the same across routes of exposure.

As with the other durations of exposure, limited publicly available data were located for heptachlor epoxide. A study submitted to EPA under FIFRA identified the liver as the most sensitive target of toxicity (IRIS 2006). Additional studies are needed that could be used to derive inhalation and oral MRLs for heptachlor epoxide and to establish the targets of toxicity for dermal exposure.

There are occupational mortality studies that have collected data appropriate for determining whether those engaged in the manufacture or application of heptachlor are at increased risk for dying of cancer. These studies have not shown an increased risk of cancer mortality (Infante et al. 1978; MacMahon et al. 1988). Occupational studies that collected cancer incidence data, rather than just mortality data, would be useful for further exploration of this issue. Carcinogenicity studies have been identified for rats and mice (NCI 1977). These data show increases in tumorigenesis following exposure to heptachlor. Chronic studies of inhalation exposure in relation to oncogenesis in animals might be useful for determining mechanism of action and the consistency of effect across routes of exposure. There are no toxicokinetic data that indicate that there will be route-specific differences.

Genotoxicity. Information on the *in vivo* genotoxic effects of heptachlor or heptachlor epoxide is limited to dominant lethality assays with negative results (Arnold et al. 1977; Epstein et al. 1972). More case reports and epidemiology studies are needed to properly evaluate genotoxic effects in humans exposed to heptachlor or heptachlor epoxide. The results of *in vitro* studies suggest that neither compound alters the frequency of gene mutations (Crebelli et al. 1986; Gentile et al. 1982; Glatt et al. 1983; Marshall et al. 1976; NTP 1987; Probst et al. 1981; Zeiger et al. 1987), and that heptachlor does not induce DNA damage in bacteria (Rashid and Mumma 1986) or rodents (Maslansky and Williams 1981; Probst et al. 1981). Alterations were observed in assays of unscheduled DNA synthesis in human fibroblasts (Ahmed et al. 1977) and chromosomal alterations in Chinese hamster ovary cells (NTP 1987). *In vivo* animal research into the effects of heptachlor and heptachlor epoxide on sister chromatid exchange, chromosomal aberrations and anomalies, DNA adduct formation, gene mutation, and other genotoxic parameters would be helpful in assessing the genotoxic potential of heptachlor and heptachlor epoxide.

Reproductive Toxicity. Although a couple of studies have attempted to establish an association between heptachlor epoxide blood levels and premature delivery or stillbirth among women presumably

exposed via ingestion (Curley et al. 1969; Wassermann et al. 1982), elevated levels of other compounds (particularly PCBs, lindane, and dieldrin) limit the interpretation of the results. Animal studies have found impaired fertility and pregnancy losses following oral exposure to heptachlor (Akay and Alp 1981; Amita Rani and Krishnakumari 1995; Green 1970; Mestitzova 1967). The mechanism of the reproductive toxicity has not been elucidated; the available data suggest that both males and females may be affected. Additional studies are needed to identify NOAELs for reproductive effects, confirm the observed results, and identify the critical targets within the reproductive system.

Developmental Toxicity. Several studies have examined the potential developmental toxicity of heptachlor or heptachlor epoxide. These studies examined potential effects in the children of women exposed to heptachlor and heptachlor epoxide in contaminated cow's milk (Baker et al. 2004b; Le Marchand et al. 1986) or examined the possible association between maternal heptachlor epoxide levels and developmental effects (Gladen et al. 2003; Hertz-Picciotto et al. 2004). Several animal studies have also examined developmental toxicity (Lawson and Luderer 2004; Moser et al. 2001; Narotsky and Kavlock 1995; Narotsky et al. 1995; Purkerson-Parker et al. 2001b; Smialowicz et al. 2001). The finding of impaired development of the nervous and immune systems was used as the basis of the intermediate-duration oral MRL for heptachlor. This study (Moser et al. 2001; Smialowicz et al. 2001) did not identify a NOAEL for these effects, additional studies would be useful for more clearly defining the threshold of toxicity. Impaired spatial memory was observed at the lowest dose tested among the offspring exposed until postnatal day 42, but not in rats exposed until postnatal day 21 (Moser et al. 2001); studies that would address the cause of the conflicting results would also be useful.

Immunotoxicity. No studies were located that specifically addressed immune function parameters following heptachlor or heptachlor epoxide exposure, although several studies have reported alterations in the lymphoreticular system (e.g., fibrosis in spleen, and increased size of spleen; decreased relative spleen weight) (Akay and Alp 1981; Aulerich et al. 1990; Pelikan 1971). A developmental toxicity study found suppression of the immune response in rats orally exposed *in utero*, during lactation, and postnatally until day 42 (Smialowicz et al. 2001). It is not known if these effects would also occur in mature animals. A study involving a battery of immune function tests would be useful for establishing whether heptachlor or heptachlor epoxide is toxic to the immune system.

Neurotoxicity. No human data on the neurotoxicity of heptachlor or heptachlor epoxide were identified. No data exist describing neurologic effects in animals following inhalation or dermal exposure of any duration. Several studies have demonstrated that exposure to heptachlor can result in neurological

effects, in particular, excitability and decreased motor activity (Akay and Alp 1981; Aulerich et al. 1990; Crum et al. 1993; Moser et al. 1995, 2003). As discussed in the Developmental Toxicity section, exposure to heptachlor (and presumably heptachlor epoxide) can result in impaired learning and memory; studies are needed to evaluate whether exposure of mature animals to heptachlor or heptachlor epoxide can also result in impaired learning and memory.

Epidemiological and Human Dosimetry Studies. The existing epidemiological studies are primarily of occupational cohorts (Blair et al. 1983; MacMahon et al. 1988; Shindell and Associates 1981; Wang and MacMahon 1979a), case reports of health effects seen in groups exposed to contaminated milk (Baker et al. 2004b; Chadduck et al. 1987; Le Marchand et al. 1986; Stehr-Green et al. 1986, 1988), or studies examining the possible association between elevated heptachlor/heptachlor epoxide blood levels and adverse health effects (Cantor et al. 2003; Cassidy et al. 2005; Curley et al. 1969; Gladen et al. 2003; Hertz-Picciotto et al. 2004; Pines et al. 1986; Quintana et al. 2004; Sturgeon et al. 1998; Wang and Grufferman 1981; Ward et al. 2000; Wassermann et al. 1982). These studies have generally not included good quantitation of the exposure to heptachlor or heptachlor epoxide. In many cases, it is not possible to determine the exact identity of the contaminants involved. Although use of this compound has been discontinued, exposure could nevertheless occur through food grown in contaminated soil, through contact with pesticides applied to homes and other structures, or from hazardous waste sites. Analytical methods are available to determine exposure to heptachlor or heptachlor epoxide (Curley et al. 1969; Klemmer et al. 1977; Radomski et al. 1968). However, no information is available that correlates levels of heptachlor epoxide in tissue with either level or duration of exposure. Occupational exposure levels are likely to be high enough to enable distinction from background levels. However, many epidemiological studies examining outcomes of exposure are limited by the accuracy of determining the exposure status of those individuals who show adverse health effects and those who show none. The precision and reliability of categorizing exposed individuals and non-exposed individuals contribute significantly to the statistical power of a study and greatly assist in accurate estimation of an increased risk. If data on exposure parameters are sparse or show very wide variation, it is difficult to determine what constitutes an exposure. More data on the correlation of tissue levels to exposure parameters would be useful for increasing the power of epidemiological studies to measure statistically significant associations between heptachlor exposure and health effects in cohorts from both occupational and contaminated community environments. Additionally epidemiology studies should focus on critical end points identified in animal studies including developmental toxicity (including neurological and immunological end points), liver effects, and cancer.

Biomarkers of Exposure and Effect.

Exposure. Exposure to heptachlor and heptachlor epoxide is currently measured by determining the level of these chemicals in the blood or adipose tissue in living organisms (Curley et al. 1969; Klemmer et al. 1977; Radomski et al. 1968). This measure is specific for both heptachlor and heptachlor epoxide. Heptachlor epoxide is also a metabolite of chlordane, and thus its presence is not specific for exposure to heptachlor alone. However, in the absence of stable chlordane residues (e.g., nonachlor and oxychlordane), the heptachlor epoxide would most likely have been derived from heptachlor. Because heptachlor is believed to be converted rapidly in the body to heptachlor epoxide, it is impossible to determine whether the exposure was to one or the other of these two compounds. Heptachlor and heptachlor epoxide accumulate in adipose tissue and are released slowly over long periods of time. Therefore, it is not possible to accurately identify whether the exposure was recent or what the duration of exposure was. However, the ratio of heptachlor epoxide to heptachlor increases over time and therefore may be used as a biomarker of possible exposure to heptachlor. The sensitivity of the methods for identifying these compounds in human tissue appears to be only sufficient to measure background levels of heptachlor epoxide in the population. Additional biomarkers of exposure to heptachlor would be helpful at this time.

Effect. There is no clinical disease state unique to heptachlor. A major problem in developing a biomarker of effect for heptachlor or heptachlor epoxide is that human exposures to these compounds have occurred concomitantly with exposures to other chemicals, and it is difficult to attribute the health effects to heptachlor or heptachlor epoxide alone. More data that quantify the biological effects as well as data that distinguish heptachlor and heptachlor epoxide exposures from those of other chemicals would be useful for developing biomarkers of effect for population monitoring. Biomarkers that could indicate the length of time since exposure would also be useful.

Absorption, Distribution, Metabolism, and Excretion. There are very few data available to assess the relative rates of pharmacokinetic parameters with respect to route of exposure for either heptachlor or heptachlor epoxide. There are no human or animal inhalation or dermal studies on absorption, distribution, metabolism, or excretion. The only human data on metabolism come from *in vitro* studies using liver microsomes that indicate that, qualitatively, human microsomes metabolize heptachlor to the same end products as do rat microsomes (Tashiro and Matsumura 1978). Oral exposure in members of farm families led to elevated serum levels of heptachlor metabolites (Stehr-Green et al. 1986), indicating that the compound is absorbed through the gastrointestinal tract. Animal studies also

suggest that uptake occurs through the gastrointestinal tract following oral dosing; excretion of these doses occurs primarily through the bile duct into the feces (Tashiro and Matsumura 1978). Lethality data suggest that heptachlor can be absorbed through the skin (Gaines 1969), but there are no data on absorption, distribution, metabolism, or excretion of dermally absorbed doses. Heptachlor epoxide is more toxic than heptachlor and has a longer half-life. Additional absorption, distribution, metabolism, and excretion data would be useful in order to gain a thorough understanding of the pharmacokinetic parameters of heptachlor and heptachlor epoxide.

Comparative Toxicokinetics. There are limited available data with which to compare humans and other animal species. Although human toxicity data are available (Baker et al. 2004b; Blair et al. 1983; Cantor et al. 2003; Cassidy et al. 2005; Chadduck et al. 1987; Curley et al. 1969; Gladen et al. 2003; Hertz-Picciotto et al. 2004; Le Marchand et al. 1986; MacMahon et al. 1988; Pines et al. 1986; Quintana et al. 2004; Shindell and Associates 1981; Stehr-Green et al. 1986, 1988; Sturgeon et al. 1998; Wang and Grufferman 1981; Wang and MacMahon 1979a; Ward et al. 2000; Wassermann et al. 1982), the results of these studies are difficult to compare with the animal studies (Akay and Alp 1981; Amita Rani and Krishnakumari 1995; Aulerich et al. 1990; Berman et al. 1995; Crum et al. 1993; Izushi and Ogata 1990; Krampl 1971; Moser et al. 2001; Narotsky and Kavlock 1995; Narotsky et al. 1995; NCI 1977; Pelikan 1971; Purkerson-Parker et al. 2001b; Smialowicz et al. 2001) because the exposure was not well characterized in the human studies and often involved exposure to multiple chemicals. As discussed in the previous section, there are limited data on the toxicokinetics of heptachlor and heptachlor epoxide. With the exception of human monitoring studies examining the levels of heptachlor/heptachlor epoxide in various tissues (Adeshina and Todd 1990; Barquet et al. 1981; Burns 1974; Greer et al. 1980; Klemmer et al. 1977; Polishuk et al. 1977b; Radomski et al. 1968; Stehr-Green et al. 1988; Wassermann et al. 1974), the available toxicokinetic data are in animals. Thus, direct comparisons between humans and animals can not be made. An *in vitro* comparative study found that the metabolites produced in humans and rats are identical, but the amounts differ (Tashiro and Matsumura 1978). Moreover, the rate of metabolism is not similar in both species. Thus, the rat may not be an appropriate metabolic model for humans. Additional studies, particularly *in vivo* studies, are needed to support these findings and identify the most appropriate animal model. There is a lack of information regarding kinetic changes after prolonged exposure. This kind of information would be useful because most exposures in the general population (e.g., from contaminated food or improperly applied pesticides) are likely to be long-term and low-dose.

Methods for Reducing Toxic Effects. The mechanism by which heptachlor and heptachlor epoxide are absorbed from the gastrointestinal tract is unknown. Current methods for reducing absorption

from the gastrointestinal tract involve removing these chemicals from the site of absorption (Haddad and Winchester 1990; HSDB 2007a; Morgan 1989). Additional studies examining the method of absorption would provide valuable information for developing methods that can interfere with gastrointestinal absorption. Numerous studies have examined the distribution of heptachlor and heptachlor epoxide (Barquet et al. 1981; Burns 1974; Curley et al. 1969; Greer et al. 1980; Jonsson et al. 1977; Polishuk et al. 1977b; Radomski et al. 1968). Additional studies on distribution are not necessary at this time. No established methods exist for reducing body burden of heptachlor and heptachlor epoxide. However, available information suggests that removal of these compounds via biliary-gastrointestinal excretion can be accelerated (Morgan 1989). Reducing enterohepatic recirculation before these chemicals partition to tissues may be effective (Haddad and Winchester 1990; HSDB 2007a). Thus, studies examining the effectiveness of repeated doses of activated charcoal or cholestyramine in reducing body burden would be useful. Adipose tissue serves as a major storage repository for both heptachlor and heptachlor epoxide (Barquet et al. 1981; Burns 1974; Greer et al. 1980; Harradine and McDougall 1986). Losing fat can mobilize the stored compound and increase the rate of its elimination. However, it may temporarily increase the blood levels of heptachlor epoxide. Studies that would examine the benefits of reducing body burden with accompanying fat reduction while balancing against harmful effects from temporary increase in blood level would be useful. Since heptachlor undergoes epoxidation to produce heptachlor epoxide which is more toxic than the parent compound, studies examining drugs that would inhibit the enzyme catalyzing this conversion would be helpful. Neurotoxicity of heptachlor epoxide is believed to result, at least in part, from interference with GABA receptor function (Yamaguchi et al. 1980). The available data suggest that benzodiazepenes and barbiturates may be useful in mitigating some of the neurological symptoms of heptachlor epoxide (Bronstein and Currance 1988; HSDB 2007b; Morgan 1989). However, additional studies examining the effectiveness of GABAergic function in mitigating heptachlor epoxide's neurologic effects would be useful. The liver also appears to be a major target organ for the toxic effects of heptachlor and heptachlor epoxide in animals (Akay and Alp 1981; Krampl 1971; Pelikan 1971). An understanding of the mechanism of action in the liver may identify new approaches for reducing the 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.

There are suggestive data indicating that children, particularly children exposed *in utero* and during infancy, may be unusually susceptible to the toxicity of heptachlor. A study in adolescents exposed to

heptachlor and heptachlor epoxide during gestation found significant alterations in neurobehavioral function (Baker et al. 2004b). Similarly, alterations in neurobehavioral function were observed in rats exposed during gestation through postnatal day 42 (Moser et al. 2001). Because neurobehavioral performance has not been investigated in adults, it is difficult to determine whether children are more susceptible to the neurotoxicity of heptachlor than adults. Additionally, no studies have investigated whether there are age-specific differences in the toxicokinetic properties of heptachlor or heptachlor epoxide. Additional studies are needed to evaluate potential age-related differences in the toxicity of heptachlor and heptachlor epoxide.

