

**TOXICOLOGICAL PROFILE FOR  
HEXACHLOROBENZENE**

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

September 2002

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## **UPDATE STATEMENT**

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry  
Division of Toxicology/Toxicology Information Branch  
1600 Clifton Road NE, E-29  
Atlanta, Georgia 30333



## FOREWORD

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

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

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

- (A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;
- (B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and
- (C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels; interested private sector organizations and groups; and members of the public.

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

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

### \*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepared toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on November 17, 1997 (62 FR 61332). For prior versions of the list of substances, see *Federal Register* notices dated April 29, 1996 (61 FR 18744); 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); and February 28, 1994 (59 FR 9486). 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.

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### *Primary Chapters/Sections of Interest*

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

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

**Chapter 3: Health Effects:** Specific health effects of a given hazardous compound are reported by *type of health effect* (death, systemic, immunologic, reproductive), by *route of exposure*, and by *length of exposure* (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.

**NOTE:** Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

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

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

### **Other Sections of Interest:**

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

### **ATSDR Information Center**

**Phone:** 1-888-42-ATSDR or (404) 498-0110     **Fax:** (404) 498-0057  
**E-mail:** [atsdric@cdc.gov](mailto:atsdric@cdc.gov)     **Internet:** <http://www.atsdr.cdc.gov>

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

*Case Studies in Environmental Medicine: Taking an Exposure History*—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards*; *Skin Lesions and Environmental Exposures*; *Cholinesterase-Inhibiting Pesticide Toxicity*; and numerous chemical-specific case studies.

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

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

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### ***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.

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### ***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](mailto: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, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-818-1800 • FAX: 847-818-9266.

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### THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.
2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.
3. Data Needs Review. The Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.



## PEER REVIEW

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

1. Dr. Syed M. GhiasUddin, Indiana Department of Environmental Management, 1815 Beckenbauer Lane, Indianapolis, IN 46214;
2. Dr. Kannan Krishnan, University of Montreal, Faculty of Medicine, 2375 Chemin de la Cote Ste-Catherine, Room 4105, Montreal, QC H3T 1A8; and
3. Dr. Clint Skinner, Skinner Associates, Consultants in Toxicology, 3985 Shooting Star Road, Creston, CA 93432.

These experts collectively have knowledge of hexachlorobenzene'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. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

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 hexachlorobenzene and the effects of exposure. The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. Hexachlorobenzene has been found in at least 107 of the 1,613 current or former NPL sites. However, the total number of NPL sites evaluated for this substance is not known. As more sites are evaluated, the sites at which hexachlorobenzene is found may increase. This information is important because exposure to this substance may harm you and because these sites may be sources of exposure.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You are 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 hexachlorobenzene, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider the other chemicals you're exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

### 1.1 WHAT IS HEXACHLOROBENZENE?

Hexachlorobenzene is a white crystalline solid. This compound does not occur naturally. It is formed as a by-product during the manufacture of chemicals used as solvents (substances used to dissolve other substances), other chlorine-containing compounds, and pesticides. Small amounts of hexachlorobenzene can also be produced during combustion processes such as burning of city wastes. It may also be produced as a by-product in waste streams of chlor-alkali and wood-preserving plants. Hexachlorobenzene was widely used as a pesticide until 1965. It was also used to make fireworks, ammunition, and synthetic rubber. Currently, the substance is not used

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commercially in the United States. For more information on the physical and chemical properties of this substance, see Chapter 4.

## **1.2 WHAT HAPPENS TO HEXACHLOROBENZENE WHEN IT ENTERS THE ENVIRONMENT?**

Hexachlorobenzene tends to remain in the environment for a long time. If it is released to the soil, it has a half-life of 3–6 years. This means that half of the total amount will disappear after 3–6 years, half of the remaining amount will disappear in another 3–6 years, and this process will continue each 3–6 years thereafter. If it is released to surface waters such as lakes, rivers, and streams, the half-life is 2.7–5.7 years, and if it is released to groundwater, the half-life is 5.3–11.4 years. Since hexachlorobenzene does not dissolve in water very well, most of it will remain in particles on the bottom of lakes, rivers, or streams. The evaporation of hexachlorobenzene into the air is not significant under ordinary conditions. Once in the air, it can be carried over wide geographic areas. Its half-life in air ranges from 0.63 to 6.28 years. For more information on the releases, occurrence, and movement of this substance, see Chapters 4, 5, and 6.

## **1.3 HOW MIGHT I BE EXPOSED TO HEXACHLOROBENZENE?**

You may be exposed to hexachlorobenzene if you live near an industrial site where it is produced as an unintentional by-product or as a minor part of another chemical product. You may also be exposed if you live near a hazardous waste site where hexachlorobenzene has been discarded. At these sites, hexachlorobenzene may be carried in the air on dust particles. The levels of it in the air around these sites are not known. The amount you might breathe in urban air is very small, about 0.00003 parts per million (ppm). If you work in an industry that uses or produces it unintentionally as a by-product, you may also breathe in hexachlorobenzene particles or dust that carries it, and it may touch your skin. In workplaces where hexachlorobenzene is used or disposed, an estimated 1–1.4 ppm of this substance has been measured in the air. You can also be exposed to it through contact with soil or dust particles contaminated with hexachlorobenzene, or by breathing air contaminated by industrial releases into the environment.

## 1. PUBLIC HEALTH STATEMENT

Because it does not dissolve easily in water, this substance is usually not present in high concentrations in drinking water. Based on a national survey, it was detected at very low levels in surface water and groundwater systems. Drinking water in three cities contained only trace amounts of hexachlorobenzene. Therefore, exposure to this substance through drinking water is limited.

Eating foods such as shellfish, fish, and certain vegetables can also expose people to hexachlorobenzene. Additionally, you can be exposed to hexachlorobenzene by eating and drinking foods and liquids, such as milk, other dairy products, meat, and poultry, if the animals from which these products are obtained have been exposed to it through their feed or other sources of contamination. Additionally, fat and oil in food may increase the amount of hexachlorobenzene that enters the body from food.

Low levels of hexachlorobenzene have been found in the fatty tissues of almost all people tested. These amounts are most likely the result of low levels in food. An estimated average yearly uptake of 1 microgram per kilogram ( $\mu\text{g}/\text{kg}$ ) of body weight has been calculated for exposure to contaminated food. Exposure by breathing contaminated air is estimated to be  $0.01 \mu\text{g}/\text{kg}/\text{year}$ . This is 100 times less than the exposure from eating contaminated foods. Drinking contaminated water is estimated to contribute only very small amounts ( $0.00085 \mu\text{g}/\text{kg}/\text{year}$ ). For more information, see Chapter 6.

### **1.4 HOW CAN HEXACHLOROBENZENE ENTER AND LEAVE MY BODY?**

Hexachlorobenzene can enter your body when you eat food contaminated with it, when you breathe particles of it in the air, or when it gets on your skin. After it enters your body, it rapidly spreads through your blood to many tissues in the body, especially to fat. This probably happens within a few hours. Based on the results of a survey of this substance in people's tissues, it will remain in your body, especially in fat, for years. A large portion of hexachlorobenzene in the fat of a mother can be transferred to her baby in breast milk. During pregnancy, this substance can transfer to the unborn child through the mother's blood. Most of it leaves your body in the feces; smaller amounts are found in urine. For more information, see Chapter 3.

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**1.5 HOW CAN HEXACHLOROBENZENE AFFECT MY HEALTH?**

To protect the public from the harmful effects of toxic chemicals and to find ways to treat people who have been harmed, scientists use many tests.

One way to see if a chemical will hurt people is to learn how the chemical is absorbed, used, and released by the body; for some chemicals, animal testing may be necessary. Animal testing may also be used to identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method to get information needed to make wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines.

A study of people in Turkey who, over a period of several years, ate grain that was accidentally contaminated with hexachlorobenzene, showed a high death rate in young children of mothers who ate it and in young children who ate it themselves. Nursing infants may be in particular danger from the transfer of hexachlorobenzene through breast milk if their mothers have been exposed. Unborn children may also be at particular risk because of the transfer of hexachlorobenzene through the mother's blood during pregnancy. This has been confirmed by experiments in animals.

People in Turkey who, over a long time, ate grain that was accidentally contaminated with hexachlorobenzene suffered from a liver disease called porphyria cutanea tarda. The main effect of porphyria is slowed or stopped formation of heme, the oxygen-carrying part of the hemoglobin molecule found in red blood cells and an important chemical in the body. Porphyria is identified by elevation of heme precursors called porphyrins in the blood, urine, and stool. This disease can cause red-colored urine, skin sores, change in skin color, arthritis, and problems of the liver, nervous system, and stomach. Studies in animals also show that eating hexachlorobenzene for a long time can harm mostly the liver, thyroid, and nervous systems; the studies in animals also show that eating hexachlorobenzene for months or years can damage bones,

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kidneys, and blood, and the immune, endocrine (hormone-releasing), and nervous systems. Unborn children and young children may be more sensitive to these effects than adults.

Studies in animals also suggest that eating this substance for months or years can cause cancer of the liver, kidney, and thyroid, but there is no strong evidence that the substance causes cancer in people. The U.S. Department of Health and Human Services (DHHS) has determined that the substance may reasonably be anticipated to be a human carcinogen. The International Agency for Research on Cancer (IARC) has determined that hexachlorobenzene is possibly carcinogenic to humans. EPA has determined that hexachlorobenzene is a probable human carcinogen. See Chapter 3 for more information.

There is no information on levels of hexachlorobenzene in air that affect people. No information is available on the taste or lowest levels at which you can taste or smell it in air or water. Therefore, people may not know when hexachlorobenzene is present in air or water. Studies conducted with rats indicate that breathing hexachlorobenzene may harm the immune system. The health effects from getting it on your skin are not known.

For more information on the levels of this substance that have caused health effects in people and animals, see Chapters 2 and 3.

### **1.6 HOW CAN HEXACHLOROBENZENE AFFECT CHILDREN?**

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

Infants and young children appeared to be especially sensitive to the effects of hexachlorobenzene in the Turkish grain poisoning epidemic. Breast-fed infants of mothers known to have ingested the contaminated bread developed a disease known as pembe yara or "pink sore." The disease was named for the skin lesions that were produced. Other symptoms were weakness and convulsions. Many of the sickened infants died from this disease. Young children beyond

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2 years of age did not get pink sore, but they did develop numerous skin, nervous system, and bone abnormalities later in life.

One study found higher levels of hexachlorobenzene in mother's milk in babies who had ear infections than in the milk of babies without ear infections. Another study found higher levels of hexachlorobenzene in the fat of boys with a specific type of birth defect, undescended testis, than in the fat of normal boys. We do not know if hexachlorobenzene caused the infection or the birth defect.

Animal studies support the suggestion that young animals exposed to hexachlorobenzene before and soon after birth are especially sensitive to hexachlorobenzene. Effects on the liver, nervous system, and immune function occurred at lower doses in the young developing animals than in adults. Animal studies also showed that hexachlorobenzene has effects on various endocrine organs, including the thyroid gland (hypothyroidism), parathyroid gland (hyperparathyroidism), adrenal gland, and ovaries. These tissues produce hormones that are important to normal growth and development of the organism.

You can find more information about how hexachlorobenzene can affect children in Sections 3.7 and 6.6.

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**1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO HEXACHLOROBENZENE?**

If your doctor finds that you have been exposed to significant amounts of hexachlorobenzene, ask whether your children might also be exposed. Your doctor might need to ask your state health department to investigate.

The primary way most people are exposed is through food. Fatty food may be higher in hexachlorobenzene than less fatty food. Additionally, when hexachlorobenzene is present in food, more may be absorbed when the food is fatty than when the food is less fatty. Therefore, eating less fatty food may reduce the risk of exposure to hexachlorobenzene.

If you live near an industrial site where hexachlorobenzene was produced or is produced as an unintentional by-product or you live near a hazardous waste site where it has been discarded, there may be high levels of hexachlorobenzene in the water and soil. Substituting cleaner sources of water and limiting contact with soil (for example, through use of a dense ground cover or thick lawn) would reduce family exposure to hexachlorobenzene. Produce grown in contaminated soil should not be eaten. By paying careful attention to dust and dirt control in the home (air filters, frequent cleaning), you can reduce family exposure to contaminated dirt. Some children eat a lot of dirt. You should prevent your children from eating dirt. You should discourage your children from putting objects in their mouths. Make sure that they wash their hands frequently and before eating. Discourage your children from putting their hands in their mouths or from other hand-to-mouth activity.

It is sometimes possible to carry hexachlorobenzene from work on your clothing, skin, hair, tools, or other objects removed from the workplace. This is particularly likely if you work in the chemical or pesticide industries. You may contaminate your car, home, or other locations outside work where children might be exposed to hexachlorobenzene. You should know about this possibility if you work where hexachlorobenzene exposure may occur.

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Your occupational health and safety officer at work can and should tell you whether chemicals you work with are dangerous and likely to be carried home on your clothes, body, or tools and whether you should be showering and changing clothes before you leave work, storing your street clothes in a separate area of the workplace, or laundering your work clothes at home separately from other clothes. Material safety data sheets (MSDS) for many chemicals used should be found at your place of work, as required by the Occupational Safety and Health Administration (OSHA) in the U.S. Department of Labor. MSDS information should include chemical names and hazardous ingredients, and important properties, such as fire and explosion data, potential health effects, how you get the chemical(s) in your body, how to properly handle the materials, and what to do in the case of emergencies. Your employer is legally responsible for providing a safe workplace and should freely answer your questions about hazardous chemicals. Your state OSHA-approved occupational safety and health program or OSHA itself can answer any further questions and help your employer identify and correct problems with hazardous substances. Your state OSHA-approved occupational safety and health program or OSHA will listen to your formal complaints about workplace health hazards and inspect your workplace when necessary. Employees have a right to seek safety and health on the job without fear of punishment.

### **1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO HEXACHLOROBENZENE?**

Blood, breast milk, urine, and feces may be tested to determine if you have ever been exposed to hexachlorobenzene. These tests are not usually available at a doctor's office because they require special equipment found at county, state, university, and independent analytical laboratories. Because this compound can collect and remain in human fat for several years, the test for this substance in breast milk can tell you only that you have been exposed, but not when or to how much. The blood, urine, and feces tests can indicate more recent exposure. However, the levels measured cannot be used to predict what health effects might occur in people. Blood, urine, and feces can also be monitored for porphyrins. High porphyrin levels indicate slowed formation of heme, which is a major effect of hexachlorobenzene in the body. The usefulness of

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this test as a sign of hexachlorobenzene exposure is limited, however, because there are many other potential causes of high porphyrin levels. For more information, see Chapters 3 and 7.

### **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. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA).

Recommendations provide valuable guidelines to protect public health but cannot be enforced by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

Regulations and recommendations can be expressed in not-to-exceed levels in air, water, soil, or food that are usually based on levels that affect animals; then they are adjusted to help protect people. Sometimes these not-to-exceed levels differ among federal organizations because of different exposure times (an 8-hour workday or a 24-hour day), the use of different animal studies, or other factors.

Recommendations and regulations are also periodically updated 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 hexachlorobenzene include the following:

EPA has developed advisories to protect people from the potential health effects of exposure to hexachlorobenzene in drinking water. EPA has proposed that drinking water should not contain more than 0.05 parts of hexachlorobenzene per million parts of water (ppm) in water that children drink, and should not exceed 0.2 ppm in water that adults drink for longer periods (approximately 7 years). No other health standards or recommendations exist for this substance.

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You can find more information on regulations and guidelines that apply to hexachlorobenzene in 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

Agency for Toxic Substances and Disease Registry  
Division of Toxicology  
1600 Clifton Road NE, Mailstop E-29  
Atlanta, GA 30333  
Web site: <http://www.atsdr.cdc.gov>

\* Information line and technical assistance

Phone: 1-888-42-ATSDR (1-888-422-8737)  
Fax: 1-404-498-0057

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

\* To order toxicological profiles, contact

National Technical Information Service  
5285 Port Royal Road  
Springfield, VA 22161  
Phone: (800) 553-6847 or (703) 605-6000

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### 2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO HEXACHLOROBENZENE IN THE UNITED STATES

Hexachlorobenzene is a fully chlorinated hydrocarbon industrial chemical that is practically insoluble in water, but is very soluble in fat, oils, and organic solvents. Hexachlorobenzene is one of the most persistent environmental pollutants, and bioaccumulates in the environment, in animals, and in humans. It is not currently manufactured as a commercial product in the United States, and virtually all commercial production ended in the late 1970s. However, some hexachlorobenzene is produced as a by-product or impurity in the manufacture of chlorinated solvents and other chlorinated compounds (e.g., carbon tetrachloride, chlorophenols, mirex, tetrachloroethylene, trichlorobenzenes, trichloroethylene, trichlorotoluenes, and vinyl chloride), including several pesticides currently in use (pentachloronitrobenzene, chlorothalonil, Dacthal<sup>®</sup>, picloram, pentachlorophenol, atrazine, simazine, and lindane). It is estimated that 3,500–11,500 kg of hexachlorobenzene were inadvertently produced in the manufacture of chlorinated solvents in 1984. There are no current commercial uses of hexachlorobenzene in the United States, although hexachlorobenzene was used as a fungicide on the seeds of onions, sorghum, wheat, and other grains until 1984, when its registration as a pesticide was voluntarily canceled. Hexachlorobenzene had also been used in the production of pyrotechnic and ordinance materials for the military and in the production of synthetic rubber.

The general population is not likely to be exposed to large amounts of hexachlorobenzene, but some exposure is likely, as many studies have detected small amounts in food and air samples. Traces of hexachlorobenzene have been found in almost all people tested for hexachlorobenzene or its metabolites. These amounts of hexachlorobenzene are most likely the result of consumption of low levels in food, with an estimated yearly uptake of 68, 22, and 5 µg for adults, toddlers, and infants, respectively. Other sources of exposure may include contact with contaminated soil and air. Hexachlorobenzene has been detected in agricultural soil at levels up to 440 ng/g, and in lake sediment at #15 ng/g. Ambient air samples have usually been reported to range from 0.1 pg/m<sup>3</sup> to 1.5 ng/m<sup>3</sup>. Hexachlorobenzene has a very low solubility in water, so exposure by water is not likely to be significant; ambient water samples have usually been below 0.1 parts per trillion (ppt).

Children are expected to be exposed to hexachlorobenzene by the same routes as adults. Additionally, if hexachlorobenzene is present in their mothers, unborn children may be exposed through the placenta and

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nursing children may be exposed to hexachlorobenzene present in milk. Human milk samples from the general population found hexachlorobenzene concentrations in the range of 11–70 ng/g fat.

See Chapter 6 for more detailed information regarding concentrations of hexachlorobenzene in environmental media.

## 2.2 SUMMARY OF HEALTH EFFECTS

Hexachlorobenzene is a toxic organochlorine that has been shown to cause death, systemic (e.g., liver, skin, bone, and thyroid), neurological, developmental, endocrine, and immunological toxicity in humans. Animal studies have demonstrated that hexachlorobenzene causes reproductive toxicity and increases the risk for cancer formation. The most sensitive target organs for hexachlorobenzene are the liver, ovary, and central nervous system.

A limited number of occupational studies have associated inhalation of hexachlorobenzene with liver effects (strongly with increased porphyrins and weakly with hepatocellular carcinoma), immunological effects (decreased neutrophil activity, increased immunoglobulins, and susceptibility to infection), and renal effects (microproteinuria) Queiroz et al. 1997, 1998a; Richter et al. 1994; Selden et al. 1999). Most data for the inhalation effects of hexachlorobenzene in humans were presented by studies of workers from an organochlorobenzene factory and the residents of a nearby rural town (Flix, Spain). Exposure to hexachlorobenzene (primarily airborne) pollution has been linked with elevated blood levels of hexachlorobenzene and hepatic effects (increased porphyrins and hepatic enzymes), thyroid effects (decreased thyroxine levels; weakly with hypothyroidism, goiter, and thyroid cancer), and impaired development of locomotor skills in infants.

Striking epidemiological evidence was found in studies of a population orally exposed to hexachlorobenzene in southeast Anatolia, Turkey. In the 1950s, widespread ingestion of bread made from grain that had been treated with hexachlorobenzene as a pesticide caused an epidemic in this region. The ingested dose of hexachlorobenzene was estimated to be in the range of 0.05–0.2 g/day, equivalent to 0.7–2.9 mg/kg/day for an average person. An extremely high (95%) rate of mortality occurred in infants under 2 years of age who had been breast fed by mothers who had ingested the contaminated bread. Poisoned infants displayed a condition known as *pembe yara* or "pink sore" because of the associated skin lesions (annular erythema). The infant deaths were primarily associated with cardiorespiratory failure secondary to this disease. Other clinical symptoms in these infants included weakness and

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convulsions. A disease called *kara yara* or “black sore” was observed most frequently in children between the ages of 6 and 15 years, although some younger children and adults were also affected. It appeared after approximately 6 months of exposure; symptoms included photosensitivity, skin fragility (causing ulcers and scarring), hyperpigmentation, and hirsutism. There was a 10% mortality rate among *kara yara* patients. These skin lesions were diagnosed as porphyria cutanea tarda, a specific type of vesiculobullous porphyria. The porphyrias are a class of inherited and acquired diseases caused by enzymatic defects in heme biosynthesis, leading to the generation of porphyrins, which may cause tissue damage, especially in the skin. The human studies and supporting animal studies have clearly demonstrated that hexachlorobenzene causes porphyria.

Other symptoms diagnosed in this hexachlorobenzene-exposed population were: loss of appetite, weakness, arthritis (a swelling and spindling of the fingers, but with little pain), hepatomegaly, enlarged thyroid, and inability to perform simple, everyday activities such as handling eating utensils, rising from a squat, and climbing stairs. Clinical findings persisted in most subjects, including high porphyria, dermal lesions, multiple neurological effects, skeletomuscular effects, enlarged liver, and enlarged thyroid. In adult pregnant women who had been exposed as children, suggestive (but not conclusive) evidence of elevated incidences of miscarriages and stillbirths was found. Similar irreversibility has been seen in animal studies: developmentally exposed rats exhibited a significantly increased response to startling as adults and acutely exposed rats still exhibited porphyria more than 500 days after exposure.

No studies were located regarding health effects in humans or animals following dermal exposure to hexachlorobenzene. However, an acute study in rats suggested that hexachlorobenzene can be absorbed across the skin.

The primary target systems for hexachlorobenzene are hepatic toxicity, reproductive toxicity, developmental toxicity, and carcinogenesis; these are discussed below. The reader is referred to Section 3.2, Discussion of Health Effects by Route of Exposure, for more detailed information and discussions of additional effects.

**Hepatic Effects.** The most consistently identified effect following exposure of humans or animals to hexachlorobenzene is porphyria. The porphyrias are a class of inherited and acquired diseases caused by enzymatic defects in heme biosynthesis, leading to the generation of porphyrins (see Section 3.5, Mechanisms of Action). The build-up of high levels of porphyrins in the body is known to cause liver (including cirrhosis, siderosis [accumulation of iron], focal necrosis, hyperplasia), and kidney (renal

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failure) damage. Additionally, phototoxicity occurs as porphyrins accumulated in the skin are activated by sunlight to generate reactive oxygen species, causing tissue damage. As a result, skin lesions occur most commonly on areas exposed to sunlight, such as the hands and face. Available data also suggest that porphyrins may activate the immune system. Porphyria, diagnosed by the presence of high levels of porphyrins in the blood, feces, or urine, has been detected following exposures to hexachlorobenzene in workers, in the residents of Flix, Spain (primarily inhalation exposures resulting from a nearby organochlorine factory), and in the Turkish epidemic (oral exposure with contaminated grain). Exposed patients from the Turkish epidemic also exhibited hepatomegaly.

Several studies in rats and mice have observed porphyria, but no clear relationship has been established between porphyria and other hepatic effects seen in animals, such as peribiliary lymphocytosis and fibrosis, hepatomegaly and increased liver weight, enzyme induction, and degenerative pathological changes.

**Reproductive Effects.** Although no reliable evidence of reproductive toxicity has been observed in humans, the reproductive performance of rats has been adversely affected at doses as low as 16 mg/kg/day of hexachlorobenzene (decreased fertility, increased numbers of stillborn pups).

Distribution studies have identified the ovaries as a site of hexachlorobenzene accumulation, and intermediate-duration exposures to doses of hexachlorobenzene as low 0.01 mg/kg/day have been shown to cause ovarian lesions in adult female *Cynomolgus* monkeys. At higher doses, studies in *Cynomolgus* monkeys, Rhesus monkeys, and rats have reported changes in organ weight, degenerative changes, and disruptions in steroidogenesis (estrogen and progesterone).

**Developmental Effects.** Human and animal studies have demonstrated that hexachlorobenzene crosses the placenta to accumulate in fetal tissues and is transferred in breast milk.

The poisoning epidemic in Anatolia, Turkey, demonstrated that hexachlorobenzene is a developmental toxin. Children exposed under 2 years of age were the most susceptible (95% mortality, skin lesions). However, children under 15 were also more susceptible than adults, and exhibited both immediate (10% mortality, skin lesions) and persistent (dermal, neurological, skeletomuscular, hepatic, and thyroid effects) symptoms. Exposure for adults was estimated at 0.05–0.2 g/day of hexachlorobenzene (in bread made from contaminated grain) between 1955 and 1959.

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Other human studies investigating developmental toxicity have been limited by small study size and low levels of hexachlorobenzene exposure; they have found suggestive evidence of an increased risk of undescended testis and impaired development of locomotor skills in newborn babies.

Animal studies have verified that hexachlorobenzene impaired neurological development and reduced neonatal viability and growth. Although an increased risk of undescended testis has not been observed in animals, the occurrence of cleft palate, renal agenesis, and minor skeletal abnormalities in mice are consistent with a possible teratogenic role for hexachlorobenzene.

**Cancer.** Among the general population, case-control studies have generally found no association between hexachlorobenzene levels in blood or tissues and incidence of breast or other cancers. Data from men exposed to hexachlorobenzene by inhalation (occupationally or as a result of nearby air pollution from an organochlorine factory in Flix, Spain) provide weak evidence for an association between hexachlorobenzene exposure and cancer of the liver, thyroid, and brain. Because hexachlorobenzene produces porphyria, it is noteworthy that several human studies have associated porphyria with the increased incidence of liver cancer.

Several animal studies have demonstrated that oral exposure to hexachlorobenzene increases the incidence of tumor formation. The evidence of carcinogenicity is strongest in the liver; hexachlorobenzene has been shown to induce hyperplasia (in rats, mice, pigs, dogs, and monkeys), metaplasia (in rats), benign tumors (hepatoma in mice and rats; hemangiohepatoma and bile duct adenoma in rats), and malignant tumors (hepatocarcinoma in rats, mice, and hamsters; bile duct adenocarcinoma in rats). Additionally, exposure to hexachlorobenzene has been shown to induce renal metaplasia, adenomas and renal cell carcinomas (in rats, mice, and hamsters); lymphosarcomas (in rats, mice, and hamsters); adrenal hyperplasia and pheochromocytoma (in rats); parathyroid adenomas (in rats); and hemangioendothelioma and thyroid tumors (in hamsters). In the Ninth Report on Carcinogens, the NTP classified hexachlorobenzene as *reasonably anticipated to be a human carcinogen*. The EPA classified hexachlorobenzene as a *probable human carcinogen*, Group B2, on the basis that oral administration of hexachlorobenzene has been shown to induce tumors in the liver, thyroid, and kidney in three rodent species. IARC has classified hexachlorobenzene as possibly carcinogenic to humans (Group 2B), based on inadequate evidence in humans and sufficient evidence in experimental animals for carcinogenicity. For more information, see Sections 3.2.1.7 and 3.2.2.7, Cancer.

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**2.3 MINIMAL RISK LEVELS (MRLs)*****Inhalation MRLs***

Although limited evidence identified organs (liver, kidneys) and systems (endocrine, neurological and immune) that may be targets of hexachlorobenzene toxicity following inhalation exposures in humans and animals, these data are qualitatively and quantitatively inadequate for use in developing acute, intermediate, or chronic inhalation MRLs for hexachlorobenzene.

***Oral MRLs***

- C An MRL of 0.008 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) for hexachlorobenzene.

This MRL is based on a critical evaluation of a developmental study (Goldey and Taylor 1992) that observed a lowest-observed-adverse-effect level (LOAEL) of 2.5 mg/kg/day for hyperactivity in offspring rats. An uncertainty factor of 300 was used (10 for extrapolation from rats to humans, 10 for human variability, and 3 for use of a minimal LOAEL).

Human data have shown that the developing central nervous system is a target of hexachlorobenzene toxicity. Many breast-fed infants of mothers who ingested hexachlorobenzene-contaminated bread during an epidemic of hexachlorobenzene poisoning in Turkey between 1955 and 1959 showed symptoms of *pembe yara*, which included weakness, convulsions, and annular erythema prior to death (Cripps et al. 1984; Peters et al. 1982, 1987). In children exposed (at an average age of 7 years) to hexachlorobenzene-contaminated grain, neurological effects persisted into adulthood (weakness, paresthesia, sensory shading, myotonia, and cogwheeling [irregular jerkiness of movement due to increased muscle tone as seen in Parkinson's disease]) (Cripps et al. 1984; Peters et al. 1982). Additionally, a preliminary report of infants from Flix, Spain, found an association between high hexachlorobenzene levels in milk and blood and impaired development of locomotor skills (Sala et al. 1999a).

Toxicology experiments have identified the same targets in developing animals. A developmental study in rats (Goldey and Taylor 1992) provided the most appropriate data from which to derive an acute-duration oral MRL for hexachlorobenzene. Virgin female rats were fed 2.5 or 25 mg/kg/day hexachlorobenzene for 4 days, 2 weeks prior to mating with unexposed males, and the developmental neurotoxicity of hexachlorobenzene was assessed in offspring using a battery of tests (Goldey and Taylor 1992). Pups

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treated with either dose reoriented themselves significantly more quickly in a negative geotaxis test (on postnatal days 6 and 8), required less time in an olfactory discrimination test, and demonstrated increased exploratory activity in a motor activity test (on postnatal days 9–11). No significant effects on learning (swim T-maze) or motor activity (measured in older offspring on postnatal days 40 and 50, respectively) were detected. Hexachlorobenzene-exposed offspring at the 25 mg/kg/day dose level exhibited significantly altered acoustic startle responses (decreased at 23 days of age and increased at 90 days of age compared to controls). Thus, the study identified a LOAEL of 2.5 mg/kg/day for hyperactivity in the offspring rats, and this was the most sensitive LOAEL identified for the acute toxicity of hexachlorobenzene.

Other animal studies have demonstrated that exposure to hexachlorobenzene can produce neurological effects. In rats exposed prenatally through adulthood, decreased operant learning ability (“post-reinforcement pause” and “index of curvature”) was observed on postnatal day 150 (Lilienthal et al. 1996). Moreover, oral exposure to hexachlorobenzene has also been shown to interfere with the function of the nervous system, inducing mild reduction in conduction velocity of the sciatic nerve and denervation (fibrillations, chronic repetitive discharges) (Sufit et al. 1986), hyperexcitability, tremors, muscle fasciculations, clonic convulsions, ataxia, lethargy, and paralysis in adult rats (Kennedy and Wigfield 1990; Kimbrough and Linder 1974; Koss et al. 1978; Nikolaev et al. 1986; Ockner and Schmid 1961); convulsions, tremors, and progressive weakness in litters of female rats (Cripps 1990); tremor in adult C57B1/6J mice (Hahn et al. 1988); dysrhythmic electroencephalogram in adult Beagle dogs (Sundlof et al. 1981); severe tremors and muscular weakness in adult Rhesus monkeys (Knauf and Hobson 1979); hypoactivity, lethargy, and ataxia in infant Rhesus monkeys (Iatropoulos et al. 1978); and tremors, panting, and unsteady gait in adult SPF pigs (Den Tonkelaar et al. 1978).

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

This MRL is based on a LOAEL of 0.01 mg/kg/day for minimal ovarian effects in monkeys (Babineau et al. 1991). An uncertainty factor of 90 was used (3 for extrapolation from monkeys to humans, 10 for human variability, and 3 for use of a minimal LOAEL). Ultrastructural studies of ovaries collected from monkeys (Babineau et al. 1991; Bourque et al. 1995; Jarrell et al. 1993) provide the most appropriate data for use deriving an intermediate oral MRL for hexachlorobenzene. Female *Cynomolgus* monkeys were fed doses of 0.01–10 mg/kg/day of hexachlorobenzene in glucose in gelatin capsules for 90 days; the studies focused exclusively on end points relevant to reproductive toxicity (ovarian function and

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histopathology). The LOAEL of 0.01 mg/kg/day for reproductive effects is the most sensitive LOAEL for the intermediate toxicity of hexachlorobenzene (Babineau et al. 1991).

Two early studies (Babineau et al. 1991; Jarrell et al. 1993) used doses of 0.1, 1, and 10 mg/kg/day of hexachlorobenzene. In all treated animals, hexachlorobenzene decreased the total number of oocytes and primary follicles, caused oocyte necrosis and follicular degeneration, and induced histopathological changes in the ovarian epithelium (cell stratification; decreased nuclear membrane distinction; increased density and granularity of oocyte nuclei; and increased numbers of aggregated lysosomes, vesicles, and vacuoles). The severity was dose-dependent.

The Bourque et al. (1995) follow-up study extended the observation of ultrastructural effects in the ovary to 0.01 mg/kg/day. At this dose, mitochondria in developing follicles were condensed and deformed. At higher doses (up to 10 mg/kg/day), the mitochondria were progressively more damaged and other changes were noted, such as indentation of nuclear membranes and abnormal accumulation of lipid in the cytoplasm of follicular cells. Because these effects were not associated with changes in oocyte fertility (measured *in vitro*), they were considered minimally adverse. Thus, these studies identify a LOAEL of 0.01 mg/kg/day for minimal reproductive effects in the treated monkeys.

Other monkey studies have also observed evidence of ovarian effects. In female *Cynomolgus* monkeys given capsules with at least 0.1 mg/kg/day of hexachlorobenzene for 90 days, a dose-related decrease in serum progesterone levels during the luteal (but not follicular and periovulatory) phase of the menstrual cycle, lengthening of the menstrual cycle, ultrastructural changes in surface epithelium of the ovary (indicative of cellular degeneration), and changes in ovary surface epithelial cell shape (length to width ratio) were detected (Foster et al. 1992a; Sims et al. 1991). In female Rhesus monkeys, gavage doses of at least 64 (but not lower doses up to 32) mg/kg/day of hexachlorobenzene for 60 days induced degenerative changes of the ovarian follicle, stroma, and germinal epithelium (Iatropoulos et al. 1976), and suggestive evidence of unusual steroidogenic activity (depressed serum potassium) was seen in Rhesus monkeys given 128 mg/kg/day for at least 60 days (Knauf and Hobson 1979).

Rat studies have confirmed the reproductive toxicity of hexachlorobenzene in the ovary. Increased serum progesterone levels and elevated ovarian weights were observed in superovulated female Sprague-Dawley rats orally administered 1 mg/kg/day hexachlorobenzene by gavage for 21 days (Foster et al. 1992b).

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Super-ovulated (but not normal cycling) female Sprague-Dawley rats gavaged with 50 mg/kg/day of hexachlorobenzene for 5 days exhibited significant elevation of serum levels of progesterone (Foster et al. 1993). In a subsequent study with ovariectomized female Sprague-Dawley rats, gavage doses of at least 1 mg/kg/day for 30 days significantly decreased circulating corticosterone and cortisol levels, without affecting levels of circulating aldosterone and progesterone levels or adrenal gland weight (Foster et al. 1995a). The investigators concluded that hexachlorobenzene exposure induces alterations in steroidogenesis of cells of the adrenal cortex inner zone.

Although clear evidence of reproductive toxicity has not been observed in humans, suggestive data indicated that hexachlorobenzene may increase the risk for spontaneous abortion (miscarriages and stillbirths). Therefore, the intermediate-duration oral MRL is considered relevant to human health.

- C An MRL of 0.00005 mg/kg/day has been derived for chronic-duration oral exposure (365 days or more) for hexachlorobenzene.

This MRL was based on a critical evaluation of a multigenerational study (Arnold et al. 1985), which observed a LOAEL of 0.016 mg/kg/day for hepatic effects in F<sub>1</sub> male rats. An uncertainty factor of 300 was used (10 for extrapolation from rats to humans, 10 for human variability, and 3 for use of a minimal LOAEL).

Although studies designed to detect liver histopathology have not been conducted in humans, epidemiological studies have detected hepatic effects as indicated by increased porphyrin and enzyme levels in people exposed for chronic durations to hexachlorobenzene (Herrero et al. 1999; Sala et al. 1999b; Seldon et al. 1999). Analysis of the available human and animal chronic oral toxicity data for hexachlorobenzene indicated that a 130-week study in rats reported by Arnold et al. (1985) provided the most appropriate data for use in the development of an oral chronic MRL for hexachlorobenzene. Briefly, male and female weanling Sprague-Dawley rats were fed 0, 0.016, 0.08, 0.4, or 2 mg/kg/day of hexachlorobenzene for 3 months prior to mating and through weaning of F<sub>1</sub> offspring, when they were sacrificed. The F<sub>1</sub> offspring were continued on their parents' diet from weaning throughout the remainder of their lives (130 weeks). Statistically significant increases in the incidences of peribiliary lymphocytosis and fibrosis were observed in the livers of male rats at \$0.016 mg/kg/day in the F<sub>1</sub> generation lifetime study. Significant dose-dependent trends were also found for hepatic basophilic chromogenesis at \$0.4 mg/kg/day in both genders of rats. The 2 mg/kg/day dose group rats also exhibited increased pup mortality (in both genders) and severe chronic nephrosis (in males only).

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The increased incidences of peribiliary lymphocytosis and fibrosis in treated males were considered to represent a minimal effect. These are common spontaneous lesions in aging rats and occurred in approximately 30% of controls in this study. For peribiliary fibrosis, incidence was increased in all treated groups (statistically significant in the 0.016 and 2 mg/kg/day groups), but there was no clear evidence of a dose-response (13/48, 23/48, 21/48, 21/49, and 23/49, respectively, in the control, 0.016, 0.08, 0.4, and 2 mg/kg/day groups). For peribiliary lymphocytosis, the incidence was increased in all treated groups (statistically significant in the 0.016, 0.08, and 2 mg/kg/day groups), and the trend was also statistically significant (16/48, 27/48, 26/48, 21/49, and 32/49, respectively, in the control, 0.016, 0.08, 0.4, and 2 mg/kg/day groups). Because incidences of these lesions in the control and treated females were similar to the control males (ranging from 6/49 to 14/49), the incidence levels in control males do not appear unusually low. Overall, these findings suggest that hexachlorobenzene produced a minimal hepatic effect in male rats at the lowest doses administered by increasing the incidence of age-related hepatic lesions. The LOAEL of 0.016 mg/kg/day reported in this study for hepatic effects is the most sensitive LOAEL for the characteristic chronic toxicity of hexachlorobenzene, liver toxicity. However, the study did not identify a no-observed-adverse-effect level (NOAEL).