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

Patrick Wong at the University of California at Davis is investigating ligand-independent endocrine disruption by several pesticides include heptachlor epoxide. Ongoing research by D.E. Wooley, also at the University of California at Davis, is investigating the neurotoxic effects and mechanisms of action of environmental toxicants including heptachlor following acute and chronic exposure.

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Information regarding the chemical identity of heptachlor and heptachlor epoxide is located in Table 4-1.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of heptachlor and heptachlor epoxide is located in Table 4-2.

Table 4-1. Chemical Identity of Heptachlor and Heptachlor Epoxide[a]

Characteristic	Heptachlor	Heptachlor epoxide
Synonym(s)	3-Chlorochlordene; 1,4,5,6,7,8,8a-hepta-chloro-3a,4,7,7a-tetrahydro-4,7-methanoindene; 1,4,5,6,7,8,8-heptachloro-3A,4,5,5a tetrahydro; alpha-dicylcopentadiene, 3,4,5,6,8,8a heptachloro, and others	Epoxyheptachlor; 1,4,5,6,7,8,8a-hepta-chloro-2,3-epoxy-3a,4,7,7a-tetra-hydro-4,7-methanoindene; 4,7-methanoindan, 1,4,5,6,7,8, 8-heptachloro-2,3-epoxy-3a,4,7,7a-tetrahydro-; 2,5-methano-2h-indeno (1,2-b)oxirene, 2,3,4,5,6,7, 7-heptachloro-1a,1b, 5,5a,6,6a-hexahydro-, (1aalpha,1bbeta,2alpha,5alpha, 5abeta,6beta,6aalpha)-
Registered trade name(s)	Basaklor; Gold Crest H-60; Termide; Heptagran; Heptagranox; Heptamak; Heptamul; Soleptax; Velsicol 104	Velsicol 53-CS-17
Chemical formula	$C_{10}H_5Cl_7$	$C_{10}H_5Cl_7O$
Chemical structure		
Identification numbers:		
CAS registry	76-44-8	1024-57-3
NIOSH RTECS	PC0700000	
EPA hazardous waste	P059	D031
OHM/TADS	7216526	833300216
DOT/UN/NA/IMDG shipping	UN 2761, UN2782, UN 2995, UN2996, IMO 3.0, IMO 6.1	UN 2761, UN2782, UN 2995, UN2996, IMO 3.0, IMO 6.1
HSDB	554	6182
NCI	C00180	

[a]All information obtained from HSDB 2007a for heptachlor or HSDB 2007b for heptachlor epoxide unless otherwise noted.

CAS = Chemical Abstracts Services; DOT/UN/NA/IMDG = 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 Heptachlor and Heptachlor Epoxide[a]

Property	Heptachlor	Heptachlor epoxide
Molecular weight	373.32	389.40
Color	White (pure); tan (technical grade)[b]	White[b]
Physical state	Crystalline solid	Crystalline solid[b]
Melting point	95–96 °C (pure); 46–74 °C (technical grade)[c]	160–161.5 °C
Boiling point	145 °C	No data
Specific Gravity:		
at 9 °C	1.57	No data
Odor	Camphor-like	No data
Odor threshold:		
Water	No data	No data
Air	0.3 mg/m^3	0.3 mg/m^3
Solubility:		
Water at 25 °C	0.05 mg/L[d]	0.275 mg/L[d]
Organic solvent(s)	Soluble in most organic solvents	Soluble in most organic solvents[b]
Partition coefficients:		
Log K_{ow}	6.10	5.40
Log K_{oc}	4.34[e]	3.34–4.37[f]
Vapor pressure		
	3x10^{-4} mmHg[g] at 20 °C	1.95x10^{-5} mmHg at 30 °C[h]
	3x10^{-4} mmHg at 25 °C	No data
Henry's law constant:		
at 25 °C	2.94x10^{-4} atm-m^3/mol	3.2x10^{-5} atm-m^3/mol
Autoignition temperature	No data	No data
Flashpoint	No data	No data
Flammability limits	Highly flammable	Non-combustible
Conversion factors	1 ppm=15.27 mg/m^3 at 25 °C, 1 atm	1 ppm=15.93 mg/m^3 at 25 °C, 1 atm
Explosive limits	Non-combustible	Containers may explode when heated

[a]All information obtained from HSDB 2007a for heptachlor or HSDB 2007b for heptachlor epoxide unless otherwise noted
[b]IARC 1974
[c]Worthing and Walker 1987
[d]EPA 1987
[e]Chapman 1989
[f]Estimated from Lyman et al. 1982
[g]ACGIH 1986
[h]Nash 1983

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

5.1 PRODUCTION

Heptachlor was first registered for use in the United States as an insecticide in 1952 and commercial production began the following year (EPA 1986a). Nearly all registered uses of heptachlor were canceled in 1974 by EPA because of its potential cancer risk and its persistence and bioaccumulation throughout the food chain (EPA 1986a). The sale of heptachlor was voluntarily canceled in 1987 by its sole U.S. manufacturer, the Velsicol Chemical Corporation. The sale, distribution, and shipment of existing stocks of all canceled chlordane and heptachlor products were prohibited in the United States as of April 1988 (EPA 1990a; SRI 1990). Heptachlor is a constituent of technical-grade chlordane, approximately 10% by weight (HSDB 2007a). Heptachlor epoxide is an oxidation product of heptachlor and of chlordane; it is not produced commercially in the United States (IARC 1979).

Crown chemical company, the last company in the United States reported to have manufactured heptachlor, transferred its registry to Wood Protection Products, Inc. on October 8, 1985. Since 1985, heptachlor use in the United States has been limited to treatment of fire ants in power transformers. All other heptachlor uses have been banned in the United States.

Table 5-1 summarizes the facilities in the United States that manufacture or process heptachlor. It also lists the maximum amounts of heptachlor that are allowed at these sites and the end uses of the heptachlor. This information is based on the release data reported to the Toxics Release Inventory (TRI) in 2004 (TRI04 2006). The majority of facilities that reported heptachlor release in 2004 were hazardous waste treatment plants that processed heptachlor for safe disposal.

Heptachlor is produced commercially by the free-radical chlorination of chlordene in benzene containing 0.5–5.0% of fuller's earth. The reaction is run for up to 8 hours. The chlordene starting material is prepared by the Diels-Alder condensation of hexachlorocyclopentadiene with cyclopentadiene (Sittig 1980). Technical-grade heptachlor usually consists of 72% heptachlor and 28% impurities such as *trans*-chlordane, *cis*-chlordane, and nonachlor (HSDB 2007a).

The U.S. International Trade Commission (USITC) did not report the domestic production volume of heptachlor separately for the years 1981–1985 (USITC 1982b, 1983b, 1984b, 1985, 1986). Only yearly totals were reported for all cyclic insecticides. The USITC reports production volume data only for

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AR	3	0	99,999	7, 12
CA	1	0	99	12
FL	1	10,000	99,999	7
GA	1	1,000	9,999	7
IL	3	0	9,999	12
KY	2	100	9,999	12
LA	2	0	9,999	12
MI	1	0	99	12
MS	1	0	99	12
NE	2	100	9,999	12
NJ	2	0	9,999	12
NV	1	100	999	2, 3, 12
OH	3	100	99,999	12
OR	2	100	9,999	12
PA	1	0	99	12
SC	1	100,000	999,999	12
TN	4	10,000	999,999	1, 4, 7
TX	5	0	999,999	12
UT	3	0	9,999	12

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

1. Produce
2. Import
3. 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

Source: TRI04 2006 (Data are from 2004)

chemicals for which three or more manufacturers report volumes that exceed certain minimum output levels.

5.2 IMPORT/EXPORT

The USITC did not report separate import data for heptachlor for the years 1981, 1982, or 1983 (USITC 1982a, 1983a, 1984a). The sale, distribution, and shipment of existing stocks of all canceled heptachlor products were prohibited by EPA in 1988 (EPA 1990a). According to the USITC, heptachlor has not been imported into the United States from 1986 to 2007 (USITC 2007).

No information was located regarding the exportation of heptachlor or heptachlor epoxide.

5.3 USE

Heptachlor is a persistent insecticide that kills insects by both ingestion and dermal contact. It is nonphytotoxic at insecticidal concentrations (Worthing and Walker 1987). Heptachlor was used extensively from 1953 to 1974 as a soil and seed treatment to protect corn, small grains, and sorghum from pests. It was used to control ants, cutworms, maggots, termites, thrips, weevils, and wireworms in both cultivated and uncultivated soils. Heptachlor was also used nonagriculturally during this time period to control termites and household insects (EPA 1986a; Worthing and Walker 1987).

EPA proposed cancellation of nearly all registered uses of heptachlor in 1974 because of its potential cancer risk and its persistence and bioaccumulation throughout the food chain. The few agricultural uses that were not canceled in 1974, treatment of field corn, seed (for corn, wheat, oats, barley, rye, and sorghum), citrus, pineapple, and narcissus bulbs, were phased out gradually over a 5-year period ending on July 1, 1983 (EPA 1986a). By April 1988, heptachlor could no longer be used for the underground control of termites. That same year, EPA prohibited the sale, distribution, and shipment of existing stocks of all canceled chlordane and heptachlor products. Subsequently, virtually all uses of heptachlor products were voluntarily canceled by the registrant, Velsicol Chemical Corporation (EPA 1990a). The only current use of heptachlor is in the treatment of fire ants in underground power transformers. This use was specifically exempted from EPA's suspension and cancellation actions because it was believed to result in insignificant exposure and, consequently, insignificant risk. It is unclear whether or not this exempted use is currently supported since Velsicol voluntarily chose not to renew their registration for technical-grade heptachlor in 1999 (EPA 1999a). A search of the National Pesticide Information Retrieval System, which

lists all of the labels for currently registered pesticides, produced no active labels for heptachlor (NPIRS 2007).

5.4 DISPOSAL

Heptachlor and heptachlor epoxide are Resource Conservation and Recovery Act (RCRA) hazardous wastes and hazardous constituents (EPA 1986b); as such, they must be disposed of in secure landfills in compliance with all federal, state, and local regulations. They may also be incinerated at 1,500 °F for 0.5 seconds for primary combustion and at 3,200 °F for 1 second for secondary combustion, with adequate scrubbing of incinerator exhaust and disposal of ash (Sittig 1985).

6. POTENTIAL FOR HUMAN EXPOSURE

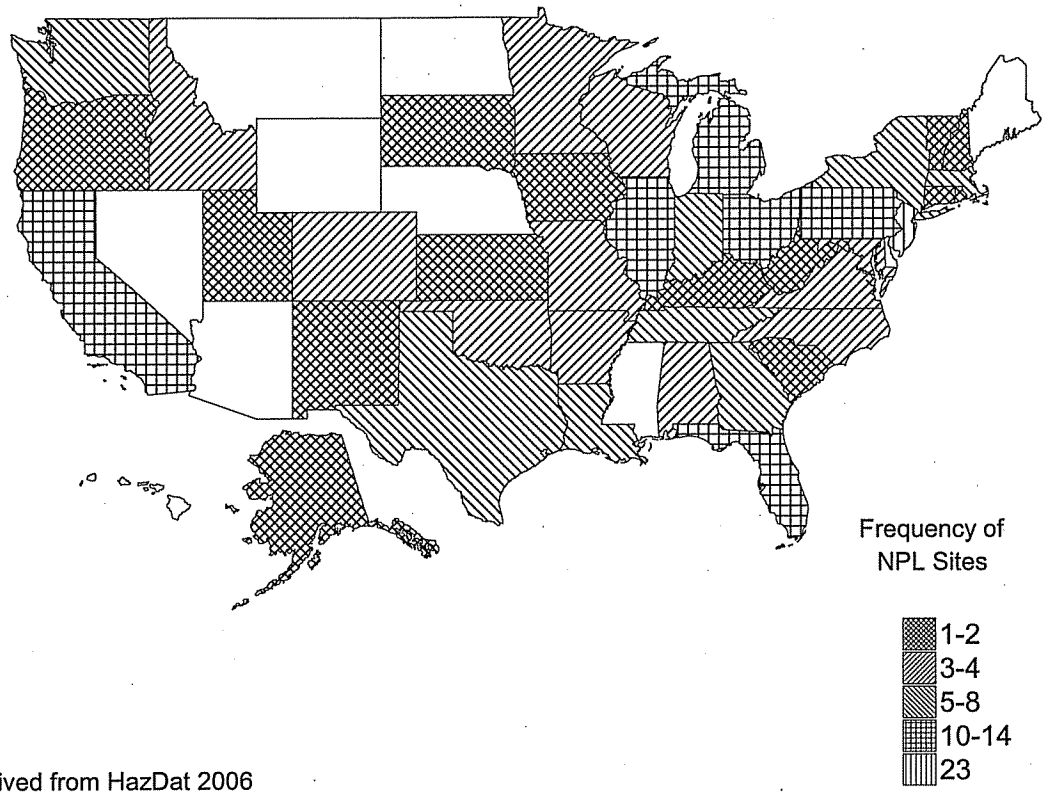
6.1 OVERVIEW

Heptachlor and heptachlor epoxide have been identified in at least 210 and 200 of the 1,684 hazardous waste sites, respectively, that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2006). However, the number of sites evaluated for heptachlor is not known. The frequency of these sites can be seen in Figure 6-1 and 6-2, respectively. Of these sites for heptachlor, 207 are located within the United States, 2 are located in the Commonwealth of Puerto Rico (not shown), and 1 is located in the Virgin Islands. For heptachlor epoxide, 195 of these sites are located within the United States, 2 are located in Guam, 2 are located in the Commonwealth of Puerto Rico, and 1 is located in the Virgin Islands.

Heptachlor was used extensively until the 1970s as a broad-spectrum insecticide on a wide variety of agricultural crops, with the major use on corn. It also had nonagricultural uses including seed treatment, home and garden uses, and termite control. In 1974, EPA proposed cancellation of nearly all registered uses of heptachlor except termite and fire ant control and dipping of roots or tops of nonfood plants, a use that was subsequently voluntarily canceled by the registrant in 1983 (EPA 1986a). In 1988, the sale, distribution, and shipment of existing stocks of all heptachlor products were prohibited in the United States with an exemption for the use of fire ant control. As of April 1988, heptachlor could no longer be used for the underground control of termites. Currently, the only commercial use of heptachlor still permitted in the United States is fire ant control in underground power transformers (EPA 1990a); however, in 1999, the sole manufacturer of heptachlor chose not to renew its registration with the EPA (EPA 1999a). As of April 2007, there were no active pesticide labels containing heptachlor (NPIRS 2007). Therefore, it is unclear whether heptachlor is still available in the United States.

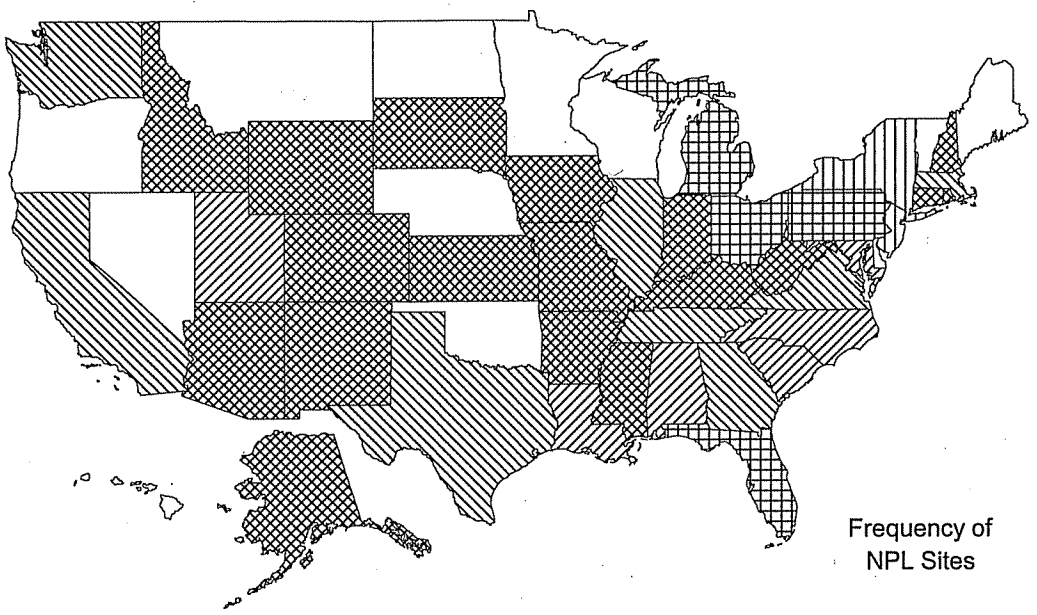
Heptachlor is converted to heptachlor epoxide and other degradation products in the environment. Heptachlor epoxide degrades more slowly and, as a result, is more persistent than heptachlor. Heptachlor epoxide has been found in food crops grown in soils treated with heptachlor many years before. Both heptachlor and heptachlor epoxide adsorb strongly to sediments, and both are bioconcentrated in aquatic and terrestrial organisms. Biomagnification of heptachlor and heptachlor epoxide in aquatic food chains is significant. Because heptachlor is readily metabolized to heptachlor epoxide by higher trophic level organisms, biomagnification of heptachlor itself is not significant. Because of the more persistent nature of heptachlor epoxide and its lipophilicity, biomagnification of heptachlor epoxide in terrestrial food chains is significant.

Figure 6-1. Frequency of NPL Sites with Heptachlor Contamination



Derived from HazDat 2006

Figure 6-2. Frequency of NPL Sites with Heptachlor Epoxide Contamination



Derived from HazDat 2006

In the past (prior to 1974), exposure of humans to heptachlor and heptachlor epoxide was directly related to the application of heptachlor as an insecticide. However, because of the persistence and bioaccumulation of heptachlor and heptachlor epoxide, exposure of the general population can occur through ingestion of contaminated food (especially cow or human milk), inhalation of vapors from contaminated soil and water, or direct contact with residual heptachlor from pesticide application. People whose homes have been treated may continue to be exposed to these chemicals in the air over long periods. Occupational exposure can occur in the manufacture of the chemical or from use of heptachlor to control fire ants. The most likely routes of exposure at hazardous waste sites are unknown. Heptachlor has been found infrequently in soil and groundwater at hazardous waste sites. Children who eat contaminated soil or people who obtain tap water from wells located near hazardous waste sites might be exposed to heptachlor. Further, since both compounds can volatilize from soil, people living near hazardous waste sites may be exposed to the compounds in the air. People whose homes have been professionally treated for termites, either by spraying or subsurface injection, may continue to be exposed to heptachlor and possibly to its transformation product, heptachlor epoxide, in the indoor air over long periods. Releases can also occur from the use of existing stocks in the possession of homeowners (EPA 1990a).

6.2 RELEASES TO THE ENVIRONMENT

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

6.2.1 Air

Estimated releases of 2 pounds of heptachlor and heptachlor epoxide to the atmosphere from 14 domestic manufacturing and processing facilities in 2004, accounted for <0.1% of the estimated total environmental releases from facilities required to report to the TRI (TRI04 2006). These releases are summarized in Table 6-1.

6.2.2 Water

Estimated releases of 9 pounds of heptachlor and heptachlor epoxide to surface water from 14 domestic manufacturing and processing facilities in 2004, accounted for about 0.3% of the estimated total environmental releases from facilities required to report to the TRI (TRI04 2006). These releases are summarized in Table 6-1. These releases were predominantly from hazardous waste disposal agencies (TRI04 2006).

Heptachlor and heptachlor epoxide may enter surface water and groundwater in runoff from contaminated soils or in discharges of waste water from production facilities.

6.2.3 Soil

Estimated releases of 3,140 pounds of heptachlor and heptachlor epoxide to soils from 14 domestic manufacturing and processing facilities in 2004, accounted for >99% of the estimated total environmental releases from facilities required to report to the TRI (TRI04 2006). These releases are summarized in Table 6-1. These releases were predominantly from hazardous waste disposal agencies (TRI04 2006).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Heptachlor has a low vapor pressure ($3.0x10^{-4}$ mmHg at 25 °C) and low water solubility (0.056 mg/L) (EPA 1987; Jury et al. 1987). The experimental value for the Henry's law constant is $1.48x10^{-3}$ suggesting that heptachlor partitions somewhat rapidly to the atmosphere from surface water and that volatilization is significant (EPA 1987; Lyman et al. 1982). Heptachlor is also subject to long-range transport and wet deposition.

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Heptachlor[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	2	0	No data	No data	0	0	0	0	0
LA	1	0	No data	No data	7	0	7	0	7
NE	1	0	No data	No data	0	0	0	0	0
NJ	1	0	9	No data	7	0	16	0	16
NV	1	0	No data	No data	162	0	162	0	162
OH	2	1	0	No data	1	0	1	1	2
OR	1	0	No data	No data	2,962	0	2,962	0	2,962
PA	1	0	No data	No data	0	0	0	0	0
TX	3	0	0	No data	0	0	0	0	0
UT	1	0	No data	No data	0	0	0	0	0
Total	14	2	9	No data	3,140	0	3,149	1	3,150

[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, waste water 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

Source: TRI04 2006 (Data are from 2004)

The log soil organic carbon adsorption coefficient (log K_{oc}) for heptachlor was estimated to be 4.34 (Chapman 1989). The log K_{oc} value indicates a very high sorption tendency, suggesting that it will adsorb strongly to soil and is not likely to leach into groundwater in most cases (Chapman 1989). The leaching potential at 15 cm (concentration in soil water/concentration in soil) for heptachlor is 0.06, and the volatilization potential at 15 cm (concentration in soil air/concentration in soil) determined in laboratory studies is $5.5x10^{-3}$, again suggesting that heptachlor is unlikely to leach appreciably in soil but has some volatilization potential (McLean et al. 1988). These are important properties since heptachlor can remain deep in soil for years. The organic matter content of the soil is another factor affecting mobility. Heptachlor is less likely to leach from soil with a high organic matter content. When released into water, it adsorbs strongly to suspended and bottom sediment.

Volatilization from soil particles to the atmosphere is possible (McLean et al. 1988). Volatilization is an important mechanism of transport of heptachlor from land surfaces (Jury et al. 1987). When heptachlor was applied to orchard grass, approximately 90% was lost in 7 days. When it was applied to moist soil surfaces, 50% was lost in 6 days. When it was applied to dry soil surface, 14–40% was lost in approximately 2 days (50 hours). Volatilization was much less—only 7% in 167 days—when incorporated to a shallow depth of 7.5 cm (Jury et al. 1987). Temperature and humidity affect the persistence of heptachlor and total heptachlor (heptachlor plus heptachlor epoxide) in soil (Shivankar and Kavadia 1989). An increase in temperature resulted in a decrease in the volatilization half-lives of heptachlor and total heptachlor. For example, at 18±1 °C (90±5% relative humidity [RH]) and 35±1 °C (90±5% RH), the half-lives of heptachlor (6 ppm) were 44.8 days and 38 days, respectively. Persistence of heptachlor and total heptachlor was found to be greater at higher humidity, irrespective of temperature. At the combination of higher temperature (25±1 °C) and low humidity (55±5% RH), faster dissipation of heptachlor occurred (half-life=24.67 days). At lower temperatures (18±1 °C) and low humidity (55±5% RH), greater persistence of heptachlor was found (40.67 days). Half-lives of total heptachlor (6 ppm) were longer because of the more persistent nature of heptachlor epoxide (Shivankar and Kavadia 1989).

The logarithm of the *n*-octanol/water partition coefficient (log K_{ow}) is a useful preliminary indicator of bioconcentration potential of a compound. The log K_{ow} for heptachlor is 5.44 (Chapman 1989; MacKay 1982), suggesting a high potential for bioaccumulation and biomagnification in the aquatic food chain. The bioconcentration factors (BCFs) for heptachlor were 10,630 in Asiatic clam fat (*Corbicula*

manilensis), 2,570 in soft clams (*Mya arenaria*), and 8,511 in oysters (*Crassostrea virginica*) (Hawker and Connell 1986).

Heptachlor epoxide is soluble in water at a concentration of 0.275 mg/L (EPA 1987). The experimental value for Henry's law constant is $3.2x10^{-5}$ (EPA 1987), suggesting that heptachlor epoxide partitions slowly to the atmosphere from surface water (Lyman et al. 1982). Based on regression equations, the log K_{oc} for heptachlor epoxide was estimated to range between 3.34 and 4.37 (Lyman et al. 1982). These log K_{oc} values suggest a high sorption tendency, meaning that this compound is not mobile in soil and has a low potential to leach. The organic matter content of soil affects the mobility of heptachlor epoxide. Heptachlor epoxide is less likely to leach from soil with a high organic matter content. If released into water, it adsorbs strongly to suspended and bottom sediments.

The log K_{ow} for heptachlor epoxide is 5.40 (MacKay 1982), indicating a high potential for bioconcentration and biomagnification in the aquatic food chain. Estimated BCFs for heptachlor epoxide are 1,698 in mussels (*Mytilus edulis*), 851 in oysters (*C. virginica*) (Hawker and Connell 1986; Geyer et al. 1982), and 2,330 in Asiatic clam fat (*C. manilensis*) (Hartley and Johnston 1983). The bioconcentration potentials of heptachlor and heptachlor epoxide differ, with the more polar epoxide being concentrated to a lesser degree than the parent compound (Hartley and Johnston 1983). Biomagnification of heptachlor and heptachlor epoxide in aquatic food chains is significant. Because heptachlor is readily metabolized to heptachlor epoxide by higher trophic level organisms, biomagnification of heptachlor itself is not significant. Because of the more persistent nature of heptachlor epoxide and its lipophilicity, biomagnification of heptachlor epoxide in terrestrial food chains is significant.

Heptachlor and heptachlor epoxide are subject to long-range transport and removal from the atmosphere by wet deposition. Snowpack samples were collected at 12 sites in the Northwest Territories, Canada, in the winter of 1985–1986. Heptachlor epoxide was present in 20 of 21 samples at a mean concentration of 0.18 ng/L ($1.8x10^{-4}$ ppb) with reported concentrations ranging from 0.02 to 0.41 ng/L (from $2x10^{-5}$ to $4.1x10^{-4}$ ppb). Heptachlor epoxide was present in both the Bering and Chukchi Seas in 1993 at mean concentrations of 2.4 and 2.8 ng/m^3, respectively (Macdonald et al. 2000).

Heptachlor and heptachlor epoxide are also taken up by plants (translocated into plants by absorption through the roots). Loamy soils were treated with heptachlor at a total of 25 pounds per 5-inch acre over a 5-year period (1958–1962) (Lichtenstein et al. 1970). The commercial formulation of heptachlor used also contained γ-chlordane and nonachlor. Insecticide residues were absorbed by crops grown in these

soils, with carrots absorbing the largest amounts. Although residue levels in soils increased up to 1962, the residue concentrations in both carrots and potatoes peaked during the 1960 growing season. During that year, the concentration of total heptachlor in carrots was 1,900 ppb. Residue levels of total heptachlor on potatoes never exceeded 540–510 ppb (1960–1962). Apparently, a threshold had been reached beyond which the content of insecticidal residues remained constant in these two crops. When insecticide residue levels in soil started to decline (1963), both carrots and potatoes also contained proportionally smaller amounts of residue. In the fall of 1968, residues of total heptachlor were found in the following crops: carrots, 413 ppb (92% heptachlor epoxide); potatoes, 70 ppb (98% heptachlor epoxide); beets, 60 ppb (100% heptachlor epoxide); radishes, 140 ppb (100% heptachlor epoxide); and cucumbers, 90 ppb (95% heptachlor epoxide) (Lichtenstein et al. 1970). Despite being banned in Argentina, trace amounts of heptachlor and heptachlor epoxide (<10 ng/g dry weight) were found in organically grown tomato plants that had never been sprayed with any pesticide outside of Buenos Aires (Gonzalez et al. 2003). Heptachlor epoxide was detected in spruce and pine trees of western Canada and the concentration of heptachlor in these trees seemed to increase as the altitude increased (Davidson et al. 2003).

6.3.2 Transformation and Degradation

6.3.2.1 Air

Heptachlor may undergo direct photolysis in sunlight and is also susceptible to photosensitized reactions (Graham et al. 1973; Ivie et al. 1972). Heptachlor epoxide is converted to intermediate and final photoproducts when exposed to sunlight or ultraviolet light on the surface of plants (Podowski et al. 1979). About 40–50% conversion occurred in 4 hours on bean leaves treated with rotenone, an insecticide, acting as a photosensitizer. No detectable photoproducts (photoheptachlor epoxide) were formed in the absence of rotenone. The photolysis products were ketones. The intermediate photoproduct possesses a reduced toxicity in mice as compared to heptachlor epoxide, and it is completely nontoxic to houseflies. The final photoproduct is more toxic to flies and mice than the parent heptachlor epoxide (Ivie et al. 1972). The photoisomers of heptachlor epoxide are not expected to form in appreciable amounts in the environment unless a potent photosensitizer is present (Ivie et al. 1972). The photolysis of heptachlor epoxide as a solid (pressed) disk, as a powder, and as 0.5% heptachlor epoxide in a potassium bromide (a photosensitizer) disk was studied. The physical nature of the sample and the intensity of illumination affected the rate of photolysis. After 121 hours of exposure to sunlight in July, 93, 98, and 0% heptachlor epoxide remained in the solid disk, powder, and potassium bromide disk, respectively. When a powdered sample of heptachlor epoxide was irradiated on a rooftop of an

unspecified location from January through mid-September, degradation was almost negligible until May, then increased through July, reaching a maximum decomposition rate of 1% per day at the end of July. By the end of the experiment (8.5 months), 39% of the original sample had decomposed (Graham et al. 1973).

6.3.2.2 Water

Heptachlor is hydrolyzed in surface water and distilled water to 1-hydroxychlordene and heptachlor epoxide. When heptachlor was added to a sample of river water maintained at room temperature and exposed to sunlight, only 25% remained after 1 week, and no heptachlor remained after the second week. The 75% loss of heptachlor after 1 week corresponds to a half-life of 3.5 days. It was observed that an equilibrium exists at the end of 4 weeks between 1-hydroxychlordene and heptachlor epoxide, so that approximately 60% of the converted heptachlor remained as 1-hydroxychlordene and 40% was converted to the epoxide. When heptachlor epoxide was added to a sample of river water (pH 7.3–8) and to distilled water, it remained unchanged for 8 weeks. A half-life of at least 4 years was calculated for heptachlor epoxide (Eichelberger and Lichtenberg 1971).