Numerous animal studies have clearly demonstrated that the liver is a major target organ of hexachlorobenzene exposure. Short-term experiments in rats have observed increased liver weight, increased hepatic porphyrins, liver histopathology (cytoplasmic vacuolation, anisokaryosis, and pyknotic hepatocytes), and increased serum cholesterol (Krishnan et al. 1991; Lecavalier et al. 1994; Rajamanickam and Padmanaban 1974; Richter et al. 1981). Intermediate- and chronic-duration experiments in rats have observed these and other signs, including additional liver histopathology (degeneration, hypertrophic hepatocytes with eosinophilic cytoplasm with thready basophilic structures, as well as inflammatory cell infiltrates), decreased liver retinoid levels, and elevated liver enzymes (Andrews et al. 1989, 1990; Den Besten et al. 1993; Elder and Urquhart 1986; Kennedy and Wigfield 1990; Koss et al. 1978, 1983; Kuiper-Goodman et al. 1977; Ockner and Schmid 1961; Smith and Cabral 1980; van Raaij et al. 1993b). Similar effects have been observed in intermediate-duration experiments in Rhesus monkeys (Iatropoulos et al. 1976; Knauf and Hobson 1979), beagle dogs (Sundlof et al. 1981), and pigs (Den Tonkelaar et al. 1978).





## 3. HEALTH EFFECTS

**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 hexachlorobenzene. 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

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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 hexachlorobenzene are indicated in Table 3-2 and Figure 3-2. Because cancer effects could occur at lower exposure levels, Figure 3-2 also shows a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 ( $10^{-4}$  to  $10^{-7}$ ), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for hexachlorobenzene. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

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

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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**

No studies were located regarding death in humans or animals following inhalation exposure to hexachlorobenzene.

**3.2.1.2 Systemic Effects**

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, dermal, or ocular effects in humans or animals following inhalation exposure to hexachlorobenzene.

**Hepatic Effects.** It is well known that ingestion of hexachlorobenzene can produce porphyria (see Section 3.2.2.2), but there are few data to suggest a similar effect from inhalation exposure. There was a small, but statistically significant, increase (in comparison to matched controls) in total urinary porphyrins in a group of nine workers exposed for 1–19 years to hexachlorobenzene and other organochlorine compounds (including octachlorostyrene, another porphyrinogenic substance [Smith et al. 1986d]) while using hexachloroethane as an aluminum degassing agent at aluminum smelters (Selden et al. 1999). The prevalence of porphyria-related symptoms did not differ between groups. Serum levels of hexachlorobenzene were positively correlated to urine porphyrin levels, but urine porphyrin levels also correlated, to a similar degree, with serum octachlorostyrene levels. Therefore, this study cannot ascertain whether the preclinical porphyria observed in aluminum smelter workers is due to hexachlorobenzene, octachlorostyrene, or both chemicals. End points of hepatic toxicity have been investigated in residents of Flix, Spain, a small village in Catalonia; a nearby electrochemical factory that manufactures organochlorines has been implicated in the village's high environmental levels of hexachlorobenzene (35 ng/m<sup>3</sup> as a 24-hour average in air). Analysis of blood hexachlorobenzene and urinary porphyrins in 604 residents of Flix, including 185 factory workers, showed that blood hexachlorobenzene levels were roughly 5-fold higher in factory workers than in other residents. However, there were no cases of clinical porphyria cutanea tarda in either group and no evidence that preclinical porphyria was more prevalent in the factory workers than in other residents or that there was any association between urinary porphyrin

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levels and blood hexachlorobenzene levels (Herrero et al. 1999; Sala et al. 1999b). A subsequent study verified the 5-fold increase in 75 factory workers, and detected a positive, statistically significant correlation between blood hexachlorobenzene levels and serum  $\gamma$ -glutamyltransferase (Sala et al. 2001a). However, no correlation was seen for serum levels of either aspartate or alanine aminotransferase. The NOAEL for liver effects in the village residents are shown in Table 3-1 and Figure 3-1. In 52 workers employed for 1–25 years at a chemical plant where hexachlorobenzene was the primary byproduct, compared with controls drawn from a local blood bank (Queiroz et al. 1998a), serum aspartate and alanine transaminase levels were increased but no correlation was detected between serum levels of transaminase and blood hexachlorobenzene. The available human data, while suggestive, have not conclusively shown hepatic effects due to inhaled hexachlorobenzene. No studies were located regarding the hepatic effects of airborne hexachlorobenzene in animals.

**Renal Effects.** Based on analysis of blood samples from 608 individuals, workers (n=189) at an electrochemical factory near Flix, Spain did not have a significantly increased risk of high serum creatinine, a marker for glomerular disease, in comparison to other Flix residents (n=419) despite hexachlorobenzene blood levels that were approximately 5-fold higher (Sala et al. 1999b). However, the power of this study to find an effect was limited by the small sample size (only nine individuals with high serum creatinine were found in the study population). “Marked changes in kidney functions” including microproteinuria were observed in Czechoslovakian workers with high blood hexachlorobenzene levels following occupational inhalation exposure to hexachlorobenzene, originally at 2.1–10.8 mg/m<sup>3</sup> and then at 0.012–0.022 mg/m<sup>3</sup>, from 1983 to 1990 (Richter et al. 1994). No studies were located regarding renal effects of inhaled hexachlorobenzene in animals.

**Endocrine Effects.** Although oral exposure to hexachlorobenzene has been clearly associated with thyroid effects, only limited information is available regarding the endocrine effects of hexachlorobenzene following inhalation exposure. A study of residents (192–558, depending on end point) of Flix, Spain, where a nearby electrochemical factory had resulted in high air and blood levels of hexachlorobenzene, detected statistically significant correlations between increased blood hexachlorobenzene levels and decreased levels of total thyroxine (T<sub>4</sub>); serum levels of thyroid stimulating hormone (TSH) were not affected (Sala et al. 2001a). Similarly, an earlier study did not detect changes in serum levels of TSH in 189 workers at the factory in comparison to 419 other Flix residents despite 5-fold higher blood hexachlorobenzene levels in the workers (Sala et al. 1999b). Both studies were limited by small sample size,

Table 3-1. Levels of Significant Exposure to Hexachlorobenzene - Inhalation

Key to <sup>a</sup> figure	Species (strain)	Exposure/ duration/ frequency	System	LOAEL			Reference Chemical Form
				NOAEL (mg/m3)	Less serious (mg/m3)	Serious (mg/m3)	
<b>ACUTE EXPOSURE</b>							
<b>Immunological/Lymphoreticular</b>							
1	Rat (Sprague- Dawley)	1-4 d 4 hr/d		4.4 M	33 M (slight impairment of pulmonary immune defenses)		Sherwood et al. 1989

Table 3-1. Levels of Significant Exposure to Hexachlorobenzene - Inhalation (continued)

Key to <sup>a</sup> figure	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL		Reference Chemical Form
					Less serious (mg/m3)	Serious (mg/m3)	
<b>INTERMEDIATE EXPOSURE</b>							
<b>Immunological/Lymphoreticular</b>							
2	Rat (Sprague- Dawley)	4 wk 4 d/wk 4 hr/d			35 M (slight impairment of pulmonary immune defense)		Sherwood et al. 1989

Table 3-1. Levels of Significant Exposure to Hexachlorobenzene - Inhalation (continued)

Key to <sup>a</sup> figure	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL		Reference Chemical Form
					Less serious (mg/m3)	Serious (mg/m3)	
<b>CHRONIC EXPOSURE</b>							
<b>Systemic</b>							
3	Human	40 yr	Hepatic	0.000035			Herrero et al. 1999

<sup>a</sup>The number corresponds to entries in Figure 3-1.

d = day(s); hr = hours(s); LOAEL = lowest-observable-adverse-effect level; M = male; NOAEL = no-observable-adverse-effect level; wk = week(s); yr = year(s)

Figure 3-1. Levels of Significant Exposure to Hexachlorobenzene - Inhalation  
Acute ( $\leq 14$  days)

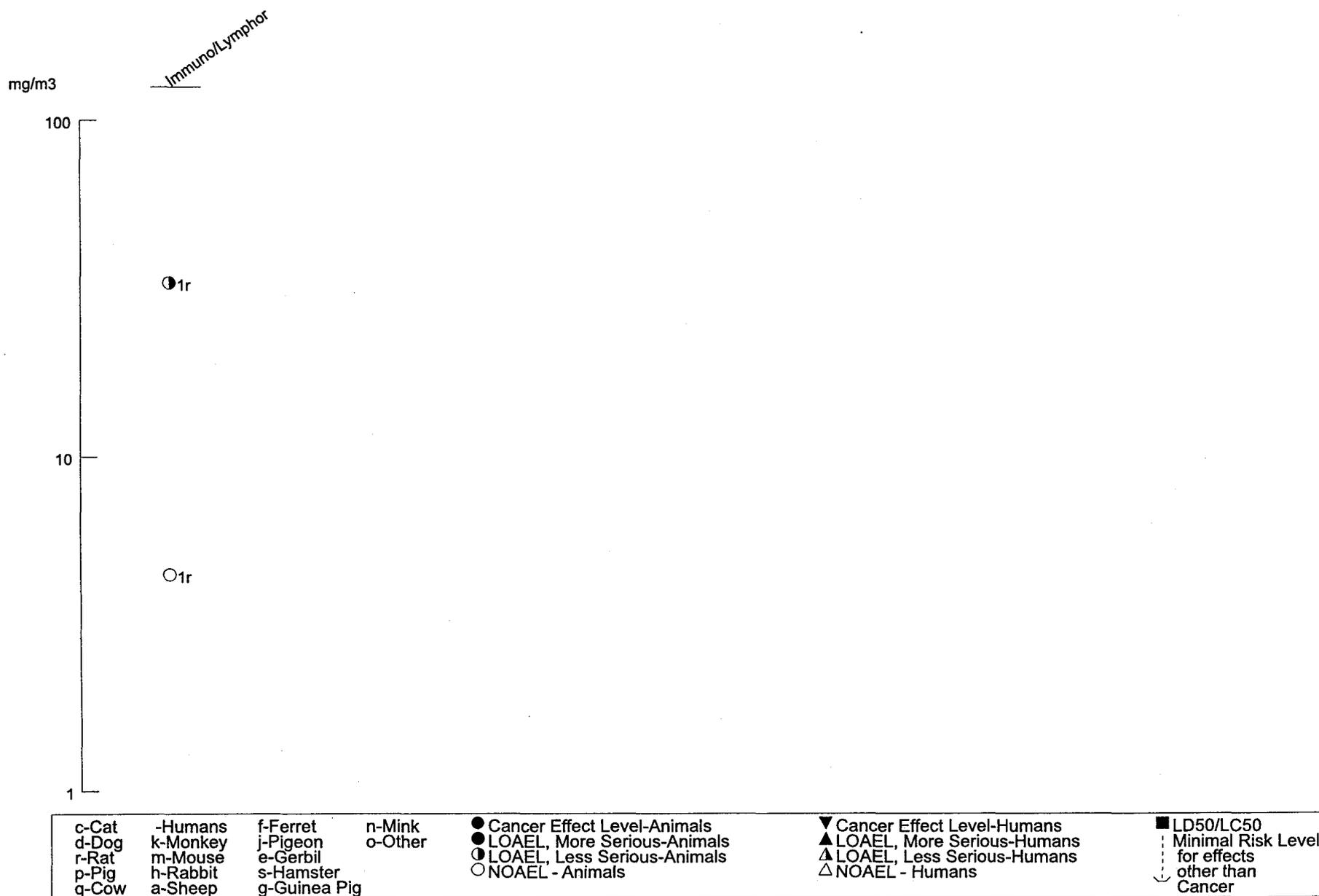


Figure 3-1. Levels of Significant Exposure to Hexachlorobenzene - Inhalation (Continued)  
Intermediate (15-364 days)

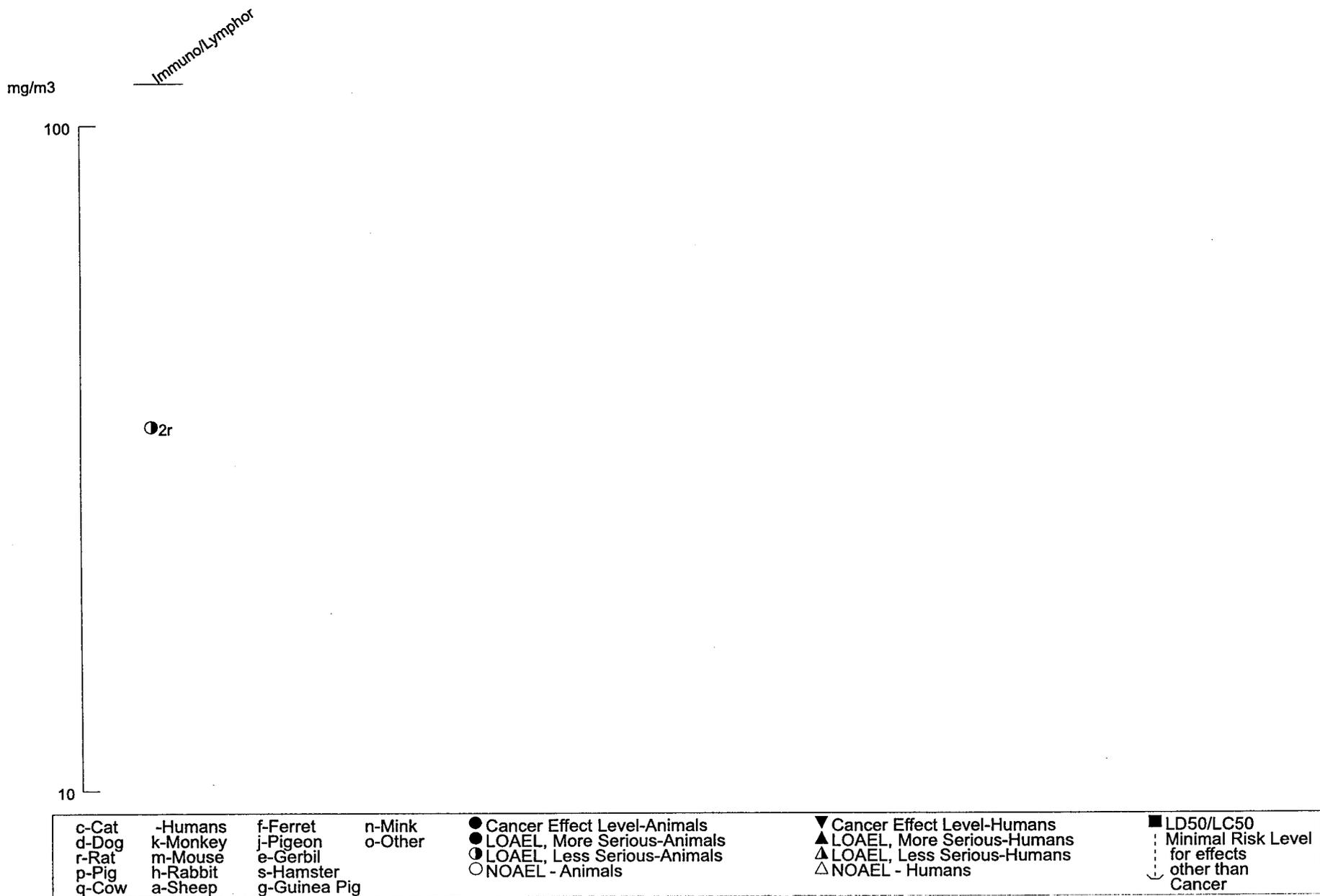


Figure 3-1. Levels of Significant Exposure to Hexachlorobenzene - Inhalation (Continued)

Chronic (≥365 days)



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as only 10 cases of elevated TSH were observed in each of the study populations. A larger survey found that the prevalences of goiter and hypothyroidism were similar in ever exposed workers (n=507) and nonexposed residents (n=1,293) (Sala et al. 1999b). No studies were located regarding endocrine effects in animals following inhalation exposure to hexachlorobenzene.

#### **3.2.1.3 Immunological and Lymphoreticular Effects**

Occupational studies indicate that inhaled hexachlorobenzene may cause physiological changes in immune parameters, but these effects are not clearly toxic. Queiroz et al. (1997, 1998a, 1998b) studied a group of Brazilian workers (n=51–66) employed for up to 25 years at a chemical plant whose primary waste product was hexachlorobenzene. Although it is not clear from the report, workers were presumably exposed to hexachlorobenzene by inhalation. Findings in blood samples of exposed workers compared to controls selected from a local blood bank were significant decreases in neutrophil chemotaxis, impaired neutrophil cytolytic activity (but not phagocytic activity) and significant increases in serum immunoglobulins (IgG and IgM, but not IgA). Blood hexachlorobenzene levels were elevated in exposed workers, but were not correlated with changes in immunological parameters. Serum immunoglobulins (IgG, IgA, IgM, and IgE, but not IgD) were also increased in Czechoslovakian workers with high blood hexachlorobenzene levels who had been exposed to hexachlorobenzene in the workplace air from 1983 to 1990, originally at 2.1–10.8 mg/m<sup>3</sup> and then at 0.012–0.022 mg/m<sup>3</sup> (Richter et al. 1994). Immunological parameters and serum organochlorine levels were measured in a group of 141 German medical patients presenting with variety of acute symptoms (mainly lack of concentration, exhaustion, and common cold) who had been occupationally exposed (as teachers, construction workers, and telecommunication technicians) for at least 6 months to multiple organochlorines (Daniel et al. 2001). A strong, statistically significant, association was detected between high blood levels of hexachlorobenzene and decreased levels of interferon- $\gamma$  blood (IFN- $\gamma$ ) levels. Moreover, patients with low overall organochlorine levels had elevated IFN- $\gamma$  levels. The authors note that IFN- $\gamma$  is important for increasing the secretion of immunoglobulins by plasma cells, and speculate that decreased IFN- $\gamma$  might increase susceptibility to infection. It is not clear whether hexachlorobenzene exposure is responsible for the observed effects, because significant cross-correlations were detected between hexachlorobenzene levels and several polycyclic biphenyl compounds.

The animal data provide weak support for an immunological effect of inhaled hexachlorobenzene. Observations in male rats exposed to 33–35 mg/m<sup>3</sup> of hexachlorobenzene aerosol for durations ranging from 4 hours to 4 weeks (4 days/week, 4 hours/day) included a slight decrease in pulmonary macrophage

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bactericidal activity to inhaled *Klebsiella pneumoniae*, a slight increase in phagocytic activity of alveolar (but not peritoneal) macrophages *in vitro*, and altered lymphocyte mitogenesis induced by T-cell (phytohemagglutinin [PHA]) and B-cell (*Salmonella typhimurium* lipopolysaccharide) mitogens in lung-associated and mesenteric lymph nodes *in vitro* (Sherwood et al. 1989). No effects were found at 4.4 mg/m<sup>3</sup> (1-day exposure only). The authors concluded that exposure to hexachlorobenzene at about 35 mg/m<sup>3</sup> resulted in slight changes to humoral and pulmonary cellular defenses. However, the reported changes were only marginally different from controls, the magnitude of the reported effects did not generally increase with exposure duration, and some of the results were contradictory (e.g., there was a significant increase in PHA-induced mitogenesis in lung-associated lymph nodes, but a significant decrease in PHA-induced mitogenesis in mesenteric lymph nodes, in rats exposed to hexachlorobenzene for 4 weeks). The NOAEL and LOAEL values from this experiment are recorded in Table 3-1 and plotted in Figure 3-1.

#### 3.2.1.4 Neurological Effects

No clear evidence of neurological effects following inhalation exposure to hexachlorobenzene is available. The prevalence of Parkinson's disease was not significantly increased in workers at an electrochemical factory near Flix, Spain (4/507) compared with other Flix residents (4/1,293) despite 5-fold higher blood hexachlorobenzene levels in the workers (Sala et al. 1999b). The small number of cases is a limitation of this study. A preliminary report (Sala et al. 1999a), based on 63 cases, detected a statistically significant association between prenatal hexachlorobenzene exposure and impaired development of locomotor skills in newborn babies in Flix, compared with those of nearby villages. A different study conducted in Oswego, New York was unable to correlate hexachlorobenzene levels in umbilical blood or breast milk with infant intelligence test results (Darvill et al. 2000). The apparent discrepancy between these studies may be explained by differences in exposure. No studies were located regarding neurological effects in animals following inhalation exposure to hexachlorobenzene.

#### 3.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals following inhalation exposure to hexachlorobenzene.

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**3.2.1.6 Developmental Effects**

Developmental effects (spontaneous abortions, low birth weight, and congenital malformations) occurred with a similar prevalence among females who ever worked at an electrochemical factory near Flix, Spain (n=46–60 for the different end points) and never exposed female residents (n=719–936), despite 5-fold higher blood hexachlorobenzene levels in the workers (Sala et al. 1999b). The small number of women factory workers is a limitation of this study. No studies were located regarding developmental effects in animals by inhalation exposure to hexachlorobenzene.

**3.2.1.7 Cancer**

In comparison to the surrounding Province of Tarragona, the incidences of thyroid cancer and soft-tissue sarcoma were significantly increased, and brain tumors marginally increased, for the years 1980–1989 in male residents of Flix, Spain, where a nearby organochlorine factory had produced high levels of hexachlorobenzene in the ambient air for decades (40 measurements in 1989–1992 averaged 35 ng/m<sup>3</sup>, and the researchers suspected concentrations had been higher in years past) (Grimalt et al. 1994). Tumor incidences were not elevated in female Flix residents, but exposures of the females (few of whom worked at the factory) may have been considerably lower than those of the males (many of whom, including all those with tumors, worked at the factory). The findings in males were based on very small numbers of observed cases (2–4 for the various tumor types), and were not duplicated in a companion analysis of cancer mortality reported in the same paper. Therefore, this study was not conclusive. Hepatocellular carcinoma was diagnosed in 1985 in a 65-year-old male who had been exposed to airborne hexachlorobenzene and, to a lesser extent, other organochlorine compounds (e.g., chlorinated benzenes, chlorophenols, dioxins, and dibenzofurans) at an aluminum smelter from 1967 to 1973 while using hexachloroethane as an aluminum degassing agent (Selden et al. 1989). This finding is suggestive, but does not provide rigorous evidence for an association between tumor development and inhalation exposure to hexachlorobenzene. No other data were located specifically associating cancer with exposure to hexachlorobenzene, but several studies have investigated an apparent association between porphyria and subsequent development of liver cancer in humans. These data are relevant because hexachlorobenzene is porphyrogenic in humans. However, factors such as cancer evolution times, liver pathology (hepatitis viral infection, fibrosis, or cirrhosis), and age were found to be better predictors of subsequent tumor development than porphyrin status in these studies (Axelson 1986; Keczkes and Barker 1976; Salata et al. 1985; Siersema et al. 1992; Topi et al. 1980; Waddington 1972).

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Animal data regarding the carcinogenicity of hexachlorobenzene via the inhalation route were not located, although there is evidence that hexachlorobenzene produces liver tumors in animals by the oral route (see Section 3.2.2.8).

#### 3.2.2 Oral Exposure

##### 3.2.2.1 Death

Evidence of human lethality following oral exposure to hexachlorobenzene is derived mainly from epidemiologic data from 1955 to 1959. An estimated 3,000–4,000 people ingested bread prepared from grain treated with fungicides composed of 10% hexachlorobenzene, at an estimated 2 kg/1,000 kg wheat. There was an extremely high rate of mortality in breast fed children (under 2 years of age) of mothers known to have ingested this bread. All children born to porphyric mothers during that epidemic died (Gocmen et al. 1989; Peters et al. 1982) and an estimated 1,000–2,000 infants died due to a condition known as *pembe yara* or "pink sore" because of the associated skin lesions (blistering and epidermolysis and annular erythema) (Cripps et al. 1984; Peters et al. 1982, 1987). Although a 10% rate of mortality in exposed adults has been reported, it is not clear how that figure relates to the expected mortality rates for comparable cohorts (Peters et al. 1982, 1987). No quantitation of exposure (dose and duration) was presented in any of these clinical reports. However, an estimated dose of 0.05–0.2 g/day (0.7–2.9 mg/kg/day for a 70-kg person) is considered to be reliable by the original investigators of the Turkey epidemic (Cam and Nigogosyan 1963). Analysis of human milk from exposed women and unexposed controls in this epidemic showed hexachlorobenzene concentrations of 0.51 and 0.07 ppm, respectively (Cripps et al. 1984; Gocmen et al. 1989; Peters et al. 1982, 1987). A report on an epidemiological study in New South Wales, Australia, which gave hexachlorobenzene concentrations ranging from trace amounts to 8.2 ppm in human body fat and #0.41 ppb in whole blood, found no adverse health effects or mortality associated with these levels of body burden (Brady and Siyali 1972; Siyali 1972).

The acute lethality of ingested hexachlorobenzene in animal studies is relatively low. LD<sub>50</sub> data are limited to a report from the Russian literature of single-dose oral LD<sub>50</sub> values of 3,500 mg/kg for rats, 4,000 mg/kg for mice, 2,600 mg/kg for rabbits, and 1,700 mg/kg for cats (Savitskii 1964, 1965). Although these LD<sub>50</sub> values were determined under unknown experimental conditions, they are consistent with the remainder of the database showing low acute lethality of hexachlorobenzene. One death was observed among 10 rats given a single dose of 600 mg/kg by gavage in corn oil (Lecavalier et al. 1994),

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but it is not clear from the report that the death was due to hexachlorobenzene. Lethal levels in animal studies are progressively lower as exposure duration is increased. Lethal levels ranged from 19 to 245 mg/kg/day in most (the exception is discussed below) intermediate-duration feeding studies (Cuomo et al. 1991; De Matteis et al. 1961; Den Besten et al. 1993; Den Tonkelaar et al. 1978; Kennedy and Wigfield 1990; Kimbrough and Linder 1974; Kuiper-Goodman et al. 1977; Ockner and Schmid 1961) and from 6 to 16 mg/kg/day in chronic oral studies (Cabral et al. 1977, 1979; Gralla et al. 1977a). Death in these studies was closely associated with occurrence of neurological symptoms (e.g., tremors, paresis, weakness, convulsions) and, in some cases, weight loss (Cabral et al. 1977; Cuomo et al. 1991; De Matteis et al. 1961; Den Besten et al. 1993; Den Tonkelaar et al. 1978; Gralla et al. 1977a; Ockner and Schmid 1961).

Aside from duration of exposure, other factors that appear to influence susceptibility to hexachlorobenzene-induced mortality include species, strain, sex, age, pregnancy status, diet, nutritional status (fasting versus normal diet), and dosing protocol (including the vehicle used and the method of exposure). A direct comparison of multiple species was performed by De Matteis et al. (1961), who treated rats, mice, guinea pigs, and rabbits with 5,000 ppm of hexachlorobenzene in the diet, providing estimated doses of 250, 650, 200, and 245 mg/kg/day, respectively. Guinea pigs, with the lowest estimated daily dose, and mice, with the highest dose, were the most severely affected of the species tested, with severe neurological effects and death occurring as soon as 8–10 days after the start of exposure. Rats and rabbits also developed neurological symptoms and died, but only after 8 weeks of exposure. The severe effects in guinea pigs despite the low dose suggest that this species may be especially sensitive to hexachlorobenzene; however, additional supporting data are lacking. Although death was reported in both male and female animals in various studies, studies that included both sexes generally reported a higher incidence of mortality in females than in males treated with the same doses (Gralla et al. 1977a; Kimbrough and Linder 1974; Kuiper-Goodman et al. 1977). Pregnant females in particular seem to be especially susceptible to hexachlorobenzene-induced mortality. Two pregnant rats fed hexachlorobenzene during gestation were much more severely affected than the nonpregnant rats in the De Matteis et al. (1961) study, with one dying before giving birth and the other dying 4 weeks after giving birth. Grant et al. (1977) observed death of pregnant dams at doses as low as 8 mg/kg/day in an intermediate-duration reproduction study, which is considerably lower than the lethal dose range to nonpregnant animals in other intermediate-duration studies (19–245 mg/kg/day).

Toxicity of hexachlorobenzene is enhanced by use of an oil vehicle in animal studies. This was demonstrated by Kennedy and Wigfield (1990), who fed female Wistar rats a diet to which hexachloro-

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benzene was added either in corn oil or as crystalline chemical. At 1,000 ppm (50 mg/kg/day), 2 deaths occurred within 23 days of the start of exposure in the corn oil group and the remaining 27 animals were removed from the study 2 days later due to obvious ill health. No deaths occurred in the crystalline chemical group (n=27) fed the same dose for 56 days. The increased toxicity of hexachlorobenzene fed with corn oil appeared to be related to increased accumulation of the chemical in the body (measured in liver, kidney, and spleen) under these conditions.

Reliable LOAEL values for mortality in each species and duration category are presented in Table 3-2 and plotted in Figure 3-2.

#### 3.2.2.2 Systemic Effects

The available data in humans and laboratory animals indicate that the liver, and specifically, the heme biosynthesis pathway, is the major systemic target of hexachlorobenzene toxicity. Human data have also shown effects on other systemic targets, including the skin, bone, and thyroid. These effects were less common than inhibition of heme biosynthesis in exposed people. No information was located regarding respiratory, cardiovascular, gastrointestinal, hematological, renal, ocular, or body weight effects in humans following oral exposure to hexachlorobenzene. However, animal data are available for these systemic effects and suggest that the blood, lungs, and kidneys may be additional systemic targets of hexachlorobenzene.

The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are presented in Table 3-2 and plotted in Figure 3-2.

**Respiratory Effects.** No studies were located regarding respiratory effects of oral hexachlorobenzene exposure in humans.

Animal studies have shown that ingested hexachlorobenzene can produce pathological effects in the lungs. The most widely reported lesions were hypertrophy and proliferation of the lining endothelial cells of the pulmonary venules and intra-alveolar accumulation of foamy-looking macrophages. The foamy appearance of macrophages is a result of increased lipid content (Goldstein et al. 1978). These

Table 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	LOAEL		Reference Chemical Form
				NOAEL (mg/kg/day)	Less serious (mg/kg/day)	
<b>ACUTE EXPOSURE</b>						
<b>Death</b>						
1	Mouse (NS)	10 d (F)				650 F (death) De Matteis et al. 1961
2	Gn Pig (NS)	10 d (F)				200 F (death) De Matteis et al. 1961
<b>Systemic</b>						
3	Rat (Wistar)	1, 2, 3, or 4 wks 5 d/wk (GW)	Hepatic		1000 F (increased porphyria, altered hepatic enzyme levels)	Billi de Catabbi et al. 2000a
4	Rat (Wistar)	1 or 7 wks, # of doses per wk unknown (GW)	Hepatic		1000 F (increased urinary porphyrin excretion)	Billi de Catabbi et al. 2000a
5	Rat (Sprague- Dawley)	2 wk 5 d/wk 1 x/d (GO)	Renal		100 M (incr kidney wt, degenerative and regenerative foci in tubules, accumulation of protein droplets in tubular cells)	Bouthillier et al. 1991
6	Rat (Sprague- Dawley)	5 d 1 x/d (GO)	Endocr		50 F (decr serum thyroxine)	Foster et al. 1993
7	Rat (CD)	1 wk (F)	Hepatic	5 F	16 F (incr hepatic ALA-S activity)	Goldstein et al. 1978
			Bd Wt	159 F		

Table 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less serious (mg/kg/day)	Serious (mg/kg/day)	
8	Rat (Wistar)	1 d (F)	Hepatic		50 F (incr highly carboxylated porphyrins in liver)		Kennedy and Wigfield 1990
9	Rat (Wistar)	Gd 6-21, 6-16, 6-9 or 10-13 1x/d (GO,GW)	Bd Wt	40 F		80 F (loss of body weight by pregnant rats)	Khera 1974a
10	Rat (Sprague- Dawley)	2x (GW)	Hepatic	700 F	1400 F (incr ornithine decarboxylase in the liver)		Kitchin and Brown 1989
11	Rat (Wistar)	7 d 1 x/d (GW)	Hepatic  Endocr	250 F	500 F (decr hepatic URO-D activity)  250 F (decr serum T4 levels)		Kleiman de Pisarev et al. 1990
12	Rat (Sprague- Dawley)	2-16 d 1 x/d (GO)	Hepatic		25 F (incr urinary and hepatic porphyrins)		Krishnan et al. 1991
13	Rat (Sprague- Dawley)	6 d 1 x/d (GO)	Hepatic  Bd Wt		10 M (incr liver wt)		Mehendale et al. 1975
14	Rat (Brown- Norway)	7 or 21 d daily (GW)	Hepatic		45 F (increased liver weight)		Michielsen et al. 2001
15	Rat (NS)	5 d 1 x/d (GO)	Bd Wt	221 M			Simon et al. 1979

Table 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/duration/frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
16	Rat (Wistar)	2 wk 3 d/wk 1 x/d (GW)	Endocr	484 M	740 M (decr serum total and free T4)		van Raaij et al. 1993a
			Bd Wt	997 M			
17	Mouse (CD-1)	Gd 7-16 (GO)	Hepatic		100 F (incr liver wt in pregnant dams)		Courtney et al. 1976
			Bd Wt	100 F			
18	Gn Pig (NS)	10 d (F)	Hepatic		200 F (fatty change)		De Matteis et al. 1961
			Renal				
<b>Neurological</b>							
19	Rat (Wistar)	Gd 6-21, 6-16, 6-9 or 10-13 1x/d (GO,GW)		40 F		80 F (hyperesthesia, tremors, and convulsions in pregnant rats)	Khera 1974a
20	Gn Pig (NS)	10 d (F)				200 F (marked weakness, hyperexcitability, tremors, convulsions)	De Matteis et al. 1961
<b>Reproductive</b>							
21	Rat (Sprague-Dawley)	5 d 1 x/d (GO)			50 F (incr serum progesterone)		Foster et al. 1993
22	Rat (NS)	5 d 1 x/d (GO)		70 M	221 M (decr male impregnation of females)		Simon et al. 1979

Table 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
<b>Developmental</b>							
23	Rat (Sprague- Dawley)	4 d 1x/d (GO)			2.5 <sup>b</sup>	(hyperactivity in young pups)	Goldey and Taylor 1992
24	Rat (Wistar)	Gd 6-21, 6-16, 6-9 or 10-13 1x/d (GO,GW)			40	(incr skeletal variations)	Khera 1974a
25	Mouse (CD-1)	Gd 7-16 (GO)				100 (incr abnormal fetuses per litter)	Courtney et al. 1976

Table 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
<b>INTERMEDIATE EXPOSURE</b>							
<b>Death</b>							
26	Rat (Wistar)	80 d (F)				100 F (60/90 died)	Cuomo et al. 1991
27	Rat (Wistar)	13 wk (F)				19 F (4/9 died)	Den Besten et al. 1993
28	Rat (Sprague- Dawley)	4 gen (F)				8 F (1/20 dams died)	Grant et al. 1977
29	Rat (Wistar)	56 d (F)				50 F (2/29 died)	Kennedy and Wigfield 1990
30	Rat (Sherman)	4 mo (F)				25 (2/10 males and 14/20 females died)	Kimbrough and Linder 1974
31	Rat (Wistar)	15 wk 3-4 d/wk 1 x/d (GO)				50 F (5/19 died)	Koss et al. 1978
32	Rat (COBS)	15 wk (F)				32 F (incr mortality in females)	Kuiper-Goodman et al. 1977
33	Rat (Sprague- Dawley)	56 d (F)				100 M (13/33 died within 1 month)	Ockner and Schmid 1961
34	Rabbit (NS)	12 wk (F)				245 F (4/4 died)	De Matteis et al. 1961

Table 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (continued)

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
35	Pig (SPF)	90 d (F)				50 M (5/5 died)	Den Tonkelaar et al. 1978
<b>Systemic</b>							
36	Monkey (Cynomolgus)	90 d 1 x/d (C)	Hemato	10 F			Foster et al. 1995a
			Bd Wt	10 F			
37	Monkey (Rhesus)	60 d 1x/d (GW)	Resp	128 F			Iatropoulos et al. 1976
			Cardio	128 F			
			Gastro	128 F			
			Musc/skel	128 F			
			Hepatic		8 F (hepatocellular hypertrophy, cloudy swelling)		
			Renal		8 F (vacuolization of proximal renal tubules)		
			Endocr	128 F			
			Ocular	128 F			
38	Monkey (Cynomolgus)	90 d 1x/d (C)	Hepatic	0.1 F	1 F (hepatocellular vacuolation, intrahepatic cholestasis)		Jarrell et al. 1993
			Endocr	1 F	10 F (incr adrenal weight)		
			Bd Wt	10 F			
39	Monkey (Rhesus)	60 d 1 x/d (GW)	Hemato	128 F			Knauf and Hobson 1979
			Hepatic	64 F	128 F (incr serum AST)		
			Renal	64 F	128 F (incr blood urea nitrogen)		
			Bd Wt		8 F (unspecified weight loss)		

Table 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (continued)

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
40	Rat (Fischer 344)	5 wk 5 d/wk 1 x/day  (GO)	Hepatic	0.1	1 M (incr liver wt)		Andrews et al. 1988
			Renal	25 M			
			Endocr	10 M (incr serum 1,25-dihydroxy- vitamin D3 and parathyroid hormone)			
41	Rat (Fischer 344)	15 wk 5 d/wk 1 x/d  (GO)	Musc/skel	0.1 M	1 M (incr femur density)		Andrews et al. 1989
			Hepatic	1 M	10 M (incr liver wt)		
			Renal	1 M	10 M (incr kidney wt, incr urinary LDH and alkaline phosphatase)		
			Endocr	0.1 M	1 M (incr serum 1,25-dihydroxy- vitamin D3)		
			Bd Wt	25 M			
42	Rat (Fischer 344)	15 wk 5 d/wk 1 x/d  (GO)	Musc/skel	0.1 M	1 M (incr femur density and cortical area)		Andrews et al. 1990
			Renal	0.1 M	1 M (incr urinary LDH)		
			Endocr	1 M	10 M (incr serum parathyroid hormone)		
43	Rat (Wistar)	1, 2, 3, or 4 wks 5 d/wk  (GW)	Hepatic		1000 F (increased porphyria, altered hepatic enzyme levels)		Billie de Catabbi et al. 2000a
44	Rat (Wistar)	1 or 7 wks # of doses per wk unknown  (GW)	Hepatic		1000 F (increased urinary porphyrin excretion)		Billie de Catabbi et al. 2000a

Table 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (continued)