When a ^{14}C-heptachlor-treated model aquatic ecosystem was examined for transformation of heptachlor in water, the relative amounts of various transformation products in water were determined as the percentage of the total ^{14}C label in the water sample. Heptachlor was found to decrease from 100% to approximately 10% of total ^{14}C material in 1 day (Lu et al. 1975). After 1 day, 1-hydroxychlordene epoxide was present as 50% of the total ^{14}C, rose to 70% on day 3, and then remained constant until day 13 of the experiment. The heptachlor hydrolysis product, 1-hydroxychlordene, reached a maximum of 10% of the total ^{14}C at day 1 and decreased thereafter. A relatively small proportion of heptachlor epoxide was formed. Heptachlor epoxide was never found to be >10% of the total ^{14}C in the water sample. The authors concluded that the major pathway of heptachlor in aquatic systems is rapid abiotic hydrolysis of heptachlor to 1-hydroxychlordene followed by metabolism to 1-hydroxychlordene epoxide (Lu et al. 1975).

Heptachlor is metabolized by the freshwater microcrustacean, *Daphnia magna*, to heptachlor epoxide or 1-hydroxychlordene. 1-Hydroxychlordene is then converted to 1-ketochlordene, 1-hydroxy2,3-epoxy-chlordene, and their glucosides, sulfates, and other conjugates (Feroz et al. 1990).

6.3.2.3 Sediment and Soil

Incubations of heptachlor with a mixed culture of soil microorganisms for 12 weeks showed slow conversion of heptachlor to chlordene, 1-exohydroxychlordene, heptachlor epoxide, and chlordene epoxide. A mixed culture of soil microorganisms, obtained from a sandy loamy soil, degraded heptachlor epoxide to the less toxic 1-exohydroxychlordene at a rate of 1% per week during the 12-week test period (Miles et al. 1971).

Soil samples that contained heptachlor were taken from five locations selected to represent typical soil types and rainfall patterns in portions of the United States. The samples were taken from places where subterranean termites were a major problem and where heptachlor was applied for treatment (Carter and Stringer 1970). Residues were found in the soil 1, 2, and 3 years after application of heptachlor. Relatively high values for 1-hydroxychlordene, representing approximately 60% of the insecticide in the soil, were obtained from extracts of a Quincy loamy fine sand from Oregon 2 years after application. Significant amounts of 1-hydroxychlordene were also found in extracts of Lakeland sand from Florida. Generally, heptachlor epoxide represented only a small fraction of the insecticide present in the soils (Carter and Stringer 1970). Because the distribution and penetration of heptachlor were uneven, there were large variations in concentration in the soils and therefore, no general trends were recognized (Carter and Stringer 1970).

Loamy soils treated with heptachlor at 25 pounds per 5-inch acre, over a 5-year period from 1958 through 1962, contained about 5% of the applied dosages in the fall of 1968, primarily in the form of heptachlor epoxide. In addition to γ-chlordane and nonachlor, which were present in the original heptachlor formulation, two toxic metabolites (heptachlor epoxide and α-chlordane) as well as three unidentified compounds were detected, thus indicating the breakdown in soils of heptachlor and related compounds (Lichtenstein et al.1970).

Experiments with thick anaerobically digested waste water sludge at 35°C showed that heptachlor was converted to an extractable degradation product that was more persistent than the initial heptachlor. About a 50% loss of heptachlor epoxide was found in anaerobic thick sludge after approximately 60 days. No information was given as to the identity of the product. No heptachlor epoxide loss occurred in aerobic dilute sludge, and only slight heptachlor epoxide loss occurred in anaerobic dilute sludge (Hill and McCarty 1967).

6.3.2.4 Other Media

Heptachlor was reported to degrade up to 45% after 3 weeks of composting. Heptachlor and heptachlor epoxide were found in concentrations of 8.5–26 and <3.8 μg/kg of municipal solid waste, respectively. Concentrations of biosolid and municipal solid waste compost were recorded at levels <0.23 and <0.63 μg/kg for heptachlor and heptachlor epoxide, respectively (Buyuksonmez et al. 2000).

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

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

6.4.1 Air

Indoor air levels of heptachlor were measured in various homes in Bloomington, Indiana, that had been professionally treated with a termiticide either by spraying or subsurface injection. Heptachlor was detected at concentrations ranging from 1.1 to 110 ng/m^3 (0.0001–0.007 ppb) (Anderson and Hites 1989). Three houses in North Carolina were treated with a termiticide containing both chlordane (0.5%) and heptachlor (0.25%). Immediately after treatment, the average ambient air level of heptachlor was 1.41 ± 0.64 μg/m^3 (0.092 ppb). At 12 months post-treatment, the heptachlor level in the air was 1.00 ± 0.70 μg/m^3 (0.065 ppb) (Wright and Leidy 1982). Heptachlor was detected at levels ranging from 1.64 to 13.2 ppb in workplace air in 1977 at the Velsicol Chemical Corporation plant in Tennessee that manufactured heptachlor (Netzel 1981). No heptachlor epoxide levels in air were detected (Netzel 1981). A study of nine households selected on the basis of high pesticide usage in an urban-suburban area in the southeastern United States found outdoor air levels of heptachlor ranging from not detectable (0.0006 ppb) to 0.003 ppb, with a mean of 0.001 ppb (Lewis et al. 1986). Heptachlor was found in seven of nine households at levels in indoor air ranging from not detectable to 0.02 ppb, with a mean of 0.006 ppb (Lewis et al. 1986). Air samples taken from Corpus Christi, Texas in 1998 had a mean heptachlor concentration of 0.04 ng/m^3 (Park et al. 2002). Heptachlor was measured in Alabama air from

January to October 1996. Heptachlor was found in concentrations ranging from 20 to 50 pg/m^3 with the highest concentrations in the summer months and the lowest concentrations in April and May. No heptachlor was detected in October (Jantunen et al. 2000). Heptachlor and heptachlor epoxide were also detected in air in Galveston, Texas in concentrations ranging from 6.1 to 77.2 and from not detected to 30.4 pg/m^3, respectively (Park et al. 2001).

Since heptachlor was used for termite control, monitoring the levels of heptachlor when applied in a home is of interest. In a study of 19 homes where heptachlor was used in the treatment of subterranean termite control, a mean concentration of 5 μg/m^3 was observed during treatment. After 24 hours, the concentration of heptachlor decreased to about 2 μg/m^3. However, even after 180 days, heptachlor levels remained around 2 μg/m^3, which was much higher than the 0.5 μg/m^3 mean from before treatment. Concentrations of heptachlor were highest in the basement of these homes with mean concentrations of 9 and 2 μg/m^3 during treatment and after 180 days, respectively (Kamble et al. 1992).

6.4.2 Water

A statewide survey (December 1985–February 1986) was conducted in Kansas to determine the degree and extent of pesticide contamination of drinking water from approximately 100 private farmstead wells. Heptachlor was detected in 1% of the wells tested at a concentration range of 0.023–0.026 ppb with an average concentration of 0.025 ppb (detection limit=0.02 ppb) (Steichen et al. 1988).

Heptachlor was included in EPA's Pesticides in Groundwater Database for 17 states and was found in 6 states: Illinois, Indiana, Missouri, New Jersey, South Carolina, and Virginia. Concentrations of heptachlor in groundwater from these six states ranged from $6.6x10^{-5}$ to 0.052 ppb (EPA 1992). Heptachlor epoxide was included in EPA's Pesticides in Groundwater Database for 16 states and was found in 7 states: Alabama, Illinois, Indiana, Kansas, Massachusetts, South Carolina, and Virginia. Concentrations of heptachlor in groundwater from these seven states ranged from a trace to 0.014 ppb (EPA 1992).

Heptachlor and heptachlor epoxide were detected in water column samples at different depths in Lake Pontchartrain in New Orleans, Louisiana. Heptachlor was detected in the 1.5-m ebb- and flood-tide samples and in the 10-m flood-tide samples at concentrations of 0.6, 9.1, and 9.3 ppt, respectively. Heptachlor epoxide was detected in the 1.5-m ebb- and flood-tide samples and in the 10-m flood-tide sample at concentrations of 2, 3.9, or 2.5 ppt, respectively (McFall et al. 1985).

Findings from the Nationwide Urban Runoff Program priority pollutant samples collected in 1982 showed that heptachlor and heptachlor epoxide were detected at a concentration of 0.1 ppb for both compounds (Cole et al. 1984). Heptachlor and heptachlor epoxide were detected in 5 and 1%, respectively, of the 86 urban storm water runoff samples taken from 15 cities.

Despite being banned in 1988, heptachlor and heptachlor epoxide are still found in the water. Heptachlor was found in concentrations ranging from 180 to 22 ng/sample of lower Missouri River water (Petty et al. 1995). Heptachlor epoxide was found in samples taken from the Mississippi Delta in May and July of 1997 at concentrations of about 10 ng/g (Zimmerman et al. 2000). Heptachlor was found in 7% of the influent and 10% of the effluent of 84 New York City municipal waste water samples. Concentrations were 0.021–0.35 and 0.02–0.447 ng/L, respectively, for the years 1989–1993. Heptachlor epoxide was found in 1% the influent and 2% of the effluent out of 84 New York City municipal waste water samples in concentrations of 0.012 and 0.018–0.03 µg/L, respectively, for the years 1989–1993 (Stubin et al. 1996). Heptachlor epoxide was found in 11 out of 242 groundwater samples taken from areas near golf courses in concentrations lower than the maximum contaminant level (MCL), 0.16 µg/L (Cohen et al. 1999).

Analysis of rain samples demonstrates how heptachlor can be deposited at sites where it was not applied. Heptachlor epoxide was detected in rain samples at concentrations ranging from 0.03 to 1 ppt at four widely separated sites in Canada from May to October in 1984. The sites are representative of overlake and shoreline locations (Strachan 1988). Snowpack samples representing snow accumulation for the winter of 1985–1986 were collected at a total of 12 widely distributed sites throughout the Northwest Territories, Canada, during the spring of 1986. Heptachlor epoxide was detected at 11 of the 12 sites at concentrations ranging from 0.2 to 0.41 ng/L ($2x10^{-4}$–$4x10^{-4}$ ppb). The only reasonable source for these compounds is long-range atmospheric transport and deposition (Gregor and Gummer 1989). Heptachlor was detected in wet precipitation samples (rain/snow) from Lake Erie at a volume-weighted mean concentration (based on the total volume collected over the 12-month period) of 0.1 ng/L ($1x10^{-5}$ ppb) (Chan and Perkins 1989). Heptachlor epoxide was detected at volume-weighted mean concentrations of 0.05 ng/L ($5x10^{-5}$ ppb), 0.24 ng/L ($2.4x10^{-4}$ ppb), and 0.02 ng/L ($2x10^{-5}$ ppb) in wet precipitation samples from Lake Superior, Lake Erie, and Lake Ontario, respectively (Chan and Perkins 1989). Heptachlor and Heptachlor epoxide were detected in rain water near Galveston Bay, Texas in concentrations ranging as high as 139.7 and 155.7 pg/L, respectively (Park et al. 2001). Heptachlor epoxide was found in two of eight samples of rain water from horticultural areas in Denmark and in two of eight background areas in

Denmark at concentrations of above the detection limit (0.011), 0.002, 0.005, and 0.002 μg/L, respectively (Hamers et al. 2001). In January 1997, heptachlor was found in rain water in farm, urban, and Oakdale samples in Iowa at concentrations of 0.016, 0.011, and 0.0073 μg/L, respectively (Hochstedler et al. 2000).

Data maintained in the STORET database for 2003–2005 included heptachlor and heptachlor epoxide concentrations in industrial. Heptachlor was reported in 53% of the 804 water samples taken around the country in concentrations ranging from 1 μg/L to below quantification limits. Heptachlor epoxide was reported in 49% of the 809 water samples taken around the country in concentrations ranging from 1 μg/L to below quantification limits (EPA 2007).

6.4.3 Sediment and Soil

Data from the 1971 National Soils Monitoring Program at 1,486 sampling sites in 37 states showed that heptachlor was detected in 4.9% of the samples from cropland soils at concentrations ranging from 10 to 1,370 ppb. Heptachlor epoxide was detected in 6.9% of the samples at concentrations ranging from 100 to 430 ppb (Carey et al. 1978). A survey of agricultural soils (pasture soils) in the New South Wales North Coast region in Australia (1983–1984) showed soils contaminated with organochlorine residues. Heptachlor levels in the pasture soils generally averaged <100 ppb. Heptachlor epoxide residues were quantitatively higher. Heptachlor and heptachlor epoxide were generally highest in the top 22.5 cm of soil (McDougall et al. 1987). Heptachlor epoxide was detected in 17 out of 822 soil samples at 10 out of 49 agricultural sites in Illinois with a mean concentration of 17 μg/kg. In the same study, heptachlor was detected in 26 soil samples from 14 different sites with a mean concentration of 50 μg/kg (Krapac et al. 1995). Heptachlor was found in 3 out of 39 samples of Alabama soil with a geometric mean concentration of 0.037 ng/g. In the same study, heptachlor epoxide was found in 12 of the 26 soil samples with a geometric mean concentration of 0.099 ng/g (Harner et al. 1999).

Heptachlor epoxide was detected in grab and core samples of southern Lake Michigan sediments (period of sampling, 1969–1970) at trace levels up to 0.7 ppb (Leland et al. 1973). The U.S. Geological Survey investigated the sediment quality of the upper Rockaway River in New Jersey. Sediment samples were collected from seven stations along the upper Rockaway River. Stations 1 and 2 drain primarily forested areas of the upper Rockaway basin. Stations 3–7 drain an area consisting primarily of residential, commercial, and industrial land usage, including six NPL sites. Concentrations of heptachlor epoxide

were <0.1 ppb for stations 1 and 2. Heptachlor epoxide concentrations ranged from <0.1 to 10 ppb for stations 3–7 (Smith et al. 1987).

Heptachlor and heptachlor epoxide were monitored at six different sites in the sediment of San Pablo Bay, California. Heptachlor was not detected in four of the samples, while the other two samples contained 2.14 and 1.63 µg/kg of heptachlor. Heptachlor epoxide concentrations were below detection levels for all six samples (Baum et al. 2001). Heptachlor was found in the sediment of Casco Bay, Washington in concentrations ranging from 0.04 to 0.13 ppb (Kennicutt et al. 1994).

Heptachlor, which may have been applied to the World Trade Center for termite control, was detected in concentrations too low to quantify in the dust that settled across lower Manhattan after September 11, 2001 (Offenberg et al. 2003).

Heptachlor and heptachlor epoxide have been monitored in all 50 states and parts of Canada by the United States Geological Society (USGS). Heptachlor was detected in sediment at 9 out of 1,148 sites in 49 major hydrological basins at a maximum concentration of 8.3 µg/kg (USGS 2003); these data were collected from 1992 to 2001. In the same monitoring study, heptachlor epoxide was detected at 20 of the 1,148 sites, at a maximum concentration of 19.7 µg/kg. Data maintained in the STORET database for 2003–2005 included heptachlor and heptachlor epoxide concentrations in industrial effluent and ambient water. Heptachlor epoxide was reported in 4 of the 176 sediment samples taken with a maximum concentration of 0.621 µg/kg. Heptachlor was not reported in any of the 186 sites reporting data from 2003 to 2005 (EPA 2007).

6.4.4 Other Environmental Media

Heptachlor and heptachlor epoxide have been detected in several aquatic species. Heptachlor was measured in shrimp collected from the Calcasieu River/Lake Complex in Louisiana at concentrations ranging from 10 to 750 ppb (Murray and Beck 1990). A survey of organic compound concentrations in whole body tissues of the Asiatic clam, *C. manilensis*, was conducted on the Apalachicola River in northwest Florida in 1979–1980 as part of the Apalachicola River Quality Assessment. Heptachlor epoxide was detected in the whole body tissue of the clam at concentrations ranging from <0.1 to 0.6 ppb, with a median concentration of 0.3 ppb (Elder and Mattraw 1984).