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	LOAEL		Reference Chemical Form
				NOAEL (mg/kg)	Less serious (mg/kg)	
45	Rat (Wistar)	1x/d 5 d/wk 7, 14, 21, or 28 d  (GW)	Hepatic		50 F (hepatic porphyria changes in hepatic sphingolipid levels)	Billie de Catabbi et al. 2000b
46	Rat (Chbb THOM)	1x/d 5 d/wk 7, 14, 21, or 28 d  (GW)	Hepatic		50 F (hepatic porphyria changes in hepatic sphingolipid levels)	Billie de Catabbi et al. 2000b
47	Rat (Sprague- Dawley)	7 wk 5 d/wk 1 x/d  (GO)	Renal		50 M (incr kidney wt, glucosuria, proteinuria, degenerative and regenerative foci in tubules, accumulation of protein droplets in tubular cells)	Bouthillier et al. 1991
48	Rat (Wistar)	80 d  (F)	Hepatic		100 F (incr liver wt, decr hepatic URO-D, incr hepatic porphyrins, incr lipid peroxidation)	Cantoni et al. 1990
49	Rat Chbb THOM)	1x/d 5 d/wk 1, 2, 3, 4, or 8 wks  (GW)	Hepatic		1000 F (Hepatic porphyria)	Cochon et al. 2001

Table 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	LOAEL		Reference Chemical Form
				NOAEL (mg/kg)	Less serious (mg/kg)	
50	Rat (Wistar)	1x/d 5 d/wk 1, 2, 3, 4, or 8 wks (GW)	Hepatic		1000 F (Hepatic porphyria)	Cochon et al. 2001
51	Rat (Wistar)	80 d (F)	Hepatic		100 F (porphyria, incr liver wt, fatty degeneration)	Cuomo et al. 1991
			Dermal		100 F (photosensitive skin lesions)	
			Bd Wt	100 F		
52	Rat (Wistar)	13 wk (F)	Hepatic		9.5 F (incr liver wt, incr urinary and liver porphyrins)	Den Besten et al. 1993
			Renal	9.5 F	19 F (incr kidney wt, basophilic renal tubules, protein casts)	
			Endocr	9.5 F	19 F (adrenal: incr wt, cortical hypertrophy and hyperplasia thyroid: decr serum T4 and T3)	
			Dermal Bd Wt	9.5 F	9.5 F (skin lesions) 19 F (severe wt loss in 4/9)	
53	Rat (Wistar)	107 d (F)	Hepatic		150 F (marked decr in hepatic URO-D activity, massive incr in hepatic porphyrin content)	Elder and Urquhart 1986
54	Rat (Wistar)	4 wk 5 d/wk 1 x/d (GW)	Renal		1000 F (porphyria and lipid peroxidation in cortex)	Fernandez-Tome et al. 2000

Table 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
55	Rat (Sprague- Dawley)	30 d 1 x/d (GO)	Endocr		1 F (decr serum corticosterone)		Foster et al. 1995b
			Bd Wt	100 F			
56	Rat (CD)	4 mo (F)	Resp	4 F	12 F (hypertrophy and proliferation of endothelial cells, incr macrophages)		Goldstein et al. 1978
			Cardio	36 F			
			Hepatic	4 F	12 F (incr urinary and hepatic porphyrins, enlarged hepatocytes)		
			Endocr	36 F			
			Dermal	12 F	36 F (small sores)		
57	Rat (Fischer- 344)	daily 5 wks (GO)	Hepatic		28 M (liver enlargement, porphyria, increased enzyme expression, increased protooncogene expression)		Gustafson et al. 2000
58	Rat (Wistar)	56 d (F)	Hepatic		5 F (incr highly carboxylated porphyrins in liver)		Kennedy and Wigfield 1990
			Renal		5 F (incr highly carboxylated porphyrins in kidney)		
			Bd Wt	5 F		50 F (large decr body wt gain)	

Table 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (continued)

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form		
					Less serious (mg/kg/day)	Serious (mg/kg/day)			
59	Rat (Sherman)	4 mo (F)	Resp		5	(incr macrophages, focal areas of fibrosis)	25 F (extensive intra-alveolar hemorrhage, edema in females)	Kimbrough and Linder 1974	
			Cardio	5		25	(fibrosis, degeneration)		
			Hemato		5	(decr hemoglobin and hematocrit)			
			Hepatic		5	(incr liver wt, enlarged hepatocytes)	25		(necrosis, fibrosis)
			Renal	5	25	(incr kidney wt)			
			Endocr		5	(hyperplasia of the adrenal cortex)			
			Dermal	5	25	(skin eruptions)			
			Bd Wt	5	25	(decr body wt gain in males)			
60	Rat (Sprague-Dawley)	1 gen (F)	Resp		3 F	(intraalveolar foamy histiocytes, hypertrophy and proliferation of endothelial cells of pulmonary venules in dams)	Kitchin et al. 1982		
			Bd Wt	7 F					
61	Rat (Wistar)	4 wk 1 x/d (GW)	Endocr		1000 F	(decr serum T4, incr T4 metabolism, incr serum TSH, incr thyroid iodine uptake)	Kleiman de Pisarev et al. 1989		
			Bd Wt	1000 F					
62	Rat (Wistar)	30 d 1 x/d (GW)	Endocr	125 F	500 F	(decr serum T4 levels)	Kleiman de Pisarev et al. 1989		

Table 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
63	Rat (Wistar)	8 wk 7 d/wk 1 x/d  (GW)	Hepatic		1000 F (incr liver wt, decr URO-D activity, incr hepatic and urinary porphyrins, incr dehalogenation of T4)		Kleiman de Pisarev et al. 1990
			Endocr		1000 F (decr serum T4, incr serum TSH)		
64	Rat (Wistar)	4 wk 7 d/wk 1 x/d  (GW)	Hepatic		1000 F (incr liver wt)		Kleiman de Pisarev et al. 1995
			Endocr		1000 F (decr serum T4, incr serum TSH)		
			Bd Wt	1000 F			
65	Rat (Wistar)	15 wk 3-4 d/wk 1 x/d  (GO)	Hepatic		50 F (incr liver wt, massive incr liver and urine porphyrins)		Koss et al. 1978
			Renal		50 F (incr kidney wt)		
			Endocr		50 F (incr adrenal wt)		
			Dermal		50 F (rough appearance of fur, hair loss, skin lesions)		
			Bd Wt	50 F			
66	Rat (Sprague- Dawley)	3-6 wk 5 d/wk 1x/d  (GO)	Hepatic		50 (incr urinary and hepatic porphyrins)		Krishnan et al. 1991
67	Rat (Sprague- Dawley)	6 wk 5 d/wk 1 x/d  (GO)	Hepatic		50 F (incr hepatic and urinary porphyrins)		Krishnan et al. 1992

Table 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (continued)

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
68	Rat (COBS)	15 wk (F)	Hemato	8	32 F (decr red blood cell count, hematocrit, and hemoglobin; leukocytosis in females)		Kuiper-Goodman et al. 1977
			Musc/skel	32			
			Hepatic	0.5	2 (basophilic clumping in hepatocytes)		
			Renal	8	32 (incr kidney wt)		
			Dermal	8	32 (alopecia)		
			Bd Wt	8	32 M (13% decr in terminal body wt in males)		
69	Rat (Wistar)	30 d (F)	Resp		22 F (cuboidal venule endothelial cells, perivascular infiltrate, accumulation of alveolar macrophages)		Michielsen et al. 1997
			Hepatic		22 F (incr liver wt, hepatocyte hypertrophy with cytoplasmic inclusions)		
			Renal	45 F			
			Dermal		22 F (gross skin lesions, epidermal hyperplasia, inflammatory infiltrate in the dermis)		
			Bd Wt	45 F			

Table 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (continued)

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
70	Rat (Lewis)	29 d (F)	Resp		8 F (cuboidal venule endothelial cells, perivascular infiltrate, accumulation of alveolar macrophages)		Michielsen et al. 1997
			Hepatic		8 F (incr liver wt, hepatocyte hypertrophy with cytoplasmic inclusions)		
			Renal	22 F			
			Dermal		8 F (gross skin lesions, epidermal hyperplasia, inflammatory infiltrate in the dermis)		
			Bd Wt	22 F			
71	Rat (Brown Norway)	28 d (F)	Resp		8 F (cuboidal venule endothelial cells, perivascular infiltrate, accumulation of alveolar macrophages)		Michielsen et al. 1997
			Hepatic		8 F (incr liver wt, hepatocyte hypertrophy with cytoplasmic inclusions)		
			Renal	22 F			
			Dermal		8 F (gross skin lesions, epidermal hyperplasia, inflammatory infiltrate in the dermis)		
			Bd Wt	22 F		45 F (sudden weight loss)	

Table 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (continued)

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
72	Rat (Brown-Norway)	daily 4 wks (F)	Hepatic		67 F (increased liver weight)		Michielsen et al. 2000
			Resp		67 F		
			Dermal		67 F (dermal lesions- hyperplasia, deep venules with activated endothelium, inflammation)		
73	Rat (Brown-Norway)	7 or 21 d daily (GW)	Hepatic		45 F (increased liver weight)		Michielsen et al. 2001
			Dermal		45 F (lesions with inflammatory mg/kg response)		
			Resp		45 F (airway mg/kg hyperresponsiveness, granuloma (non-neoplastic lesions) formation)		
74	Rat (Brown-Norway)	7 or 21 d daily (GW)	Hemato		45 F (increased total IgE)		Michielsen et al. 2001
			Dermal		45 F (lesions, inflammatory mg/kg cellular immune response)		
			Resp		45 F (airway mg/kg hyperresponsiveness, granuloma (non-neoplastic lesions) formation )		
75	Rat (Wistar)	60 d (F)	Hepatic		430 M (incr serum ALT, bilirubin, and glutamate dehydrogenase)		Nikolaev et al. 1986

Table 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
76	Rat (Sprague- Dawley)	56 d (F)	Hemato	100 M			Ockner and Schmid 1961
			Musc/skel		100 M (porphyrin accumulation in cortex of long bones)		
			Hepatic		100 M (porphyria, hepatomegaly, hepatocellular degeneration)		
77	Rat (Wistar)	3 wk (F)	Hepatic		25 M (incr liver wt)		Schielen et al. 1993
			Dermal		25 M (transient lesions on face and ears)		
			Bd Wt	50 M			
78	Rat (Wistar)	3 wk (F)	Dermal		50 (skin lesions)		Schielen et al. 1995b
			Bd Wt	50			
79	Rat (Agus)	112 d (F)	Hepatic		5 F (incr hepatic porphyrin content, decr hepatic URO-D activity, incr hepatic ALA-S activity)		Smith et al. 1979
80	Rat (Porton- Wistar)	112 d (F)	Hepatic	5 F			Smith et al. 1979

Table 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
81	Rat (Fischer- 344)	15 wk (F)	Hepatic		10	(incr liver wt, hepatocellular hypertrophy, incr hepatic porphyrin levels in females)	Smith et al. 1985
			Renal		10 F	(incr renal porphyrin levels in females)	
82	Rat (Wistar)	60 d 1 x/d (GW)	Hepatic		1000 F	(decr URO-D activity in liver)	Sopena de Kracoff et al. 1994
			Endocr		1000 F	(decr serum T4, incr serum TSH)	
83	Rat (Wistar)	6 wk (F)	Hepatic	8 M	22 M	(incr liver wt)	Van Loveren et al. 1990
84	Rat (Wistar)	4 wk 3 d/wk 1 x/d (GW)	Hepatic		1000 M	(incr liver wt)	van Raaij et al. 1993b
			Endocr		1000 M	(decr serum T4 levels)	
85	Rat (Wistar)	3 wk (F)	Hemato		25 M	(incr extramedullary hematopoiesis in spleen; neutrophilia)	Vos et al. 1979b
			Hepatic		25 M	(incr liver wt, liver cell hypertrophy and cytoplasmic hyalinization)	
			Renal	100 M			
			Endocr	100 M			
			Bd Wt	100 M			

Table 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/duration/frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
86	Rat (BD VI)	5 wk 7 d/wk 1 x/d (GW)	Hepatic		1000	(decr URO-D activity in males and females; incr hepatic and urinary porphyrins in females)	Wainstok de Calmanovici et al. 1991
87	Mouse (Balb/c)	6 wk (F)	Resp  Hepatic	22 M		22 M (incr liver wt, hepatocellular hypertrophy)	Loose et al. 1977
88	Mouse (C57BL/10ScSn)	7 wk (F)	Hepatic			26 M (incr hepatic porphyrin levels)	Vincent et al. 1989
89	Dog (Beagle)	21 d 1 or 2 x/d (C)	Resp  Cardio Hemato Hepatic  Renal Endocr	100 F  100 F 100 F  100 F 100 F		50 F (fatty changes in liver, swollen hepatocytes and hepatomegaly)	Sundlof et al. 1981

Table 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less serious (mg/kg/day)	Serious (mg/kg/day)	
90	Rabbit (NS)	12 wk (F)	Hemato	245 F			De Matteis et al. 1961
			Musc/skel			245 F (necrosis, degeneration, and focal calcification in muscle, incr porphyrins in bone)	
			Hepatic			245 F (incr urinary and hepatic porphyrins, fatty change, necrosis)	
			Bd Wt			245 F (weight loss)	
91	Pig (SPF)	90 d (F)	Hemato	50 M			Den Tonkelaar et al. 1978
			Hepatic	0.05 M	0.5 M (hepatocellular hypertrophy)		
			Renal	0.5 M	5 M (incr kidney wt)	50 M (degeneration of proximal tubules and loop of Henle)	
			Endocr Bd Wt	0.5 M 5 M	5 M (incr thyroid wt)	50 M (depressed growth)	
<b>Immunological/Lymphoreticular</b>							
92	Monkey (Rhesus)	60 d (GW)			8 F (thymic cortical atrophy)		Iatropoulos et al. 1976
93	Rat (Wistar)	56 d (F)		5 F	50 F (incr spleen weight, incr highly carboxylated porphyrins in spleen)		Kennedy and Wigfield 1990
94	Rat (Wistar)	15 wk 3-4 d/wk 1 x/d (GO)			50 F (incr spleen wt)		Koss et al. 1978

Table 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	LOAEL		Reference Chemical Form
				NOAEL (mg/kg/day)	Less serious (mg/kg/day)	
95	Rat (COBS)	15 wk (F)		8	32 (incr lymphocyte count, incr spleen wt, congestive splenomegaly in females)	Kuiper-Goodman et al. 1977
96	Rat (Wistar)	30 d (F)			22 F (incr spleen wt, "high endothelial" venules in popliteal lymph node, incr serum IgM)	Michielsen et al. 1997
97	Rat (Lewis)	29 d (F)			8 F ("high endothelial" venules in popliteal lymph node)	Michielsen et al. 1997
98	Rat (Brown Norway)	28 d (F)			8 F (incr spleen wt, "high endothelial" venules in popliteal lymph node; incr serum IgM autoantibodies)	Michielsen et al. 1997
99	Rat (Brown- Norway)	daily 4 wks (F)			67 F (increased spleen weight)	Michielsen et al. 2000
100	Rat (Brown- Norway)	7 or 21 d daily (GW)			45 F (Increased spleen weight)	Michielsen et al. 2001
101	Rat (Wistar)	3 wk (F)			25 M (incr IgM autoantibodies)	Schielen et al. 1993
102	Rat (Wistar)	13 wk (F)			8 F (incr spleen wt, incr total serum IgM, incr serum IgM autoantibodies)	Schielen et al. 1995a

Table 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
103	Rat (Wistar)	3 wk (F)			50	(incr spleen and lymph node wt, altered size distribution of splenocytes, selective activation of splenic B-1 cells)	Schielen et al. 1995b
104	Rat (Wistar)	6 wk (F)			8 M	(decr NK cell activity in lung)	Van Loveren et al. 1990
105	Rat (Wistar)	3 wk (F)			25 M	(incr wt and proliferation of high-endothelial venules in lymph nodes, enlarged white pulp [marginal zones and follicles] in spleen, incr neutrophil count)	Vos et al. 1979b
106	Mouse	6 wk (F)			22	(incr susceptibility to hepatitis infection)	Carthew et al. 1990
107	Mouse (Balb/c)	6 wk (F)			22 M	(immunosuppression, decr antibody production)	Loose et al. 1977
108	Mouse (Balb/c)	6 wk (F)			22 M	(incr susceptibility to bacterial endotoxin and protozoan infection)	Loose et al. 1978
109	Mouse (Balb/c)	18 wk (F)		22 M			Loose et al. 1981

Table 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (continued)

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	LOAEL		Reference Chemical Form
				NOAEL (mg/kg/day)	Less serious (mg/kg/day)	
110	Mouse	18 wk (F)			0.6 M (incr susceptibility to tumor challenge <i>in vivo</i> , decr killing of tumor cells <i>in vitro</i> )	Loose et al. 1981
111	Mouse (C57BL/6)	40 wk (F)			22 M (decr graft-host activity)	Silkworth and Loose 1981
112	Pig (SPF)	90 d (F)		5 M	50 M (atrophy of lymph nodes)	Den Tonkelaar et al. 1978
<b>Neurological</b>						
113	Monkey (Rhesus)	60 d 1 x/d (GW)		32 F		64 F (severe tremors, muscular weakness) Knauf and Hobson 1979
114	Rat (Wistar)	1x/d 5 d/wk 1, 2, 3, 4, or 8 wks (GW)			1000 F (altered phospholipid levels in brain)	Cochon et al. 2001
115	Rat (Chbb THOM)	1x/d 5 d/wk 1, 2, 3, 4, or 8 wks (GW)			1000 F (altered phospholipid levels in brain)	Cochon et al. 2001
116	Rat (CD)	4 mo (F)		12 F		36 F (excessive irritability) Goldstein et al. 1978
117	Rat (Sprague-Dawley)	4 gen (F)		4		8 F (convulsions in dams) Grant et al. 1977

Table 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less serious (mg/kg/day)	Serious (mg/kg/day)	
118	Rat (Wistar)	56 d (F)		5 F		50 F (lethargy, tremor, convulsions)	Kennedy and Wigfield 1990
119	Rat (Sherman)	4 mo (F)		5		25 (tremor, hyperexcitability)	Kimbrough and Linder 1974
120	Rat (Wistar)	15 wk 3-4 d/wk 1 x/d (GO)				50 F (muscle fasciculations, tremors)	Koss et al. 1978
121	Rat (COBS)	15 wk (F)		8		32 (tremors, ataxia, hind limb paralysis)	Kuiper-Goodman et al. 1977
122	Rat (Wistar)	60 d (F)				430 M (clonic convulsions, tremors, hyperexcitability)	Nikolaev et al. 1986
123	Rat (Sprague- Dawley)	56 d (F)				100 M (ataxia, tremor, paralysis)	Ockner and Schmid 1961
124	Rat (Sprague- Dawley)	20 wk (F)			40 M (decr nerve conduction velocity)		Sufit et al. 1986
125	Dog (Beagle)	21 d 1 or 2 x/d (C)				50 F (dysrhythmic electro- encephalogram)	Sundlof et al. 1981
126	Rabbit (NS)	12 wk (F)				245 F (tremor, paresis)	De Matteis et al. 1961
127	Pig (SPF)	90 d (F)		5 M		50 M (tremors, unsteady gait)	Den Tonkelaar et al. 1978

Table 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (continued)

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	LOAEL		Reference Chemical Form
				NOAEL (mg/kg/day)	Less serious (mg/kg/day)	
<b>Reproductive</b>						
128	Monkey (Cynomolgus)	90 d 1 x/d (C)			0.1 F (cellular degeneration of ovarian surface epithelium)	Babineau et al. 1991
129	Monkey (Cynomolgus)	90 d 1 x/d (C)			0.01 <sup>c</sup> F (mitochondrial degeneration in developing ovarian follicles)	Bourque et al. 1995
130	Monkey (Cynomolgus)	13 wk 7 d/wk 1 x/d (C)		0.1 F	1 F (decr serum progesterone levels during the luteal phase of menstruation)	Foster et al. 1992a
131	Monkey (Cynomolgus)	90 d 1 x/d (C)		1 F	10 F (incr length of menstrual cycle, decr ovulatory levels of estradiol)	Foster et al. 1995a
132	Monkey (Rhesus)	60 d (GW)			8 F (degeneration of the germinal epithelium, reduced number of primary follicles, and multiple follicular cysts in the ovaries)	Iatropoulos et al. 1976
133	Monkey (Cynomolgus)	90 d 1x/d (C)			0.1 F (degenerative lesions in oocytes)	Jarrell et al. 1993
134	Monkey (Rhesus)	24 d 1 x/d (GW)				4 F (blocked ovulation) Muller et al. 1978

Table 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
135	Monkey (Cyno- molgus)	12 wk 7 d/wk 1 x/d (C)			0.1 F (altered morphology of ovary surface epithelium cells)	1 F (necrosis of ovary surface epithelium cells, denuding of ovary)	Sims et al. 1991
136	Rat (Wistar)	30 d 1 x/d (GW)			1000 F (incr estrus duration, altered hormone levels, reduced ovulation, degenerative ovarian lesions)		Alvarez et al. 2000
137	Rat (Sprague- Dawley)	21 d 1 x/d (GO)			1 F (incr serum progesterone levels)		Foster et al. 1992b
138	Rat (Sprague- Dawley)	4 gen (F)		8		16 (decr fertility and litter size)	Grant et al. 1977
139	Rat (Sprague- Dawley)	daily 28 d pre-mating - weaning (GO)	Bd Wt	0.008 F			Nakashima et al. 1997
140	Pig (SPF)	90 d (F)		5 M	50 M (retarded development of the testes)		Den Tonkelaar et al. 1978
<b>Developmental</b>							
141	Monkey (Rhesus)	22-60 d 1 x/d (GW)				64 (2/3 infants died with lethargy, ataxia, and listlessness)	Iatropoulos et al. 1978

Table 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (continued)

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
142	Rat (Sprague- Dawley)	4 gen (F)		2	4 (decr pup weight gain)	8 (decr pup viability)	Grant et al. 1977
143	Rat (Sprague- Dawley)	1 gen (F)			3 (decr pup weight gain)	4 (decreased survival)	Kitchin et al. 1982
144	Rat (Wistar)	2 gen (F)		0.6 M	1.3 M (reduced efficiency of pups in operant behavior task)		Lilienthal et al. 1996
145	Rat (Wistar)	gestation + lactation + 2 wks post-weaning (F)			2.5 (decr resistance to infection, incr IgG response to tetanus toxoid, and proliferation of high endothelial venules in lymph nodes in pups)		Vos et al. 1979a
146	Rat (Wistar)	gestation + lactation + 2 wks or 7 mo post-weaning (F)			0.2 (incr IgG and IgM response to tetanus toxoid, incr delayed-type hypersensitivity reaction to ovalbumin, and accumulation of foamy macrophages in the lung in offspring)	5 (high pup mortality)	Vos et al. 1983

Table 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (continued)

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ duration/ frequency/ (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
<b>CHRONIC EXPOSURE</b>							
<b>Death</b>							
147	Mouse (Swiss)	120 wk (F)				24 (decr survival)	Cabral et al. 1979
148	Hamster (Syrian)	lifespan (F)				16 (decr lifespan)	Cabral et al. 1977
149	Dog (Beagle)	1 yr 1x/d (C)				11 F (2/6 females died)	Gralla et al. 1977
<b>Systemic</b>							
150	Rat (Sprague- Dawley)	2 gen (F)	Hemato	2			Arnold et al. 1985
			Hepatic	0.08	0.4 M (incr liver wt)		
			Renal	2			
			Bd Wt	2			
151	Rat (Fischer- 344)	daily 5 wks (F)	Hepatic	6.25	6.25 (increased liver weight, centrilobular hypertrophy, foci of GST-P)		Kishima et al. 2000
152	Rat (Sprague- Dawley)	1 yr (F)	Hepatic	0.05	0.25 (mitochondrial swelling and elongation)		Mollenhauer et al. 1975
153	Rat (Agus)	90 wk (F)	Hepatic		7 F (porphyria)		Smith and Cabral 1980
			Dermal		7 F (alopecia)		
			Bd Wt		7 F (decr body wt gain)		

Table 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
154 Rat (Fischer- 344)		90 wk (F)	Hepatic		10	(decr URO-D activity, incr hepatic porphyrin levels, hepatocyte hypertrophy, fatty degeneration, bile duct hyperplasia)	Smith et al. 1985
			Renal		10	(incr kidney wt, incr renal porphyrin levels, nephrosis in males)	
			Endocr Bd Wt	10	10	(decr body wt)	
155 Rat (Fischer- 344)		65 wk (F)	Hepatic		10 F	(incr liver wt; biliary hyperplasia; incr liver porphyrins; induction of microsomal enzymes and glutathione S-transferase)	Smith et al. 1993
			Bd Wt	10 F			
156 Mouse (C57BL/10Sc Sn)		18 mo (F)	Hepatic		13 M	(hepatocyte hypertrophy)	Smith et al. 1989
			Bd Wt		13 M	(decr body wt)	
157 Hamster (Syrian golden)		lifespan (F)	Bd Wt			16 M (marked decr in wt gain)	Cabral et al. 1977

Table 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
158	Dog (Beagle)	1 yr (C)	Cardio	11		110 (arteriopathy)	Gralla et al. 1977a
			Gastro	1		11 (diarrhea, necrotic and inflammatory lesions of the omentum and abdominal serosa)	
			Hemato	1	11 (neutrophilia)	110 (anemia)	
			Hepatic	1		11 (hepatomegaly, bile duct hyperplasia, pericholangitis, periportal fibrosis, incr serum alkaline phosphatase and AST)	
			Bd Wt	1		11 (loss of body weight)	
<b>Immunological/Lymphoreticular</b>							
159	Dog (Beagle)	1 yr (C)			0.1 (incr severity of nodular hyperplasia of the gastric lymphoid tissue)		Gralla et al. 1977a
<b>Neurological</b>							
160	Mouse (Swiss)	120 wk (F)				24 (tremors, convulsions)	Cabral et al. 1979
<b>Reproductive</b>							
161	Rat (Sprague-Dawley)	2 gen (F)		2			Arnold et al. 1985

Table 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency/ (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
<b>Developmental</b>							
162	Rat (Sprague- Dawley)	2 gen (F)			0.016 <sup>d</sup> M (peribiliary lymphocytosis and fibrosis of the liver in F1 adult males)	2 (decr neonatal viability of F1 pups; incr neoplastic liver nodules, parathyroid adenoma, and adrenal pheochromocytoma in F1 adults)	Arnold et al. 1985
<b>Cancer</b>							
163	Rat (Sprague- Dawley)	104 wk (F)				4 (CEL: hepatoma, bile-duct adenoma, hepatocarcinoma, renal adenoma)	Ertürk et al. 1986
164	Rat (Agus)	90 wk (F)				7 F (CEL: liver-cell tumors)	Smith and Cabral 1980
165	Rat (Wistar)	75 wk (F)				5 F (CEL: liver-cell tumors)	Smith and Cabral 1980
166	Rat (Fischer- 344)	90 wk (F)				10 (CEL: hepatocarcinoma)	Smith et al. 1985
167	Rat (Fischer- 344)	65 wk (F)				10 F (CEL: liver tumors)	Smith et al. 1993
168	Mouse (Swiss)	120 wk (F)				12 (CEL: liver tumors)	Cabral et al. 1979

Table 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (continued)

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less serious (mg/kg/day)	Serious (mg/kg/day)	
169	Hamster (Syrian)	lifespan (F)				4 (CEL: hepatoma, liver hemangioendothelioma, thyroid alveolar adenoma)	Cabral et al. 1977

<sup>a</sup>The number corresponds to entries in Figure 3-2.

<sup>b</sup>Used to derive an acute oral minimal risk level (MRL) of 0.008 mg/kg/day; dose divided by uncertainty factor of 300 (10 for extrapolation from rats to humans, 10 for human variability, and 3 for use of a minimal LOAEL).

<sup>c</sup>Used to derive an intermediate oral MRL of 0.0001 mg/kg/day; dose divided by an uncertainty factor of 100 (3 for extrapolation from monkeys to humans, 10 for human variability, and 3 for use of a minimal LOAEL).

<sup>d</sup>Used to derive a chronic oral MRL of 0.00005 mg/kg/day; dose divided by an uncertainty factor of 300 (10 for extrapolation from rats to humans, 10 for human variability, and 3 for use of a minimal LOAEL).

ALA-S = delta-aminolevulinic acid synthetase; AST = aspartate aminotransferase; Bd wt = body weight; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); CNA = central nervous system; Decr = decreased; Endocr = endocrine; F = female; (F) = feed; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; gen = generation; (GO) = gavage in oil; (GW) = gavage in water; Hemato = hematological; Incr = increased; LD<sub>50</sub> = lethal dose, 50% kill; LDH = lactose dehydrogenase; LOAEL = lowest-observable-adverse effect level; M = male; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; Resp = respiratory; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; URO-D = uroporphyrinogen decarboxylase; wk = week(s); wt = weight; x = times; yr = year(s)

Figure 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral  
Acute ( $\leq 14$  days)

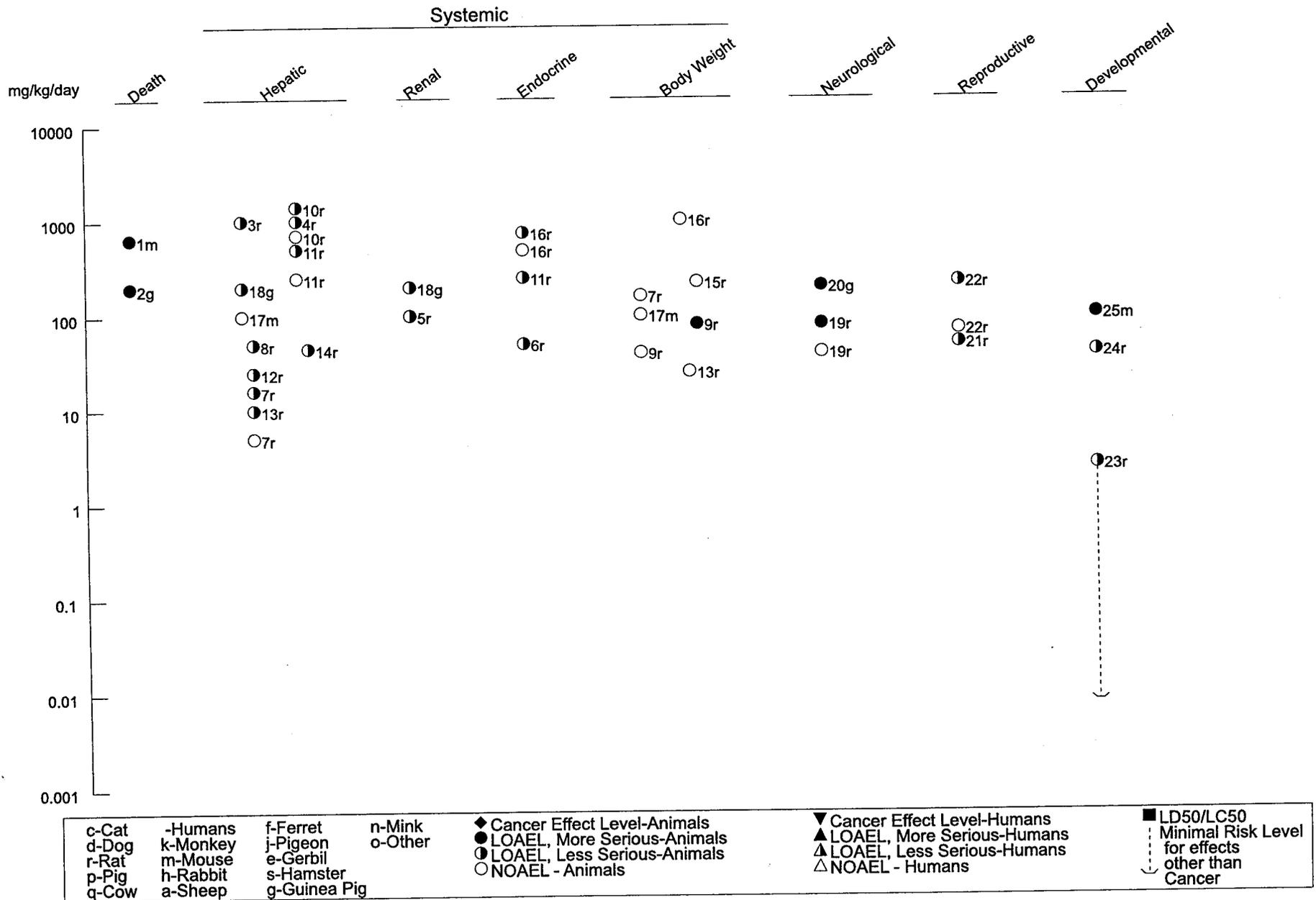


Figure 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (Continued)  
Intermediate (15-364 days)

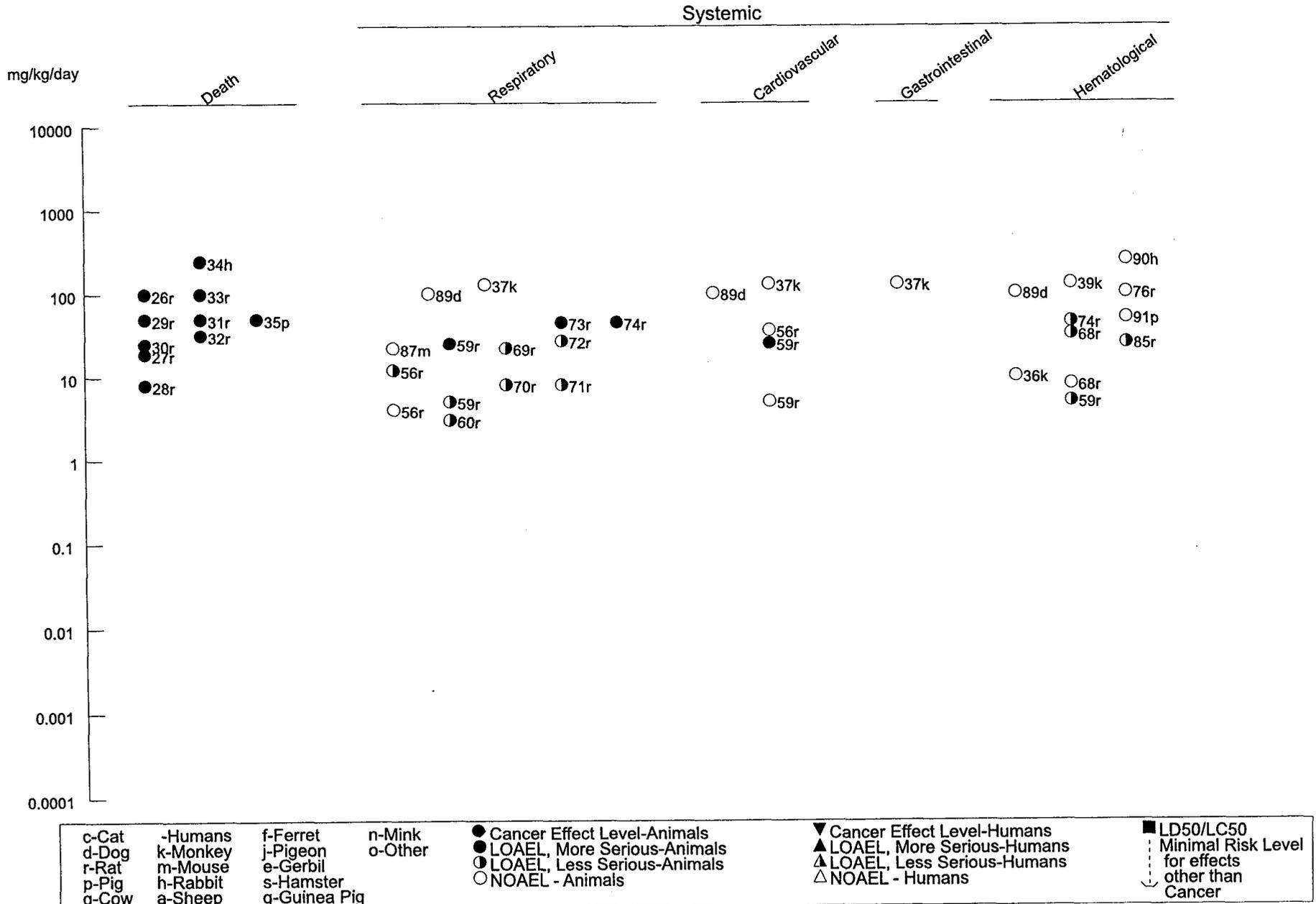
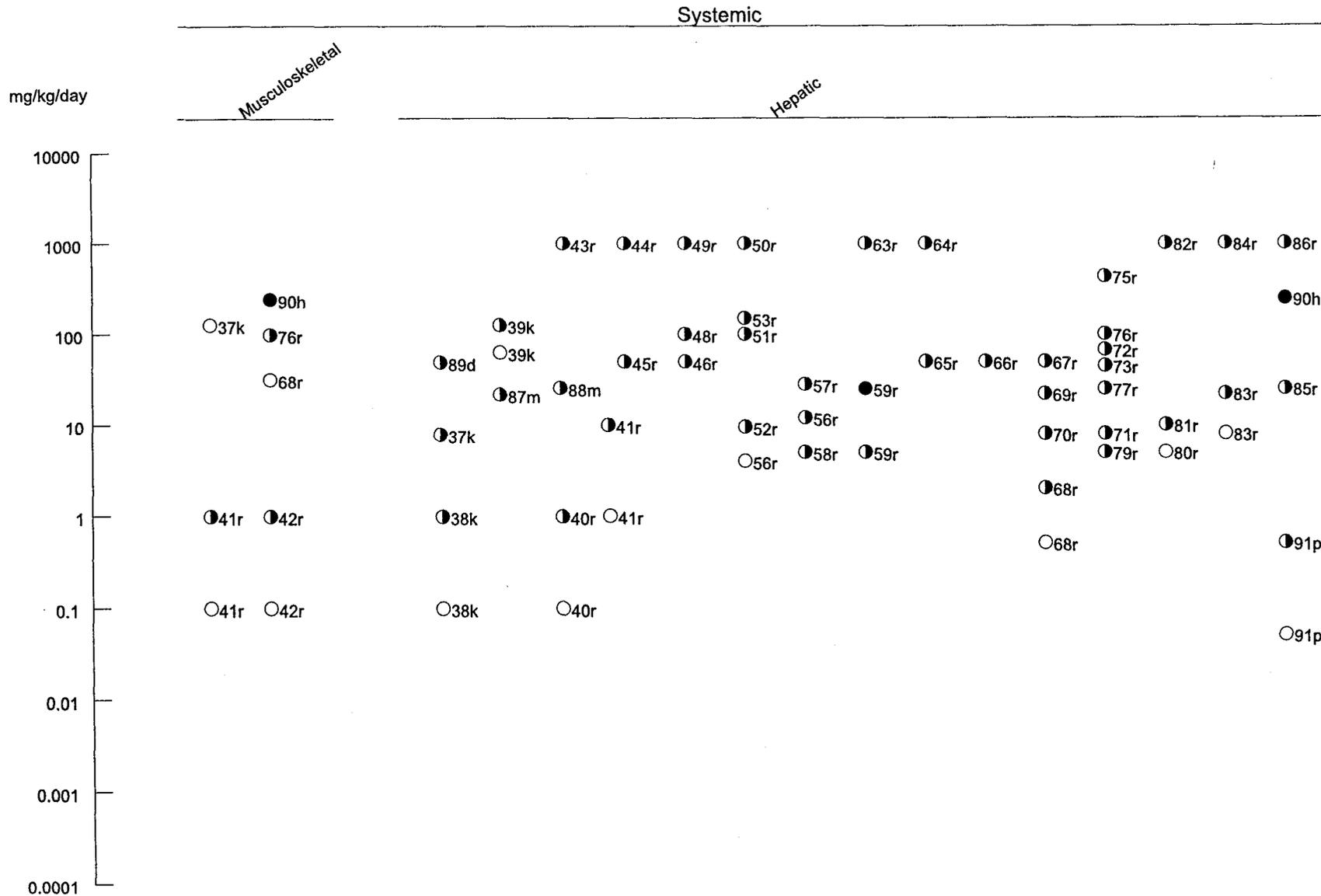