Composite whole fish samples taken from tributary rivers around the Great Lakes in 1980–1981 had heptachlor levels of <0.002 mg/kg (<2 ppb) at all sites except the Ashtabula River where a maximum concentration of 0.30 mg/kg (300 ppb) occurred. Heptachlor epoxide was detected at concentrations ranging from 0.003 to 0.48 mg/kg (3–480 ppb) (DeVault 1985). Freshwater fish collected in 1984 for the National Contaminant Biomonitoring Program run by the U.S. Fish and Wildlife Service contained a geometric mean residue concentration of total heptachlor (heptachlor epoxide plus traces of heptachlor) of 0.01 ppm (wet weight). Heptachlor residues in fish were present in 49.1% of the collection stations (n=112) located at major rivers throughout the United States, including Alaska and Hawaii. Concentrations of heptachlor epoxide in whole fish samples remained highest in Hawaii and in the Midwest, especially in Lake Michigan and in the Mississippi, Missouri, Ohio, and Illinois Rivers (Schmitt et al. 1990).

Average residue levels of total heptachlor detected in Illinois soybeans in 1980 (6.6 ppb) showed an increase from 1974 levels (5.3 ppb), even though the usage of heptachlor declined during that period (MacMonegle et al. 1984). Heptachlor residues above maximum residue limits were reported in Australian beef in 1987. Upon removing the animals from contaminated pastures, the proportion of samples of beef with residue levels above the permitted limits decreased from 0.42% in 1986–1987 to 0.22% in 1987–1988 (Corrigan and Seneviratna 1989). In an earlier study, heptachlor epoxide levels in cow's milk reached a maximum of 0.22 ppm within 3–7 days after the animals had grazed on pastures immediately following treatment of the grasses with heptachlor (Gannon and Decker 1960).

Heptachlor concentrations in pork and beef have decreased from 1974 to 1996. In 1974–1984, heptachlor was detected in beef and pork in concentrations of 0.1–54 and 11.2–970 ppb, respectively. By 1988, heptachlor was not detected in beef and was detected in 33% of the pork samples studied in concentrations ranging from 1 to 8 ppb with no other detections in pork after 1988. Heptachlor epoxide was detected in concentrations of 1.9–2.9 and 0.5–5.9 ppb in pork and beef, respectively, during studies from 1974 to 1984. During the years 1985–1988, heptachlor epoxide was not detected in pork, but was detected in 35% of beef samples at concentrations ranging from 19 to 27 ppb. Heptachlor epoxide was still found in 3% of pork samples and 12% of beef samples taken from 1993 to 1996 (Cantoni and Comi 1997).

Monitoring data collected by the USGS from 1992 to 2001 at 1,148 sites in 49 U.S. major hydrological basins indicated that heptachlor and heptachlor epoxide were infrequently detected in fish (USGS 2003).

Heptachlor was detected in fish at 3 sites at a maximum concentration of 12 µg/kg and heptachlor epoxide was detected in fish at 88 sites at a maximum concentration of 270 µg/kg (USGS 2003).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The general population is primarily exposed to heptachlor and heptachlor epoxide through diet. The food classes most likely to contain residues are milk and other dairy products, vegetables, meat, fish, and poultry. In the FDA Total Diet Study conducted between 1981 and 1982, levels of chemicals in the diet were determined by analyzing samples from retail markets in 13 cities throughout the continental United States. These samples represent the typical 14-day diet. Approximately 120 individual food items, including drinking water, were collected for each market basket sample; the infant diet consisted of about 50 of these foods, and the toddler diet included 110. The average daily intake of heptachlor epoxide for infants was estimated to be 0.01 µg/kg/day. The 1981–1982 average daily intake of heptachlor epoxide for toddlers was reported to be 0.009 µg/kg/day. Whole milk, with an average concentration of 0.1 ppb, contributed the highest daily intake of heptachlor epoxide for both toddlers and infants (Gartrell et al. 1986b). In the FDA Total Diet Study conducted between 1982 and 1984, analyses were performed of 234 items depicting the diets of eight population groups with members ranging in age from infants to elderly adults. The data represent eight food collections in regional metropolitan areas during the 2-year period. Toddlers (2 years old) had the highest daily intake of heptachlor epoxide (6.1 ng/kg/day). Infants had a daily intake of heptachlor epoxide of 2.7 ng/kg/day. Daily intake from whole milk was not included in this study. Adults had heptachlor epoxide intakes that ranged from 1.5 ng/kg/day (60–65-year-old females) to 2.8 ng/kg/day (14–16-year-old males). Heptachlor epoxide was found in 8% of the food samples analyzed between 1982 and 1984. Heptachlor intake was <0.1 ng/kg/day for all age/gender groups. Between 1980 and 1982–1984, daily intakes of heptachlor epoxide decreased from 19 to 3 ng/kg/day for infants, from 20 to 6 ng/kg/day for toddlers, and from 7 to 2–3 ng/kg/day for adults (Gunderson 1988). Heptachlor epoxide was found in 45 different food items from a total diet study. From this information and from questionnaires, it was estimated that heptachlor epoxide was found at a mean concentration of 0.3 µg/day in people surveyed in 1990 (MacIntosh et al. 1996).

The 1988 Acceptable Daily Intake (ADI) established by the United Nation's Food and Agriculture Organization and the World Health Organization (FAO/WHO) for total heptachlor was 0.5 µg/kg/day (FDA 1989). Total heptachlor intakes found in the Total Diet Analysis (1988) were 0.004 µg/kg/day for 6–11-month-old infants, 0.017 µg/kg/day for 14–16-year-old males, and 0.0007 µg/kg/day for 60–63-year-old females (FDA 1989).

Adipose tissue samples from various body parts of people living in northeast Louisiana, an area of heavy agriculture, were taken during pathological examination. Heptachlor epoxide levels in the individual tissue samples ranged from 20 to 790 ppb (average=239 ppb) for the 1980 study and from 60 to 220 ppb (average=159 ppb) from adipose tissue samples taken from other donors for the 1984 study (Holt et al. 1986).

Heptachlor and heptachlor epoxide have been found in human milk samples (Al-Omar et al. 1986; Fytianos et al. 1985; Larsen et al. 1971; Mes et al. 1986; Ritcey et al. 1972; Savage et al. 1981). Breast milk samples (n=210) taken from Canadian women from five different regions who had resided in Canada for at least 5 years were analyzed for chlorinated hydrocarbon contaminants as part of a monitoring program. Trends from 1967 to 1982 showed heptachlor epoxide levels decreased from a mean of 3 ppb in 1967 to a mean of <1 ppb in 1982 (maximum, 7 ppb) (Mes et al. 1986). Heptachlor epoxide was found in 62% of all samples taken in 1982 (Mes et al. 1986). Human milk samples obtained from 1,436 women residing in the United States were analyzed for chlorinated hydrocarbon insecticides. While heptachlor was recovered in <2% of the samples, heptachlor epoxide was found in 63% of the samples. The proportion of breast milk samples containing heptachlor epoxide varied significantly among the five geographic regions (66.1–128 ppb) with the southeastern states having the highest mean residual level. The reasons for higher levels of these chemicals in samples from women in the southeastern United States are not clear, but there may be several contributing factors. For example, more people in the southeast use pesticides in the home, lawn, and garden, and a larger proportion of southeastern U.S. homes have been treated with heptachlor for termite control. The mean residual level of heptachlor epoxide in breast milk for the whole United States was 91.4 ppb (Savage et al. 1981). A 5-month follow-up study of four pregnant Iraqi women without occupational exposure to organochlorine pesticides found total heptachlor levels in the placenta immediately after delivery ranging from not detectable to 28 ppb total tissue weight. Milk samples were then taken for 20 consecutive weeks. Average total heptachlor levels in the mothers' milk ranged from 15 to 68 parts per billion parts of whole milk (Al-Omar et al. 1986). There was considerable fluctuation in the residue concentrations over the 20 weeks. The authors suggest that the fluctuations could be attributed to changes in daily diet intake of residues and daily variations in milk production and fat content of the milk.

A pilot study for EPA's Non-Occupational Exposure Study was conducted in August 1985 in order to assess nonoccupational exposures to pesticides, including heptachlor, in indoor air and personal respiratory air. The study was conducted in nine households selected on the basis of high pesticide usage

in an urban-suburban area in the southeastern United States. The residents of these households were generally retired or semi-retired persons, who spent the majority of their time indoors (average=18 hours) and, consequently, do not represent the general adult population. The results showed that heptachlor was found in seven of nine households at levels in indoor air ranging from not detectable (at 0.0001 ppb) to 0.31 μg/m^3 (0.02 ppb), with a mean of 0.088 μg/m^3 (0.006 ppb). When residents wore personal monitors, operated only during periods of activity, heptachlor was detected in six of nine households at personal exposure levels of not detectable to 0.18 μg/m^3 (0.01 ppb), with a mean of 0.06 μg/m^3 (0.004 ppb). Outdoor air levels of heptachlor were lower, ranging from not detectable to 0.048 μg/m^3 (0.003 ppb), with a mean of 0.016 μg/m^3 (0.001 ppb), and were detected in five of nine households (Lewis et al. 1986).

Heptachlor has been routinely found in human breast milk as well as in animal and commercial milk products and has been studied extensively. A 25-year study of contaminants in human breast milk found that heptachlor in breast milk of Canadian mothers decreased from 3 ng/g in 1965 to 0.11 ng/g in 1992 (Craan and Haines 1998). Heptachlor has been detected in milk and umbilical cord fluid of 13.5% of the 385 mothers tested in the Arctic region of Canada with a mean concentration of 0.6 μg/L (Butler Walker et al. 2003). Termite control was associated with high heptachlor body burden as analyzed through breast milk in Australia where heptachlor epoxide was found in the breast milk of 575 of the 797 women tested in Victoria, Australia with concentration median of 0.007 mg/kg in 1997 (Sim et al. 1998). Average heptachlor epoxide levels in whole blood samples from non-occupationally exposed mothers and their newborns in Argentina were 0.23±0.29 ppb in 13 mothers and 0.06±0.01 ppb in 13 newborn infants (Radomski et al. 1971a). Heptachlor and heptachlor epoxide were found in 50 samples (51.5%) of pasteurized milk samples tested in Spain. Of the samples with heptachlor and heptachlor epoxide, eight of them contained levels that exceeded the limits stated by the European Union (Martinez et al. 1997). Heptachlor and heptachlor epoxide were found in cows' milk at concentrations of 6.5–28.5 and 8.5–34 ng/g, respectively (Armendariz et al. 2004).

In a study of non-occupationally exposed people in Jacksonville, Florida and Springfield/Chicopee, Massachusetts from 1986 to 1988, heptachlor was found in personal, outdoor, and indoor air samples. While Springfield/Chicopee did not have any samples that contained heptachlor, the concentration of heptachlor in samples from Jacksonville ranged from 0.1 to 0.8 ng/m^3 (Whitmore et al. 1994).

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.

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).

Infants and toddlers are exposed to higher levels (based on their greater dose to surface area [or body weight] ratio) of heptachlor epoxide in the diet (particularly from milk) than are adults. Higher exposure rates in indoor air may occur for at least 1 year in homes that have been treated for termites with heptachlor in the past. Although the most likely routes of exposure at hazardous waste sites are unknown, exposure may result from ingestion of contaminated soil near these sites particularly by children. Since both heptachlor and heptachlor epoxide volatilize from soil, inhalation exposure may also be important for persons living near hazardous waste sites. Exposure via ingestion of contaminated drinking water obtained from wells near hazardous waste sites is unlikely. Heptachlor and heptachlor epoxide are considered too lipophilic to leach to groundwater. While some samples have been found in well water, this trend is not universal. Workers involved in the manufacture of heptachlor and in the application of heptachlor for fire ant control are at risk of exposure to heptachlor. People living in the southeastern United States may be exposed to higher than background levels of heptachlor or heptachlor epoxide because of the larger proportion of southeastern U.S. homes that have been treated with heptachlor for termite control and the greater usage of pesticides in the home, lawn, and garden. Infants living in this region may be more likely to ingest heptachlor or heptachlor epoxide from maternal breast milk, although this exposure pathway is not restricted to the southeastern United States.

The average daily intake of heptachlor epoxide for infants was estimated to be 0.01 μg/kg/day. The 1981–1982 average daily intake of heptachlor epoxide for toddlers was reported to be 0.009 μg/kg/day. Whole milk, with an average concentration of 0.1 ppb, contributed the highest daily intake of heptachlor

epoxide for both toddlers and infants (Gartrell et al. 1986b). In the FDA Total Diet Study conducted between 1982 and 1984, analyses were performed of 234 items depicting the diets of eight population groups with members ranging in age from infants to elderly adults. The data represent eight food collections in regional metropolitan areas during the 2-year period. Toddlers (2 years old) had the highest daily intake of heptachlor epoxide (6.1 ng/kg/day). Infants had a daily intake of heptachlor epoxide of 2.7 ng/kg/day. The 1988 Acceptable Daily Intake (ADI) established by the United Nation's Food and Agriculture Organization and the World Health Organization (FAO/WHO) for total heptachlor was 0.5 μg/kg/day (FDA 1989). Total heptachlor intakes found in the Total Diet Analysis (1988) were 0.004 μg/kg/day for 6–11-month-old infants, 0.017 μg/kg/day for 14–16-year-old males, and 0.0007 μg/kg/day for 60–63-year-old females (FDA 1989).

Heptachlor epoxide was found in whole blood samples from nonoccupationally exposed mothers and their newborns in Argentina (Radomski et al. 1971a). The average level of heptachlor epoxide was 0.23±0.29 ppb in 13 mothers and 0.06±0.01 ppb in 13 newborn infants, although no blood samples were taken from the mothers during pregnancy (Radomski et al. 1971a).

In order to understand the exposure of children to pesticides, studies have been done to monitor pesticide levels in areas and food that are specific to children. Heptachlor was not detected in apple, pear, squash, or carrot baby food. Both organic and traditional manufacturers were studied (Moore et al. 2000). Studies of school areas along the Mexican-Texas border found heptachlor in 63% of all soil samples tested in concentrations ranging from a trace to 5 ppb (Miersma et al. 2003). Heptachlor was one of the most frequent chemicals found in a study of children's exposure to pesticides and was found in 8/9 home dust samples, 3/8 play areas, and 3/4 children's hand rinse samples (Lewis et al. 1994). In a study of pesticide exposure of children of farmworkers in Virginia and North Carolina, heptachlor was found in 10% of the floors at a mean concentration of 2 $\mu g/m^2$. Heptachlor, however, was not detected on any of the toys or hands of the children (Quandt et al. 2004).

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Data concerning occupational exposure levels of heptachlor are very limited. An industrial hygiene survey conducted in 1977 at the Velsicol Chemical Corporation, Memphis, Tennessee, a plant that manufactured heptachlor, detected heptachlor in workplace air at levels ranging from 0.025 to 0.202 mg/m^3 (1.64–13.2 ppb) (Netzel 1981). Data from the National Occupational Exposure Survey

(NOES) conducted by NIOSH from 1981 to 1983 were not available for heptachlor or heptachlor epoxide.

People who worked with pesticides from 1954 to 1988, such as farmers and pest control workers, were at potentially higher risk of being exposed to heptachlor and heptachlor epoxide. People who worked in termite control before 1988 may have higher exposures to heptachlor since it was commonly used as a pesticide in the treatment of termites. High concentrations of heptachlor were found on applicators' hands and forearms with exposure rates calculated at 83 and 23 ng/cm^2/hour (Kamble et al. 1992). Heptachlor was not found in the blood of Japanese termite control workers in 1987, 1 year after chlordane, which contained heptachlor, was banned in Japan. Heptachlor epoxide, however, was found in all of the Japanese termite workers monitored from 1987 to 1990. The highest level of heptachlor epoxide was in the blood of a worker who had been working in pest control for 20 years and almost all of the workers still had heptachlor epoxide in their blood in 1990 (Jitunari et al. 1995). A study showed that farmers and their spouses in Iowa and North Carolina were exposed to heptachlor epoxide at concentration ranges of 0.21–0.55 ng/mL. With the exception of two of the spouses, everyone in the study had exposure limits of 0.21 ng/mL or greater as analyzed from serum concentrations (Brock et al. 1998).