Figure 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (Continued)

Intermediate (15-364 days)



HEXACHLORO BENZENE

3. HEALTH EFFECTS

c-Cat	-Humans	f-Ferret	n-Mink	● Cancer Effect Level-Animals	▼ Cancer Effect Level-Humans	■ LD50/LC50
d-Dog	k-Monkey	j-Pigeon	o-Other	● LOAEL, More Serious-Animals	▲ LOAEL, More Serious-Humans	⋯ Minimal Risk Level
r-Rat	m-Mouse	e-Gerbil		○ LOAEL, Less Serious-Animals	△ LOAEL, Less Serious-Humans	for effects other than
p-Pig	h-Rabbit	s-Hamster		○ NOAEL - Animals	△ NOAEL - Humans	Cancer
q-Cow	a-Sheep	g-Guinea Pig				

Figure 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (Continued)  
Intermediate (15-364 days)

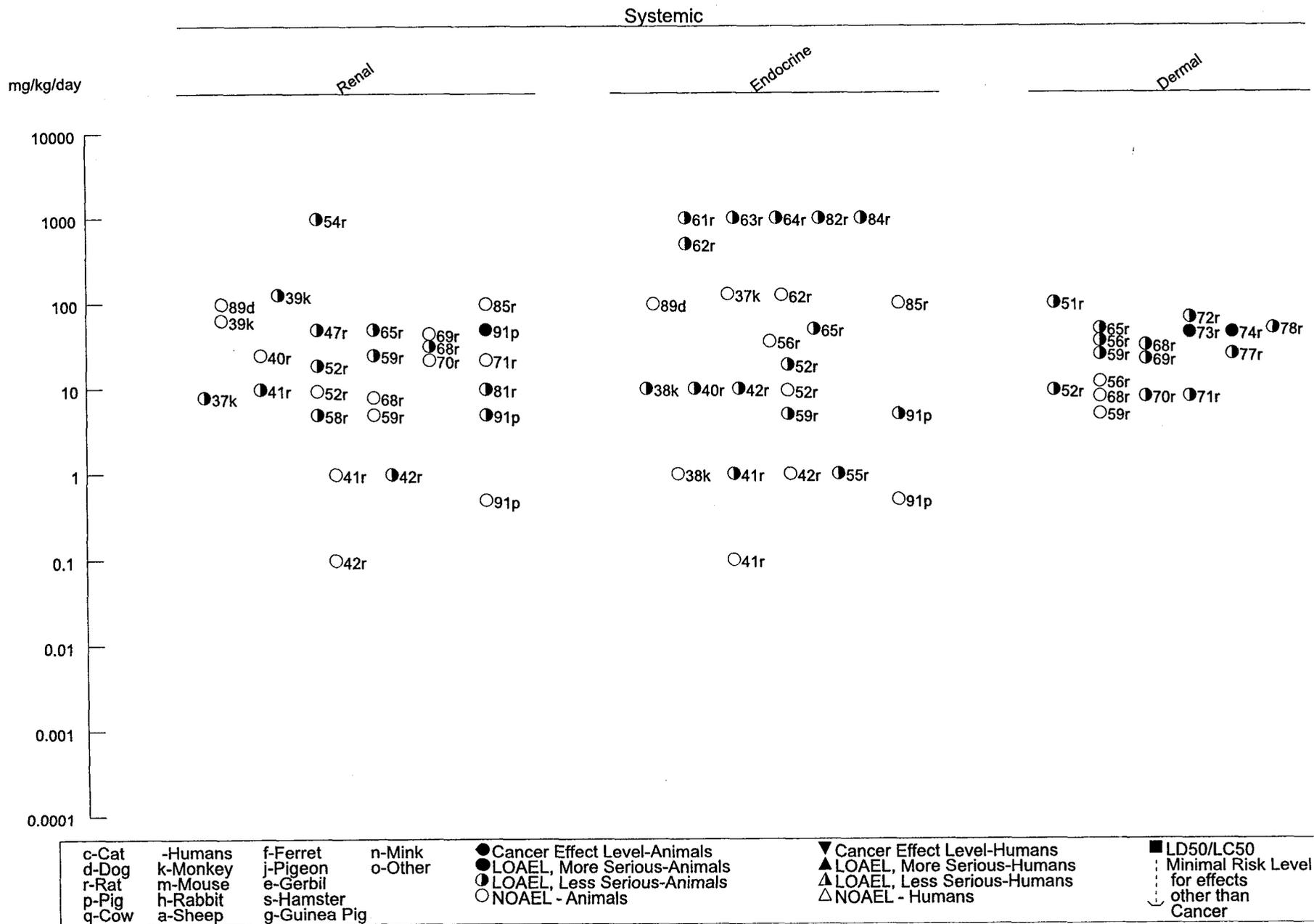
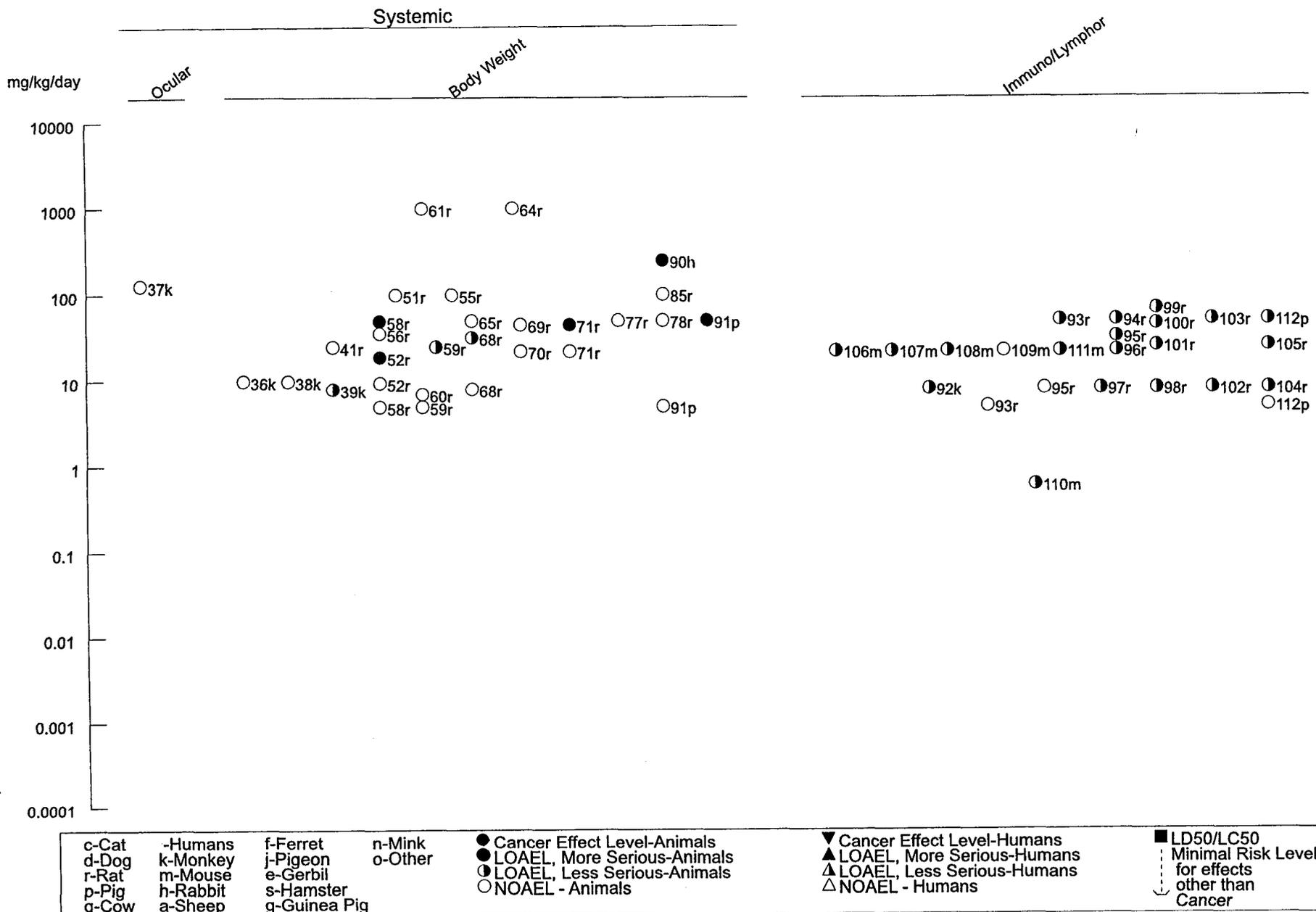


Figure 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (Continued)

Intermediate (15-364 days)

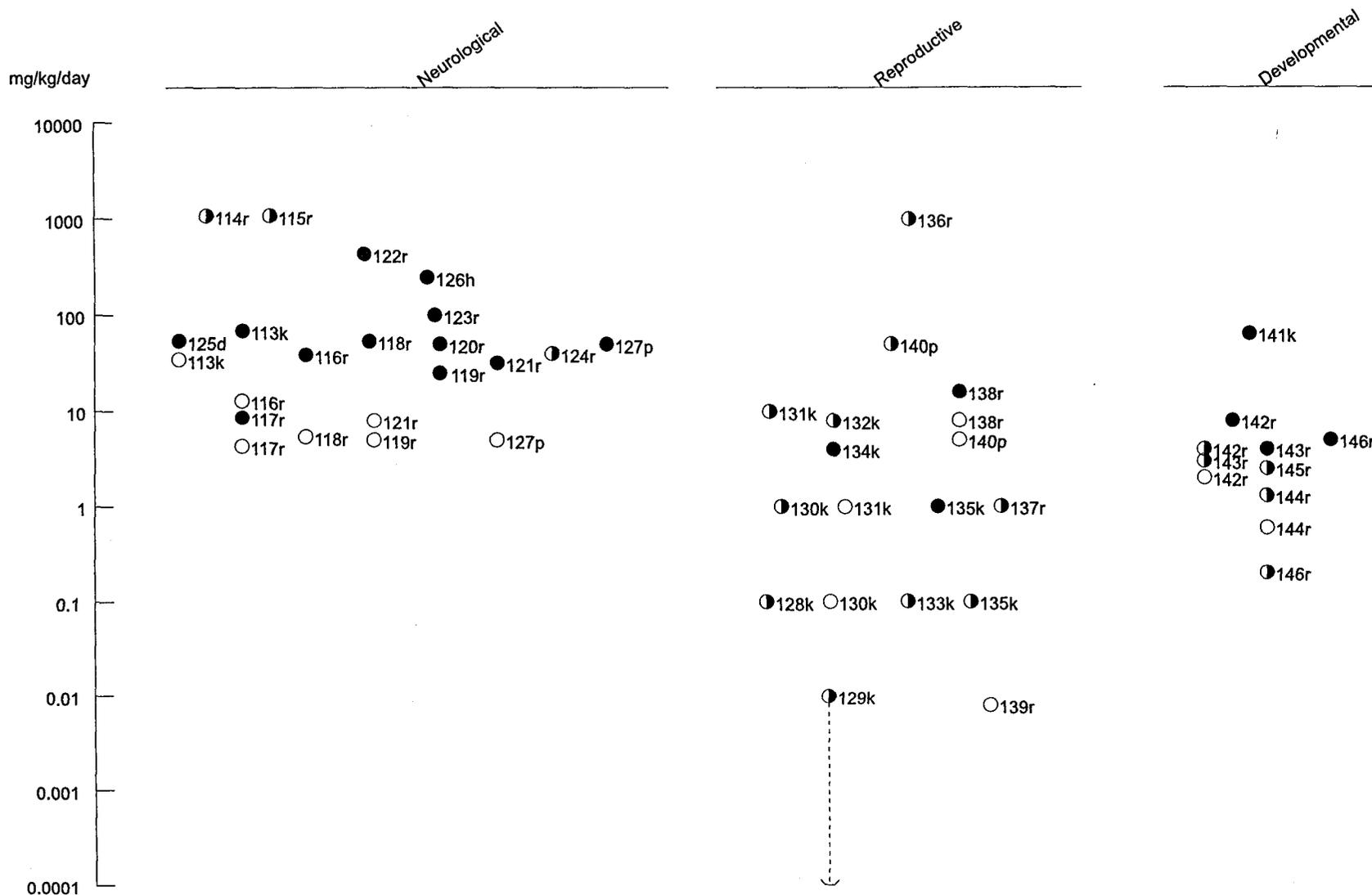


HEXACHLOROBENZENE

3. HEALTH EFFECTS

Figure 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (Continued)

Intermediate (15-364 days)

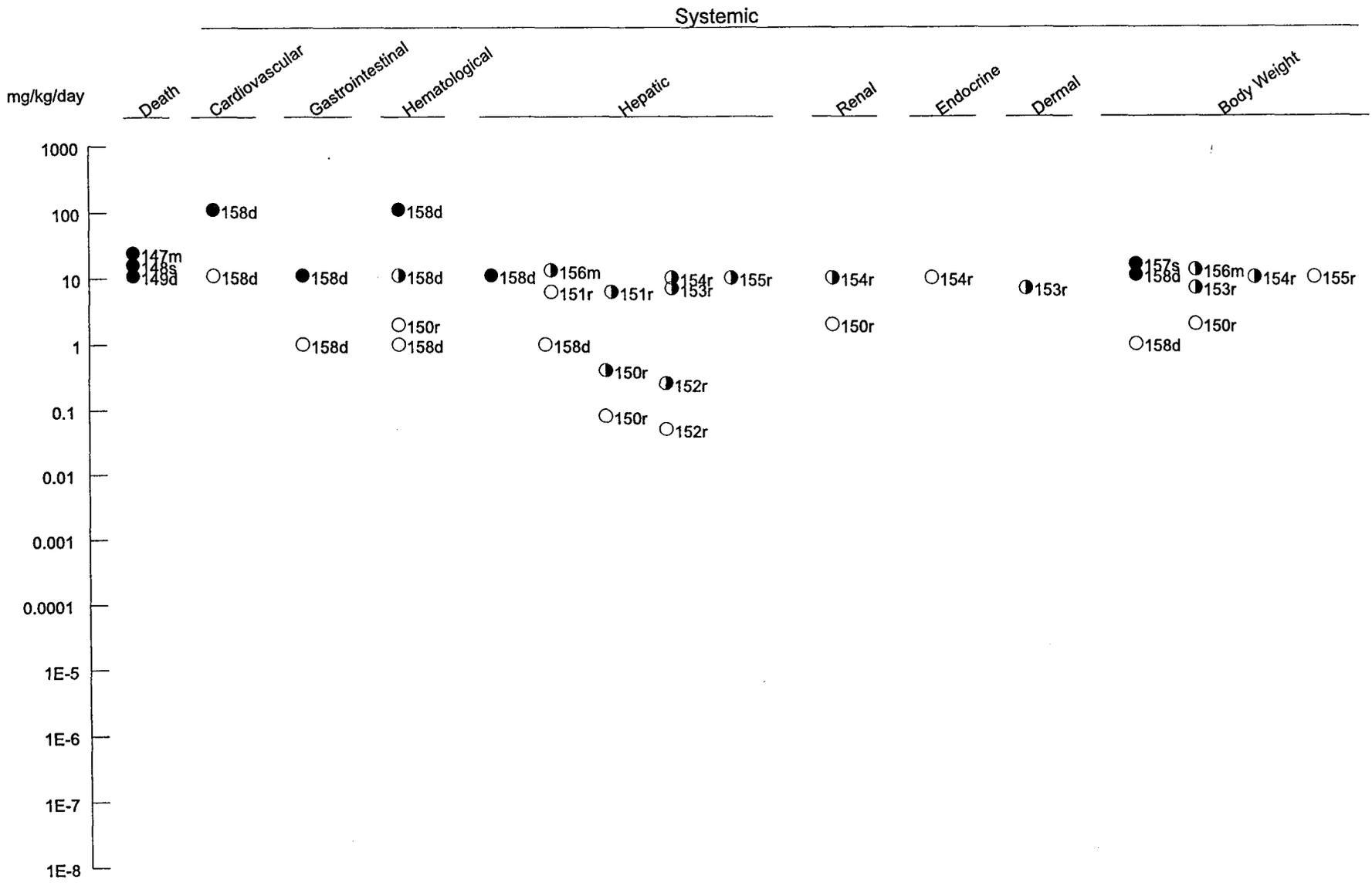


HEXACHLOROBENZENE

3. HEALTH EFFECTS

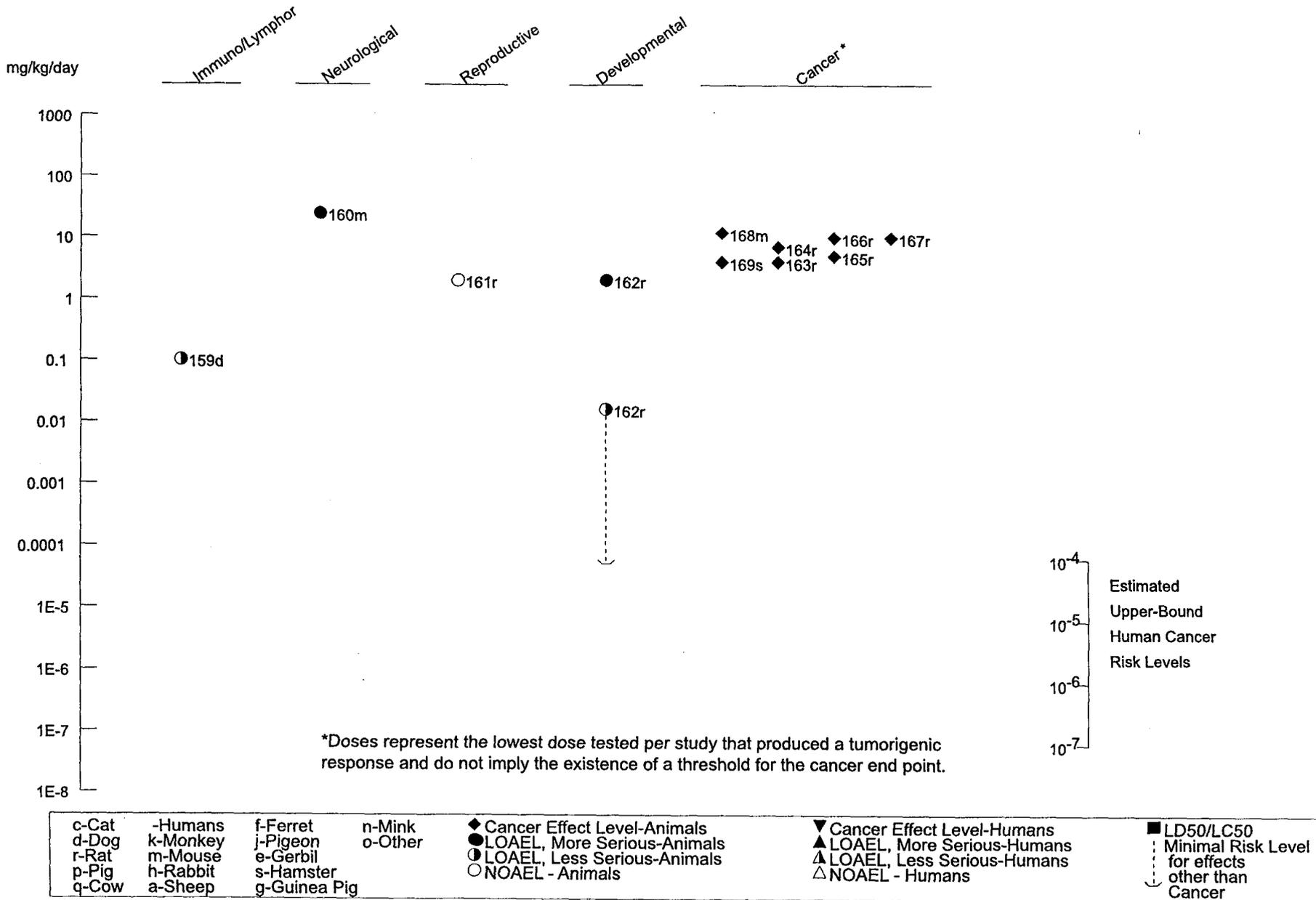
c-Cat	-Humans	f-Ferret	n-Mink	● Cancer Effect Level-Animals	▼ Cancer Effect Level-Humans	■ LD50/LC50
d-Dog	k-Monkey	j-Pigeon	o-Other	● LOAEL, More Serious-Animals	▲ LOAEL, More Serious-Humans	⋮ Minimal Risk Level
r-Rat	m-Mouse	e-Gerbil		○ LOAEL, Less Serious-Animals	△ LOAEL, Less Serious-Humans	for effects
p-Pig	h-Rabbit	s-Hamster		○ NOAEL - Animals	△ NOAEL - Humans	other than
q-Cow	a-Sheep	g-Guinea Pig				Cancer

Figure 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (Continued)  
Chronic (≥365 days)



c-Cat	-Humans	f-Ferret	n-Mink	● Cancer Effect Level-Animals	▼ Cancer Effect Level-Humans	■ LD50/LC50
d-Dog	k-Monkey	j-Pigeon	o-Other	● LOAEL, More Serious-Animals	▲ LOAEL, More Serious-Humans	⋮ Minimal Risk Level
r-Rat	m-Mouse	e-Gerbil		○ LOAEL, Less Serious-Animals	△ LOAEL, Less Serious-Humans	for effects
p-Pig	h-Rabbit	s-Hamster		○ NOAEL - Animals	△ NOAEL - Humans	other than
q-Cow	a-Sheep	g-Guinea Pig				Cancer

Figure 3-2. Levels of Significant Exposure to Hexachlorobenzene - Oral (Continued)  
Chronic (≥365 days)



## 3. HEALTH EFFECTS

lesions, typically occurring together, were found in six different strains of rats and both sexes, at doses as low as 3 mg/kg/day in intermediate-duration feeding studies (Goldstein et al. 1978; Kimbrough and Linder 1974; Kitchin et al. 1982; Michielsen et al. 1997, 1999, 2001). They were seen at doses as low as 1 mg/kg/day, with a NOAEL of 0.2 mg/kg/day, in rats that received both pre- and postnatal exposure (Vos et al. 1979a, 1983). (The Vos studies are included as developmental toxicity studies in Table 3-2 and Figure 3-2.) Michielsen et al. (1997) hypothesized an immunomodulated etiology for these lesions, but the lesions occurred to a similar extent in five rat strains (Wistar, Lewis, Brown Norway; athymic and euthymic WAG/Rij) with very different responses to immunomodulating agents and did not correlate with observed immune changes, providing no support for this hypothesis (Michielsen et al. 1997, 1999, 2001). More severe pulmonary effects have also been observed in rats at higher doses. In addition to macrophage accumulation and focal areas of interstitial fibrosis, which they observed in male and female rats exposed to 5 mg/kg/day in the diet for 4 months, Kimbrough and Linder (1974) also observed extensive intra-alveolar hemorrhage, inflammation, and edema, accompanied by an increase in lung weight, in females exposed to 25 or 50 mg/kg/day. Michielsen et al. (2001) observed an adverse effect on respiratory function, and airway hyperresponsiveness, as well as granulomatous lung inflammation, in rats exposed to 45 mg/kg/day. Only limited pulmonary histopathology data are available for other species, and pulmonary lesions were not seen in available studies on monkeys, dogs, or mice (Iatropoulos et al. 1976; Loose et al. 1977; Sundlof et al. 1981).

**Cardiovascular Effects.** No studies were located regarding cardiovascular effects of oral hexachlorobenzene exposure in humans.

There have been a few reports of cardiovascular lesions in animals exposed to hexachlorobenzene. Gralla et al. (1977a) described an arteriopathy affecting multiple organs in dogs treated with 110 mg/kg/day of hexachlorobenzene for 1 year. The lesion was characterized by inflammation of small arteries and arterioles, with focal proliferative endarteritis, fibrinoid necrosis, and thrombosis, and occasionally involved fibrosis and inflammation adjacent to the arterioles in the heart and the liver. Although features of the lesion suggested a hypersensitivity reaction, an immune etiology was not supported by serum electrophoretic data. The arteritis was seen in 4 of 12 beagle dogs treated with 110 mg/kg/day, a dose that produced weight loss, mortality, and other frank toxic effects, but was not seen in dogs treated with lower doses. It is not known if these effects were produced by a direct effect of hexachlorobenzene or were secondary to general poor health of the dogs in this study. However, similar observations in the heart were made by Kimbrough and Linder (1974) in rats. These researchers found fibrosis and degeneration of muscle fibers in the heart of rats exposed to 25 mg/kg/day or more in the diet for 4 months.

## 3. HEALTH EFFECTS

Degenerated tissue was infiltrated by inflammatory cells. Other studies that included pathological examination of cardiovascular tissues in dogs, rats, and monkeys did not find treatment-related lesions (Goldstein et al. 1978; Iatropoulos et al. 1976; Sundlof et al. 1981).

**Gastrointestinal Effects.** No studies were located regarding gastrointestinal effects of oral hexachlorobenzene exposure in humans.

Gastrointestinal effects have not been commonly reported in animal studies of hexachlorobenzene. Dogs given 11 mg/kg/day by capsule for 1 year experienced intermittent episodes of diarrhea (Gralla et al. 1977a). Necropsy revealed necrotic and inflammatory lesions of the omentum and abdominal serosa, but there were apparently no findings in the stomach, small intestines, or large intestines. Pathological examination of female pigs exposed to 0.025 or 0.5 mg/kg/day for 212 days throughout mating, gestation, and lactation showed gastrointestinal lesions ranging from catarrhal exudation to mild ulceration, but microscopic signs of gastritis were also found in some control group animals, suggesting that the observed lesions were not an effect of hexachlorobenzene (Hansen et al. 1979). Gastrointestinal lesions were not observed in female Rhesus monkeys given oral hexachlorobenzene at doses of up to 128 mg/kg/day for 60 days (Iatropoulos et al. 1976).

**Hematological Effects.** No data were located on the hematological effects of hexachlorobenzene in humans.

Animal data suggest that hexachlorobenzene can produce anemia and leukocytosis. Several studies reported decreases in hemoglobin, hematocrit, and/or red blood cell count in rats at doses ranging from 5 to 32 mg/kg/day in 1–4-month studies (Kimbrough and Linder 1974; Kuiper-Goodman et al. 1977; Richter et al. 1981). Female rats were much more sensitive than male rats in these studies (Kimbrough and Linder 1974; Kuiper-Goodman et al. 1977). Other studies in rats did not find changes in these parameters, but used lower doses (Arnold et al. 1985), a much shorter exposure period (Lecavalier et al. 1994), or only the less sensitive male rats (Ockner and Schmid 1961). Other reported findings in rats consistent with the hypothesis that hexachlorobenzene can produce anemia were increased extramedullary hematopoiesis in the spleen, which was seen at doses as low as 5 mg/kg/day with combined pre- and postnatal exposure (Vos et al. 1979a, 1979b, 1983), and reduced medullary area in the femur, which was found at 10 mg/kg/day and above in a 15-week study (Andrews et al. 1990). Limited data are available regarding hematological effects in other species. Anemia was observed in dogs exposed to 110 mg/kg/day for 1 year (Gralla et al. 1977a), but not in dogs exposed to 100 mg/kg/day for only

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3 weeks (Sundlof et al. 1981), in rabbits exposed to 245 mg/kg/day for 12 weeks (De Matteis et al. 1961), in pigs exposed to 50 mg/kg/day for 13 weeks (Den Tonkelaar et al. 1978), or in monkeys exposed to 128 mg/kg/day for 60 days (Knauf and Hobson 1979) or 10 mg/kg/day for 90 days (Foster et al. 1995a).

Many of the same studies that reported anemia and related findings also reported neutrophilia and/or leukocytosis. In rats, the white blood cell increases were found at the same or higher doses than the red cell changes (25 mg/kg/day in 3–16 week feeding studies), and there appeared to be less of a disparity in response between males and females (Kimbrough and Linder 1974; Kuiper-Goodman et al. 1977; Vos et al. 1979b). In dogs, afebrile neutrophilia was observed at 11 mg/kg/day, while anemia was found only at the high dose of 110 mg/kg/day (Gralla et al. 1977a). Negative studies in these species used lower doses (Arnold et al. 1985) or a much shorter exposure period (Lecavalier et al. 1994; Sundlof et al. 1981). Although values remained within normal ranges, Den Tonkelaar et al. (1978) identified a tendency towards leukocytosis and relative neutrophilia in male pigs treated with dietary doses as low as 0.05 mg/kg/day for 90 days. However, studies in monkeys given doses up to 10 mg/kg/day for 90 days (Foster et al. 1995a) or doses up to 128 mg/kg/day for 60 days (Knauf and Hobson 1979) were negative.

**Musculoskeletal Effects.** Hexachlorobenzene has been associated with painless arthritis (swelling of the joints distinct from rheumatoid arthritis), osteoporosis, and small distinctive hands in patients exposed to the chemical from consumption of bread prepared from contaminated grain. Although there was severe shortening of digits due to osteoporosis in the bones of the hands (phalangeal, carpal, and metacarpal), particularly at the ends, no limitation of movement was reported. Painless arthritic changes were also reported in the patients (Cripps et al. 1984; Peters et al. 1982, 1987).

Effects on both bone and muscle have been reported in animal studies of hexachlorobenzene. Detailed studies of bone effects were conducted by Andrews et al. (1989, 1990) in male rats treated by gavage in corn oil for up to 15 weeks. These researchers found significant, dose-related increases in femur density (osteosclerosis) at doses of 1 mg/kg/day and above, and identified a NOAEL of 0.1 mg/kg/day for this effect. Femur length, weight, volume, and cross-sectional area were not consistently altered, indicating no effect on the rate of bone growth. The other dose-related changes in bone were an increase in cortical area at 1 mg/kg/day and above and a corresponding decrease in medullary area at 10 mg/kg/day and above. Other pertinent findings were decreases in serum alkaline phosphatase and increases in serum 1,25-dihydroxy-vitamin D<sub>3</sub> and parathyroid hormone (hyperparathyroidism). The joint findings of osteosclerosis, increased cortical and reduced medullary area without a change in the rate of bone growth, and decreased serum alkaline phosphatase are consistent with a mechanism involving reduced resorption

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of bone. The increases in serum 1,25-dihydroxy-vitamin D3 and parathyroid hormone, both of which are involved in calcium regulation and bone resorption, suggest that the hypothesized effect on bone resorption is probably secondary to hyperparathyroidism. The decrease in medullary area (bone marrow cavity) that ultimately results from these changes may, in turn, contribute to hematological and immune effects associated with hexachlorobenzene.

Studies conducted at higher doses that produced marked interference with heme metabolism found substantial accumulation of porphyrins in bone cortex, but not marrow. This was observed in rats treated with 100 mg/kg/day in the diet for 56 days (Ockner and Schmid 1961) and rabbits treated with 245 mg/kg/day in the diet for 84 days (De Matteis et al. 1961). No bone (or liver or kidney) accumulation of porphyrins was observed by Andrews et al. (1989), but the highest dose in this study was only 25 mg/kg/day.

Skeletal muscle lesions have been reported in animals exposed to hexachlorobenzene, but only with repeated exposure to high doses. Rabbits treated with 245 mg/kg/day of hexachlorobenzene for 12 weeks were observed to have necrosis, degeneration, and focal calcification in skeletal muscle (De Matteis et al. 1961). Skeletal muscle lesions were not found in rats fed up to 32 mg/kg/day for 15 weeks (Kuiper-Goodman et al. 1977).

**Hepatic Effects.** The major evidence that oral exposure to hexachlorobenzene by humans can result in hepatopathology is derived from studies of an outbreak of porphyria in Turkey attributed to the consumption of bread prepared from hexachlorobenzene-contaminated grain from 1955 to 1959 (Cam and Nigogosyan 1963; Cripps et al. 1984; Peters et al. 1982, 1987). These adverse hepatic effects were mainly characterized by porphyria. The appearance of abnormal levels of porphyrin precursors in the urine suggests that hexachlorobenzene disturbed the body's porphyrin metabolism in the liver, which caused histopathologic changes in the liver. Uroporphyrin and  $\delta$ -aminolevulinic acid (d-ALA) synthase increased in the urine, and uroporphyrin and coproporphyrin increased in the stool of patients who had ingested hexachlorobenzene-contaminated bread (Cripps et al. 1984; Peters et al. 1982, 1987). No quantitation of exposure (dose and duration) was presented in any of these clinical reports. However, an estimated dose of 0.05–0.2 g/day (0.7–2.9 mg/kg/day for a 70-kg person) is considered to be reliable by the original investigators of the Turkey epidemic (Cam and Nigogosyan 1963).

Studies in animals have confirmed that the liver is an important target organ for hexachlorobenzene following ingestion. Hepatic effects associated with oral exposure to hexachlorobenzene in animal

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studies include disruption of heme synthesis (culminating in porphyria), induction of microsomal enzymes, hepatomegaly, and cellular damage.

Disruption of hepatic heme synthesis by hexachlorobenzene has been well studied in rats (see below). Hexachlorobenzene inhibits the activity of hepatic uroporphyrinogen decarboxylase, an enzyme in the heme biosynthesis pathway, leading to build up of heme precursors (porphyrins) in the liver and other tissues and their excessive excretion in the urine (porphyria). The activity of other enzymes in the heme biosynthesis pathway may also be altered; in particular, an increase in the activity of  $\delta$ -aminolevulinic acid synthetase has been reported in some studies (see Section 3.5, Mechanisms of Action). This pattern of effects is very similar to what is seen in human porphyria cutanea tarda.

Following acute exposure, the lowest dose reported to induce outright porphyria in an animal study was 25 mg/kg/day in an 8-day study in female rats in which hexachlorobenzene was administered by gavage in corn oil; the rats were monitored for urinary and hepatic porphyrins after 35–50 days (Krishnan et al. 1991). Goldstein et al. (1978) observed a statistically significant increase in hepatic  $\delta$ -aminolevulinic acid synthetase activity in female rats fed 16 mg/kg/day of hexachlorobenzene in the diet for 1 week, but there was little or no effect on hepatic porphyrin levels at that time, possibly because of insufficient latency time for the effect to develop. (Time course studies have shown that there may be a delay of approximately 4 weeks between treatment with hexachlorobenzene and development of porphyria [Krishnan et al. 1991; Mylchreest and Charbonneau 1997; Billi de Catabbi et al. 2000a], although there may be little or no delay if the hexachlorobenzene is administered in a form that is readily absorbed [e.g., predissolved in corn oil] at high doses [Kennedy and Wigfield 1990].) There was no increase in hepatic  $\delta$ -aminolevulinic acid synthetase activity at 5 mg/kg/day in the Goldstein et al. (1978) study. The dose level at which hexachlorobenzene will produce porphyria depends on the exposure protocol. When hexachlorobenzene was administered to female rats by gavage for 7 days in an aqueous suspension rather than oil, no effect on hepatic uroporphyrinogen decarboxylase (monitored at 7 days) was observed even at 250 mg/kg/day, and only doses of 500 mg/kg/day or higher were effective (Kleiman de Pisarev et al. 1990), reflecting the fact that hexachlorobenzene administered in water is only minimally absorbed from the gastrointestinal tract, and also perhaps, the short latency time. Even at 1,000 mg/kg/day in this study, uroporphyrinogen decarboxylase activity was decreased only 25%, while  $\delta$ -aminolevulinic acid synthetase activity and liver porphyrin levels were unchanged from controls. Billi de Catabbi et al. (2000a) observed that acute (5-day) exposure above a threshold (1 g/kg) caused persistent porphyria (lasting at least as long as the 20-week observation period).

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Hexachlorobenzene doses as low as 5–12 mg/kg/day have been reported to produce porphyrinogenic effects, such as increased liver weight, inhibition of hepatic uroporphyrinogen decarboxylase, accumulation of porphyrins in liver, excretion of porphyrins in urine, and increased hepatic  $\delta$ -aminolevulinic acid synthetase activity, in female rats exposed for intermediate durations (Alvarez et al. 2000; Den Besten et al. 1993; Goldstein et al. 1978; Kennedy and Wigfield 1990; Kuiper-Goodman et al. 1977; Smith et al. 1979, 1985; Sweeney et al. 1986). One of these studies, Goldstein et al. (1978), identified a NOAEL of 4 mg/kg/day for increases in liver porphyrins and  $\delta$ -aminolevulinic acid synthetase activity after a 4-month dietary exposure. In male rats, there was little or no evidence of porphyria at doses up to 25 mg/kg/day (Andrews et al. 1989; Kuiper-Goodman et al. 1977; Smith et al. 1985), but mild changes were noted at 32–50 mg/kg/day (Krishnan et al. 1991; Kuiper-Goodman et al. 1977) and severe porphyria was observed at 100 mg/kg/day (Ockner and Schmid 1961). The reduced sensitivity of male rats in comparison to females may be related to differences in metabolism of hexachlorobenzene between the sexes in this species, particularly with regard to glutathione conjugation (D'Amour and Charbonneau 1992; Richter et al. 1981; Rizzardini and Smith 1982), which have been linked to the presence of estradiol in the females (Legault et al. 1997). Among female rats, strain-related differences in sensitivity have also been reported (Billi de Catabbi et al. 2000a; Michielsen et al. 1997), possibly related, at least in one case, to differences in nonheme iron content of the liver between strains (Smith et al. 1979). In other species, there was no evidence of porphyria in female monkeys treated with up to 10 mg/kg/day by capsule for 3 months (Jarrell et al. 1993) or in male pigs exposed to up to 50 mg/kg/day in the diet for 3 months (Den Tonkelaar et al. 1978); these results appear to reflect species differences, but may be influenced by the lack of oil vehicle to enhance absorption.

In studies of chronic exposure duration, hexachlorobenzene doses of 7–10 mg/kg/day in the feed produced complete inhibition of uroporphyrinogen decarboxylase and high levels of porphyrins in the liver and urine in both male and female rats (Smith and Cabral 1980; Smith et al. 1985, 1993). Although uroporphyrinogen decarboxylase activity was completely inhibited in both sexes, liver accumulation of porphyrins was 5-fold higher in females than in males (Smith et al. 1985). Chronic rat studies that employed lower dose levels did not monitor porphyrin levels (Arnold et al. 1985; Mollenhauser et al. 1975). Male mice exposed to slightly higher dietary doses of hexachlorobenzene (13 mg/kg/day) showed only a modest transitory increase in hepatic porphyrin levels after 6 months of treatment, which was not found at subsequent sacrifices at 12 and 18 months (Smith et al. 1989). There was no evidence of porphyrin accumulation in the liver or other tissues of dogs treated with hexachlorobenzene doses as high as 110 mg/kg/day for 1 year (Gralla et al. 1977a, 1977b).

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As in human porphyria cutanea tarda, porphyria in rats produced by hexachlorobenzene typically occurs along with other effects on the liver, such as induction of microsomal enzymes, increased liver weight, hepatocellular hypertrophy, cytoplasmic vacuolation, fatty degeneration, and biliary hyperplasia (Cuomo et al. 1991; Den Besten et al. 1993; Kimbrough and Linder 1974; Koss et al. 1978; Kuiper-Goodman et al. 1977; Michielsen et al. 1997; Smith et al. 1985, 1993; Sweeney et al. 1986; Vos et al. 1979b). The relationship between porphyria and these other hepatic effects is uncertain. In some instances, effects on liver weight, enzymes, and/or histopathology occurred in rats at lower doses than porphyria or in the absence of porphyria (e.g., Arnold et al. 1985; Gustafson et al. 2000; Kishima et al. 2000; Mehendale et al. 1975; Mollenhauer et al. 1975; Michielsen et al. 2000). Liver lesions have also been observed in species, such as monkeys, dogs, and pigs, where there is no evidence of a porphyrinogenic effect (Den Tonkelaar et al. 1978; Gralla et al. 1977a; Iatropoulos et al. 1976; Jarrell et al. 1993). Kishima et al. (2000) reported that the hepatotoxicity of hexachlorobenzene was increased by an energy-restricted diet. The most sensitive hepatic end points following acute, intermediate, and chronic exposure, respectively, were increased liver weight and induction of microsomal enzymes in male rats exposed to 10 mg/kg/day for 6 days (Mehendale et al. 1975), hepatocellular hypertrophy in male pigs exposed to 0.5 mg/kg/day for 90 days (Den Tonkelaar et al. 1978), and peribiliary lymphocytosis and fibrosis in F<sub>1</sub> adult male rats exposed to 0.016 mg/kg/day *in utero* and throughout their lifetime in a 2-generation study (Arnold et al. 1985; listed as a developmental effect in Table 3-2 and the basis for the chronic oral MRL of 0.00005 mg/kg/day, as described in the footnote to Table 3-2 and in Appendix A).

**Renal Effects.** No studies were found regarding renal effects in humans following oral exposure to hexachlorobenzene.

Animal studies have demonstrated that the kidney is a target for hexachlorobenzene. Renal effects that have been widely reported in animal studies are increased kidney weight, accumulation of porphyrins in association with disruption of heme metabolism (as in the liver), and direct and indirect evidence of renal tissue damage. Increases in kidney weight have been observed in many studies, primarily those involving 7 weeks of exposure (Andrews et al. 1989; Bouthillier et al. 1991; Den Besten et al. 1993; Den Tonkelaar et al. 1978; Kimbrough and Linder 1974; Koss et al. 1978; Kuiper-Goodman et al. 1977; Smith et al. 1985). Most studies shorter than 7 weeks in duration did not find increases in kidney weight, even using doses as high as 100 mg/kg/day (Andrews et al. 1988; Richter et al. 1981; Sundlof et al. 1981; Vos et al. 1979b). This includes interim sacrifices in longer duration studies that did eventually show increases in kidney weight (Andrews et al. 1989). Multiple-dose feeding studies of 12–16 weeks identified LOAEL values of 19–32 mg/kg/day and NOAEL values of 5–9.5 mg/kg/day for increased

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kidney weight in male and female rats (Den Besten et al. 1993; Kimbrough and Linder 1974; Kuiper-Goodman et al. 1977). Lower critical values were obtained when exposure was by gavage in oil rather than in the diet (Andrews et al. 1989, 1990), when pigs were tested rather than rats (Den Tonkelaar et al. 1978), and when exposure duration was extended over 1 year (Smith et al. 1985). The lowest LOAEL and NOAEL for increased kidney weight in any study were 1 and 0.1 mg/kg/day, respectively (Andrews et al. 1989). It has been proposed that increased kidney weight in animals exposed to hexachlorobenzene may result from induction of renal microsomal enzymes (Bouthillier et al. 1991). Renal pathology (described below) may have been a contributing factor in some studies.

Among the available studies, the most sensitive indication of renal pathology due to hexachlorobenzene was increased urine enzyme levels. Male rats treated with 1 mg/kg/day of hexachlorobenzene by gavage in oil for 15 weeks had increased concentrations of alkaline phosphatase and/or lactate dehydrogenase in the urine, an effect that was not found at 0.1 mg/kg/day (Andrews et al. 1989, 1990). These effect levels correspond with those for changes in kidney weight in the same studies. Increased urinary levels of these enzymes suggest the occurrence of either glomerular damage allowing the enzymes to leak into the urine from the serum or tubular cell damage where the enzymes are released directly from the damaged cells into the urine. There was an apparent increase in calcium excretion in a higher dose group that could be interpreted to indicate impaired reabsorption of calcium by the distal tubules, which would support the hypothesis that damaged tubular cells were responsible for the observed enzymuria.

Studies that included histopathological examination of the kidneys provided more direct evidence of damage to renal tubule cells. Bouthillier et al. (1991) observed degenerative and regenerative foci of epithelial cells in the proximal tubules and accumulation of protein droplets in proximal tubular cells in male rats treated with 50 mg/kg/day for 7 weeks or 100 mg/kg/day for 2 weeks. These lesions were accompanied by glucosuria, proteinuria, and an 11-fold increase in  $\alpha_{2u}$ -globulin levels. The nature of the effects in males and near-absence of effects in females (just glucosuria and an increase in urinary  $\gamma$ -glutamyl transpeptidase were found) led the researchers to suggest that hexachlorobenzene produces a male rat specific protein droplet nephropathy, as is seen with some other chlorinated benzenes. Support for a nephrotoxic effect in rats is provided by Smith et al. (1985), who found mild to severe nephrosis in 12/12 surviving male rats treated with 10 mg/kg/day for 90 weeks, but 0/10 surviving male controls and only 1/10 surviving treated females. Similarly, Arnold et al. (1985) observed chronic nephrosis in male, but not female, rats with combined pre- and postnatal lifetime exposure to 2 mg/kg/day of hexachlorobenzene.

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Renal lesions, however, have been reported in female rats treated with hexachlorobenzene. Basophilic renal tubules and protein casts were seen in female rats exposed to 19 mg/kg/day for 13 weeks (Den Besten et al. 1993). Renal accumulation of porphyrins has been reported in female rats exposed to doses as low as 5 mg/kg/day for 56 days (see below). Renal effects have also been noted in other animal species. Female monkeys treated with 8 mg/kg/day for 60 days developed vacuolization of proximal tubules, and at 128 mg/kg/day, thickening of the basement membranes, glomerular hyperemia, and increased BUN were also found (Iatropoulos et al. 1976; Knauf and Hobson 1979). Male pigs exposed to 50 mg/kg/day in the diet all died prior to scheduled sacrifice and were found upon necropsy to have degeneration of the proximal tubules and loop of Henle (Den Tonkelaar et al. 1978). Blood ammonia levels were increased 3-fold in female guinea pigs treated with 200 mg/kg/day (De Matteis et al. 1961). There is also a brief paper by Ertürk et al. (1986), lacking detail regarding experimental methods or results, that reports marked renal lesions, including severe hyperemia, necrotic tubular degeneration, hemorrhage, and nephritis in male and female rats, mice, and hamsters given 90-day dietary exposure to 10–33 mg/kg/day (although the effects were most severe in male rats, they were seen in all groups). The occurrence of renal effects in female rats and in other species of laboratory animal shows that the nephrotoxic effects of hexachlorobenzene are not limited to the  $\alpha_2\mu$ -globulin nephropathy demonstrated by Bouthillier et al. (1991), and suggests that this chemical may produce renal effects by multiple mechanisms.

Renal accumulation of porphyrins has been related to disruption of heme metabolism and lipid peroxidation. Female rats treated with 1,000 mg/kg/day of hexachlorobenzene by gavage in aqueous Tween 20 had a significant decrease in uroporphyrinogen decarboxylase (URO-D) activity in the renal cortex after 3 weeks of exposure and a subsequent increase in porphyrin levels in the renal cortex, but not the renal medulla or papilla, after 4 weeks of exposure (Fernandez-Tome et al. 2000). Lipid peroxidation, indicated by measurement of conjugated dienes and malondialdehyde (MDA), was significantly increased throughout most of the exposure period in the renal cortex, but was not increased at all in the renal medulla or papilla. Based on these findings, the researchers suggested that disruption of heme metabolism and accumulation of porphyrins in the renal cortex are secondary to lipid peroxidation produced by hexachlorobenzene in this tissue. Distribution of porphyria in kidney is consistent with fact that enzymes of heme metabolism are localized in the renal cortex; the occurrence of lipid peroxidation in the renal cortex is consistent with its relative susceptibility to oxidative stress, compared to the papilla or medulla. The use of such a high dose in this study reflects the fact that hexachlorobenzene is not well absorbed from water. Renal accumulation of porphyrins was observed at much lower doses (as low as 5 mg/kg/day) in feeding studies in female rats (Kennedy and Wigfield 1990; Smith et al. 1985),

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particularly when hexachlorobenzene was added to the diet in an oil vehicle (Kennedy and Wigfield 1990). No experimental evidence was found for renal accumulation of porphyrins in male rats treated with up to 25 mg/kg/day for 15 weeks in the diet or by gavage in oil (Andrews et al. 1989; Smith et al. 1985).

Despite the numerous data supporting an effect of hexachlorobenzene on the kidney, it should be noted that several well-conducted investigations of kidney histopathology failed to find any treatment-related lesions in either male or female rats, even with high exposures (up to 50 mg/kg/day for 4 months) that, based on the database as a whole, would have been expected to produce tissue damage (Kimbrough and Linder 1974; Kuiper-Goodman et al. 1977; Michielsen et al. 1997; Vos et al. 1979b).

**Endocrine Effects.** Human data suggest that hexachlorobenzene adversely affects the endocrine system; specifically, the thyroid is a target organ. Two follow-up studies conducted 25 (Peters et al. 1982) and 20–30 years (Cripps et al. 1984) after patients (n=161–225) were exposed as children to bread contaminated with hexachlorobenzene in Southeast Turkey detected thyromegaly in 60% of women and 25% of men (Cripps et al. 1984; Peters et al. 1982). The background incidence for this area was 5%. Additionally, hirsutism and small stature were observed in 47 and 44%, respectively, of the study population. However, a study of serum hormone and organochlorine levels in a cohort of 110 Swedish or Latvian men who consumed Baltic sea fish (Hagmar et al. 2001) found no age-adjusted correlation between hexachlorobenzene levels and any of the measured serum hormones (follicle-stimulating hormone, luteinizing hormone, prolactin, plasma thyrotropin, free and total T3, free and total T4, and free testosterone). The authors considered the fish to be a diet high in persistent organohalogens, but did not quantitate intake.

Animal studies have demonstrated that hexachlorobenzene has multiple endocrine effects; the most striking are the induction of hypothyroidism and hyperparathyroidism in rats. Limited evidence suggests that hexachlorobenzene also affects serum retinoid levels, the adrenal gland and serum levels of corticosterone and cortisol (see below). Moreover, studies have shown that hexachlorobenzene affects serum levels of estrogen and progesterone (discussed in Section 3.2.2.5, Reproductive Effects).

Multiple studies have demonstrated that serum T4 levels decrease rapidly in rats following gavage treatment with hexachlorobenzene (Den Besten et al. 1993; Den Tonkelaar et al. 1978; Foster et al. 1993; Kleiman de Pisarev et al. 1989, 1990, 1995; Smith et al. 1986b; Sopena de Kracoff et al. 1994; van Raaij et al. 1993a, 1993b). Effects on serum TSH levels (both increases and decreases) are delayed and appear

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secondary to decreases in T4. The most sensitive acute study observed statistically significant decreases in T4 levels in female rats at doses as low as 50 mg/kg/day for 5 days (Foster et al. 1993). A time-course in female Wistar rats gavaged with 1,000 mg/kg/day of hexachlorobenzene in corn oil found that serum T4 levels rapidly decreased, reaching a steady-state after 8 days, approximately 75% below controls. In contrast, serum TSH levels reached a steady state after 30 days, at 80% below controls (Sopena de Kracoff et al. 1994). Similarly, experiments in female Wistar rats gavaged with 1,000 mg/kg/day for at least 8 weeks observed significantly decreased serum T4 and protein-bound iodine and elevated TSH levels and thyroid weight (Kleiman de Pisarev et al. 1989, 1990, 1995).

The most sensitive intermediate-duration studies were conducted in male Syrian hamsters (Smith et al. 1986b, 1987), which responded differently than rats to hexachlorobenzene. In hamsters exposed to 10 mg/kg/day in feed for 28 weeks (the lowest effective intermediate-duration dose identified) or to a higher dose for a shorter time (50 mg/kg/day or more for 6 weeks), thyroid gland weights were significantly increased (2.5-fold), serum T3 levels were decreased, and sodium iodide uptake was increased (~3-fold), while serum T4 levels were unchanged. Thyroid weight increased significantly, and correlated with histopathological observations of large and irregularly shaped follicles in the thyroid. Notably, two other studies did not observe treatment-related thyroid histopathology at effective doses; Den Besten et al. (1993) observed decreased T3 and T4 levels in female Wistar rats exposed to hexachlorobenzene in the feed at doses up to 19.0 mg/kg/day for 13 weeks, and Den Tonkelaar et al. (1978) detected significantly increased thyroid weight in male Landvarken pigs fed 5 mg/kg/day of hexachlorobenzene for 12 weeks.

Increased hepatic metabolism and hepatic excretion (into bile) appear to be important to the mode-of-action for the thyroid effects of hexachlorobenzene. Kleiman de Pisarev et al. (1989, 1990, 1995) observed that gavage administration of 1,000 mg/kg/day of hexachlorobenzene in corn oil to female Wistar rats for 28–30 days not only significantly decreased serum T4 levels, but also increased both the metabolism (deiodination) and fecal excretion of T4. In male Wistar (WAG/MBL) rats orally dosed with 120 mg/kg/day of hexachlorobenzene 3 times/week for 4 weeks, levels of T4 glucuronide increased but levels of serum T4 and nonconjugated T4 decreased (van Raaij et al. 1993b). Hepatic T4 UDP-glucuronyltransferase (UDPGT) activity was increased while T4 iodothyronine deiodinase activity was decreased. Bile flow and T4 excretion were increased. However, serum T3 levels were unaffected. Taken together, these data indicate that hexachlorobenzene induces liver activity that results in decreased serum levels of T4. Treatment of female Sprague-Dawley rats with 50 mg/kg/day of hexachlorobenzene by gavage for 5 days significantly decreased serum T4 levels and free thyroxine index without affecting

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T3 uptake (Foster et al. 1993). However, following gonadotropin pretreatment to induce superovulation, 3-day treatment with 50 mg/kg/day of hexachlorobenzene significantly decreased both serum T4 levels and serum T3 uptake. The authors concluded that the acute induction of hypothyroidism was augmented by ovulation (Foster et al. 1993). Gavage treatment of inbred male Wistar (WAG/RIJ) rats with 27 mg/kg/day pentachlorophenol was more effective than 780 mg/kg/day of hexachlorobenzene at reducing free and total T4 levels (van Raaij et al. 1993a). The authors concluded that metabolites of hexachlorobenzene, rather than hexachlorobenzene itself, may be involved in the reduction of serum thyroid hormones.

Andrews et al. (1988, 1989, 1990) have conducted detailed studies into hexachlorobenzene-induced hyperparathyroidism and osteoporosis in male Fischer 344 rats. Gavage treatment of rats with doses as low as 1.0 mg/kg for 5 weeks, 5 days/week, significantly increased serum levels of vitamin D<sub>3</sub> and urinary levels of phosphorous. Treatment with at least 10 mg/kg significantly increased serum levels of PTH, increased urinary levels of calcium, and decreased serum levels of alkaline phosphatase (an enzyme important in bone mineralization). The combination of high PTH and vitamin D<sub>3</sub> is expected to cause calcium resorption from bone and calcium conservation by the kidneys, and this is consistent with the adverse skeletal effects seen by authors at 1.0 mg/kg (see Section 3.2.2.2, Musculoskeletal Effects).

Animal studies have shown that hexachlorobenzene affects the adrenal gland (weight, histopathology, and hormone levels). Adrenal gland weight was significantly increased in male and female Sherman rats fed at least 25 mg/kg/day of hexachlorobenzene for 4 months (Kimbrough and Linder 1974). Adrenal gland weight was also significantly increased in Wistar rat pups exposed to at least 2.5 mg/kg/day of hexachlorobenzene (starting early in pregnancy and continuing through gestation and lactation, and an additional 2 weeks after weaning) (Vos et al. 1979a). In female Wistar rats that were fed 9.5 or 19.0 mg/kg/day of hexachlorobenzene for 13 weeks (Den Besten et al. 1993), adrenal gland weight (69%) was significantly increased in the high-dose group. Histopathology (reported only for the high-dose group) observed adrenal cortex hypertrophy, hyperplasia, occasional hemorrhaging, cortical cell vacuolation, and inflammatory cell infiltrates. In female ovariectomized Sprague-Dawley rats gavaged for 30 days with 1, 10, or 100 mg/kg/day of hexachlorobenzene, corticosterone was decreased at all doses, but serum cortisol levels were only decreased by 100 mg/kg/day (Foster et al. 1995a). Moreover, no effect was seen on serum progesterone and aldosterone levels or adrenal weight. Koss et al. (1978) detected statistically significant increases in relative adrenal weight (up to 43%) in female Wistar rats that were treated with 50 mg/kg hexachlorobenzene every other day by gavage for 9–15 weeks; this effect had reversed after a 38-week posttreatment period. In another experiment, single adult female monkeys

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received 0, 8, 32, or 64 mg/kg and two monkeys received 128 mg/kg of hexachlorobenzene by gavage in methylcellulose daily for 60 days (Iatropoulos et al. 1976). One of the monkeys given 128 mg/kg exhibited moderate adrenal medullary hyperplasia and the monkey given 64 mg/kg/ exhibited slight hyperplasia of the adrenal zona fasciculata; however, these findings are not conclusive due to the small numbers of animals used.

Limited animal evidence suggests that hexachlorobenzene affects retinoid levels. In blood samples taken from 101 polar bears from Svalbard, Norway, statistically significant correlations were observed between higher blood levels of hexachlorobenzene and both lower levels of retinol and a lower ratio of total thyroxine (T4) to free triiodothyronine (T3) (Skaare et al. 2001). In female Wistar rats fed 19 (but not 9.5) mg/kg/day of hexachlorobenzene for 13 weeks (Den Besten et al. 1993), significant increases were seen in adrenal gland weight (69%) and both liver retinol and retinyl palmitate levels. Plasma retinol levels were not affected at 1 week, but were significantly increased at 13 weeks by the high dose.

**Dermal Effects.** Studies of humans exposed to hexachlorobenzene in bread prepared from contaminated grain in Turkey demonstrated that hexachlorobenzene can produce skin lesions following oral exposure. It is well known that ingestion of hexachlorobenzene can produce porphyria (see Section 3.2.2.2, Hepatic Effects). The porphyrias are a class of inherited and acquired diseases caused by enzymatic defects in heme biosynthesis, leading to the generation of porphyrins. One of the most serious symptoms of porphyria is photosensitivity; porphyrins accumulated in the skin absorb radiation (maximally at 400–410 nm) and then generate reactive oxygen species, causing tissue damage (Lim and Cohen 1999; Meola and Lim 1993; Sandberg et al. 1982). Skin lesions occur most commonly on areas exposed to sunlight, such as the hands and face. Porphyria cutanea tarda, a specific type of vesiculobullous porphyria, was widespread in southeast Anatolia, Turkey in the late 1950s (approximately 1955–1959). The disease was traced to ingestion of bread made from seed grain that had been treated with hexachlorobenzene as a fungicide (Cam and Nigogosyan 1963). The ingested dose of hexachlorobenzene by exposed persons was estimated to be in the range of 0.05–0.2 g/day (0.7–2.9 mg/kg/day for a 70-kg person) during the episode (Cam and Nigogosyan 1963). Symptoms of what was called *kara yara* or “black sore” appeared after approximately 6 months of exposure (Gocmen et al. 1989). The disease was observed most frequently in children between the ages of 6 and 15 years, although some younger children and adults were also affected (Cam and Nigogosyan 1963; Dogramaci 1964). The initial lesions resembled comedones (blackhead acne) and milia (small whitish epidermal cysts caused by hair follicle and sweat gland obstruction) with photosensitivity and the development of erythema on sun-exposed areas; moreover, the skin was sensitive to minor trauma. These lesions

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progressed to include large bullous lesions that ulcerated and healed leaving severe mutilating scars, hyperpigmentation that was most prominent on exposed areas but usually affected the entire skin, and hypertrichosis (hirsutism) that occurred principally on the forehead, cheeks, arms, and legs but occasionally involved the whole body (Gocmen et al. 1989). Infants who had been breast fed by mothers who had ingested the contaminated bread displayed a condition known as *pembe yara* or "pink sore" because of the associated skin lesions (annular erythema) (Peters et al. 1966, 1982). The medical history of people who were exposed to hexachlorobenzene in the Turkish poisoning episode was followed for up to 30 years (Cripps et al. 1984; Gocmen et al. 1989; Peters et al. 1982, 1987). A total of 252 patients who had become porphyric during the Turkish epidemic were studied over a 10-year period from 1977 to 1987 (Gocmen et al. 1989). Subjects had an average age of 7.6 years at onset of symptoms and an average age at follow-up of 35.7 years. Thirty years after onset, clinical findings persisted in most subjects, including severe scarring (83.7%), hyperpigmentation (65%), hypertrichosis (44.8%), pinched face appearance with perioral scarring (40.1%), and fragile skin (33.7%). Dermal lesions were more prominent in sun-exposed areas of the skin.

Studies into the mode of action of porphyria (unrelated to hexachlorobenzene-exposure) have suggested that the dermal toxicity of porphyrins is exacerbated by involvement of the immune system; following irradiation, porphyrins may activate the complement system and stimulate mast cells and neutrophils to damage nearby tissues (Lim and Cohen 1999; Meola and Lim 1993). Additionally, an increased risk of porphyria cutanea tarda has been associated with human immunodeficiency virus (HIV) infection (Drobacheff et al. 1998; Egger et al. 2002).

Although several animal studies have demonstrated that oral exposure to hexachlorobenzene (for at least 4 weeks) results in dermal lesions and causes immunological effects with dermal lesions, none established a casual relationship (Koss et al. 1978; Michielsen et al. 1997, 2000; Schielen et al. 1995a; Torinuki et al. 1981). Additionally, it is unclear whether porphyrin-induced phototoxicity occurs in rats; the combination of hexachlorobenzene and sunlight exposure induced dermal lesions in rats similar to those reported in people (Torinuki et al. 1981). However, hexachlorobenzene-treated rats have exhibited skin lesions without detectable dermal porphyrin accumulation (assayed with fluorescence microscopy) (Michielesen et al. 1997). Dermal lesions in rats following hexachlorobenzene exposure have been seen most frequently on the head, neck, and shoulders (similar to humans) although the rats' exposure to sunlight was presumably limited by experimental design and body fur (Koss et al. 1978; Michielsen et al. 1997, 2000). These data seem to suggest that additional modes-of-action are important.

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Dermal effects were noted in a study of female Wistar rats that were gavaged with 50 mg/kg hexachlorobenzene in olive oil every other day for 9–15 weeks, followed by a 38-week observation period (Koss et al. 1978). The fur had a roughened appearance during treatment, and round, ulcerous lesions on the head, ears, throat, and shoulders, with diameters of 2–20 mm, were observed in 10% of treated animals after 4 weeks and 50% of animals after 9 weeks. These lesions resolved 12–16 weeks after discontinuation of treatments. At 15 weeks only, spleen weight was significantly increased. A subsequent study, using lower doses and more sensitive end points, observed strain specificity in rats fed hexachlorobenzene for 4 weeks (Michielsen et al. 1997). Brown Norway and Lewis rats received 18 or 53 mg/kg/day, while Wistar rats were fed 50 or 97 mg/kg/day. Increased incidence of skin lesions were statistically significant for all treatment groups compared to controls. In Brown Norway rats, skin lesions were very severe, and their incidence was correlated with signs of immunomodulation (increased IgG, IgE, and IgM levels, spleen weight, and lung inflammation). In Lewis rats, skin lesions were moderate, and correlated less strongly with evidence of immune effects. In Wistar rats, lesions were observed only at the high dose, and were considered negligible; immune effects were also minor. Grossly, the lesions were found in the head and neck region and ranged from redness only to large exudating sores with crusts. Histopathology of both lesional and non-lesional skin observed epidermal hyperplasia, deep dermal venules with activated endothelial cells, and deep inflammatory cell infiltrates. A subsequent experiment (Michielson et al. 2000) verified that doses as low as 58 mg/kg/day in the feed of female Brown Norway rats for 4 weeks induced skin lesions in the head and neck areas, the severity of which increased with time. Likewise, a study in female Wistar rats fed 15 or 30 mg/kg/day of hexachlorobenzene for 13 weeks observed statistically significant increases in the incidence of wounds appearing by weeks 5–7 on the face, neck, shoulders, and behind the ears of treated animals (Schielen et al. 1995a). The incidence (but not severity) increased with increasing dose. Treatment also induced porphyria and increased serum levels of IgM, IgA, and autoantigen-specific IgM. Torinuki et al. (1981) treated rats for 2 months with hexachlorobenzene with repeated exposure to sunlight. In addition to porphyria, gross pathology of the skin observed erythema, erosion, crusting, skin thickening, and scarring. Histopathology found acanthosis (abnormal dermal thickening), vacuolization of malpighian cells, subepidermal vesicles, blood vessel dilation, and perivascular cell infiltration of lymphocytes, histiocytes, and mast cells. In addition to lesions, hexachlorobenzene has induced dermal effects that are not clearly toxic. In female Wistar rats, skin cytochrome P450-dependent 7-ethoxyresorufin-O-deethylase was induced after 60 or 70 days (but not 10 days) of feeding with 50 mg/kg/day of hexachlorobenzene (Goerz et al. 1978, 1994). No dermal lesions were observed in female Agus Wistar rats fed diets containing 5 mg/kg/day of hexachlorobenzene for 90 weeks, although treated animals “possessed less hair than controls” (Smith and Cabral 1980).

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**Ocular Effects.** No studies were found regarding adverse ocular effects in humans following oral exposure to hexachlorobenzene.

Only one relevant animal study was identified. In adult female Rhesus monkeys treated by gavage with hexachlorobenzene in methylcellulose at doses up to 32 mg/kg/day for 60 days, gross pathology and histopathology of the eyes did not detect any adverse effects (Iatropoulos et al. 1976).

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

Decreases in body weight following oral exposure of animals to hexachlorobenzene were not observed following acute exposure and were observed in intermediate- and chronic-duration experiments only in the presence of other adverse effects such as mortality, clinical evidence of weakness or lethargy, increased incidences of tumors, or liver toxicity (see below and Section 3.3.2). The available data suggest that body weight loss may be secondary to organ-specific toxicity.

No acute studies have reported changes in body weight. Body weight was not affected in rats dosed once by gavage with 400 or 600 mg/kg of hexachlorobenzene in corn oil (Lecavalier et al. 1994) or in male rats gavaged with doses up to 221 mg/kg/day for 5 consecutive days (Simon et al. 1979).

Similarly, many intermediate-duration experiments did not detect significant changes in body weight in Wistar rats fed up to 1,000 mg/kg/day of hexachlorobenzene for 4 weeks (Alvarez et al. 2000; Kleiman de Pisarev et al. 1995; Michielsen et al. 1997; Schielen et al. 1993, 1995b; Vos et al. 1979b), in Brown Norway rats and Lewis rats fed up to 45 mg/kg/day for 4 weeks (Michielsen et al. 1997, 2000), in ovariectomized adult female Sprague-Dawley rats gavaged with doses up to 100 mg/kg/day of hexachlorobenzene in corn oil for 30 days (Foster et al. 1995b), in female CD rats fed up to 36 mg/kg/day for 4 months (Goldstein et al. 1978), in female Wistar rats fed 5 mg/kg/day of hexachlorobenzene in arachis oil for 75 weeks (Smith and Cabral 1980), or in male BALB/c mice fed 22 mg/kg/day for 6 weeks (Loose et al. 1977). Intermediate-duration experiments that did report statistically significant weight loss in rats (Kuiper-Goodman et al. 1977; Smith and Cabral 1980; Smith et al. 1985) or mice (Cabral et al. 1979; Shirai et al. 1978) usually considered it to be slight-to-moderate. The most rapid onset of weight loss was a slight decrease at doses as low as 22 mg/kg/day in male Wistar rats for 6 weeks, in the presence of increased liver, spleen, and lymph node weight and decreased natural killer cell activity (Van Loveren et al. 1990). Although one study reported statistically significant decreases in body weight in male

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Fisher 344 rats at doses as low as 0.1 mg/kg of hexachlorobenzene by gavage in corn oil 5 days/week for 5 weeks (Andrews et al. 1988), subsequent studies using the same protocols in 15-week experiments saw no effects on body weight (Andrews et al. 1989, 1990). Oral intermediate-dosing studies that observed hexachlorobenzene-induced mortality also found significant weight loss. In a 13-week feeding study, four of nine female Wistar rats receiving the high dose of 19 mg/kg/day of hexachlorobenzene in corn oil for 13 weeks were euthanized during the study due to severe weight loss and distress, while no body weight effects were seen in surviving or lower dose animals (Den Besten et al. 1993). Male Syrian golden hamsters fed 16 (but not lower doses up to 8) mg/kg/day of hexachlorobenzene in the diet for life, males exhibited “marked weight reduction” and significantly increased mortality (Cabral et al. 1977). However, similar mortality was observed in treated female hamsters without corresponding weight loss.

Similar findings have also been demonstrated in dogs, monkeys, and pigs. No treatment-related effects on body weight were observed in adult female beagle dogs that received hexachlorobenzene in corn oil orally in capsules for 3 weeks at doses up to 100 mg/kg/day (Sundlof et al. 1981) or in male and female beagle dogs fed capsules of hexachlorobenzene at doses up to 110 mg/kg/day for up to 12 months (Gralla et al. 1977a). Similarly, experiments in which female *Cynomolgus* monkeys were dosed with hexachlorobenzene in gelatin capsules at doses up to 10 mg/kg/day for 90 days, did not detect changes in body weight (Foster et al. 1992a, 1995a; Jarrell et al. 1993). In contrast, unspecified weight loss was reported beginning at 4 weeks in adult female Rhesus monkeys given hexachlorobenzene by daily gavage (in aqueous methylcellulose) for 60 days at doses as low as 8 mg/kg/day; renal and neurological effects were also reported (Knauf and Hobson 1979). All male SPF pigs fed 50 mg/kg/day (but not lower doses up to 5 mg/kg/day) for 90 days exhibited depressed growth (beginning at week 4) prior to death between weeks 8 and 12 (Den Tonkelaar et al. 1978).

In fetal and immature pups, hexachlorobenzene-induced changes body weight were observed only in the presence of maternal toxicity. No decreases in maternal or pup body weight were observed at doses as high as 100 mg/kg/day on gestation days 7–16 in CD-1 mice or as long as *in utero* and lifetime exposure of Sprague-Dawley rats to 2 mg/kg/day (Arnold et al. 1985; Courtney et al. 1976; Goldey and Taylor 1992; Lilienthal et al. 1996; Taylor and Goldey 1990; Vos et al. 1979a, 1983). In Wistar rats, maternal and fetal body weight were decreased by gavage doses of at least 80 mg/kg/day of hexachlorobenzene in corn oil on gestation days 6–21 (Khera et al. 1974a); however, slight changes in the dosing protocols (fewer treatment days, use of aqueous gum tragacanth instead of corn oil) prevented weight loss.

Likewise, Sprague-Dawley rat pup weight and viability were significantly reduced at birth, 5 days, and 24 days, following lifetime dietary exposure of both male and female parent rats to at least 4 mg/kg/day

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(Grant et al. 1977). Maternal signs reported by these two studies (Grant et al. 1977; Khera et al. 1974a) included mortality, convulsions, and reduced fertility.

### 3.2.2.3 Immunological and Lymphoreticular Effects

Although epidemiological studies have suggested that consumption by mothers of fish high in organochlorines may affect the immune system of their infants, oral exposure of people to hexachlorobenzene has not been clearly associated with immunological effects. The levels of hexachlorobenzene, dieldrin, and *p,p'*-dichlorodiphenyldichloroethylene (*p,p'*-DDE) in milk samples collected shortly after the birth of Canadian Inuit infants correlated with increased risk of otitis media in their first year of life, but not with other serum immune parameters (immunoglobulins, cytokines, lymphocyte activation markers) (Dewailly et al. 2000). A similar study of immune parameters in umbilical blood of Canadian mothers with high or low consumption of fish from the Lower-North-Shore of the St. Lawrence River detected a statistically significant association only between decreased lymphocyte secretion of cytokine IL-10 and increased levels of hexachlorobenzene, *p,p'*-DDE, and mercury (Belles-Isles et al. 2000). However, evidence suggests that hexachlorobenzene may indirectly affect the immune system by inducing porphyria (see Section 3.2.2.2 Hepatic Effects). Mode-of-action studies of individuals with inherited and acquired porphyria (unrelated to hexachlorobenzene) have found that irradiated porphyrins may activate the complement system and stimulate mast cells and neutrophils to damage nearby tissues (Lim and Cohen 1999; Meola and Lim 1993). Additionally, an increased risk of porphyria cutanea tarda has been associated with HIV infection (reviewed Drobacheff et al. 1998; Egger et al. 2002).

The effects of oral exposure to hexachlorobenzene to the immune system of animals appear to be species- and strain- (Michielsen et al. 1997) dependent, with immunosuppression observed in mice (see below), monkeys (Iatropoulos et al. 1976) and bears (Bernhoft et al. 2000), and at least a partial stimulation of the immune system in rats (see below) and dogs (Gralla et al. 1977a). Additionally, a number of animal studies have observed inflammation and immune cell infiltration in tissues such as the liver (Arnold et al. 1985; Ertürk et al. 1986), respiratory tract (Goldstein et al. 1978; Kimbrough and Linder 1974; Kitchin et al. 1982; Michielsen et al. 1997, 1999, 2001; Vos et al. 1979a, 1983), and skin (Koss et al. 1978; Michielsen et al. 1997, 2000; Schielen et al. 1993, 1995b; Torinkui et al. 1981) following oral exposure to hexachlorobenzene. The lowest dose to cause an immune response was 0.016 mg/kg/day, which induced peribiliary lymphocytosis in F<sub>1</sub> Sprague-Dawley rats exposed for life to dietary doses (Arnold et al. 1985). Because the mode-of-action is unclear, it is not known if these immune effects are secondary following toxicity to target organs or if they are involved in the etiology of disease in these organs.

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Mode-of-action studies in rats have suggested that the immune effects of hexachlorobenzene may be secondary to the accumulation of porphyrins produced by the liver in the spleen or other organs of immunological importance (Kennedy and Wigfield 1990; Kuiper-Goodman et al. 1977) or by the metabolic products of hexachlorobenzene (Schielen et al. 1995a).

Immunosuppression has been observed in male mice following oral exposure to hexachlorobenzene. The most sensitive effects were seen at dietary doses as low as 0.6 mg/kg/day; 6 weeks of exposure significantly reduced spleen cell cytotoxic activity (Loose et al. 1981) and 18 weeks of exposure decreased the mean survival time of mice following challenge with injected ascites tumor cells. Immune effects were seen as early as 3 weeks; feeding of 13 mg/kg/day decreased survival time following ascites tumor cell challenge (Loose et al. 1981), and feeding with 22 mg/kg/day decreased resistance to bacterial endotoxin (*Salmonella typhosa* lipopolysaccharide [LPS]) and to malarial infection (*Plasmodium berghei*) (Loose et al. 1978). Feeding at the same dose (22 mg/kg/day) for 6 weeks reduced primary and secondary plaque-forming cell responses to sheep red blood cells, reduced serum IgG, IgM, and IgA levels, increased spleen weight (Loose et al. 1977), increased susceptibility to infection by hepatitis (but not cytomegalovirus or pneumonia) virus (Carthew et al. 1990), and reduced ability of spleen cells to lyse P388 tumor cells (Silkworth and Loose 1981). Feeding of 22 mg/kg/day for 37 (but not 13 or fewer) weeks of treatment decreased graft-versus-host response (measured by injecting harvested spleen cells into neonatal BDF1 mice) (Silkworth and Loose 1981). In addition to the effects seen in adult male mice, similar effects were observed in a developmental study. Pups of pregnant BALB/c mice fed doses as low as 0.5 mg/kg/day on gestation days 1–18 exhibited a marked, significant decrease in delayed type hypersensitivity (DTH) response when tested on postnatal day 45 (Barnett et al. 1987). Analyses of collected spleen cells found that 5 (but not 0.5) mg/kg/day decreased mixed lymphocyte response and decreased B cell numbers; neither dose affected spleen blastogenesis induced by T- or B-cell mitogens.