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 heptachlor and heptachlor epoxide is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of heptachlor and heptachlor epoxide.

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. The physical and chemical properties of heptachlor and heptachlor epoxide are sufficiently well defined to allow assessments of the environmental fate of the compounds to be made (ACGIH 1986; Chapman 1989; HSDB 2007a; MacKay 1982). Some physical and chemical properties of heptachlor epoxide that are not relevant to environmental fate are lacking. Knowledge of these properties, such as odor, flashpoint, and flammability limits, would be useful for workers involved in the manufacture, use, or clean-up of heptachlor and heptachlor epoxide.

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 2004, became available in May of 2006. This database is updated yearly and should provide a list of industrial production facilities and emissions.

The United States International Trade Commission (USITC) did not report separate import data for heptachlor for the years 1981, 1982, or 1983 (USITC 1982a, 1983a, 1984a). The sale, distribution, and shipment of existing stocks of all canceled heptachlor products were prohibited by EPA in 1988 (EPA 1990a). According to the USITC, no heptachlor has been imported into the United States from 1996 through 2007 (USITC 2007).

Currently, heptachlor use in the United States is limited to fire ant control in power transformers (EPA 1990a). However, because of former widespread use of heptachlor and the persistence of heptachlor epoxide, these compounds and their degradation products can still be found at low levels in indoor air, water, soil, and food. Disposal methods are well documented in the literature (EPA 1986b; Sittig 1985); however, more current information would be useful. Information on historical disposal practices would be helpful in evaluating the potential for environmental contamination. More information on the volume of heptachlor used in fire ant control would be useful in estimating potential occupational exposure.

Environmental Fate. Heptachlor and heptachlor epoxide are partitioned to the air, water, and soil (EPA 1987; Jury et al. 1987; Lichtenstein et al. 1970; Shivankar and Kavadia 1989). They are both transported in air and water and sorb to soils and sediment (Chapman 1989; MacKay 1982). They are biotransformed in soil and surface water, with biotransformation occurring faster for heptachlor than for heptachlor epoxide. Current data on the biotransformation (including half-life data) of both compounds

in surface water, surface soil, and subsurface soil would be useful in assessing the environmental persistence of these substances. Data on the toxicity of the biotransformation products of both compounds would assist in better characterizing the potential public health threat. Both heptachlor and heptachlor epoxide undergo photolysis (Graham et al. 1973; Ivie et al. 1972; Podowski et al. 1979). Data regarding the half-lives for photolysis would be helpful in determining the persistence of both compounds.

Bioavailability from Environmental Media. The limited pharmacokinetic data indicate that both compounds are absorbed following inhalation, oral, and dermal exposure (Arthur et al. 1975; Gaines 1969; Harradine and McDougall 1986). Additional information on the absorption of these compounds following inhalation and following ingestion of contaminated drinking water and soil would be useful in evaluating the relative importance of various routes of exposure to populations living in the vicinity of hazardous waste sites and those whose homes have been treated for termites with heptachlor or chlordane.

Food Chain Bioaccumulation. Heptachlor and heptachlor epoxide accumulate in aquatic and terrestrial organisms (Elder and Mattraw 1984; Murray and Beck 1990; Schmitt et al. 1990). Biomagnification of heptachlor and heptachlor epoxide in aquatic food chains is significant (Connell et al. 2002; Cullen and Connell 1994; Geyer et al. 1982; Hawker and Connell 1986). Because heptachlor is readily metabolized to heptachlor epoxide by higher trophic level organisms, biomagnification of heptachlor itself is not significant (Feroz et al. 1990). Because of the more persistent nature of heptachlor epoxide and its lipophilicity, biomagnification of heptachlor epoxide in terrestrial food chains is significant (Connell et al. 2002; Cullen and Connell 1994; Hartley and Johnston 1983). More current information regarding biomagnification of heptachlor epoxide in terrestrial food chains would be helpful in evaluating the extent of environmental contamination.

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

Heptachlor and heptachlor epoxide have been detected in indoor and outdoor air, surface water, groundwater, soil, sediment, food (Larsen et al. 1971; Lewis et al. 1986; MacIntosh et al. 1996; Park et al. 2002; USGS 2003), and fish (USGS 2003). Current monitoring data on levels of both compounds in

outdoor and indoor air and soil would be useful. Dietary intake data for the general population were located (FDA 1989; Gartrell et al. 1986b; Gunderson 1988; MacIntosh et al. 1996). Intake data for other media (air and water) are needed to estimate the risk of exposure of the general population.

Exposure Levels in Humans. Heptachlor epoxide has been detected in human blood, tissues (including adipose tissue), and breast milk (Al-Omar et al. 1986; Butler Walker et al. 2003; Craan and Haines 1998; Holt et al. 1986; Larsen et al. 1971; Savage et al. 1981). The presence of heptachlor epoxide is used as an indicator of exposure to heptachlor. Current monitoring studies of heptachlor epoxide in these tissues and fluids would be helpful in assessing the extent to which populations, particularly in the vicinity of hazardous waste sites, have been exposed to heptachlor. Reliable data regarding heptachlor levels in the elderly were not found. The elderly who may have been exposed to heptachlor have reduced capability to eliminate toxicants.

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

Exposures of Children. Heptachlor levels have been monitored in human breast milk as well as baby food (Moore et al. 2000). Heptachlor exposure of children at the Mexican-American border was studied as well as the exposure of children of farm workers and children whose homes were treated for termites (Lewis et al. 1994; Miersma et al. 2003; Quandt et al. 2004). Current monitoring studies of heptachlor and heptachlor epoxide in blood, fluids and tissues of children would be helpful in assessing the extent to which populations, particularly in the vicinity of hazardous waste sites, have been exposed to heptachlor.

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 heptachlor 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 in Progress (FEDRIP 2006) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs identified in Section 6.8.1. The only current study pertaining to heptachlor was of the direct and indirect photolytic fate of persistent organic pollutants in Arctic surface waters. The principal investigator of this study is Yu-Ping Chin of Ohio State University. This research is funded by the National Science Foundation (NSF).

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7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring heptachlor and heptachlor epoxide, their metabolites, and other biomarkers of exposure and effect to heptachlor and heptachlor epoxide. 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

Analytical methods exist for measuring heptachlor, heptachlor epoxide, and/or their metabolites in various tissues (including adipose tissue), blood, human milk, urine, and feces. The common method used is gas chromatography (GC) coupled with electron capture detection (ECD) followed by identification using GC/mass spectrometry (MS). Since evidence indicates that heptachlor is metabolized to heptachlor epoxide in mammals, exposure to heptachlor is usually measured by determining levels of heptachlor epoxide in biological media. A summary of the detection methods used for various biological media is presented in Table 7-1.

Heptachlor and heptachlor epoxide are measured in adipose tissue, blood, and serum using GC/ECD (Adeshina and Todd 1990; Burse et al. 1990; Polishuk et al. 1977a, 1977b; Radomski et al. 1971a, 1971b) and identified by GC/MS (LeBel and Williams 1986). Sample preparation steps for adipose tissue vary but, in general, involve a lipid extraction step followed by a clean-up procedure involving gel permeation chromatography (GPC) and/or Florisil column clean-up. Using GPC with methylene chloride and cyclohexane as solvents, individual organochlorine contaminants can be separated from adipose tissue to produce extracts clean enough for direct GC analysis. Clean-up efficiency using GPC is 99.9% (LeBel and Williams 1986). The sensitivity obtained using GC/ECD is in the low-ppb range. Recoveries for heptachlor are adequate (72–87%); recoveries for heptachlor epoxide are good (84–98%). Precision is good for both (Adeshina and Todd 1990; LeBel and Williams 1986). The preparation step used for measuring heptachlor epoxide in blood and serum involves lipid extraction, clean-up with column chromatography, and elution with acetonitrile, hexane, and methylene chloride (Burse et al. 1990;

Table 7-1. Analytical Methods for Determining Heptachlor and Heptachlor Epoxide in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Adipose tissue	Lipid extraction with acetone-hexane; fractionation from fat by gel permeation chromatography; Florisil column clean-up.	GC/ECD; GC/MS	1.4 ng/g (heptachlor); 1.1 ng/g (heptachlor epoxide)	72–87% (heptachlor); 86–98% (heptachlor epoxide)	LeBel and Williams 1986
Adipose tissue	Lipid extraction with petroleum ether; concentration; clean-up on Florisil column.	GC/ECD	0.001 ppm (heptachlor epoxide)	84%	Adeshina and Todd 1990
Human liver and brain tissue	Grind liver tissue and extract with petroleum ether. Dry brain tissue and grind with petroleum ether. Centrifuge and inject.	GC/ECD	NR	NR	Radomski et al. 1968
Human tissues	Homogenize. Extract with hexane containing anhydrous sodium sulfate. Evaporate. Redissolve in hexane. Clean-up on Florisil.	GC/ECD	NR	NR	Klemmer et al. 1977
Blood	Lipid extraction with chloroform/methanol; clean-up with column chromatography; elution with acetonitrile, hexane and methylene chloride.	GC/ECD	NR	NR	Polishuk et al. 1977a, 1977b
Serum	Add methanol and extract with hexane/ethyl ether. Clean-up on Florisil column. Acid treatment and clean-up on silica gel column.	GC/ECD	NR	80–96%	Burse et al. 1990
Human milk	Homogenize with chloroform/methanol; lipid extract with petroleum ether or hexane; clean-up by column chromatography; elution with acetonitrile, hexane, and methylene chloride.	GC/ECD	NR	NR	Polishuk et al. 1977b

Table 7-1. Analytical Methods for Determining Heptachlor and Heptachlor Epoxide in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Human milk	Lipid extraction with acetone-hexane. Dissolve in benzene-acetone. Clean-up on Florisil. Elute with dichloromethane-petroleum ether. Concentrate and add hexane.	GC/ECD	0.001 ppm (heptachlor epoxide)	NR	Ritcey et al. 1972
Urine and feces (heptachlor, heptachlor epoxide, and metabolites)	Extract with acetone and hexane. Combine solvents and concentrate. Mix with silicic acid and air dry. Clean-up on Florisil column and silicic acid column. Metabolites extracted into hexane for GC analysis.	GC/ECD	NR	NR	Tashiro and Matsumura 1978

ECD = electron capture detector; GC = gas chromatography; MS = mass spectrometry; NR = not reported

Polishuk et al. 1977a, 1977b). Recovery is adequate (80–96%). Precision is good (9–15%). Sensitivity was not reported (Burse et al. 1990).

GC/ECD and GC equipped with a microcoulometric detector have been used to determine heptachlor and heptachlor epoxide in a variety of human tissues, including the liver, brain, adrenals, lungs, heart, kidneys, spleen, and pancreas (Curley et al. 1969; Klemmer et al. 1977; Radomski et al. 1968). Details of a sample preparation method were not reported for GC equipped with a microcoulometric detector (Curley et al. 1969). Sample preparation steps for GC/ECD include homogenization, extraction with petroleum ether or hexane, usually followed by a clean-up procedure (Klemmer et al. 1977; Radomski et al. 1968). Recovery, sensitivity, and precision data were not reported (Curley et al. 1969; Klemmer et al. 1977; Radomski et al. 1968).

Heptachlor and heptachlor epoxide have been measured in samples of human milk using GC/ECD and GC/MS (Mussalo-Rauhamaa et al. 1988; Polishuk et al. 1977b; Ritcey et al. 1972). Sample preparation steps for milk involve homogenization with chloroform/methanol, lipid extraction with petroleum ether, hexane or acetone-hexane, clean-up by column chromatography, and elution with acetonitrile, hexane, methylene chloride, or dichloromethane-petroleum ether. Precision, accuracy, and sensitivity were not reported for most of the studies; however, one study reported a sensitivity in the low-ppb range (Ritcey et al. 1972).

Heptachlor, heptachlor epoxide, and their metabolites have been measured in urine and feces using GC/ECD (Tashiro and Matsumura 1978). Sample preparation steps involve extraction with acetone and hexane, clean-up on Florisil and silicic acid columns, and extraction of the derivatized metabolites into hexane for GLC analysis. Precision, accuracy, and sensitivity were not reported (Tashiro and Matsumura 1978).

7.2 ENVIRONMENTAL SAMPLES

Methods exist for measuring heptachlor and heptachlor epoxide in air, water, soil, and food. The most common methods are GC/ECD and GC/MS. A summary of methods for detecting heptachlor and heptachlor epoxide in various environmental samples is presented in Table 7-2.

Heptachlor is measured in indoor and outdoor air samples using GC/ECD and GC/MS (Anderson and Hites 1989; Leone et al. 2000; Lewis et al. 1986; Savage 1989). Heptachlor has also been measured in

Table 7-2. Analytical Methods for Determining Heptachlor and Heptachlor Epoxide in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Outdoor air	Sample collected with low-volume sampler consisting of a constant flow pump and a cartridge containing polyurethane foam. Extract with diethylether in hexane.	GC/ECD; GC/MS	0.0006 ppb	99% (heptachlor)	Lewis et al. 1986
Indoor air	Sample collected with a polyurethane foam plug sampler. Soxhlet extraction with petroleum ether.	GC/ECD	<3 ppt	NR	Leone et al. 2000
House dust	Sample collected with high-volume surface sampler; extract with diethyl ether in hexane.	GC/ECD; GC/MS	NR	NR (heptachlor)	Roberts and Camann 1989
Water	Extract with methylene chloride.	GC/MS	NR	52–68% (heptachlor)	Alford-Stevens et al. 1988
Waste water	Extract with methylene chloride; exchange to hexane.	GC/ECD (EPA Method 8080)	0.003 µg/L (heptachlor); 0.083 µg/L (heptachlor epoxide)	69% (heptachlor); 89% (heptachlor epoxide)	EPA 1994a
Waste water	Extract with methylene chloride	GC/MS (EPA Method 8250)	1.9 µg/L (heptachlor); 2.2 µg/L (heptachlor epoxide)	87% (heptachlor); 92% (heptachlor epoxide)	EPA 1994b
Drinking water	Extract with methylene chloride; solvent exchange to methyl *tert*-butyl ether.	GC/ECD (EPA Method 508)	0.01 µg/L (heptachlor); 0.015 µg/L (heptachlor epoxide)	99% (heptachlor); 95% (heptachlor epoxide)	Lopez-Avila et al. 1990
Soil/ sediment and solid waste	Extract with methylene chloride; clean-up extract.	GC/MS (EPA Method 8250)	1.9 µg/L (heptachlor); 2.2 µg/L (heptachlor epoxide)	87% (heptachlor); 92% (heptachlor epoxide)	EPA 1994a
Foodstuff (butterfat)	Lipid extraction with automated gel permeation chromatography; direct injection.	GC/ECD	NR	100% (heptachlor epoxide)	Hopper and Griffitt 1987
Milk	Extract on solid-matrix disposable columns by means of acetonitrile-saturated light petroleum; Florisil® clean-up.	GC/ECD	NR	99% (heptachlor epoxide)	DiMuccio et al. 1988
Water and soft drink	Extracted with ethyl acetate; dried with sodium sulfate and then evaporated before taken up in methanol water solvent mixture	LC/MS/MS	NR	NR	Chandramouli et al. 2004

Table 7-2. Analytical Methods for Determining Heptachlor and Heptachlor Epoxide in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	Extract placed on extraction well plates loaded with sorbent; standard solutions were added before injecting onto column	SPE-GC-MS	0.01–2.5 µg/L	90–99% (heptachlor)	Li et al. 2000
Water	800 mL extracted with hexane; extract concentrated and reconstituted in toluene	GC/MS	0.5 µg/L	NR	Canadian Ministry of the Environment 2003

ECD = electron capture detector; EPA = Environmental Protection Agency; GC = gas chromatography; LC = liquid chromatograph; MS = mass spectrometry; NR = not reported; SPE = solid phase extraction

house dust (Roberts and Camann 1989). Preparation methods involve the use of a variety of air trapping samplers. Examples of these include the Greenburg-Smith impinger, Chromosorb 102, low-volume samplers, and the Millipore miniature vacuum pump with a sampling tube. The next step includes extraction with diethyl ether, acetone-hexane, or toluene (Anderson and Hites 1989; Roberts and Camann 1989). For indoor air, sensitivity is in the sub-ppt range (Leone et al. 2000). For outdoor air, precision is good (13%) and recovery is excellent (99%). Sensitivity is in the sub-ppb range (Lewis et al. 1986).