In contrast to the immunosuppression observed in mice exposed to hexachlorobenzene, studies in rats have generally found stimulation of the immune system, as indicated by such effects as increased spleen and lymph node weights, increased neutrophil counts, and increased serum immunoglobulins. In feeding studies with male rats, exposure to at least 25 mg/kg/day of hexachlorobenzene for 3 weeks caused increased neutrophil counts, elevated popliteal lymph node weight with a corresponding proliferation of popliteal lymph node high-endothelial venules (Vos et al. 1979b), and spleen histopathology consisting of extramedullary hematopoiesis, enlarged marginal zones and follicles, and increased macrophage density in the marginal zones (Schielen et al. 1993; Vos et al. 1979b). In Wistar rats fed doses as low as 50 mg/kg/day for 3 weeks, immunological effects observed included increased spleen and lymph node

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(popliteal, inguinal, and mediastinal, but not parathyroid) weight; increased basophil, monocyte, and total leukocyte counts (Kennedy and Wigfield 1990; Koss et al. 1978; Schielen et al. 1995b; Vos et al. 1979a, 1979b); increased splenic (but not lymph nodal) cell size; selectively activated B cell (but not T cell) subpopulations (Schielen et al. 1995b); increased splenic and serum levels of total IgM; and increased serum levels of specific IgM (anti-phosphatidylcholine IgM, and anti-single stranded DNA IgM) without increases in IgM against foreign antigens (tetanus toxoid, sheep erythrocytes, and bovine serum albumin) (Schielen et al. 1993, 1995b). These reported changes in B cell populations and IgM levels strongly suggest an autoimmune response. Remarkably, no changes were seen immune function tests for thymus-independent (*Escherichia coli* lipopolysaccharides) and thymus-dependent (tetanus toxoid) antibody responses, cell-mediated immunity (rejection of skin transplants, resistance to *Listeria monocytogenes* infection, or delayed-type hypersensitivity to *Mycobacterium tuberculin*), phagocytic competence (clearance of carbon particles), the mitogenic response of peripheral blood lymphocytes (to pokeweed mitogen, concanavalin A, and phytohemagglutinin), or susceptibility to *E. coli* endotoxin in Wistar rats at doses up to 100 mg/kg/day for 3 weeks (Vos et al. 1979b). Feeding of male Wistar rats with doses as low as 8 mg/kg/day for 6 weeks reduced natural killer cell activity (Van Loveren et al. 1990). Atrophy of the thymus was observed in male rats fed 100 mg/kg/day for 3 weeks (Vos et al. 1979b) and in female Wistar rats fed 15 mg/kg/day for 13 weeks (Schielen et al. 1995a).

Two developmental studies in rats by the same laboratory reported hexachlorobenzene effects on humoral and cellular immunity (Vos et al. 1979a, 1983). The first study reported that hexachlorobenzene exposure strongly enhanced humoral immunity (antibody response to tetanus toxoid), but slightly depressed cellular immunity (as evaluated by susceptibility to infection, skin graft rejection time, and response to mitogens) in pups whose mothers were fed 2.5 or 7.5 mg/kg/day of hexachlorobenzene from early pregnancy and continuing through gestation and lactation; after weaning pups were fed the same doses for an additional 2 weeks prior to testing (Vos et al. 1979a). In both treatment groups, resistance to infection (*L. monocytogenes* and *Trichinella spiralis*) was reduced, the IgG response to tetanus toxoid was significantly increased, and histopathology found proliferation of high-endothelial venules in the paracortex of the lymph nodes. At 7.5 mg/kg/day, the IgG response to *Trichinella* was increased, increases were seen in blood levels of eosinophils, basophils, IgM and IgG, and histopathology found accumulation of foamy macrophages in the lung and increased extramedullary hematopoiesis in the spleen. Neither dose affected rejection of skin transplant, passive cutaneous anaphylaxis, IgM response to LPS, mitogenic responsiveness of lymphocytes, clearance of carbon particles, or clearance of *Listeria monocytogenes*. However, the follow-up study found that hexachlorobenzene stimulated both humoral and cell-mediated immunity in the Wistar rat pups whose mothers were fed 0.2, 1, or 5 mg/kg/day of

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hexachlorobenzene from early pregnancy through lactation; weaning pups were fed the same doses up to 7 months (Vos et al. 1983). Cytotoxicity of spleen cells (to injected lymphoma cells) was not affected by treatment. Treatment with at least 0.2 mg/kg/day significantly increased the IgG and IgM response to tetanus toxoid and delayed-type hypersensitivity reaction to ovalbumin, and induced accumulation of foamy macrophages in the lungs. At 1 mg/kg/day and above, increased popliteal lymph node weight with a corresponding increase in lymph node cellular proliferation were observed, and cell proliferation was also detected in the endothelial cells lining pulmonary capillaries and venules. At 5 mg/kg/day, increases were observed in spleen, lung, and mesenteric lymph node weight; serum IgM (but not IgG) levels; the relative number of basophils in the blood; and extramedullary hematopoiesis of the spleen. These effects demonstrated stimulation of both humoral and cell-mediated immunity.

A strain-dependent correlation between immunological and dermal effects was observed in female rats (Michielsen et al. 1997). For 28 days, Wistar rats were fed 22 or 45 mg/kg/day, while Lewis rats were fed 8 or 22 mg/kg/day, and Brown Norway rats were fed 8, 22, or 45 mg/kg/day of hexachlorobenzene. Brown Norway rats were the most sensitive to hexachlorobenzene exposure, and correlations were observed between the incidence and severity of immune responses and dermal lesions. In contrast, Wistar rats were the most resistant, and correlations were not apparent, while some correlations were seen in Lewis rats. Hexachlorobenzene induced skin lesions in all treatment groups, most severe in Brown Norway rats and least severe in Wistar rats, characterized by epidermal hyperplasia, inflammatory infiltrate in the dermis, and activation (due to hypertrophy and proliferation) of endothelial cells in dermal vessels. Relative spleen weights were significantly increased in a dose-related fashion in all three strains while popliteal lymph node weight was increased in the high-dose Lewis and Brown Norway rats, but not in Wistar rats. All strains showed increases in IgM, but only Brown Norway rats exhibited increases in serum IgE and IgG. However, lung pathology was not strain dependent; histopathology observed lung lesions consisting of venules lined with unusually plump endothelial cells and surrounded by large perivascular infiltrate and accumulation of alveolar macrophages. The authors concluded that the inflammatory responses in the skin and lungs were of different etiologies, and speculated an involvement of the immune system in the observed dermal lesions.

Studies of the immunological effects of hexachlorobenzene in nonrodents observed evidence of immunosuppression in monkeys and bears, and stimulation of the immune system in dogs. In female Rhesus monkeys, gavage with hexachlorobenzene in methylcellulose at doses as low as 8 mg/kg for 60 days caused thymic cortical atrophy, consisting of a reduction or absence of individual lobules, increased numbers of thymic corpuscles, and medullar hyperplasia or reticular cells, macrophages, plasma

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cells, and lymphocytes. However, the use of only one or two monkeys in this study diminishes the reliability of these data (Iatropoulos et al. 1976). A significant correlation between hexachlorobenzene levels and decreased IgG was observed in an analysis of sera from 56 polar bears in Svalbard, Norway, observed (Bernhoft et al. 2000). Because similar correlations were also observed for three polychlorinated biphenyl congeners (99, 194, and 206), this effect cannot be clearly attributed to hexachlorobenzene. Although no immunologically-related gross pathology or histopathology were observed in a 21-day oral study in female dogs at doses as high as 150 mg/kg/day (Sundlof et al. 1981), nodular hyperplasia of gastric lymphoid tissue was found in all beagle dogs given hexachlorobenzene in gelatin capsules daily for 12 months at doses as low as 10 mg/kg/day and an increased incidence of inflexible neutrophilia (increased numbers of blood neutrophils without fever) was observed at 10 and 110 mg/kg/day (Gralla et al. 1977a).

The highest NOAEL values and all reliable LOAEL values for immunologic effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

#### **3.2.2.4 Neurological Effects**

The evidence of neurotoxicity in humans following oral exposure to hexachlorobenzene was provided by studies of people in southeast Turkey who consumed contaminated bread in the late 1950s. The ingested dose of hexachlorobenzene by exposed persons was estimated to be in the range of 0.05–0.2 g/day (0.7–2.9 mg/kg/day for a 70-kg person) during the episode (Cam and Nigogosyan 1963).

Neurological symptoms included loss of appetite, tremors, convulsions, and “weakness that often made it impossible to eat with a knife and fork, rise from a squat, or climb stairs” (Gocmen et al. 1989; Peters et al. 1982). Follow-up studies of 25 (Peters et al. 1982) and 30 years (Cripps et al. 1984) included 161 and 204 patients, respectively. They found that neurological symptoms persisted in adults who had been exposed as children, and included weakness (62–66%), paresthesia (spontaneous tingling or burning sensations, 55%), sensory shading (graded sensory loss that diminishes upon testing more proximally and is indicative of polyneuropathy, 61–63%), myotonia (delayed muscle relaxation after an initial contraction, 38–50%), and cogwheeling (irregular jerkiness of movement due to increased muscle tone as seen in Parkinson’s disease, 29–41%). During the grain poisoning epidemic, there was an extremely high (95%) rate of mortality in infants under 2 years of age, who had been breast fed by mothers who had ingested the contaminated bread; these children exhibited convulsions, tremors, and progressive weakness prior to death (Cripps 1990; Peters et al. 1966). Analysis of human milk from exposed women and

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unexposed controls in this epidemic showed hexachlorobenzene concentrations of 0.51 and 0.07 ppm, respectively (Cripps et al. 1984; Gocmen et al. 1989; Peters et al. 1982, 1987). A study investigating the potential effects of consuming fish from the Great Lakes was unable to correlate hexachlorobenzene levels in umbilical blood or breast milk with infant intelligence test results (Darvill et al. 2000).

Multiple studies have shown that hexachlorobenzene induces serious neurological effects such as convulsions, tremors (intermittent and constant), lethargy, and progressive weakness in rats, mice, rabbits, pigs, monkeys, and quail (Cabral et al. 1979; Cripps 1990; De Matteis et al. 1961; Den Besten et al. 1993; Den Tonkelaar et al. 1978; Grant et al. 1977; Hahn et al. 1988; Kennedy and Wigfield 1990; Kimbrough and Linder 1974; Khera 1974a; Knauf and Hobson 1979; Ockner and Schmid 1961; others). In several studies, these effects were only seen prior to death or in treatment groups with significant mortality. The lowest dose to cause such serious effects was 8 mg/kg/day in Sprague-Dawley rats as part of a multigeneration study, with convulsions preceding death (Grant et al. 1977). In comparison, no tremors were seen in female Agus or Wistar rats fed diets containing 5 mg/kg/day of hexachlorobenzene for 75–90 weeks (Smith and Cabral 1980). Similar effects have been seen in other species. Mice orally exposed to 26 mg/kg/day of hexachlorobenzene for up to 17 weeks exhibited severe tremors prior to death (Hahn et al. 1988). Male SPF pigs fed 50 mg/kg/day of hexachlorobenzene for 90 days exhibited tremors, panting, and unsteady gait without histopathology (Den Tonkelaar et al. 1978). Adult female Rhesus monkeys given oral doses of hexachlorobenzene for 60 days suffered severe tremors and muscular weakness at doses as low as 64 mg/kg/day and marked lethargy and weakness were observed at 128 mg/kg/day (Knauf and Hobson 1979). Two of three infant Rhesus monkeys whose mothers were treated with 64 mg/kg/day for up to 60 days during lactation displayed hypoactivity, lethargy, and ataxia, and subsequently died (Iatropoulos et al. 1978). The offspring of pregnant rats fed 200 (but not 5) mg/kg/day for an unspecified period during gestation exhibited convulsions, tremors, and progressive weakness (Cripps 1990).

Other studies have investigated more subtle neurological effects resulting from oral exposure to hexachlorobenzene. Electrophysiological changes (dysrhythmic electroencephalogram) in the central nervous system were demonstrated in dogs receiving doses of 50 mg/kg/day for 21 days (Sundlof et al. 1981). Another functional experiment observed axonal effects in the sciatic nerve (fibrillations, repetitive or pseudomyotonic discharges, and mild slowing of conduction velocities) in rats fed 40 mg/kg/day of hexachlorobenzene for 20 weeks or at least 3.75 mg/kg/day for 2 years (Sufit et al. 1986). In male Wistar rats gavaged with doses as low as 317 mg/kg/day for 4 weeks, significant decreases were observed in the rate of T4 uptake into cerebrospinal fluid and brain tissue (van Raaij et al. 1994). Additionally, gavage

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treatment of Chbb THOM and Wistar rats with 1,000 mg/kg/day of hexachlorobenzene in a water-Tween suspension for up to 28 days induced changes in brain phospholipids (phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, phosphatidylserine, and sphingomyelin) without affecting brain porphyrin levels (Billi de Catabbi et al. 2000b; Cochon et al. 2001). Because these effects were seen prior to the onset of porphyrin accumulation in the liver, the authors concluded that the effects of hexachlorobenzene on phospholipids in the brain were different from its effects on phospholipids of the liver or Harderian gland, which reportedly occur following porphyrin accumulation.

One of two developmental studies in rats that investigated the neurobehavioral effects of hexachlorobenzene observed hyperactivity. Two weeks prior to mating, female Sprague-Dawley rats were gavaged for 4 days with 2.5 or 25 mg/kg/day (Goldey and Taylor 1992; Taylor and Goldey 1990). In the first 3 weeks postnatally, both treatment groups of pups exhibited a significantly increased level of hyperactivity compared to controls. Specifically, treated pups reoriented themselves significantly more quickly in a negative geotaxis test, required less time in an olfactory discrimination test, and demonstrated increased exploratory activity in a motor activity test (postnatal days 15–20). No significant effects on learning (swim T-maze) or motor activity (measured in older offspring on postnatal days 40 and 50, respectively) were detected. Pups exposed to 25 mg/kg/day exhibited decreased acoustic startle response (ASR) on postnatal day 23 and increased ASR on postnatal day 90. Another study fed female Wistar rats hexachlorobenzene for 90 days prior to mating through lactation and offspring were maintained on the same diet until postnatal day 150 (Lilienthal et al. 1996). In pups exposed to 1.3 mg/kg/day (but not lower doses up to 0.64 mg/kg/day), significant decreases were seen in operant learning (“post-reinforcement pause” and “index of curvature”) on postnatal day 150. However, because the rats were exposed both developmentally and as adults, the development significance of changes in operant learning is unclear. No changes were seen in an open field activity test (a measure of early locomotor skills) on day 21 or an active avoidance learning test on day 90.

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species for intermediate duration category are shown in Table 3-2 and plotted in Figure 3-2.

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**3.2.2.5 Reproductive Effects**

Epidemiological studies suggest that hexachlorobenzene may cause spontaneous abortion in women. In Southeastern Turkey, consumption of bread made from grain treated with hexachlorobenzene resulted in widespread poisoning between 1955 and 1959. Although no quantitation of exposure was presented in any of these clinical reports, an estimated dose of 0.05–0.2 g/day (0.7–2.9 mg/kg/day for a 70-kg person) is considered to be reliable by the original investigators of the Turkey epidemic (Cam and Nigogosyan 1963). A follow-up study conducted between 1977 and 1981 identified 42 porphyric mothers who had been exposed as children, with 188 pregnancies (Peters et al. 1982, 1987). Of these, 15 were fetal deaths (13 miscarriages and 2 stillbirths), and 31 produced children who died in the first several years of life. Similarly, another follow-up study conducted 20–30 years after initial exposure identified 57 porphyric mothers, who had a total of 276 pregnancies (Gocmen et al. 1989). Of these, 23 were fetal deaths, and 54 produced children who died in the first several years of life. Porphyric mothers had an average of 0.51 ppm hexachlorobenzene in their breast milk, compared to 0.07 ppm in unexposed controls (Gocmen et al. 1989). The degree to which these two exposed populations overlap and the expected frequencies of adverse pregnancy outcomes for the unexposed cohorts were unclear. Surviving offspring of porphyric mothers were clinically normal, and had urine and stool porphyrin levels similar to control children.

A subsequent retrospective study, conducted 40 years after initial exposure, compared three groups of 42 women (controls from outside the exposed area and women from the hexachlorobenzene-exposed region either with or without a diagnosis of porphyria cutanea tarda) (Jarrell et al. 1998). The incidence of women with blood levels of hexachlorobenzene exceeding 1 ng/mL was greater in women with porphyria cutanea tarda or women living in the contaminated region than country-wide controls and correlated (across exposure-groups) with an increased risk of spontaneous abortion. Notably, blood levels did not correlate with the number of pregnancies, sex ratio of born children, or onset of menopause. Statistically significant increases in the levels of inhibin (a hormone secreted by ovarian granulosa cells to decrease the release of follicle-stimulating hormone [FSH] from the pituitary) were observed in women diagnosed with porphyria cutanea tarda. Because no exposure-related differences were seen for FSH or estradiol, the biological significance is unclear, but ovarian effects would be consistent with animal studies (see below).

Studies of other populations with exposure to multiple organochlorines did not find significant differences in blood hexachlorobenzene levels between controls and cases of spontaneous abortion in Italy (Leoni et al. 1986, 1989) or Germany (Gerhard et al. 1998). Average maternal blood levels of

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hexachlorobenzene were 1.6 and 0.679 ng/mL, respectively. Similarly, no changes in reproductive outcomes in Xixin, China, were detected following the cessation of agricultural uses of hexachlorobenzene (Huang et al. 1989).

For hexachlorobenzene, animal studies have identified adverse effects in the ovaries at doses as low as 0.01 mg/kg/day (Alvarez et al. 2000; Babineau et al. 1991; Bourque et al. 1995; Foster et al. 1992a, 1992b, 1995a, 1995b; Jarrell et al. 1993; Lecavalier et al. 1994; Iatropoulos et al. 1976; Knauf and Hobson 1979; MacPhee et al. 1993; Muller et al. 1978; Sims et al. 1991), in the testes at doses as low as 10 mg/kg/day (Gralla et al. 1977a; Smith et al. 1985), and on reproductive function with doses of at least 16 mg/kg/day (Grant et al. 1977; Simon et al. 1979).

The ovaries are a sensitive target organ for hexachlorobenzene. Distribution studies have identified the ovaries as a site of hexachlorobenzene accumulation (Foster et al. 1993; Sitarska et al. 1995; others). Studies have reported changes in organ weight; histological (light microscopy) and ultrastructural (electron microscopy) degenerative changes; and altered serum levels of gonadal hormones (estrogen and progesterone). Investigations into the mode-of-action generally found disruptions in steroidogenesis.

The acute data for ovarian effects are limited (Foster et al. 1993; Lecavalier et al. 1994). Mild morphological changes in the ovary were detected in female Sprague-Dawley rats given a single gavage dose of at least 400 mg/kg in corn oil (Lecavalier et al. 1994). Serum progesterone levels were increased in female Sprague-Dawley rats that were superovulated prior to gavage treatment with 50 mg/kg/day of hexachlorobenzene in corn oil for 5 days but not in normally-cycling rats similarly treated (Foster et al. 1993).

A 90-day assay in adult female *Cynomolgus* monkeys observed ovarian toxicity at the lowest dose tested, 0.001 mg/kg/day of hexachlorobenzene (Bourque et al. 1995). Ultrastructural analyses of developing ova detected mitochondrial changes, which increased in frequency and severity with dose. Swelling of the cristae resulting in abnormal intracristae spaces was seen at 0.01 mg/kg/day; mitochondrial matrices became more coarsely granular and exhibited occasional irregular morphology at 0.1 mg/kg/day; and mitochondria had “electron-lucent” matrices and reduced membrane integrity at 10 mg/kg/day. A similar increase in frequency and severity was observed for lesions in follicular cells: abnormal nuclei were seen in “a few cells” at 0.01 mg/kg/day, while nuclear membrane infolding was clearly apparent at 0.1 mg/kg/day. Abnormal spaces between follicular cells were observed at 1 mg/kg/day, and follicular cells exhibited abnormal lipid accumulation and deeply folded and indented nuclear membranes at

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10 mg/kg/day. Thecal cells exhibited deformed nuclei only at 10 mg/kg/day. Since mitochondrial changes may represent nonspecific cell injury, the specific mode of action of degenerative ovarian changes remains unclear. The LOAEL of 0.01 mg/kg/day from this study was used to calculate an intermediate oral MRL of 0.0001 mg/kg/day as described in the footnote to Table 3-2 and in Appendix A.

Supporting data are provided by previous 90-day studies in female *Cynomolgus* monkeys that had dose-related degenerative changes in oocytes and ovaries at all doses tested, 0.1–10 mg/kg/day (Babineau et al. 1991; Foster et al. 1992a, 1995a; Jarrell et al. 1993; Sims et al. 1991). Increasing in frequency and severity, oocyte effects progressed from increased numbers of lysosomal elements and irregularly arranged thecal layer cells to altered oocyte morphology (shape irregularities, increased granularity and density, less distinct membrane), cytoplasmic vacuolation, lysosomal aggregation, and pyknosis of follicular granulosa cells. Similarly, ovarian changes progressed from cellular hypertrophy, increasing columnarization of normally cuboidal cells, and small lipid inclusions, to cellular necrosis and separation of epithelium from connective tissue, stratification and elongation of epithelial cells, and increased numbers of lysosomes, vesicles, and lipid inclusions. Additionally, luteal phase progesterone levels were reduced at 1 mg/kg/day, ovulatory surge estrogen levels were decreased at 10 mg/kg/day, and menstrual cycle length variability was increased at 10 mg/kg/day (Foster et al. 1992a, 1995a). Remarkably, doses up to 10 mg/kg/day did not affect fertility (measured in oocytes by *in vitro* tests), serum inhibin levels, or numbers or size of oocytes, follicles, or corpora lutea. Notably, liver lesions (cholestasis, accentuated zonation, increased portal density, and mid-zone vacuolation) were only seen at the higher doses of 1 and 10 mg/kg/day.

Earlier studies in female Rhesus monkeys observed similar lesions. In female Rhesus monkeys given hexachlorobenzene for 60 days, ovarian effects seen at 8 mg/kg/day included cortical degeneration, reduced numbers of primary follicles with a concurrent increase in relative corpora lutea volume, multiple follicular cysts, and a thickening of the ovarian germinal epithelium with cells exhibiting a columnar appearance progressing to pseudostratification (Iatropoulos et al. 1976). These effects increased in incidence and severity with dose. At 32 mg/kg/day and above, epithelial nuclei were pyknotic (condensed) and karyorrhectic (fragmented) and at 128 mg/kg/day, ovarian cortices were predominated by dense stroma. These ovarian changes were similar to those normally seen in menopause, and indicate that the corpora lutea were not producing steroids. A subsequent study in female Rhesus monkeys found that serum cholesterol was increased by gavage doses of 8 mg/kg/day of hexachlorobenzene in methyl cellulose for 60 days (Knauf and Hobson 1979); this effect may be secondary to changes in ovarian steroidogenic activity. These findings are supported by a study in which hexachlorobenzene blocked

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ovulation (estrogen and progesterone remained low, LH and FSH continued to climb, and menstruation was delayed) in one of four female Rhesus monkeys gavaged with 4 mg/kg/day of hexachlorobenzene in aqueous methyl cellulose for up to 78 days (Muller et al. 1978). A lower-dose study found no changes in serum levels of estrogen, progesterone, FSH, or LH in female Rhesus monkeys fed 0.03 mg/kg/day of hexachlorobenzene in monkey chow for 11 months (Rozman et al. 1978). The difference between this study and the one in *Cynomolgus* monkeys that observed changes in estrogen and progesterone levels (Foster et al. 1992a, 1995a) may reflect strain specificity or differences in absorption following disparate methods of oral exposure.

No evidence of histopathology was found in the ovaries of female beagle dogs given hexachlorobenzene in gelatin capsules with corn oil at doses up to 100 mg/kg/day for 21 days; data for other reproductive organs were not reported (Sundlof et al. 1981).

Although rat studies have not investigated doses as low as those used in monkey studies, they have identified histological evidence of degeneration and ultrastructural changes in the ovaries of animals treated with hexachlorobenzene. Gavage treatment of female Wistar rats with 1,000 mg/kg/day of hexachlorobenzene for 30 days caused degenerative lesions (increased numbers of atresic follicles, inflammatory infiltration of primary follicles, stratification and proliferation of ovarian surface epithelial cells, and irregular nuclei in epithelial cells) and changes in hormone and hormone receptor levels (decreased serum estradiol and prolactin, increased FSH, decreased estrogen receptor levels) (Alvarez et al. 2000). Similarly, a 21-day study detected increased serum progesterone levels in female Sprague-Dawley rats gavaged with at least 1 mg/kg/day of hexachlorobenzene (Foster et al. 1992b). In treated animals, the number of ova produced per rat decreased significantly and the length of estrus increased significantly. Another study in female Sprague-Dawley rats observed suggestive evidence of ovarian lesions (increased prominence of Golgi complexes, smooth endoplasmic reticulum, and free polysomes) at 10 (but not 1 or 100) mg/kg/day (MacPhee et al. 1993). The differences observed between rats and monkeys for changes in progesterone levels may be related to differences in their cycle lengths.

To investigate the contributions of adrenal steroidogenesis, adult female Sprague-Dawley rats were ovariectomized prior to treatment (Foster et al. 1995a). Gavage treatment for 30 days at doses as low as 1 mg/kg/day decreased serum corticosterone, while serum cortisol was decreased only at 100 mg/kg/day; no effects were seen on aldosterone or progesterone levels. The authors concluded that hexachlorobenzene induced alterations in steroidogenesis of cells of the inner zone of the adrenal cortex.

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Some intermediate-duration experiments have demonstrated that hexachlorobenzene adversely affects reproductive performance. In a multigenerational study in which male and female Sprague-Dawley rats were fed hexachlorobenzene at doses of 0.5–32 mg/kg/day through premating and two series of mating, gestation, and lactation for up to four generations, statistically significant decreases in fertility and increases in the number of stillborns were observed at doses as low as 16 mg/kg/day and average litter size was decreased at 8 mg/kg/day and above (Grant et al. 1977). A study which dosed only male rats were dosed with 70 mg/kg/day of hexachlorobenzene for 5 consecutive days prior to 14 weeks of consecutive mating found decreased male reproductive performance (mating index), but no changes in fertility (numbers of inseminated females made pregnant) (Simon et al. 1979). In contrast, in two studies in which only females were dosed, no reproductive toxicity was observed, either in female Sprague-Dawley rats fed 7 mg/kg/day continuously from 96 days prior to first mating through gestation of two successive litters (Kitchin et al. 1982) or in female *Cynomolgus* monkeys given 10 mg/kg/day orally for 90 days (Jarrell et al. 1993).

Similarly, no reproductive toxicity was observed in a chronic assay in which both male and female Sprague-Dawley rats were fed doses of hexachlorobenzene up to 2 mg/kg/day from 3 months prior to mating through weaning (Arnold et al. 1985).

The other chronic data available are pertinent to testicular damage (Gralla et al. 1977a; Smith et al. 1985). In male Fischer 344/N rats fed 10 mg/kg/day of hexachlorobenzene in arachis oil for 90 weeks, testicular weight was significantly increased and testicular interstitial cell tumors were more severe (although incidence was not affected) compared to controls (Smith et al. 1985). Slight testicular degeneration, with numerous spermatogonic giant cells and incomplete complement of spermatogonia in the seminiferous tubules, was observed in two of six male beagle dogs given 110 mg/kg/day of hexachlorobenzene in gelatin capsules with corn oil for 12 months (Gralla et al. 1977a). Additionally, retarded sexual maturation of the testes was observed in male SPF pigs fed 50 (but not lower doses up to 5 mg/kg/day of hexachlorobenzene for 90 days (Den Tonkelaar et al. 1978).

The highest NOAEL values and all reliable LOAEL values for reproductive effects in each species and duration category are shown in Table 3-2 and plotted in Figure 3-2.

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**3.2.2.6 Developmental Effects**

Human and animal studies have demonstrated that hexachlorobenzene crosses the placenta to accumulate in fetal tissues; additionally, hexachlorobenzene is concentrated in milk and can be transferred to the suckling neonate (for more information, see Sections 3.4.1 and 3.4.2).

Oral exposure to hexachlorobenzene has been associated with serious developmental toxicity in a study of a poisoning epidemic (Cripps et al. 1984; Gocmen et al. 1989; Peters et al. 1966, 1982, 1987). In southeast Anatolia, Turkey, ingestion of an estimated 0.7–2.9 mg/kg/day of hexachlorobenzene between 1955 and 1959 (in bread made from grain treated with hexachlorobenzene as a fungicide) resulted in dramatic developmental effects, including a 95% mortality rate in infants under 2 years of age who had been breast fed by exposed mothers (Peters et al. 1966). These infants were diagnosed with a condition known as *pembe yara* or "pink sore" because of associated skin lesions consisting of blistering, epidermolysis, and annular erythema. The cause of death in these infants was cardiorespiratory failure; weakness and convulsions were also seen frequently. Older children, between the ages of 6 and 15 years, exhibited a condition known as *kara yara* or "black sore" more frequently than younger children or adults. The symptoms of this disease began with photosensitivity and progressed within 6 months to include hyperpigmentation, dermal fragility (resulting in ulcerating lesions and severe mutilating scars), and hirsutism (Cam and Nigogosyan 1963; Dogramaci 1964; Gocmen et al. 1989). Mortality was 10% among *kara yara* patients. These skin lesions (pink sore and black sore) have been diagnosed as porphyria cutanea tarda, a specific type of vesiculobullous porphyria. The porphyrias are a class of inherited and acquired diseases caused by enzymatic defects in heme biosynthesis, leading to the generation of porphyrins, which may cause tissue damage, especially in the skin (for more information, see Sections 3.2.2.2, Hepatic Effects and Dermal Effects, and 3.5.2, Mechanisms of Toxicity). Similar dermal lesions, but no increase in mortality incidence, were reported for exposed adults, who also exhibited neurological disorders (weakness and diminished muscle control).

Follow-up studies have found persistent symptoms of developmental toxicity in a cohort of 252 adults (162 men and 90 women) who had been exposed as children in the poisoning epidemic (average age of the cohort at the time of exposure was 7.6 years) (Cripps et al. 1984; Gocmen et al. 1989; Peters et al. 1982). Short stature was seen in 42.1% of the patients, considered striking in comparison to their unexposed siblings. Additionally, 66.6% of the exposed patients exhibited osteoporosis of bones in the hands, associated with distinctive small hands, painless swelling, and spindling of fingers. Osteoporosis and osteosclerosis have been observed in adult hexachlorobenzene-exposed rats (see Section 3.2.2.2,

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Musculoskeletal Effects). In addition to the profound weakness and decreased muscle control observed in exposed adults (see Section 3.2.2.4, Neurological Effects), this cohort also presented paresthesia (spontaneous tingling or burning sensations, in 53.6% of patients) and graded sensory loss indicative of polyneuropathy (in 60.6% of patients).

Two follow-up investigations have found potential reproductive effects in women exposed as children to hexachlorobenzene in the Turkish epidemic (Gocmen et al. 1989; Jarrell et al. 1998). A study conducted 20–30 years after initial exposure identified 57 porphyric mothers with 23 fetal deaths and 54 children who died in the first several years of life from a total of 276 pregnancies (Gocmen et al. 1989). Porphyric mothers had an average of 0.51 ppm hexachlorobenzene in their breast milk, compared to 0.07 ppm in unexposed controls. The results of this study were inconclusive because no information was provided regarding the expected incidence of fetal deaths and newborn-death in this population. Another study found a statistically significant increased risk of abortion among a subset of exposed women who exhibited porphyria cutanea tarda and had blood levels of hexachlorobenzene above 1.0 ng/mL (Jarrell et al. 1998).

A German case-control study found that adipose hexachlorobenzene levels in 18 male patients who underwent orchidopexy to correct unilateral or bilateral undescended testis (mean age 4.2 years) were 3-fold higher compared to a group of 30 male control patients (mean age 3.5 years); this difference was highly significant statistically (Hosie et al. 2000). These results were inconclusive because a similar correlation was also observed for heptachloroepoxide (but not for other organochlorines measured). This study is also limited by its small study size and lack of age-adjustment.

Although epidemiological studies have suggested that consumption by mothers of fish high in organochlorines may affect the immune system of their infants, perinatal exposure to hexachlorobenzene has not been clearly associated with immunological effects. The levels of hexachlorobenzene, dieldrin, and *p,p'*-dichlorodiphenyldichloroethylene (*p,p'*-DDE) in milk samples collected shortly after the birth of Canadian Inuit infants correlated with increased risk of otitis media in their first year of life, but not with other serum immune parameters (immunoglobulins, cytokines, lymphocyte activation markers) (Dewailly et al. 2000). A similar study of immune parameters in umbilical blood of Canadian mothers with high or low consumption of fish from the Lower-North-Shore of the St. Lawrence River detected a statistically significant association only between decreased lymphocyte secretion of cytokine IL-10 and increased levels of hexachlorobenzene, *p,p'*-DDE, and mercury (Belles-Isles et al. 2000).

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Acute-duration developmental studies have verified that hexachlorobenzene impaired neurological development at doses as low as 2.5 mg/kg/day in rats (Goldey and Taylor 1992) and produced teratogenic abnormalities at doses as low as 40 mg/kg/day (Courtney et al. 1976; Khera 1974a). Intermediate-duration developmental studies in rats have seen immunodevelopmental effects at 0.5 mg/kg/day (Barnett et al. 1987); neurodevelopmental effects at 1.3 mg/kg/day (Lilienthal et al. 1996); and reduced neonatal viability and growth, and organ weight changes at 4–5 mg/kg/day (Grant et al. 1977; Kitchin et al. 1982; Vos et al. 1979a, 1983). In Rhesus monkey pups, death (accompanied by neurological effects, lung edema, and liver damage) resulted from nursing for 15–38 days from female monkeys exposed to 64 mg/kg/day of hexachlorobenzene (Bailey et al. 1980; Iatropoulos et al. 1978). One chronic study was found (Arnold et al. 1985). In a multigenerational reproductive study in Sprague-Dawley rats, hexachlorobenzene induced minor liver effects (peribiliary lymphocytosis and fibrosis) at doses as low as 0.016 mg/kg/day in F<sub>1</sub> adults and induced more serious effects (decreased F<sub>1</sub> neonatal viability; tumor formation in F<sub>1</sub> adults) at doses as low as 2 mg/kg/day of hexachlorobenzene.

The most sensitive acute study evaluated neurodevelopmental end points and detected evidence of hyperactivity in Sprague-Dawley rat pups (Goldey and Taylor 1992; Taylor and Goldey 1990). This study was considered acute because virgin female Sprague-Dawley rats were gavaged for 4 days with 2.5 or 25 mg/kg/day of hexachlorobenzene 2 weeks prior to mating. Compared to controls, pups from both treatment groups reoriented themselves significantly more quickly in a negative geotaxis test, required less time in an olfactory discrimination test (postnatal days 6, 8, and 10), and demonstrated increased exploratory activity in a motor activity test (postnatal days 15–20). Pups exposed to 25 mg/kg/day exhibited decreased acoustic startle response (ASR) on postnatal day 23 and increased ASR on postnatal day 90. The LOAEL of 2.5 mg/kg/day from this study has been used to calculate an acute oral MRL of 0.008 mg/kg/day as described in the footnote to Table 3-2 and in Appendix A.

Other acute studies have used higher doses to investigate traditional end points of developmental toxicity. An acute single-dose study found an increase in the overall incidence of fetal abnormalities (but not any specific abnormality) in the fetuses of pregnant female CD-1 mice gavaged with 100 mg/kg/day of hexachlorobenzene on gestation days 7–16; cleft palate and renal agenesis were the most common anomalies noted (Courtney et al. 1976). Three acute (3–10 days) and one intermediate (15 days) developmental toxicity experiments in pregnant Wistar rats observed increases in the incidences of sternal variations and the 14<sup>th</sup> rib formation at 40 mg/kg/day (Khera 1974a). At 80 mg/kg/day, decreased fetal and maternal body weights were seen with other maternal effects.

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The most sensitive intermediate-duration study evaluated immunodevelopmental toxicity. Pups of pregnant BALB/c mice fed doses as low as 0.5 mg/kg/day on gestation days 1–18 exhibited a marked, significant decrease in delayed type hypersensitivity (DTH) response when tested on postnatal day 45 (Barnett et al. 1987). Splenic effects (decreased B cell numbers and decreased mixed lymphocyte responses) were seen at 5 mg/kg/day (but not 0.5 mg/kg/day). Studies in Wistar rats have also demonstrated immunodevelopmental toxicity. In pups born to dams exposed through gestation and lactation to hexachlorobenzene and continued on the same diets, 0.2 mg/kg/day, increased immune responses (IgM and IgG responses to tetanus toxin, delayed-type reaction to ovalbumin, and pulmonary accumulation of foamy macrophages) were noted (Vos et al. 1983); exposure to 2.5 mg/kg/day decreased resistance to infection and caused lymph node endothelial proliferation. Additional signs of developmental toxicity were seen in these pups at higher doses: pup mortality, liver weight, and popliteal lymph node weights were increased at 5 mg/kg/day; and adrenal weight and serum immunoglobulin concentrations (IgM and IgG) were increased at 7.5 mg/kg/day (Vos et al. 1979a, 1983). Similar developmental effects were observed in an intermediate-duration reproductive study which fed female Sprague-Dawley rats were fed hexachlorobenzene for 96 days prior to mating through 2 rounds of breeding (Kitchin et al. 1982). In both F<sub>1a</sub> and F<sub>1b</sub> pups, doses as low as 3 mg/kg/day decreased body weight and doses as low as 4 mg/kg/day decreased survival (Kitchin et al. 1982).

The only animal developmental study in non-rodents used Rhesus monkey mothers (Bailey et al. 1980; Iatropoulos et al. 1978). Only one of three infant monkeys (between 21 and 118 days of age) nursing from mothers fed 64 mg/kg/day of hexachlorobenzene by daily gavage survived; the durations of dosing were 15 and 38 days (for the mortalities) and 60 days (for the survivor). Although the mothers were asymptomatic, both infant mortalities exhibited neurological effects (listlessness, lethargy, depression, and ataxia) and lung edema prior to death. Microscopic findings included mild hepatocellular hypertrophy in the infant that survived, and hepatic fatty changes, slight renal proximal tubule vacuolation, and mild cerebral gliosis in one or both infants that died.

Two chronic-duration reproductive studies in Sprague-Dawley rats observed signs of developmental toxicity (Arnold et al. 1985; Grant et al. 1977). In one study male and female rats were fed hexachlorobenzene from 3 months prior to mating through weaning, and pups were continued on the same diet for their entire lifetime. Only the highest dose tested, 2 mg/kg/day, decreased pup survival. When examined as adults (week 130), peribiliary lymphocytosis and fibrosis were observed in F<sub>1</sub> males at the lowest dose tested, 0.016 mg/kg/day, and hepatic basophilic chromogenesis was seen at 0.4 mg/kg/day (Arnold et al. 1985). A four-generation assay found increased liver weight and hepatic aniline hydroxylase activity at

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2 mg/kg/day ( $F_{1a}$  and  $F_{3a}$  animals), consistently decreased pup weight at 4 mg/kg/day (all pup generations), and decreased pup viability at 8 mg/kg/day ( $F_{1a}$  and  $F_{1b}$  animals) (Grant et al. 1977). The LOAEL of 0.016 mg/kg/day from the lower-dose study (Arnold et al. 1985) has been used to calculate a chronic oral MRL of 0.00005 mg/kg/day as described in the footnote to Table 3-2 and in Appendix A.

The highest NOAEL values and all reliable LOAEL values for developmental effects in each species and duration category are presented in Table 3-2 and plotted in Figure 3-2.

#### 3.2.2.7 Cancer

The Department of Human Health Services (DHHS) considers the evidence for the carcinogenicity of hexachlorobenzene in experimental animals sufficient, and this chemical is reasonably anticipated to be a carcinogen in humans (NTP 2001). A cancer assessment for hexachlorobenzene is available on Integrated Risk Information System (IRIS 2001) in which the chemical is assigned to U.S. EPA cancer weight-of-evidence Group B2, probable human carcinogen, on the basis that oral administration of hexachlorobenzene has been shown to induce tumors in the liver, thyroid, and kidney in three rodent species. IRIS (2001) presents an oral slope factor of 1.6 per (mg/kg)/day and inhalation unit risk of 0.00046 per ( $\mu\text{g}/\text{m}^3$ ) for hexachlorobenzene based on hepatocellular carcinoma in orally exposed female rats (Ertürk et al. 1986). This EPA assessment is currently undergoing re-evaluation.

The available epidemiology reports taken together do not support an association between hexachlorobenzene exposure and increased cancer incidence, but their limitations (including small study sizes, similar tissue hexachlorobenzene levels between cancer and control groups, and potentially confounding effects of other organochlorines) preclude considering them evidence of noncarcinogenicity. Case-control studies (ranging in size from 20 cancer cases and 20 controls to 304 cases and 186 controls) investigating organochlorine levels in serum or breast tissue samples surgically removed from groups of patients either with breast cancer or with benign breast tumors were unable to detect statistically significant differences in hexachlorobenzene levels (Dorgan et al. 1999; Falck et al. 1992; Guttes et al. 1998; Liljegren et al. 1998; Mendonca et al. 1999; Moysich et al. 1998; Mussalo-Rauhamaa et al. 1990; Zheng et al. 1999). The exception was a prospective study by Dewailly et al. (1994) in which serum and adipose organochlorine levels were measured in 41 Canadian women (ages 40-69) undergoing breast biopsy. Mammary adenocarcinoma was diagnosed in 20 women and benign breast tumors in 17 others; the former group had statistically significantly higher serum (but not adipose) levels of hexachlorobenzene compared to the latter group. No association of blood hexachlorobenzene levels with cancer

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incidence was observed in a study of 108 pancreatic cancer patients in the San Francisco Bay area (Hoppin et al. 2000), or in a study of 154 endometrial cancer patients in Sweden (Weiderpass et al. 2000). Additionally, studies analyzing hexachlorobenzene in the bone marrow of 13 German leukemia patients (Scheele et al. 1996) and in the adipose of 4 male Swedish patients with Ewing's sarcoma of the bone (Hardell et al. 1997) did not find any statistically significant increases compared to controls. No evidence of cancer was reported in a 25-year follow-up study of 161 people (Peters et al. 1982) or a 20–30-year follow-up study of 204 people (Cripps et al. 1984) who consumed hexachlorobenzene-contaminated grain in Turkey from 1955 to 1959. However, these two studies did not examine patients for internal cancer and were not designed to detect increases in cancer incidence.

Those follow-up studies (Cripps et al. 1984; Peters et al. 1982) did detect porphyria in some adults (17/204 and 33/161, respectively) who had been exposed as children to hexachlorobenzene (see Section 3.2.2.2 Hepatic Effects). This is relevant to cancer formation in humans because other epidemiology studies (unrelated to hexachlorobenzene) have found statistically significant associations between porphyria and increased risk of liver cancer. Fracanzani et al. (2001) reported that the presence of porphyria conferred a 5-fold increased risk of liver cancer. Linet et al. (1999) reported that porphyria cutanea tarda and acute intermittent porphyria were associated, respectively, with 20- and 70-fold increases in liver cancer and 3-fold increases in lung cancer. However, porphyria and liver cancer in the general population share common etiologies, so the association may not be casual (Axelson 1986; Salata et al. 1985; Topi et al. 1980; Waddington 1972).

Oral exposure of rats, mice, and hamsters to hexachlorobenzene has induced tumors in the liver ("liver cell" tumor, hepatocellular carcinoma, hepatoma, hemangiohepatoma, hemangioendothelioma, bile duct tumor) (see below). Individual studies have also reported statistically significant increases in the incidences of kidney (renal cell adenoma), thyroid (alveolar adenoma), parathyroid (adenoma), and adrenal gland (pheochromocytoma) tumors, as well as the induction of lymphosarcoma (non-Hodgkin's lymphoma) (Arnold et al. 1985; Ertürk et al. 1986). Female rats (Ertürk et al. 1986; Pereira et al. 1982; Smith and Cabral 1980) and mice (Cabral et al. 1979) appear to be more susceptible than males to the hepatocarcinogenic effects of hexachlorobenzene and limited evidence suggests that males are more susceptible to renal cancer (Ertürk et al. 1986). The cause of these gender specificities are unclear.

Chronic oral exposure to hexachlorobenzene induces liver tumors in rats, with female rats appearing more susceptible than males. Ertürk et al. (1986) fed Sprague-Dawley rats 4 or 8 mg/kg/day of hexachlorobenzene for up to 2 years, with 9 interim sacrifices. Hexachlorobenzene induced statistically significant

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increases in the incidences of hepatoma, hepatocarcinoma, and renal carcinoma in both genders. In the liver, degenerative lesions were seen after 2–3 weeks, preneoplastic changes were detected after 200 days, and hepatocarcinomas were detected beginning at 300 days. Hepatomas, hemangiohepatomas, and hepatocellular carcinomas were significantly more common in females than in males. Bile duct adenomas (statistically significant increased incidence) and bile duct adenocarcinomas (not significant) were seen only in treated females. In contrast, renal adenomas and renal cell carcinomas were more frequent in males. Smith and Cabral (1980) detected liver cell tumors in all (14/14) female Agus rats and in a majority of female Wistar rats (4/6) fed hexachlorobenzene for 90 weeks at doses of 6–8 and 5 mg/kg/day, respectively. Moreover, in those treated Wistar rats without tumors (2/6), evidence of preneoplastic changes (hepatocellular hypertrophy) was observed. Similar results were seen in a subsequent study (Smith et al. 1985). In Fischer 344/N rats fed 10 mg/kg/day of hexachlorobenzene for 90 weeks, all surviving females had multiple liver tumors and at least 50% exhibited hepatocellular carcinomas. In contrast, only 16% of males exhibited liver tumors, which were smaller and limited to one per animal. Liver tumors stained heavily for gamma-glutamyl transpeptidase. In a tumor promotion study, feeding of 10 mg/kg/day of hexachlorobenzene for 45 days induced significantly more preneoplastic changes (hepatic foci positive for gamma-glutamyl transpeptidase) in the initiated livers of female Sprague-Dawley rats than of males (Pereira et al. 1982). In female (but not male) F<sub>1</sub> Sprague-Dawley rats with lifetime exposure to 2 mg/kg/day of hexachlorobenzene, the incidence of liver neoplastic nodules was significantly increased compared to controls (Arnold et al. 1985).

Hexachlorobenzene also induced liver tumors in mice and hamsters, but gender specificity was apparent only in mice. Syrian golden hamsters were fed 0, 4, 8, and 16 mg/kg/day of hexachlorobenzene in the diet for life (Cabral et al. 1977). Statistically significant increases in incidence were seen for hepatomas and hemangioendotheliomas (liver and spleen) in all treatment groups, with a slightly higher incidence in males than in females. Thyroid tumors were not seen in control groups, but were found in all treatment groups except low dose males; however, the increased incidence was significant only for males at 16 mg/kg/day. Outbred Swiss mice were fed 6, 12, or 25 mg/kg/day of hexachlorobenzene for up to 120 weeks (Cabral et al. 1979). Statistically significant increases in the incidence of liver cell tumors were seen at 12 and 25 (but not 6) mg/kg/day for both genders. Liver tumor incidence was significantly more common in females than in males treated with 25 mg/kg/day. Tumor multiplicity and size increased with increasing dose, while the latency period decreased.

A brief paper by Ertürk et al. (1986) reported the induction of liver and other tumor types in Sprague-Dawley rats, Swiss mice, and Syrian golden hamsters after only 90 days of feeding the animals 20 or

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40 mg/kg/day of hexachlorobenzene. However, the report is limited by its lack of methodology and quantitative results. Liver effects included hepatomas, metaplasia, and stromal activation. Some support for the findings of a rapid onset of liver tumor formation is found in intermediate oral dosing (10 days to 24 weeks) experiments with hexachlorobenzene that induced hepatocellular hypertrophy in rats (Den Besten et al. 1993; Smith et al. 1985), mice (Shirai et al. 1978), pigs (Den Tonkelaar et al. 1978), dogs (Sundlof et al. 1981), and Rhesus monkeys (Iatropoulos et al. 1976; Knauf and Hobson 1979). However, other intermediate-duration studies (13 weeks to 1 year) in rats did not detect neoplasia or preneoplastic effects in the liver or other organs (Goldstein et al. 1978; Kimbrough and Linder 1974; Kuiper-Goodman et al. 1977; Mollenhauer et al. 1975; Smith et al. 1979, 1985, 1986a).

The mode-of-action for the hepatocarcinogenicity of hexachlorobenzene has been investigated. Multiple studies have indicated that non-heme iron potentiates the hepatocarcinogenic effects of hexachlorobenzene (Adjarov 1990; Elder and Urquhart 1986; Hahn et al. 1988; Smith and Francis 1983; Smith et al. 1989, 1993; Vincent et al. 1989). Two studies in rats provided limited evidence that hexachlorobenzene is a promoter but not an initiator of liver cancer. As noted above, treatment of intact Sprague-Dawley rats with 10 mg/kg/day of hexachlorobenzene for 45 days did not induce hepatic foci positive for gamma-glutamyl transpeptidase, but foci were induced following liver initiation by partial hepatectomy with and without diethylnitrosamine (Pereira et al. 1982). This finding suggests that hexachlorobenzene may act as an promoter at doses insufficient to initiate tumors. No evidence of altered foci were detected in male Fisher 344 rats pretreated with partial hepatectomy and treated with a single gavage dose of 5,000 mg/kg hexachlorobenzene followed by liver tumor promotion with carbon tetrachloride and cholic acid for 12 weeks (Tsuda et al. 1993).

Reported incidences of other tumor types have also increased following oral exposure to hexachlorobenzene. A group of five adult female Rhesus monkeys were dosed by gavage with hexachlorobenzene in methylcellulose daily for 60 days (Iatropoulos et al. 1976). Single monkeys received 0, 8, 32, or 64 mg/kg and two monkeys received 128 mg/kg. In one of the high dose monkeys (but not in the others), a benign mammary fibroadenoma was detected. This evidence is inconclusive, because of the low statistical power of the study. The other monkey given 128 mg/kg exhibited moderate adrenal medullary hyperplasia and the monkey given 64 mg/kg exhibited slight hyperplasia of the adrenal zona fasciculata; these findings support observations made in rats. In F<sub>1</sub> Sprague-Dawley rats exposed to 2 mg/kg/day for their entire lives (including *in utero* exposure and approximately 130 weeks *ex utero*, as part of a 2-generation reproductive study), statistically significant increases in adrenal pheochromocytomas were seen in both males and females, while a significantly increased incidence of parathyroid adenomas was

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observed only in females (Arnold et al. 1985). The biological significance of the adrenal effect is also supported by observations of adrenal gland cortical hyperplasia in female Wistar rats at doses as low as 9.5 mg/kg/day for 13 weeks (Den Besten et al. 1993) and in male and female Sherman rats exposed to hexachlorobenzene in the diet at doses as low as 5 mg/kg/day for 4 months (Kimbrough and Linder 1974). No other studies have reported any parathyroid histopathology caused by oral exposure to hexachlorobenzene, but parathyroid effects (changes in hormone levels) have been observed in male Fischer 344 rats (Andrews et al. 1988, 1989, 1990). The observations made during the 90-day study in which Sprague-Dawley rats, Swiss mice, and Syrian golden hamsters were fed 20 or 40 mg/kg/day of hexachlorobenzene have not been confirmed (Ertürk et al. 1986). Renal damage with metaplastic regenerative changes were seen in treated animals; renal tumors were “most frequent in rats” and “more frequent in males.” Lymphosarcomas (detected in the thymus, spleen, and lymph nodes) were apparently common in all treatment groups, with frequent lymphohematopoietic hyperplasia and lymphocytic infiltrations. These lesions occurred 2–4-fold (depending on organ) more frequently in female mice than in male mice.

The CEL (i.e., lowest dose that produced a tumorigenic response for each species), the duration category of exposure to hexachlorobenzene, and the estimated upper-bound risk levels from  $10^{-4}$  to  $10^{-7}$  are shown in Table 3-2 and plotted in Figure 3-2.

#### **3.2.3 Dermal Exposure**

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

##### **3.2.3.1 Death**

##### **3.2.3.2 Systemic Effects**

##### **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**

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**3.2.3.7 Cancer****3.3 GENOTOXICITY**

An increased incidence of micronuclei was observed in the peripheral lymphocytes of 41 chemical workers in San Paulo, Brazil, who had been exposed to a mixture of chlorinated solvents that included hexachlorobenzene, as well as carbon tetrachloride and perchlorethylene (da Silva Augusto et al. 1997). The usefulness of this study is limited by the confounding effect of multiple chemical exposure.

No studies were located regarding genotoxic effects in animals following inhalation exposure to hexachlorobenzene.

No studies were located regarding the genotoxic effects of hexachlorobenzene in humans following oral exposure.

*In vivo* studies in rats revealed the lack of significant genotoxic activity in mammals following oral exposures to hexachlorobenzene. Negative results were observed in two dominant lethal mutation assays that orally exposed rats at doses ranging from 60 to 221 mg/kg (Khera 1974a; Simon et al. 1979). No evidence of genotoxicity was observed in mouse liver, lung, kidney, spleen, or bone marrow after oral dosing (Sasaki et al. 1997). An oral exposure study to test the DNA induction potential of hexachlorobenzene in Wistar rats provided equivocal evidence that hexachlorobenzene reacts directly with DNA (Gopaldaswamy and Nair 1992). Male rats were untreated or pretreated with phenobarbital (0.1% sodium phenobarbital in drinking water for 2 weeks) and then administered 25 mg/kg (specific activity 14.0 mCi/mmol) hexachlorobenzene in 0.1 mL refined peanut oil for 24 hours. The animals were sacrificed and DNA obtained from liver extracts. Upon analysis, the DNA was found to be bound by hexachlorobenzene ( $2.23 \pm 0.27$  pmoles/mg DNA for phenobarbital untreated animals and  $3.56 \pm 0.18$  pmoles/mg DNA for phenobarbital pretreated animals). The comparative values for lindane in the same study were  $5.82 \pm 0.31$  and  $6.90 \pm 0.14$  pmoles/mg DNA, respectively. No hexachlorobenzene untreated control values were provided in the study report. It is notable, however, that there is evidence (Jackson et al. 1993) that phenobarbital is mutagenic *in vitro* in several test systems. Other studies have likewise failed to observe gene mutations or unscheduled DNA repair in microbial assays (Gopaldaswamy and Nair 1992; Haworth et al. 1983; Siekel et al. 1991).

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No studies were located regarding genotoxic effects in humans or animals following dermal exposure to hexachlorobenzene.

Hexachlorobenzene did not produce chromosomal aberrations in human peripheral lymphocytes *in vitro* (Siekel et al. 1991). However, hexachlorobenzene produced weak positive results in assays for DNA fragmentation and micronuclei formation in primary cultures of human hepatocytes (Canonero et al. 1997). Treatment with hexachlorobenzene induced only minimal formation of DNA adducts in cultured human Hep G2 hepatoma cells (Dubois et al. 1997).

The micronucleus assay, but not the DNA fragmentation assay, was positive in cultured rat hepatocytes (Canonero et al. 1997). The researchers concluded that hexachlorobenzene is a weak genotoxic carcinogen and that negative responses in standard genotoxicity assays were due to limitations in the ability of exogenous metabolic activation systems to duplicate the complex interactions of the intact liver cell. Hexachlorobenzene was also positive in an assay for replicative DNA synthesis in mouse hepatocytes (Miyagawa et al. 1995). Treatment with hexachlorobenzene induced only minimal formation of DNA adducts in fetal hepatocytes from rats and quail (Dubois et al. 1997).

Hexachlorobenzene tested negative or ambiguous in reverse mutation assays in *S. typhimurium* (Gopaldaswamy and Aiyar 1986; Gopaldaswamy and Nair 1992; Haworth et al. 1983; Siekel et al. 1991) and *E. coli* (Siekel et al. 1991) with and without metabolic activation, although an assay for reverse mutation in the yeast *Saccharomyces cerevisiae* was positive (Guerzoni et al. 1976). Hexachlorobenzene also tested negative in a DNA repair assay in *E. coli* (Siekel et al. 1991).

Data from a study in male Long Evans rats suggested that the metabolism of hexachlorobenzene to pentachlorobenzene and other more polar metabolites proceed either through a free-radical mechanism or by initial formation of an arene oxide. These reactive intermediates may form covalent bonds with cellular constituents (such as protein amino acids or DNA nucleic acids) leading to irreversible cell damage (Lui and Sweeney 1975). Several other studies have also found evidence of binding to cellular proteins by reactive electrophilic metabolites of hexachlorobenzene formed by cytochrome P-450 system (Gopaldaswamy and Nair 1992; Rajamanickam and Padmanaban 1974; van Ommen et al. 1985).

Key *in vivo* genotoxicity studies are presented in Table 3-3 and *in vitro* genotoxicity studies are presented in Table 3-4.

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**3.4 TOXICOKINETICS**

In humans, inhalation accounts for an unknown, but probably low, amount of exposure due to the low vapor pressure of hexachlorobenzene. Current information indicates that human absorption of inhaled hexachlorobenzene is poor; approximately two orders of magnitude less than the exposure estimate for the oral route (Burns et al. 1974; Burton and Bennett 1987; Currier et al. 1980). Other data of absorption following inhalation exposure come from studies of occupational exposures (Queiroz et al. 1997, 1998a, 1998b; Richter et al. 1994; Selden et al. 1997) and citizens of Flix, Spain, who have been exposed to airborne hexachlorobenzene from an organochlorine factory (Grimalt et al. 1994; Herrero et al. 1999; Sala et al. 1999b; To-Figueras et al. 1997). Based on information from an epidemic resulting from ingestion of hexachlorobenzene-contaminated bread in Turkey, ingested hexachlorobenzene is moderately absorbed from the gastrointestinal tract (Albro and Thomas 1974; Cam and Nigogosyan 1963; Gocmen et al. 1989; Peters et al. 1982). However, most of the hexachlorobenzene body burden in the U.S. population derives from dietary intake of fatty foods (Burton and Bennett 1987). Schlummer et al. (1998) estimated that 85.4% of ingested hexachlorobenzene will be absorbed when the blood contains no hexachlorobenzene, and that this percentage will be reduced by 0.2% for each ng of hexachlorobenzene per g lipid in blood, and hypothesized a “fat-flush” theory of hexachlorobenzene absorption: temporary increases in lipid content in the gut dilute hexachlorobenzene concentrations and increase the diffusion gradient from the gut into the lymph and blood. Data from animal studies indicate that the gastrointestinal absorption of hexachlorobenzene is quite variable, depending upon the solvent vehicle used for administration, ranging from 6% when administered in aqueous solution to 82% when administered with squalene in cottonseed oil (Albro and Thomas 1974), olive oil (Freeman et al. 1989);

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**Table 3-3. Genotoxicity of Hexachlorobenzene *In Vivo***

End point	Species (test system)	Exposure route	Results	Reference
Mammalian systems:				
Dominant lethals	Rat	Oral	–	Khera 1974a
	Rat	Oral	–	Simon et al. 1979
DNA binding	Rat (Wistar)	Oral	±	Gopaldaswamy and Nair 1992

– = negative result; ± = weakly positive; DNA = deoxyribonucleic acid

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**Table 3-4. Genotoxicity of Hexachlorobenzene *In Vitro***

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Reverse mutation				
<i>Salmonella typhimurium</i>	Gene mutation	–	–	Haworth et al. 1983
<i>S. typhimurium</i>	Gene mutation	±	–	Gopaldaswamy and Nair 1992
<i>S. typhimurium</i>	Gene mutation	–	–	Siekel et al. 1991
<i>Escherichia coli</i>	Gene mutation	–	–	Siekel et al. 1991
DNA Repair Assays				
<i>E. coli</i>	DNA repair	–	–	Siekel et al. 1991
Eukaryotic cells:				
Human peripheral blood lymphocytes	Chromosomal aberration	–	–	Siekel et al. 1991
Mammalian system:				
Rat (Wistar)	DNA binding	±	–	Gopaldaswamy and Nair 1992

– = negative result; ± = weakly positive; DNA = deoxyribonucleic acid

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Goldey et al. 1990; Knauf and Hobson 1979; Koss and Koransky 1975; Mehendale et al. 1975; Sundlof et al. 1982; Villeneuve and Hierlihy 1975), or peanut oil (Ingebrigtsen and Nafstad 1983; Ingebrigtsen et al. 1981). The lymphatic system has been shown to play an important role in the gastrointestinal uptake of hexachlorobenzene in animals (Iatropoulos et al. 1975). Although no empirical data are available on the dermal absorption of hexachlorobenzene in humans, data from a rat study were used to develop a compartment model for application to a 70-kg worker. Using these data, the dermal absorption constant for hexachlorobenzene was calculated as  $1.4 \times 10^{-3}$  per hour (Koizumi 1991).

Information on distribution in people following inhalation exposure to hexachlorobenzene is limited (Ataniyazova et al. 2001; Sala et al. 2001b) and no information is available on the distribution of inhaled hexachlorobenzene in animals. However, orally absorbed hexachlorobenzene distributes widely in mammalian tissue, rapidly partitioning to blood, liver, breast milk, adipose tissue, endocrine organs, bone marrow, and ovarian follicular fluid (Ellenhorn and Barceloux 1988; Foster et al. 1995a; Ingebrigtsen 1986; Ingebrigtsen and Nafstad 1983; Knauf and Hobson 1979; Wickstrom et al. 1983), and preferentially distributing to adipose tissue or organs with high fat content (Burton and Bennett 1987; Cohn et al. 1978; Koss and Koransky 1975; Lecavalier et al. 1994; Mehendale et al. 1975; Robinson et al. 1990; Teufel et al. 1990; van Raaij et al. 1993a; Verschueren 1983). Animal studies of oral dosing have showed that levels of hexachlorobenzene increase in a dose-dependent manner in all tissues up to 100 mg/kg/day (Foster et al. 1995a; Jarrell et al. 1993; Sundlof et al. 1982). Hexachlorobenzene body burden is readily transferred from pregnant mother to the fetus through the placenta in animals (Courtney and Andrews 1985; Courtney et al. 1979; Cripps 1990; Goldey et al. 1990; Nakashima and Ikegari 2000; Nakashima et al. 1997, 1999; Villeneuve and Hierlihy 1975; Villeneuve et al. 1974a). Additionally, hexachlorobenzene is concentrated in the milk and can be transferred to the suckling neonate (Bailey et al. 1980; Cripps 1990; Goldey et al. 1990; Nakashima and Ikegari 2000; Nakashima et al. 1997, 1999). Evidence from animal studies indicates that protein-poor diets may promote the preferential partitioning of ingested hexachlorobenzene to fatty tissue (Rodrigues et al. 1991). In a survey of the U.S. population, it was found that concentration of hexachlorobenzene tended to increase with increasing age, a testimony to the propensity of hexachlorobenzene to bioaccumulate in mammalian tissue (Robinson et al. 1990). In a group of 350 German children, blood hexachlorobenzene levels (and levels of other organochlorines) correlated strongly with the length of breast-feeding (Karmaus et al. 2001). Weak associations were seen between decreased blood hexachlorobenzene levels and increased child body mass index (above  $18 \text{ kg/m}^2$ ), and between increased hexachlorobenzene levels and both maternal age at birth (36–45-year-old group only) and late birth order (3<sup>rd</sup> or later, with spacing between children of at least 4 years). These data suggest that increased size may dilute hexachlorobenzene in the body, and that levels of hexachloro-

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benzene in mothers may increase with age. No correlations were seen for mothers who smoked during pregnancy, or the age and gender of the child.

Hexachlorobenzene is slowly metabolized in mammals, and the majority of hexachlorobenzene is excreted unchanged (in feces). Reductive dechlorination of hexachlorobenzene—catalyzed by enzymes located in the microsomal fraction of liver, lung, kidney, and intestine—appears to be an important pathway for the metabolism of hexachlorobenzene (Ingebrigtsen et al. 1986). It has been suggested that epoxide formation also occurs in this metabolism (Lui et al. 1976). PCP has been identified in human liver preparations incubated with hexachlorobenzene (Koss et al. 1986). In animals, hexachlorobenzene is slowly metabolized to PCP by the hepatic cytochrome P-450 system, conjugated with glutathione to yield pentachlorothiophenol, or reductively dechlorinated to form pentachlorobenzene. Other metabolites include less chlorinated benzenes, chlorophenols, S-conjugated phenols, and benzenes. PCP is subsequently converted to TCHQ (Hahn et al. 1988, 1989; Linko et al. 1986; Mehendale et al. 1975; Rozman et al. 1977a). The feces contain mostly unchanged parent compound, and about 1% pentachlorobenzene and traces of PCP after oral hexachlorobenzene exposure in mammals, while urinary excretion consists of mostly the metabolites, pentachlorobenzene, 2,4,5-trichlorophenol, *N*-acetyl-*S*(pentachlorophenyl)cysteine, mercaptotetrachlorothioanisole, and tetrachlorobenzene, 2,3,5,6-tetrachlorobenzene-1,4-diol; and unchanged parent compound (Koss et al. 1978; Mehendale et al. 1975; Rizzardini and Smith 1982; Rozman et al. 1978). Pentachlorothiophenol, PCP, methylthiopentachlorobenzene, 1,4-bis-(methylthio)-2,3,5,6-tetrachlorobenzene, chlorophenols, S-conjugated phenols and benzenes, and less chlorinated benzenes have also been identified in the liver following oral exposure in animals (D'Amour and Charbonneau 1992; Engst et al. 1976a; Ingebrigtsen et al. 1981, 1986; Jansson and Bergman 1978; Koss et al. 1976, 1979; Lui and Sweeney 1975; Renner 1988; Richter et al. 1981; Stewart and Smith 1986; To-Figueras et al. 1992; van Ommen et al. 1985, 1989; Yang et al. 1978). Sex differences in the metabolism of hexachlorobenzene in the adult animals have been reported. Urinary excretion of PCP, 2,3,5,6-tetrachlorobenzene-1,4-diol, and pentachlorothiophenol was greater in females than in males in this study (Rizzardini and Smith 1982).

To-Figueras et al. (2000) observed a high correlation between fecal and blood levels of hexachlorobenzene in 53 people highly exposed to airborne hexachlorobenzene. No information is available on the excretion of hexachlorobenzene following inhalation exposure in animals or following dermal exposure in humans or animals. In humans, ingested hexachlorobenzene is excreted in the urine mainly as its metabolites, PCP and pentachlorothiophenol (To-Figueras et al. 1992). In animals, the excretion of hexachlorobenzene appears to be quite variable, depending upon the solvent vehicle used (Albro and Thomas

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1974; Rozman et al. 1977a). Based on decreasing concentrations in the liver, the biological half-life of hexachlorobenzene has been estimated to be 8 days at the start of the elimination phase, 10 weeks after 3 months, and 12 months after 1.5 years (Koss et al. 1983), suggesting differential release of hexachlorobenzene from tissue stores, perhaps as a function of lipophilicity. Ingested hexachlorobenzene is excreted predominantly in the feces, mainly as unchanged parent compound, and to a lesser extent in the urine, as its metabolites (PCP, pentachlorothiophenol, pentachlorobenzene) (Mehendale et al. 1975).

Approximately 99% of unchanged ingested hexachlorobenzene was excreted in the feces; 50% of urinary excretion was PCP, 25% was pentachlorobenzene, and 25% was unchanged hexachlorobenzene in Rhesus monkeys treated with 0.03 mg/kg/day in the diet for 15 months (Rozman et al. 1977a). Based on animal studies, the urinary excretion of hexachlorobenzene exhibits sex- and age-specific differences; the excretion of pentachlorothiophenol increases with sexual maturity in female rats and slightly decreases in male rats (To-Figueras et al. 1991). Biliary excretion was not an important excretory pathway in rats given a single hexachlorobenzene dose of 10 mg/kg by gavage in peanut oil, accounting for <4% of the administered dose (Ingebrigtsen et al. 1981).

#### 3.4.1 Absorption

##### 3.4.1.1 Inhalation Exposure

Limited data show that hexachlorobenzene can be absorbed through the respiratory tract in humans, although no information is available as to the rate and extent of respiratory tract absorption of hexachlorobenzene in either humans or animals.

Spanish researchers have studied a population with long-term exposure to high levels of hexachlorobenzene in air (Grimalt et al. 1994; Herrero et al. 1999; Sala et al. 1999b; To-Figueras et al. 1997). The rural Spanish village of Flix contains an organochlorine factory that has been producing volatile chlorinated solvents for decades, and no other large industrial facilities. Following complaints of odor, approximately 40 air samples were collected in July and November of 1989 and May and October of 1992 at diverse sites in the village. As a control, five air samples were collected in the city of Barcelona. Average air levels of hexachlorobenzene in Flix ( $35 \text{ ng/m}^3$ ) were over 100-fold higher than in Barcelona ( $0.3 \text{ ng/m}^3$ ), while other organochlorines were found at similar or lower concentrations in Flix than in Barcelona. Corresponding to the high air levels, it was found that residents of Flix had unusually high serum levels of hexachlorobenzene (mean of  $39.8 \text{ ng/mL}$  based on a total number of 604 tested) in comparison to populations in Barcelona (mean= $4.13 \text{ ng/mL}$ ,  $n=100$ ), the United States

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(mean=0.19 ng/mL, n=370), Croatia (mean=1.00, n=15), and Germany (mean=1.12, n=6). Serum levels of other organochlorines in Flix residents were much lower than hexachlorobenzene levels and did not differ from other populations. Among Flix residents, serum hexachlorobenzene levels were several fold higher in factory workers (mean=93.4 ng/mL, n=185) than other residents (mean=16.9 ng/mL, n=419). Factory workers were presumably exposed to much higher air levels of hexachlorobenzene than other village residents, and some may have had dermal exposure as well.

It is noteworthy that mean serum hexachlorobenzene levels in Flix residents who did not work at the factory (and therefore, can be assumed to have had no direct dermal exposure to hexachlorobenzene) were still 4-fold higher than Barcelona residents. However, the difference was not entirely due to inhalation exposure. In addition to working at the factory, other variables associated with serum hexachlorobenzene levels were age and consumption of local fish. Among women (very few of whom had ever worked at the factory), the geometric mean serum hexachlorobenzene level was 14.9 ng/mL in those that did not eat local fish (176/180) and 18.2 ng/mL in those that did (only 4/180). Therefore, indirect exposure to hexachlorobenzene via consumption of contaminated fish may have contributed slightly to serum hexachlorobenzene levels in nonfactory worker Flix residents, but was not a major factor. This study shows that exposure to high levels of hexachlorobenzene in air leads to high levels of hexachlorobenzene in serum, and that a significant portion of hexachlorobenzene uptake in this situation can be attributed to inhalation and absorption across the respiratory tract.

Studies of workers with occupational exposure to hexachlorobenzene, where exposure was probably primarily by inhalation, but may have involved dermal contact as well, also show increased serum levels of hexachlorobenzene in the exposed workers. Selden et al. (1997) found significantly higher serum hexachlorobenzene levels in 29 hazardous waste incineration workers (63 ng/g lipid) than in 60 matched controls (35 ng/g lipid). The exposed workers also had significantly increased serum hexachlorobenzene levels compared with their own historical samples given before the start of employment (0.40 ng/g plasma vs. 0.27 ng/g plasma). Airborne hexachlorobenzene levels in different locations in the plant ranged from 0.066 to 11 ng/m<sup>3</sup>. Queiroz et al. (1997, 1998a, 1998b) observed that each of the 51 workers on leave from a closed chemical plant had blood hexachlorobenzene levels >0.1 µg/dL (mean=4.4 µg/dL), while controls chosen from blood donors at the local blood bank to be similar in age and race to the exposed group all had blood hexachlorobenzene levels lower than the limit of detection (0.02 µg/dL). The plant produced carbon tetrachloride and tetrachloroethylene; hexachlorobenzene was generated as a byproduct of the production process as a solid residue. Richter et al. (1994) documented high serum hexachlorobenzene levels in workers exposed to 2.1–10.8 mg/m<sup>3</sup> of hexachlorobenzene in air, which persisted even

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after air concentrations of hexachlorobenzene were reduced to 0.012–0.022 mg/m<sup>3</sup>. Although dermal exposure cannot be ruled out in these studies, uptake of hexachlorobenzene across the respiratory tract is likely to have contributed significantly to hexachlorobenzene body burden in all of these studies.

No studies were located regarding inhalation exposure to hexachlorobenzene in animals.

#### 3.4.1.2 Oral Exposure

Widespread occurrence of porphyria cutanea tarda in southeast Anatolia in Turkey in the late 1950s was shown to be due to ingestion of bread made from grain that had been treated with hexachlorobenzene (Cam and Nigogosyan 1963). The ingested dose of hexachlorobenzene was estimated to be in the range of 0.05–0.2 g/day, or 0.7–2.9 mg/kg/day for a 70-kg person. The occurrence of systemic health effects following ingestion of hexachlorobenzene demonstrates that this chemical can be absorbed via the gastrointestinal tract in humans, and in amounts sufficient to produce serious health effects. Follow-up studies conducted between 1977 and 1981 found that hexachlorobenzene levels in 56 samples of human milk obtained from porphyric mothers averaged 0.51 ppm (standard deviation [SD]=0.75 ppm, highest value=2.8 ppm), while levels in women from families without porphyria or outside the affected area had an average level of 0.07 ppm (SD=0.07 ppm) (Peters et al. 1982). Therefore, even 20 years after exposure, there was a large difference in breast milk hexachlorobenzene concentrations between people from families that had consumed the contaminated grain and those that did not.

One study was located in which gastrointestinal absorption of hexachlorobenzene in humans was quantified. Schlummer et al. (1998) used a mass-balance approach to estimate absorption of hexachlorobenzene ingested at low concentrations in the diet in seven volunteers (four males and three females) ranging in age from 24 to 81 years. Hexachlorobenzene was measured in the food (uniform meals of varying portion sizes) ingested by volunteers over a 3-day period (using duplicate portions) and in the corresponding feces (first and last meals identified using iron capsules to produce black feces). Similar experiments were then conducted in which the volunteers chose their own foods. Whole blood samples were collected 3 weeks after the last mass balance experiment. Percent net absorption was calculated as the difference between ingested and excreted hexachlorobenzene, divided by the ingested amount. When fed a standardized meal, the percent absorption was a relatively uniform 70–82% in the four young adults tested (one female and three males ranging in age from 24 to 36 years). It decreased to 1% in a 53-year-old male volunteer and further to -56 and -210% in 76- and 81-year-old female volunteers, respectively.

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The negative values in the elderly volunteers indicate net excretion, rather than absorption, in these individuals. Similar results were reportedly obtained when volunteers chose their own meals.

Blood levels of hexachlorobenzene (expressed as ng/g blood lipid) also varied with age, ranging from 65 to 82 in the young adult volunteers and increasing to 230, 680, and 1,420 in the 53-, 76-, and 81-year-old volunteers, respectively (Schlummer et al. 1998). The researchers noted a trend for decreasing absorption with increasing blood levels in the volunteers, and a linear regression was fit to these data. The calculated regression equation was:

$$\text{percent absorption hexachlorobenzene} = 0.8538 - 0.0021 \times (\text{ng hexachlorobenzene/g blood lipid})$$

This equation suggests that 85.4% of ingested hexachlorobenzene will be absorbed when the blood contains no hexachlorobenzene, and that this percentage will be reduced by 0.2% for each ng of hexachlorobenzene per g lipid in blood. This regression equation provided an excellent fit to the data ( $R^2=0.98$ ), leading to the conclusion that concentration of hexachlorobenzene in the blood is a major factor influencing absorption of hexachlorobenzene from the gut. Although absorption of lipophilic compounds such as hexachlorobenzene is thought to occur by simple passive diffusion, analysis of the entire data set in this study (17 polychlorinated dibenzo-*p*-dioxins/furans [PCDD/F] congeners and 10 PCBs in addition to hexachlorobenzene) showed that absorption of these compounds could not be explained by simple gradients between lipid-based food and blood concentrations or between gut contents and gut tissue. The researchers offered a “fat-flush” hypothesis of absorption for hexachlorobenzene and related compounds whereby lipid absorbed into gut tissue would temporarily increase lipid content of the tissue, diluting contaminant concentration in the gut tissue (on a lipid basis) and increasing the diffusion gradient for the contaminant from the gut contents, before being transported from the gut tissue to the lymph and blood.

Gastrointestinal absorption of hexachlorobenzene has been well studied in laboratory animals. Ingebrigtsen and Nafstad (1983) demonstrated that gastrointestinal absorption of hexachlorobenzene in an oil vehicle is rapid. Male Wistar rats were given a single gavage dose of 0.4 mg/kg of radiolabeled hexachlorobenzene dissolved in peanut oil and examined by whole body autoradiography at various time intervals starting 2 hours after dosing. A considerable amount of radiolabeled material was absorbed and distributed throughout the body within 2 hours of dosing, and peak levels were reached within 24 hours. Rapid absorption was also shown in beagle dogs that had hexachlorobenzene levels in blood monitored during and after 7 days of daily oral dosing with 10 or 100 mg/kg of hexachlorobenzene in corn oil by

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capsule (Sundlof et al. 1982). Peak blood concentrations occurred 3 hours after dosing in low-dose dogs, and after a somewhat longer (unspecified) interval in high-dose dogs. Blood concentrations continued to increase over several days after the last dose was administered in both groups, possibly due to continued absorption from the intestines during that time. This finding suggests that while the bulk of an oral dose of hexachlorobenzene in oil is absorbed rapidly in a few hours, absorption of residual quantities can continue for a period of days.