Heptachlor and heptachlor epoxide are measured in water, drinking water, waste water, soil/sediment, and solid waste using GC/ECD, GC/MS, and liquid chromatography (LC)/MS/MS (Alford-Stevens et al. 1988; Canadian Ministry of the Environment 2003; Chandramouli et al. 2004; EPA 1994a, 1994b; Lopez-Avila et al. 1990; McDougall et al. 1987; Smith et al. 1987). Preparation of water, waste water, and drinking water samples involves extraction with methylene chloride, concentration, and solvent exchange to hexane or methyl *tert*-butyl ether. Mean recovery in water for heptachlor was low (52–68%) and precision was poor (48–57%) (Alford-Stevens et al. 1988). Poor recovery and precision data were thought to be attributable to chromatographic problems in some of the participating laboratories. For drinking water (EPA Method 508), recovery was excellent for heptachlor (99%) and heptachlor epoxide (95%). Precision was excellent for both compounds (<10%). Sensitivity was in the sub-ppb range (Lopez-Avila et al. 1990). Preparation of soil/sediment or solid waste samples involves extraction with methylene chloride, methylene chloride-acetone, methylene chloride-methanol, or acetone-hexane followed by clean-up with Florisil or GPC (Alford-Stevens et al. 1988; EPA 1994a). Overall precision was adequate to poor, ranging from 19 to 47% for heptachlor. Recovery and sensitivity were not reported (Alford-Stevens et al. 1988). EPA Test Methods 8080 and 8250 for evaluating waste water, soil sediment, and solid waste report sensitivity in the low-ppb range for both heptachlor and heptachlor epoxide (EPA 1994a, 1994b). Recovery for heptachlor is adequate (69–87%) and recovery for heptachlor epoxide is good (89–92%). Precision is adequate for both methods (EPA 1994a, 1994b).

GC/ECD is the method used to detect heptachlor and heptachlor epoxide in foods (butterfat, fruits, vegetables, milk, and animal feed) (Di Muccio et al. 1988; Hopper and Griffitt 1987; Korfmacher et al. 1987; Ober et al. 1987; Santa Maria et al. 1986). Preparation methods vary for the different types of foods. The sample preparation method for butterfat involves GPC. GPC is a rapid clean-up technique for separating pesticide residues from a lipid extract. It was developed into an automated clean-up apparatus for use on a wide variety of fats and oils. The automated GPC system is reproducible and reliable. After being cleaned on GPC, most samples can be analyzed by GC without additional clean-up (Hopper and Griffitt 1987). Recovery is complete (100%), and precision is very good (<3%). Sensitivity is in the sub-

ppm range. The sample preparation for milk samples involves selective extraction on solid-matrix disposable columns by means of acetonitrile-saturated light petroleum, followed by Florisil column clean-up. Recovery is excellent (99%); precision is very good (<7%) (Di Muccio et al. 1988). Sample preparation for fruits, vegetables, and animal feed involves cyclic steam distillation extraction in hexane or isooctane with direct injection into the gas chromatograph. Recoveries for this method are very low (15–50%). This is an indication that heptachlor is not extracted quantitatively by steam distillation and is not a recommended preparation method (Ober et al. 1987; Santa Maria et al. 1986).

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 heptachlor and heptachlor epoxide is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of heptachlor and heptachlor epoxide.

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 exist for determining levels of heptachlor, heptachlor epoxide, and/or their metabolites in various tissues (including adipose tissues) (Adeshina and Todd 1990; Curley et al. 1969; Klemmer et al. 1977; LeBel and Williams 1986; Radomski et al. 1968), milk (Mussalo-Rauhamaa et al. 1988; Polishuk et al. 1977b; Ritcey et al. 1972), blood (Polishuk et al. 1977a, 1977b), serum (Burse et al. 1990), urine, and feces (Tashiro and Matsumura 1978). Methods for determining levels in adipose tissue are sensitive for measuring levels at which health effects might occur as well as background levels in the population. Methods for determining heptachlor and heptachlor epoxide in adipose tissue are relatively precise. Recovery is better for heptachlor epoxide than for heptachlor. Data on the determination of

heptachlor and heptachlor epoxide in tissues, blood, serum, milk, urine, and feces are limited as precision, recovery, and/or sensitivity data were not reported for the existing methods. More information on the precision, accuracy, and sensitivity of these methods is needed to evaluate the value of using levels of heptachlor and heptachlor epoxide as biomarkers of exposure.

Effect. There is no known effect of heptachlor or heptachlor epoxide that can be quantitatively related to exposure.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Existing methods for determining levels of heptachlor in air are sensitive enough to measure background levels in the environment, as well as levels at which health effects might occur. Data on the determination of heptachlor and heptachlor epoxide in air (Anderson and Hites 1989; Leone et al. 2000; Lewis et al. 1986; Roberts and Camann 1989; Savage 1989), water (Alford-Stevens et al. 1988; EPA 1994a, 1994b; Lopez-Avila et al. 1990), soil (EPA 1994b; McDougall et al. 1987; Smith et al. 1987), and food (Di Muccio et al. 1988; Hopper and Griffitt 1987; Korfmacher et al. 1987; Ober et al. 1987; Santa Maria et al. 1986) are limited. Information on the accuracy, precision, and sensitivity of these methods would permit better assessment of the risk of low-level environmental exposure for these media. A preparation method for fruit and vegetable analysis that provides increased recovery would allow better assessment of the risk of dietary exposure. 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

No ongoing studies regarding analytical methods were located for heptachlor or heptachlor epoxide.

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8. REGULATIONS AND ADVISORIES

The international and national regulations and guidelines regarding heptachlor and heptachlor epoxide in air, water, and other media are summarized in Table 8-1.

ATSDR derived an acute-duration oral MRL of 0.0006 mg/kg/day for heptachlor. This MRL was based on a LOAEL of 1.8 mg/kg/day for impaired reproductive performance in female rats mated with unexposed males (Amita Rani and Krishnakumari 1995), an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability), and a modifying factor of 3 for the use of a serious end point.

ATSDR derived an intermediate-duration oral MRL of 0.0001 mg/kg/day for heptachlor. This MRL was based on a minimal LOAEL of 0.03 mg/kg/day for developmental immunological and neurological effects in rats (Moser et al. 2001; Smialowicz et al. 2001) 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).

EPA (IRIS 2005) has derived an oral reference dose (RfD) for heptachlor of $5x10^{-4}$ mg/kg/day based on NOAEL of 0.15 mg/kg/day and LOAEL of 0.25 mg/kg/day for increased liver weight in rats exposed to heptachlor for 2 years and an uncertainty factor of 300 (10 for extrapolation from animals to humans, 10 for human variability, and 3 to account for limitations in the database particularly the lack of a chronic study in a second species).

EPA (IRIS 2005) also derived an RfD of $1.3x10^{-5}$ mg/kg/day for heptachlor epoxide. This RfD is based on a LOAEL of 0.0125 mg/kg/day for increased relative liver weight identified in a dog study submitted to EPA by Dow Chemical Company and an uncertainty factor of 1,000 to account for inter and intraspecies extrapolation and because a NOAEL was not attained. The studies which serve as the basis of the RfDs for heptachlor and heptachlor epoxide were not discussed in the toxicological profile because they were submitted to EPA under FIFRA and are not publicly available.

Table 8-1. Regulations and Guidelines Applicable to Heptachlor and Heptachlor Epoxide

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification		IARC 2004
	Heptachlor	Group 2B[a]	
WHO	Air quality guidelines	No data	WHO 2000
	Drinking water quality guidelines	Guideline values have not been established[b]	WHO 2004
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV-TWA		ACGIH 2004
	Heptachlor[c]	0.05 mg/m^3	
	Heptachlor epoxide[c]	0.05 mg/m^3	
EPA	Hazardous air pollutant		EPA 2004b 42 USC 7412
	Heptachlor	Yes	
NIOSH	REL (10-hour TWA)		NIOSH 2005
	Heptachlor[d,e]	0.5 mg/m^3	
	IDLH		
	Heptachlor	35 mg/m^3	
OSHA	PEL (8-hour TWA) for general industry		OSHA 2005c 29 CFR 1910.1000
	Heptachlor[f]	0.5 mg/m^3	
	PEL (8-hour TWA) for construction industry		OSHA 2005b 29 CFR 1926.55
	Heptachlor[f]	0.5 mg/m^3	
	PEL (8-hour TWA) for shipyard industry		OSHA 2005a 29 CFR 1915.1000
	Heptachlor[f]	0.5 mg/m^3	
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311 of the Clean Water Act		EPA 2005a 40 CFR 116.4
	Heptachlor	Yes	
	Drinking-water health advisories		EPA 2004a
	Heptachlor		
	1-day health advisory for a 10-kg child[g]	0.01 mg/L	
	10-day health advisory for a 10-kg child[h]	0.01 mg/L	
	DWEL[i]	0.02 mg/L	
	10^{-4} Cancer risk[j]	0.0008 mg/L	

Table 8-1. Regulations and Guidelines Applicable to Heptachlor and Heptachlor Epoxide

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	Drinking-water health advisories		EPA 2004a
	Heptachlor epoxide		
	1-day health advisory for a 10-kg child[g]	0.01 mg/L	
	10-day health advisory for a 10-kg child[h]	No data	
	DWEL[i]	0.0004 mg/L	
	10^{-4} Cancer risk[j]	0.0004 mg/L	
	National primary drinking water regulations[k]		EPA 2002a
	Heptachlor		
	MCL	0.0004 mg/L	
	MCLG	Zero	
	Heptachlor epoxide		
	MCL	0.0002 mg/L	
	MCLG	Zero	
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act		EPA 2005b 40 CFR 117.3
	Heptachlor	1 pound	
	Water quality criteria for human health consumption of:		EPA 2002b
	Heptachlor[l]		
	Water + organism	7.9×10^{-5}	
	Organism only	7.9×10^{-5}	
	Heptachlor epoxide[l]		
	Water + organism	3.9×10^{-5}	
	Organism only	3.9×10^{-5}	
c. Food			
FDA	Action level		FDA 2000
	Heptachlor		
	Artichokes; asparagus; Brassica (cole) leafy vegetables; bulb vegetables; cereal grains; citrus fruits; eggs; figs; fruiting vegetables; leafy vegetables; legume vegetables; peanuts; pome fruits; root and tuber vegetables; salsify tops; small fruits and berries; stone fruits; and sugarcane	0.01 ppm	
	Cottonseed, cucurbit vegetables, pineapple, and rabbit (fat basis)	0.02 ppm	
	Fish (edible portion)	0.3 ppm	
	Milk (fat basis)	0.1 ppm	

Table 8-1. Regulations and Guidelines Applicable to Heptachlor and Heptachlor Epoxide

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
FDA	Bottled water		FDA 2004 21 CFR 165.110
	Heptachlor	0.0004 mg/L	
	Heptachlor epoxide	0.0002 mg/L	
d. Other			
ACGIH	Carcinogenicity classification		ACGIH 2004
	Heptachlor	A3[m]	
	Heptachlor epoxide	A3[m]	
EPA	Carcinogenicity classification		IRIS 2005
	Heptachlor	B2[n]	
	Heptachlor epoxide	B2[n]	
	RfC		
	Heptachlor	Not available at this time	
	Heptachlor epoxide	Not available at this time	
	RfD		
	Heptachlor	5.0×10^{-4} mg/kg/day	
	Heptachlor epoxide	1.3×10^{-5} mg/kg/day	
	Inhalation unit risk		
	Heptachlor	1.3×10^{-3} per ug/m^3	
	Heptachlor epoxide	2.6×10^{-3} per ug/m^3	
	Oral slope factor		
	Heptachlor	4.5 per mg/kg-day	
	Heptachlor epoxide	9.1 per mg/kg-day	
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance		EPA 2005c 40 CFR 302.4
	Heptachlor[o]		
	Reportable quantity	1 pound	
	RCRA waste number	P059	
	Heptachlor epoxide[p]		
	Reportable quantity	1 pound	
	RCRA waste number	No data	
	Effective date of toxic chemical release reporting		EPA 2005e 40 CFR 372.65
	Heptachlor	01/01/87	

Table 8-1. Regulations and Guidelines Applicable to Heptachlor and Heptachlor Epoxide

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
	Threshold amounts for manufacturing (including importing), processing, and otherwise using such toxic chemicals		EPA 2005d 40 CFR 372.28
	Heptachlor	10 pounds	
NTP	Carcinogenicity classification	No data	NTP 2005

[a]Group 2B: possibly carcinogenic to humans
[b]Guideline values have not been established: heptachlor and heptachlor epoxide occurs in drinking water at concentrations well below those at which heptachlor epoxide toxic effects may occur.
[c]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.
[d]Potential occupational carcinogen
[e]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.
[f]Skin designation
[g]1-Day health advisory: the concentration of a chemical in drinking water that is not expected to cause any adverse noncarcinogenic effects for up to 1 day of exposure. The 1-day health advisory is normally designed to protect a 10-kg child consuming 1 liter of water per day.
[h]10-Day health advisory: the concentration of a chemical in drinking water that is not expected to cause any adverse noncarcinogenic effects for up to 10 days of exposure. The 10-day health advisory is also normally designed to protect a 10-kg child consuming 1 liter of water per day.
[i]DWEL: a lifetime exposure concentration protective of adverse, noncancer health effects that assumes all of the exposure to a contaminant is from drinking water.
[j]10^{-4} Cancer risk: the concentration of a chemical in drinking water corresponding to an excess estimated lifetime cancer risk of 1 in 10,000.
[k]Potential health effects from ingestion of water include liver damage and increased risk of cancer. The contaminant in drinking water is the residue of a banned termiticide (heptachlor) and the breakdown of heptachlor from epoxide heptachlor.
[l]This criterion is based on carcinogenicity of 10^{-6} risk.
[m]A3: not classifiable as a human carcinogen
[n]B2: probable human carcinogen
[o]Heptachlor: designated CERCLA hazardous substance pursuant to Section 311(b)(2) and 307(a) of the Clean Water Act, Section 112 of the Clean Air Act, and Section 3001 of RCRA.
[p]Heptachlor epoxide: designated CERCLA hazardous substance pursuant to Section 307(a) of the Clean Water Act.

ACGIH = American Conference of Governmental Industrial Hygienists; CERCLA = Comprehensive Environmetnal Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DWEL = drinking-water equivalent level; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MCL = maximum contaminat 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; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

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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.

10. GLOSSARY

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 $\mu g/m^3$ 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 and Environmental Medicine, 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 and Environmental Medicine, 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: Heptachlor
CAS Numbers: 76-44-8
Date: August 2007
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 19
Species: Rat

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

Reference: Amita Rani BE, Krishnakumari MK. 1995. Prenatal toxicity of heptachlor in albino rats. Pharmacol Toxicol 76(2):112-114.

Experimental design: Groups of 30 female CFT-Wistar rats received gavage doses of heptachlor in groundnut oil for 14 days (presumably 7 days/week). The total administered doses were 25 and 50 mg/kg body weight; the daily doses were 1.8 and 3.6 mg/kg/day; a vehicle control group was also used. After 14 days of exposure, the animals were mated with controls.

Effect noted in study and corresponding doses: A significant decrease in the number of pregnant females (56.3 and 44.4%) and increase in the number of resorptions (18.90 and 11.40%) were observed in both groups of heptachlor-exposed rats. Significant decreases in estradiol-17beta and progesterone levels were also observed in the 1.8 mg/kg/day group. No alterations in the number of implantations were observed. The investigators noted that focal necrosis was observed in the liver; however, they did not note at which dose level and no incidence data were provided.

Dose and end point used for MRL derivation: The MRL is based on a serious LOAEL of 1.8 mg/kg/day for reproductive effects.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation: 1,000

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

Modifying Factor used in MRL derivation: 3

[X] 3 for use of a serious end point

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 dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information that lend support to this MRL: Several targets of toxicity have been identified, in addition to the impaired reproductive performance observed in the Amita Rani and Krishnakumari (1995) study. These include the liver, nervous system, and developing offspring. Gestational exposure to 4.5 or 6.8 mg/kg/day resulted in decreases in pup body weight (Narotsky and Kavlock 1995; Narotsky et al. 1995) and a decrease in pup righting reflex was observed at 4.2 mg/kg/day (Purkerson-Parker et al. 2001b). At twice these dose levels, an increase in pup mortality was observed (Narotsky et al. 1995; Purkerson-Parker et al. 2001b). Liver effects were observed at doses similar to those resulting in developmental effects. Increases in serum alanine aminotransferase and aldolase activity levels, hepatocytomegaly, and minimal monocellular necrosis were observed in rats administered 7 mg/kg/day heptachlor in oil for 14 days (Berman et al. 1995; Krampl 1971). Exposure to 7 mg/kg/day also resulted in excitability and increased arousal in rats administered heptachlor in oil via gavage for 1 or 14 days (Moser et al. 1995).

Agency Contacts (Chemical Managers): Zemoria Rosemond, B.A.; G. Daniel Todd, Ph.D.; Malcolm Williams, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Heptachlor
CAS Numbers: 76-44-8
Date: June 2007
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 49
Species: Rat

Minimal Risk Level: 0.0001 [X] mg/kg/day [ ] ppm

Reference: Smialowicz RJ, Williams WC, Copeland CB, et al. 2001. The effects of perinatal/juvenile heptachlor exposure on adult immune and reproductive system function in rats. Toxicol Sci 61(1):164-175.

Moser VC, Shafer TJ, Ward TR, et al. 2001. Neurotoxicological outcomes of perinatal heptachlor exposure in the rat. Toxicol Sci 60(2):315-326.

Experimental design: Groups of 15–20 pregnant Sprague Dawley rats were administered via gavage 0, 0.03, 0.3, or 3 mg/kg/day heptachlor in corn oil on gestational day 12 through postnatal day 7; pups were also exposed from postnatal day 7 to 21 or 42. Neurobehavorial assessment consisted of righting reflex on postnatal days 2–5, functional observational battery test, motor activity, passive avoidance test of learning and memory, and Morris water maze to assess spatial and working memory. The liver, kidneys, adrenals, thymus, spleen, ovaries, uterus/vagina, testes, epididymides, seminal vesicles/coagulating glands, and ventral and dorsolateral prostate were histologically examined in 15–17 offspring from each group on postnatal day 46. The following immunological tests were performed in the 8-week-old offspring: splenic lymphoproliferative (LP) responses to T cell mitogens (e.g., concanavalin A [ConA], phytohemagglutinin [PHA]) and to allogeneic cells in a mixed lymphocyte reaction, primary IgM antibody response to sheep red blood cells, examination of splenic lymphocytes subpopulations, and delayed-type and contact hypersensitivity. Reproductive assessment included evaluation of vaginal opening (index of female puberty) and prepuce separation (index of male puberty) beginning at postnatal days 25 and 35, respectively. The offspring were mated with an untreated mate and the dams were allowed to rear the first litter to postnatal day 10. The results of the neurobehavioral assessment were reported by Moser et al. (2001); the remaining results were reported by Smialowicz et al. (2001).

Effect noted in study and corresponding doses: No significant alterations in maternal body weight, number of dams delivering litters, litter size, or pup survival were observed. Additionally, no alterations in pup growth rates, age at eye opening, anogenital distance, or age at vaginal opening or preputial separation were observed. A significant decrease in pup body weight at postnatal day 1 was observed at 3 mg/kg/day; this effect was not observed at postnatal days 7, 14, or 21. No consistent, statistically significant alterations in offspring body weights were observed at postnatal days 21, 28, 35, or 42. Significant alterations in absolute and relative liver weights were observed in males and females exposed to 3 mg/kg/day; increases in absolute and relative ovary weights were also observed at 3 mg/kg/day. No histological alterations were observed in the examined tissues. No alterations in fertility were observed in the adult males and females mated to untreated partners, and no effects on soft tissue or gross body structure of the offspring (F_2 generation) were observed. No alterations in sperm count or sperm motility were observed.

Righting was significantly delayed in the female offspring of rats exposed to 3 mg/kg/day heptachlor; no significant alterations were observed in the male offspring. The investigators suggested that this was due to a delay in the ontogeny of righting rather than an inability to perform the task. The following significant alterations in the FOB and motor activity tests were found in the offspring dosed until postnatal day 21: increased open field activity in 3 mg/kg/day males, non-dose-related increased activity in figure-eight chambers in females (significant only in 0.03 mg/kg/day group), and faster decline in habituation of activity in 3 mg/kg/day males. Alterations in the offspring dosed until postnatal day 42 included: increased levels of urination in males in the 0.03 and 0.3 mg/kg/day groups, increased landing foot splay in males in the 0.03 mg/kg/day group, and removal reactivity in males and females in the 0.03 mg/kg/day group. No alterations in the passive avoidance test were observed in the offspring exposed until postnatal day 21; in those exposed until postnatal day 42, an increase in the number of nose pokes was observed in all groups of females. No significant alterations in performance on the water maze test were found in the offspring exposed until postnatal day 21. In those exposed until postnatal day 42, increases in latency to find the platform were observed in males and females exposed to 3 mg/kg/day and increases in the time spent in the outer zone were found in males exposed to 0.3 or 3 mg/kg/day. In the water maze memory trial, no differences in performance were found between controls and animals exposed until postnatal day 21. Alterations in significant quadrant bias were observed in 0.03, 0.3, and 3 mg/kg/day males during the first probe test and in 0.3 and 3 mg/kg/day males and 3 mg/kg/day females in the second probe test. The study investigators noted that the heptachlor-exposed rats did not develop an efficient search strategy for locating the platform; they spent more time circling the outer zone of the tank. By the second week of the test, control rats had learned to venture into the zone where the platform was located.

A dose-related, statistically significant suppression of primary IgM antibody response to sRBC was found in males, but not females. The primary IgM response to sRBCs was reduced in 21-week-old males exposed to 0.3 mg/kg/day. A second immunization with sRBCs administered 4 weeks later resulted in a significant reduction in IgG antibody response in males administered 0.03, 0.3, or 3 mg/kg/day heptachlor; no response was seen in females. A decrease in the $OX12^{+}OX19^{-}$ (i.e., B/plasma cells) population was also found in the spleen of males exposed to 3 mg/kg/day. No alterations in the following immunological parameters assessed at 8 weeks of age were found: lymphoid organ weights, splenic NK cell activity, splenic cellularity or cell viability, and lymphoproliferative responses of splenic lymphocytes to T-cell mitogens ConA and PHA or to allogenic cells in the mixed lymphocyte reaction. The results of this portion of the study suggest that exposure to heptachlor adversely affects the development of the immune system.

Dose and end point used for MRL derivation: The MRL is based on a minimal LOAEL of 0.03 mg/kg/day for developmental immunological and neurological effects. The observed alterations were considered to be minimally adverse and suggestive of immunotoxicity and neurotoxicity.

[ ] 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 dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information that lend support to this MRL: The results of the Smialowicz et al. (2001) study suggest that exposure to heptachlor adversely affects the development of the immune system. A framework for testing a chemical's potential to induce developmental immunotoxicological effects has not been established. Based on the results of studies in mature animals (Luster et al. 1992), two panels of government, industry, and academia immunotoxicology experts (Holsapple et al. 2005; Luster et al. 2003) reached a consensus that assays measuring the response to a T-cell dependent antigen (e.g., sheep red blood cells) should be included in included in a developmental immunotoxicology protocol. In mature animals, the sheep red blood cells antibody plague-forming cell test was the most reliable single test predictor of immunotoxicity (Luster et al. 1992).

Intermediate-duration oral exposure studies have identified a number of targets of heptachlor toxicity including the liver, nervous system, reproductive system, and the developing offspring. Other less documented effects have also been observed. The developing organism appears to be the most sensitive target. In the absence of maternal toxicity, heptachlor is not associated with alterations in pup mortality or body weight gain (Lawson and Luderer 2004; Purkerson-Parker et al. 2001b; Smialowicz et al. 2001) or alterations in the development of the reproductive system (Lawson and Luderer 2004; Smialowicz et al. 2001). In contrast, heptachlor appears to adversely affect the development of the nervous and immune systems. The observed effects include impaired spatial memory at 0.03 mg/kg/day and higher (Moser et al. 2001), impaired spatial learning at 0.3 mg/kg/day and higher (Moser et al. 2001), and decreased in righting reflex (Moser et al. 2001; Purkerson-Parker et al. 2001b) and increased open field activity (Moser et al. 2001) at 3 mg/kg/day. These effects were observed in rats exposed *in utero*, during lactation, and postnatally until day 42; spatial memory and learning were not adversely affected when the exposure was terminated at postnatal day 21 (Moser et al. 2001). The conflicting results may have resulted in the higher heptachlor epoxide body burden in rats exposed to postnatal day 42, testing at different ages, or exposure may have occurred during a critical window of vulnerability. The effects observed in rats are consistent with those observed in humans. Impaired performance on several neurobehavioral tests, including abstract concept formation, visual perception, and motor planning, was observed in high school students presumably prenatally exposed to heptachlor from contaminated milk products (Baker et al. 2004b). Alterations in immune function were also observed in the rats exposed until postnatal day 42. At 0.03 mg/kg/day and higher, suppression of the immune response to sheep red blood cells was observed (Smialowicz et al. 2001). A reduction in the percentage of B lymphocytes was also observed in the spleen of rats exposed to 3 mg/kg/day. Other tests of immune function were not significantly altered.

The liver effects observed in rats or mice exposed to heptachlor in the diet include increased liver weights (Izushi and Ogata 1990; Pelikan 1971), increased serum alanine aminotransferase levels (Izushi and Ogata 1990), steatosis (Pelikan 1971), and hepatitis and necrosis (Akay and Alp 1981). The lowest LOAEL values for these effects range from 5 to 8.4 mg/kg/day. Neurological signs such as hyperexcitability, seizures, and difficulty standing, walking, and righting were observed at similar dose levels; LOAELs ranged from 1.7 to 17 mg/kg/day (Akay and Alp 1981; Aulerich et al. 1990; Crum et al. 1993). The reproductive system appeared to be more sensitive to heptachlor toxicity. Decreases in epididymal sperm count were observed in rats administered 0.65 mg/kg/day heptachlor in groundnut oil for 70 days (Amita Rani and Krishnakumari 1995). This dose also resulted in increased resorptions when the exposed males were mated with unexposed females. Infertility was observed in all mice exposed to 8.4 mg/kg/day heptachlor for 10 weeks (Akay and Alp 1981).

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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

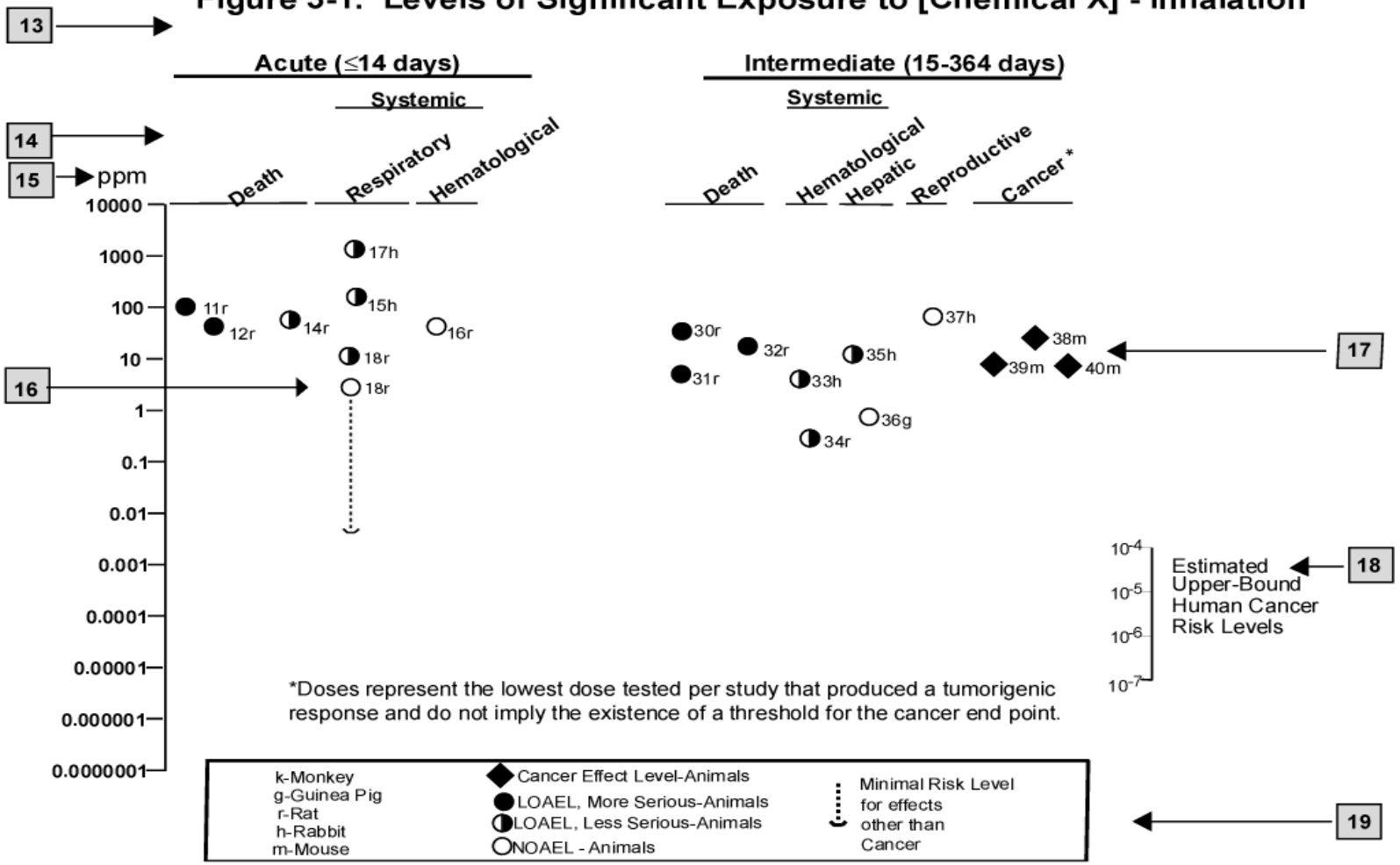
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) 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 B

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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
DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/Intergovernmental 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

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APPENDIX D. INDEX