Hexachlorobenzene administered by gavage in aqueous methylcellulose suspension is also absorbed from the gut within a few hours (Iatropoulos et al. 1975). Sprague-Dawley rats given single gavage doses of 0.15 mg (approximately 0.6 mg/kg) of radiolabeled hexachlorobenzene in 1% methylcellulose solution were sacrificed at intervals between 1 and 48 hours after dosing for determination of tissue radioactivity levels. The ingested material was absorbed by the walls of the stomach and duodenum within 1 hour of dosing, and by the jejunum and ileum within 3 hours. Peak levels in the duodenum and jejuno-ileum occurred 3 hours after dosing. The majority of ingested hexachlorobenzene was absorbed from these regions of the small intestine by the lymphatic system and deposited in the fat, bypassing portal circulation to the liver, systemic circulation, and the excretory organs.

Although absorption of hexachlorobenzene from aqueous suspension occurred in a similar time frame as absorption from an oil vehicle in the studies described above, other studies have shown that the extent of absorption from aqueous suspension is much less. Koss and Koransky (1975) measured absorption of radiolabeled hexachlorobenzene in female Wistar rats following gavage administration of the chemical in olive oil at doses of 20, 60, and 180 mg/kg, and in aqueous suspension (6% gum arabic in water) at doses of 16, 120, and 970 mg/kg. Two days after dosing in olive oil, 73–88% of the administered radioactivity was recovered in the body, while 1% was recovered in the gut contents, 18–26% in the feces, and 0.4–0.6% in the urine in the different dose groups. This finding suggests oral absorption of about 80% of ingested hexachlorobenzene, regardless of dose, when administered in oil. When administered in aqueous suspension, however, absorption was much lower and appeared to depend on dose. At the low dose of 16 mg/kg, roughly 20% of administered radioactivity was recovered in body tissues 3 days after dosing in aqueous suspension, compared with 0.4% in the gut contents, 74% in the feces, and 0.4% in the urine. At the higher doses, only 2–5% of the administered hexachlorobenzene was absorbed from the aqueous suspension.

Other studies determined absorption of hexachlorobenzene from oil vehicles to be similar to that reported by Koss and Koransky (1975). Albro and Thomas (1974) gave male CD rats single gavage doses of 12 or

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30 mg/kg of hexachlorobenzene in cottonseed oil. They found that after 96 hours, 72% (high dose) to 82% (low dose) of the dose had not been excreted in the feces. No hexachlorobenzene was detected in the bile or urine, and only about 3% of the dose was present in the intestinal tissue and contents (primarily the former), and an associated *in vitro* experiment showed that fecal bacteria do not metabolize hexachlorobenzene; this suggests that the “removed” 72–82% had been absorbed into the body. Ingebrigtsen et al. (1981) used bile duct cannulated rats to monitor biliary excretion of radiolabeled hexachlorobenzene after gavage dosing with 10 mg/kg in peanut oil. A total of 3.6% of the administered radioactivity was recovered in the bile within 48 hours, while bile flow remained steady, showing that biliary excretion is only a minor pathway for hexachlorobenzene. After 96 hours, approximately 25% of the administered radioactivity was recovered in the feces and 2% in the urine. These data again suggest oral absorption of somewhere near 80% of the ingested dose for hexachlorobenzene administered in oil.

The studies described above showed that absorption of hexachlorobenzene in the gut is much more extensive from oil vehicles than from aqueous vehicles. Zabick and Schemmel (1980) demonstrated that a high fat diet also enhances absorption of hexachlorobenzene, in comparison to a high carbohydrate diet. Groups of 6 female Osbourne-Mendel rats were fed either a high fat diet or one of two high carbohydrate diets (one using corn starch, the other using sucrose) supplemented with 32 mg/kg/day of hexachlorobenzene for 6, 12, or 18 days. The high fat diet resulted in higher carcass fat content (data not shown; cited to Shier and Schemmel 1975) and greatly increased concentrations of hexachlorobenzene in perirenal fat, liver, and gastrocnemius. At the same time, concentrations of hexachlorobenzene in the feces were much lower with the high fat diet, suggesting that the high fat diet facilitated absorption of hexachlorobenzene from the gut, thereby leading to the increase in tissue levels. The data from all of these studies showing enhanced absorption of hexachlorobenzene when administered in oil or a high fat diet are consistent with the “fat-flush” hypothesis for hexachlorobenzene absorption proposed by Schlummer et al. (1998) based on the human data.

#### **3.4.1.3 Dermal Exposure**

No studies were located regarding absorption in humans following dermal exposure to hexachlorobenzene.

Evidence from rats suggests that hexachlorobenzene can be absorbed across the skin. Using radiolabelled hexachlorobenzene, Koizumi (1991) conducted a mass-balance study of dermal absorption in male Fisher 344 rats. A dermal dose of approximately 2.5 mg/kg of <sup>14</sup>C-hexachlorobenzene dissolved in

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tetrachloroethylene was applied to a 4 cm<sup>2</sup> clipped area on the back under occlusion. The rats, 3 per group, were transferred to metabolic cages and sacrificed after 6, 24, or 72 hours. Cumulative absorption of hexachlorobenzene (the sum recovered from the urine, feces, liver, carcass, skin not directly contaminated, and subcutaneous tissue) increased with duration of exposure from 1.05% of the applied dose after 6 hours to 2.67% after 24 hours and 9.71% after 72 hours. A one-compartment linear pharmacokinetic model was used to calculate an absorption constant of  $1.40 \times 10^{-3}$  per hour.

A modeling exercise conducted by Koizumi (1991) suggests that dermal absorption of hexachlorobenzene can contribute significantly to body burden in exposed workers. Assuming the rate constant in rats applies to man and a biological half-life ranging from 100 to 730 days, a three-compartment linear pharmacokinetic model developed based on the rat data and scaled up to a 70-kg man showed that hexachlorobenzene blood levels will increase with duration of exposure and that dermal doses as low as 2.56–18.2 mg (which could result from contamination small enough to go unnoticed) could, over a period of years, lead to hexachlorobenzene blood levels in the vicinity of 200 ppb, regarded by some researchers (Currier et al. 1980) as the upper safe limit in humans.

Koizumi (1991) also collected data showing that washing can decrease the absorption of dermally-contacted hexachlorobenzene by a significant degree. In the rats, washing the test area with soap 6 hours after application of hexachlorobenzene removed 34% of the applied dose and reduced the cumulative amount absorbed after 72 hours by 50% (from 9.71 to 4.90%).

#### 3.4.2 Distribution

##### 3.4.2.1 Inhalation Exposure

Two studies have investigated hexachlorobenzene distribution in people exposed via inhalation. The Aral Sea in Uzbekistan is a putative source of airborne exposure to hexachlorobenzene, metals, and other pollutants because its water levels are decreasing, revealing sediments to wind dissemination over the surrounding area. Ataniyazova et al. (2001) analyzed 18 maternal blood samples, 28 umbilical cord blood samples, and 41 milk samples collected from mothers and infants within 200 kilometers of the southern border of the Aral Sea in Uzbekistan. The respective mean concentrations of hexachlorobenzene in maternal and cord blood were 167 ng/L (range 72–9,920 ng/L) and 70 ng/L (range 25–1,300 ng/L) and in 93% of milk samples, with a mean of 28 ng/g fat (range 10–109 ng/L). Sala et al. (2001a) compared two populations; for a group of 31 pairs of mothers and infants from Flix, Spain, who had been highly

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exposed to airborne hexachlorobenzene from a chlorinated solvent factory, the respective geometric means of hexachlorobenzene maternal and cord blood levels were 3.98 ng/mL (range 0.50–20.78 ng/mL) and 1.40 ng/mL (range 0.30–5.77 ng/mL). For subjects from villages nearby to Flix, the respective geometric means of hexachlorobenzene maternal and cord blood levels were 2.51 ng/mL (range 0.36–7.46 ng/mL) and 0.85 ng/mL (range 0.13–2.45 ng/mL). A statistically significant correlation between maternal and umbilical cord blood was detected.

No studies were located regarding distribution of hexachlorobenzene following inhalation in animals.

#### 3.4.2.2 Oral Exposure

Hexachlorobenzene rapidly distributes throughout the body following absorption. A whole-body autoradiography experiment in rats showed that hexachlorobenzene was extensively distributed throughout the body within 2 hours of receiving a single oral dose of 0.4 mg/kg in peanut oil (Ingebrigtsen and Nafstad 1983). In another experiment, radiolabeled hexachlorobenzene was found in multiple internal tissues in rats 3 hours after the rats received a single oral dose of about 0.6 mg/kg in aqueous methylcellulose (Iatropoulos et al. 1975).

Although hexachlorobenzene is widely distributed in the body, it is not evenly distributed. Due to its lipophilic nature, hexachlorobenzene distributes preferentially to fat, and to a lesser extent, other lipid-rich tissues. In the Iatropoulos et al. (1975) study, radiolabel occurred at the highest levels and was most persistent in the mesenteric lymph node and adipose tissue. Levels were much lower and declined rapidly in the lung, liver, and kidney. The researchers interpreted these findings to indicate that a significant fraction of the gastrointestinally absorbed hexachlorobenzene is transported via the lymphatic system to the fat, bypassing portal circulation to the liver and systemic circulation to the excretory organs.

Numerous studies have shown preferential distribution of hexachlorobenzene to adipose tissue. In the rat autoradiography study mentioned above, Ingebrigtsen and Nafstad (1983) found peak levels of radioactivity in the fat to be roughly 60-fold higher than peak levels in the blood and 30-fold higher than peak levels in the brain and liver. Besides the fat, other tissues found to contain relatively high concentrations of radioactivity included the skin, bone marrow, Harderian gland, nasal mucosa, preputial gland, and intestinal tract. Koss and Koransky (1975) found similar results in rats given single gavage doses of 20–180 mg/kg of radiolabeled hexachlorobenzene in oil, with radioactivity in fat two days after administration being about 60-fold higher than in blood, 30-fold higher than in liver, and 5-fold higher

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than in skin. Levels in brain and kidney were intermediate between liver and blood, while levels in muscle were lower. Lecavalier et al. (1994) also found approximately 30-fold higher concentrations of hexachlorobenzene in the fat than in the liver 14 days after a single gavage dose of 400 or 600 mg/kg of hexachlorobenzene in corn oil. Brain and kidney concentrations were slightly (within a factor of 2) lower than liver concentrations, while serum levels were an order of magnitude lower than liver concentrations. In a repeated dose study, ovariectomized adult female rats treated by gavage in oil with 1, 10, or 100 mg/kg/day of hexachlorobenzene for 30 days had hexachlorobenzene concentrations in fat that were 30-fold higher than levels in liver, which were in turn 20-fold higher than levels in serum. Levels in the adrenals were roughly 20-fold greater than levels in liver (Foster et al. 1995a). A study in which rats were dosed with 50 mg/kg of hexachlorobenzene by gavage in oil every other day for 15 weeks also showed hexachlorobenzene concentrations in the fat to be 30–60 times greater than concentrations in the liver, brain, kidney, and blood throughout dosing and a subsequent 38-week observation period (Koss et al. 1978).

Preferential distribution to fat and high lipid tissues has also been demonstrated in other animal species. Dogs given seven consecutive daily doses of 10 or 100 mg/kg/day of hexachlorobenzene in corn oil by capsule had peak hexachlorobenzene concentrations in fat that were 30-fold greater than peak liver levels (Sundlof et al. 1982). Other tissues with relatively high levels (5- to 10-fold greater than liver) were the skin, adrenal, and thyroid. Levels in the kidney, heart, brain, spleen, pancreas, and muscle were similar to levels in the liver. Cynomolgus monkeys treated with 0.1, 1, or 10 mg/kg/day of hexachlorobenzene in gelatin capsules for 90 days had hexachlorobenzene concentrations in fat that exceeded liver concentrations by 10- to 15-fold (Jarrell et al. 1993). Kidney and brain hexachlorobenzene levels were lower than in the liver, while serum and follicular fluid levels were much lower still (Foster et al. 1995b; Jarrell et al. 1993). In Rhesus monkeys given oral doses of 8–128 mg/kg/day of hexachlorobenzene by gavage in aqueous methyl cellulose for 60 days, the highest concentrations of hexachlorobenzene were found in the body fat and bone marrow, with considerably lower concentrations in the adrenals, liver, kidney, brain, ovaries, muscle, and serum (Knauf and Hobson 1979).

The animal studies showed that levels of hexachlorobenzene increased in a dose-dependent manner in all tissues, at least at doses up to around 100 mg/kg/day. The study by Foster et al. (1995a) found dose-dependent increases in tissue levels of hexachlorobenzene in rats treated with 1, 10, or 100 mg/kg/day, the study by Sundlof et al. (1982) found dose-dependent tissue levels in dogs treated with 10 or 100 mg/kg/day, and the study by Jarrell et al. (1993) found dose-dependent tissue levels in monkeys treated with 0.1, 1, or 10 mg/kg/day. In the fat, the increase in hexachlorobenzene concentration was

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directly proportional to dose at doses up to 100 mg/kg/day in dogs (Sundlof et al. 1982), 10 mg/kg/day in rats (Foster et al. 1995a), and 1 mg/kg/day in monkeys (Jarrell et al. 1993). Lecavalier et al. (1994) found no difference in tissue levels of hexachlorobenzene following dosing with 400 or 600 mg/kg in rats, showing that dose-dependence is lost at high doses. Knauf and Hobson (1979) found no clear relationship between tissue levels of hexachlorobenzene and dose in Rhesus monkeys given between 8 and 128 mg/kg. However, their highly variable results may have been due to very small group sizes (one or two monkeys per dose) and, they speculated, variation in the amount of body fat in the monkeys used. Although Koss and Koransky (1975) tested multiple dose levels, their results were not presented in sufficient detail to assess dose-dependence of tissue levels.

In humans, data regarding tissue concentrations of hexachlorobenzene are limited to autopsy cases and easily sampled tissues and fluids, such as breast milk and blood serum. Two studies were located in which both breast adipose/milk and blood serum were collected from the same individuals and analyzed for hexachlorobenzene. In a study of 36 Connecticut women between 50 and 80 years of age, hexachlorobenzene was detected in the breast adipose of all 36 women (median concentration=17.7 ng/g fat), but was not detected in the serum of any of these women (quantitation limit=0.6 ng/g) (Archibeque-Engle et al. 1997). In a study of seven pregnant/lactating New York women (each with a differing interval between collection of blood and milk samples), hexachlorobenzene was detected in the serum (0.03–0.29 ng/g), but at lower concentrations than in the milk (0.21–0.74 ng/g) (Greizerstein et al. 1999). The difference between serum and milk levels can be attributed in part to the differing lipid content of these fluids. Lipid-normalized concentrations of hexachlorobenzene were 8–48.4 ng/g lipid in serum and 11–22.5 ng/g lipid in milk. Two other studies were located that looked at both breast adipose/milk and serum levels of hexachlorobenzene in the same populations, although not necessarily in the same individuals. In Veracruz, Mexico, a group of 65 volunteer mothers in the hospital for delivery had average hexachlorobenzene blood serum concentrations of 1.1 ng/g, and a group of 60 volunteer mothers in the hospital for Cesarean delivery (extent of overlap with blood volunteers unknown) had average hexachlorobenzene concentrations in milk fat and adipose tissue of 25 and 58 ng/g fat, respectively, 30 days after delivery (Waliszewski et al. 1999a, 1999b). Similarly, a group of six women from a city in northern Germany had a mean serum hexachlorobenzene level of 1.0 ng/g, while breast milk samples from seven women from northern Germany in the same year (overlap with blood donors not known) showed a mean hexachlorobenzene concentration of about 70 ng/g fat (Petzold et al. 1999).

Other studies have found hexachlorobenzene in human blood (Rutten et al. 1988; Sala et al. 1999b; Schlummer et al. 1998; Siyali 1972), liver (Dewailly et al. 1999; Weistrand and Noren 1998), bone

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marrow (Bucholski et al. 1996; Scheele et al. 1995), brain (Dewailly et al. 1999), fat (Ansari et al. 1986; Dewailly et al. 1999; Lordo et al. 1996; Robinson et al. 1990; Scheele et al. 1995; Siyali 1972; Teufel et al. 1990; Weistrand and Noren 1998), and breast milk (Craan and Haines 1998; Czaja et al. 1997; Gladen et al. 1999; Gocmen et al. 1989; Lunden and Noren 1998; Newsome and Ryan 1999; Scheele et al. 1995; Weisenberg 1986; Wickstrom et al. 1983; and many others). In human plasma, close to half of the hexachlorobenzene present is found in the lipoprotein depleted fraction (containing primarily albumin), while the rest is split between the high density (. 20%), low density (. 20%), and very low density (. 10%) lipoprotein fractions (Noren et al. 1999).

Schlummer et al. (1998) found that blood levels of hexachlorobenzene (expressed as ng/g blood lipid) varied with age in a group of seven volunteers, ranging from 65 to 82 in four young adult volunteers and increasing to 230, 680, and 1,420 in the 53-, 76-, and 81-year-old volunteers, respectively. This result shows that hexachlorobenzene accumulates in people as they age. Tissue build up occurs because people are continually exposed to hexachlorobenzene in the environment and excretion is slow. In their rat experiments, Koss and Koransky (1975) observed an estimated elimination half-time of 8–10 days for hexachlorobenzene in the fat and other tissues following administration of a single gavage dose of 20–180 mg/kg. However, this finding was based on only a 14-day observation period. Koss et al. (1978) monitored tissue hexachlorobenzene levels 14 and 38 weeks after a 15-week dosing period (50 mg/kg every other day) in rats. Although the researchers could not produce an estimate of biological half-life, they found that the rate of elimination decreased over time and speculated that elimination of hexachlorobenzene might continue for years. This issue is discussed in more detail in Section 3.4.4 on Elimination and Excretion.

Human studies have shown that hexachlorobenzene can pass from the mother to the neonate through the placenta. In a study of 160 full-term neonates in Germany, hexachlorobenzene was found at an average concentration of 2.03 µg/L in 1984/1985 and 0.61 µg/L in 1994/1995 in neonatal blood obtained from an unblocked peripheral vein within the first 12 hours of life before the first oral feeding (Lackmann et al. 1996, 1999). Ando et al. (1985) found hexachlorobenzene in maternal blood, placenta, and neonatal cord blood in 36 pregnant Japanese women and their babies. There was a statistically significant correlation between the concentration of hexachlorobenzene in the placenta and in cord blood. Waliszewski et al. (1999c) reported a statistically significant correlation ( $R=0.87$ ) between levels of hexachlorobenzene in maternal blood serum (mean=1 µg/L, detected in 100% of samples) and umbilical cord serum (mean=0.8 µg/L, detected in 98% of samples) in a group of 65 volunteer mothers in Veracruz, Mexico. Hexachlorobenzene was also found in the cord blood of all 63 births (geometric mean [GM]=1 µg/L)

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analyzed in the village of Flix, Spain (Sala et al. 1999a), and in all 656 births (GM=0.04 µg/L) analyzed in Quebec, Canada (Rhainds et al. 1999).

Studies in laboratory animals support the findings in humans that hexachlorobenzene is transferred from pregnant mother to the fetus through the placenta. Hexachlorobenzene was found in the fetus and placenta of pregnant mice treated with 50 mg/kg/day of hexachlorobenzene by gavage in corn oil on days 7–11 of gestation and examined 24 hours after the last dose (Courtney et al. 1976). Follow-up studies by these researchers demonstrated that fetal (whole body) and placental hexachlorobenzene concentrations increased with dose, with the duration of dosing, and with the day of dosing (dosing later in gestation leads to higher levels) in mice, and that results in rats were similar to those in mice (Courtney and Andrews 1985; Courtney et al. 1979). Other studies showing transfer of maternal hexachlorobenzene to the fetus in rats were reported by Nakashima et al. (1997) and Cripps (1990). Goldey et al. (1990) measured maternal and fetal tissue levels of hexachlorobenzene in rats given a total dose of 11 mg/kg over a 3-day period 3 weeks prior to breeding. They found that fetal blood and liver concentrations were slightly lower than maternal blood concentrations, while fetal brain levels were about half of the maternal blood levels. Villeneuve and co-workers measured hexachlorobenzene levels in fetal tissues after administering hexachlorobenzene at a series of dose levels. The fetuses of pregnant rats treated with 5–120 mg/kg/day of hexachlorobenzene by gavage in corn oil on days 6–16 of gestation and sacrificed for cesarian section on day 22 of gestation showed dose-related increases in hexachlorobenzene concentration in whole fetus, fetal liver, and fetal brain (Villeneuve and Hierlihy 1975). The concentration of hexachlorobenzene in fetal liver was about 20–40% of the concentration in maternal liver. The concentration in fetal brain was about half that in fetal liver. A similar study in rabbits also demonstrated dose-dependent placental transfer of hexachlorobenzene, although in this species, fetal liver concentrations of hexachlorobenzene were 2–3-fold higher than maternal liver concentrations (Villeneuve et al. 1974a). Fetal brain levels, however, were much lower than fetal liver levels and were also less than maternal brain concentrations in rabbits.

The occurrence of hexachlorobenzene in breast milk of humans is well documented in many populations, as noted above. Many of the same animal studies that investigated placental transfer of hexachlorobenzene also studied lactational transfer from mothers to their offspring (Courtney and Andrews 1985; Cripps 1990; Goldey et al. 1990; Nakashima et al. 1997). These data are discussed in Section 3.4.4 on Elimination and Excretion.

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**3.4.2.3 Dermal Exposure**

No studies were located regarding distribution of hexachlorobenzene following dermal exposure in humans.

Male Fischer 344 rats that received a single dermal dose of approximately 2.5 mg/kg <sup>14</sup>C-hexachlorobenzene dissolved in tetrachloroethylene applied to a 4 cm<sup>2</sup> clipped area on the back absorbed only 9.7% of the dose; 90.3% of the applied dose remained unabsorbed on the skin after 72 hours. The concentration of hexachlorobenzene in the liver and blood increased steadily after dermal application. Washing decreased mean hexachlorobenzene concentrations in blood from 263 to 0.128 µg/g and in the liver from 0.68 to 0.556 µg/g liver at 72 hours. The authors developed a compartment model based on the data collected, for application to a 70-kg worker (Koizumi 1991).

**3.4.3 Metabolism****3.4.3.1 Inhalation Exposure**

No studies were located regarding metabolism in humans or animals after inhalation exposure to hexachlorobenzene.

**3.4.3.2 Oral Exposure**

Hexachlorobenzene is slowly metabolized to pentachlorophenol by the hepatic cytochrome P-450 system (CYP3A1, CYP3A2, CYP3A4 isoforms) (Den Besten et al. 1994; Mehmood et al. 1996; Schielen et al. 1995a), conjugated with glutathione to yield pentachlorothiophenol, or reductively dechlorinated to form pentachlorobenzene (Ingebrigtsen et al. 1986; Koss et al. 1979; Renner 1988). Other metabolites include less chlorinated benzenes, chlorophenols, S-conjugated phenols, and benzenes (Den Besten et al. 1994; Koss et al. 1986). Pentachlorophenol is subsequently converted to tetrachlorohydroquinone (Mehmood et al. 1996; van Ommen et al. 1985).

Pentachlorobenzene and pentachlorophenol were identified as the major metabolites of <sup>14</sup>C-labeled hexachlorobenzene (0.03 mg/kg/day) administered in the diet to Rhesus monkeys for 15 months (Rozman et al. 1977). In the urine, approximately 50% of the excreted radiolabel was pentachlorophenol, 25% was pentachlorobenzene, and the remaining 25% consisted of unidentified metabolites and unchanged hexa-

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chlorobenzene. Of the excreted radioactivity in the feces, 99% was unchanged hexachlorobenzene, with <1% pentachlorobenzene and trace amounts of pentachlorophenol. A subsequent report of a similar study in Rhesus monkeys found that fecal excretion consisted of 99% unchanged parent compound, about 1% pentachlorobenzene, and traces of pentachlorophenol (Rozman et al. 1978). Urinary metabolites consisted of 50–75% pentachlorophenol. The remainder of radioactivity (25–50%) was composed of pentachlorobenzene, hexachlorobenzene, and tetrachlorobenzene. Only unchanged parent compound was found in the plasma, and the red blood cells contained 95% unchanged parent compound and 5% pentachlorophenol.

A similar metabolic pattern was observed in the rat. Extraction and analysis of fecal radioactivity, which accounted for 16% of the administered dose, 7 days after gavage administration of 5 mg/kg of <sup>14</sup>C-labeled hexachlorobenzene in arachis oil to rats did not reveal the presence of metabolites. Urine, which contained 0.85% of the administered radiolabel, contained 2,4,5-trichlorophenol, pentachlorophenol, and several unidentified chlorinated benzenes (Mehendale et al. 1975). Gas/liquid chromatography-mass spectrometry identified 20% of the radioactivity as parental hexachlorobenzene together with the metabolites pentachlorothiophenol and pentachlorophenol in isolated perfused rat (male Wistar) liver treated with <sup>14</sup>C-hexachlorobenzene diluted with unlabeled hexachlorobenzene to yield a concentration of 0.1 mg hexachlorobenzene/mL perfusate. Most of the radioactivity was found in the perfusate and in the liver; unchanged hexachlorobenzene was responsible for most of the radioactivity. Traces of pentachlorothiophenol and pentachlorophenol were identified in the perfusate and the liver, respectively (Ingebrigtsen et al. 1981, 1986). A study reported that 98% of biliary radioactivity, which constituted 3.6% of the administered dose 48 hours after administration, was in the form of metabolites; 25% of this radioactivity was glutathione-conjugated pentachlorophenol (Ingebrigtsen et al. 1981). No sulfur-containing metabolites of hexachlorobenzene were found in the bile. However, a study of the metabolic fate of hexachlorobenzene (particularly as it relates to transformation of hexachlorobenzene into any methylthio- and methylsulfonyl-metabolites) in male Wistar rats identified methylthiopentachlorobenzene and 1,4-bis-(methylthio)-2,3,5,6-tetrachlorobenzene as metabolites of hexachlorobenzene (Jansson and Bergman 1978). These compounds were excreted to a greater extent than the corresponding monosubstituted metabolites. One methylthiotetrachlorobenzene was also found. Pentachlorophenol was the only detectable metabolite in blood, liver, urine, or feces of female Wistar rats 38 weeks after the end of 15-week gavage exposure to 50 mg/kg/day of hexachlorobenzene (Koss et al. 1978).

In other rat studies, N-acetyl-S(pentachlorophenyl)cysteine (PCTP-NAC) was the most abundant urinary product in female Wistar rats administered dietary hexachlorobenzene in 4% corn oil for 13 weeks

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resulting in doses of 7.5 or 15 mg/kg/day (Den Besten et al. 1994) or treated twice a week for 35 weeks by gavage with 50 mg/kg in olive oil (Rietjens et al. 1995). Other rats in the Den Besten et al. (1994) study were similarly administered dietary levels of 0.03 or 0.13% pentachlorobenzene to provide a basis for comparison. Pentachlorophenol and tetrachlorohydroquinone were common urinary metabolites of both hexachlorobenzene and pentachlorobenzene. Mercaptotetrachlorothioanisole (MTCTA), which was excreted as a glucuronide, was also detected in the urine of rats given hexachlorobenzene. Pentachlorophenol, pentachlorothiophenol, 2,3,4,6- and 2,3,5,6-tetrachlorophenol, and pentachlorobenzene were identified as metabolites of hexachlorobenzene in another study (Richter et al. 1981). Significant sex-related differences were observed, with higher amounts of pentachlorothiophenol observed in the livers of female rats. This was accompanied by a slower decrease in hepatic levels of hexachlorobenzene in the female rat liver compared to the male liver. Sex differences in the metabolism of hexachlorobenzene in the adult rat have also been observed. After 10 weeks of treatment, the urinary excretion of pentachlorophenol, 2,3,5,6-tetrachlorobenzene-1,4-diol, and pentachlorothiophenol was greater in females than in males in this study (Rizzardini and Smith 1982). Sex-related differences in biotransformation of hexachlorobenzene could account for differences observed in porphyrinogenic activity of hexachlorobenzene in male and female rats (D'Amour and Charbonneau 1992; Richter et al. 1981; Rizzardini and Smith 1982).

Two alternatives have been proposed for the mechanism of conversion of hexachlorobenzene to pentachlorophenol: formation of an epoxide or free radical attack on the carbon-chlorine bond. Substitution of adjacent carbons with chlorine argues against a mechanism involving an epoxide; either cleavage of the bond by free radical attack followed by hydroxylation, or conjugation with glutathione seems more plausible. However, if the presence of *o*- and *p*-hydroxy derivatives of pentachlorophenol could be confirmed, there would be a strong possibility that epoxides are intermediates in the dechlorination or hydroxylation of hexachlorobenzene or both (Lui et al. 1976). *In vitro* studies with perfused rat livers demonstrated that <sup>14</sup>C-labeled hexachlorobenzene was converted to acidic conjugates (45%), while 5% was converted to sulfate or glucuronic acid conjugates (Ingebrigtsen et al. 1986). There is evidence that mammalian metabolism of hexachlorobenzene to pentachlorophenol is mediated by the hepatic cytochrome P-450 system (CYP3A1, CYP3A2, CYP3A4 isoforms; others) (Den Besten et al. 1994; Mehmood et al. 1996; Schielen et al. 1995a).

Several other studies in laboratory animals also identified the following mammalian biotransformation products of hexachlorobenzene: pentachlorophenol (Ingebrigtsen et al. 1981; Koss et al. 1976, 1979; Lui and Sweeney 1975; van Ommen et al. 1985; Yang et al. 1978); pentachlorothiophenol (D'Amour and

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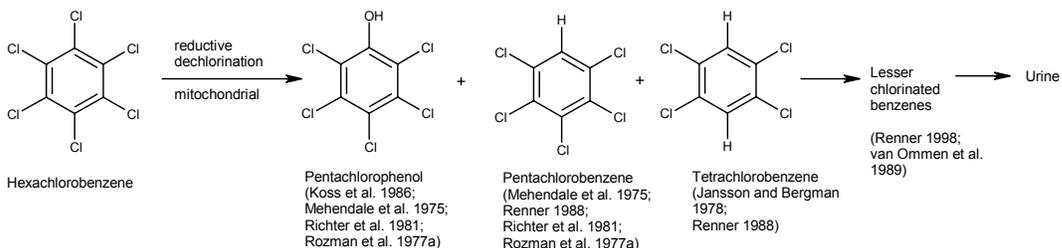
Charbonneau 1992; To-Figueras et al. 1992); less chlorinated benzenes, chlorophenols, S-conjugated phenols and benzenes (Engst et al. 1976; Koss et al. 1979; Renner 1988; Stewart and Smith 1986); and tetrachlorohydroquinone and tetrachlorocatechol (Koss et al. 1976, 1979; Lui et al. 1976; Mehmood et al. 1996; van Ommen et al. 1985, 1989). The various pathways and metabolites of hexachlorobenzene are depicted in Figure 3-3.

There is some evidence to indicate that metabolism of hexachlorobenzene to pentachlorophenol is accelerated in rats fed fish oil, in comparison to lard or soybean oil (Umegaki and Ikegami 1998). Rats fed fish oil had significant increases in liver cytochrome P-450, blood pentachlorophenol and

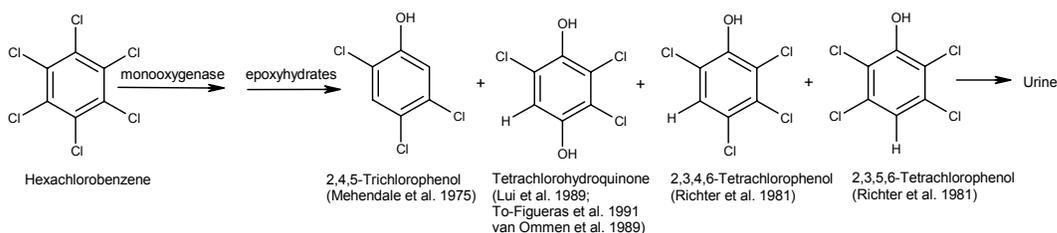
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**Figure 3-3. Metabolism and Urinary Metabolites of Hexachlorobenzene**

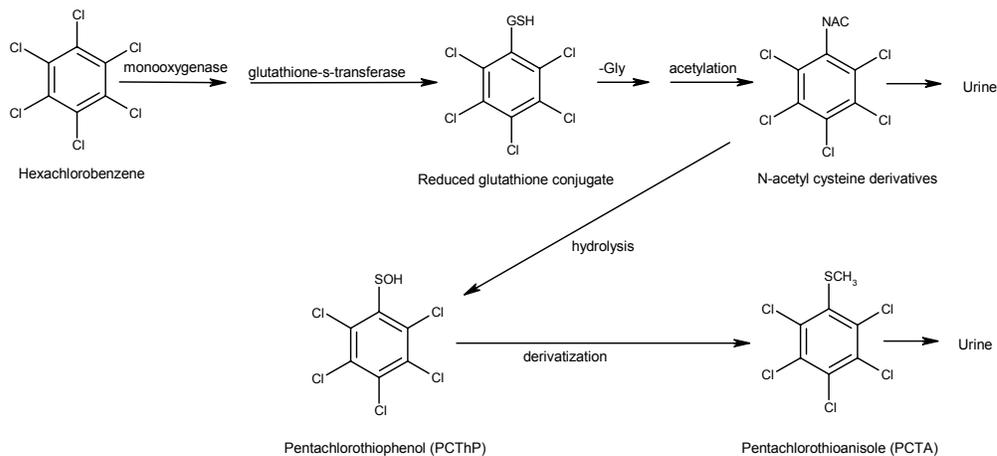
MAJOR METABOLITES



MINOR METABOLITES



GLUTATHIONE CONJUGATION: FORMATION OF SULFUR DERIVATIVES  
(Adapted from Ingebrigtsen et al. 1981; Jansson and Bergman 1978; Renner 1988; To-Figueras et al. 1992)



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pentachlorophenol:hexachlorobenzene ratio, and urinary excretion of pentachlorophenol, while levels of hexachlorobenzene in the feces were unchanged (indicating no difference in absorption between groups).

Limited human data are consistent with results from animal studies. Portions (0.5 g) of abdominal subcutaneous adipose tissue obtained as histological samples during surgery of patients and urine from these patients in Germany were extracted with benzene for hexachlorobenzene and its metabolites (Koss et al. 1986). Hexachlorobenzene was detected in the adipose tissue of the patients, while only pentachlorophenol was detected in the urine. A correlation was found between levels of hexachlorobenzene found in adipose tissue and urinary pentachlorophenol. However, it is possible that the urinary pentachlorophenol originated from other chlorinated hydrocarbons such as pentachlorobenzene, gamma-hexachlorocyclohexane, or pentachloronitrobenzene. Human cytochrome P-450 3A4 expressed in the yeast *Saccharomyces cerevisiae* metabolized hexachlorobenzene to pentachlorophenol, which was further transformed to tetrachlorohydroquinone, in both *in vitro* and *in vivo* experiments (Mehmood et al. 1996).

#### 3.4.3.3 Dermal Exposure

No studies were located regarding metabolism in humans or animals after dermal exposure to hexachlorobenzene.

#### 3.4.4 Elimination and Excretion

##### 3.4.4.1 Inhalation Exposure

To-Figueras et al. (2000) observed a high correlation between fecal and blood levels of hexachlorobenzene in a group of 25 men and 28 women from Flix, Spain. This population was highly exposed to airborne hexachlorobenzene from a nearby chlorinated solvent factory. The geometric mean of hexachlorobenzene in blood was 163  $\mu\text{g}/5.4\text{ L}$ . Estimated fecal excretion of unchanged hexachlorobenzene was 10.4  $\mu\text{g}/\text{day}$ , 4–6.4% of the estimated total blood level. No unchanged hexachlorobenzene was detected in urine; urinary excretion of metabolites was 5.1  $\mu\text{g}/\text{day}$ , 1.8–3.1% of the estimated total blood level.

No studies were located regarding excretion of hexachlorobenzene in animals following inhalation exposure.

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**3.4.4.2 Oral Exposure**

Elimination of absorbed hexachlorobenzene is slow and occurs primarily via the feces, with smaller amounts being excreted in the urine. Hexachlorobenzene eliminated in the feces is predominantly unchanged parent compound, although small amounts of various metabolites have also been found. Conversely, hexachlorobenzene in the urine is almost all in the form of metabolites. Following a single intraperitoneal injection of radiolabeled hexachlorobenzene (4 mg/kg) in rats, approximately 34% of the administered radioactivity was recovered in the feces over the following 14 days, 80% of which was unchanged parent compound (Koss and Koransky 1975). By contrast, only 5% of the administered radioactivity was recovered in the urine, and only 4% of that was unchanged parent compound. A 14-day recovery period was used due to the slow elimination of hexachlorobenzene from the body. Yang et al. (1978) conducted an experiment in which rats were injected intravenously with radiolabeled hexachlorobenzene and excreta collected over the following 48 hours. Only 1% of the administered dose appeared in the feces, and 0.2% in the urine, within 48 hours of dosing. These researchers also conducted a long-term experiment in monkeys (Yang et al. 1978). One year after intravenous injection, only 28.2% of the administered dose had been excreted in the feces (90% unchanged hexachlorobenzene) and 1.6% in the urine (all metabolites). The researchers attributed slow elimination of hexachlorobenzene to long-term storage of the chemical in the fat. Neither Koss and Koransky (1975) nor Yang et al. (1978) detected radioactivity in the expired air from treated animals.

Both biliary and intestinal excretion contribute to fecal excretion of hexachlorobenzene. Hexachlorobenzene and/or its metabolites were found in the bile after intravenous injection of hexachlorobenzene in monkeys, suggesting the possibility of biliary excretion (Yang et al. 1978). Bile duct cannulated rats given hexachlorobenzene by gavage excreted 3.6% of the administered dose in the bile within 48 hours (Ingebrigtsen et al. 1981). Although one report suggested that biliary excretion was more important than intestinal excretion (Sundlof et al. 1982), other studies have shown that biliary excretion is a minor contributor to fecal excretion. Rozman et al. (1981) estimated biliary excretion to account for about 10% of fecal excretion in rats and monkeys treated with oral hexachlorobenzene. Intestinal excretion was responsible for the bulk of the fecal excretion in this study. Feeding with aliphatic hydrocarbons (mineral oil, hexadecane) enhanced fecal excretion in both rats and monkeys, with a corresponding decrease in blood and adipose hexachlorobenzene concentrations, primarily due to increased elimination of hexachlorobenzene in the large intestine (Rozman et al. 1981). In contrast to aliphatic hydrocarbons, cholestyramine, which interferes with enterohepatic recycling, had no effect on fecal excretion of hexachlorobenzene (confirming the minor role of biliary excretion for this chemical), and sesame oil produced

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only a very small increase in fecal hexachlorobenzene excretion (possibly by increasing gastrointestinal absorption). Richter and Schafer (1981) showed that addition of hydrocarbons (light liquid paraffin and squalane) to the perfusion medium enhanced elimination of unchanged hexachlorobenzene in perfused intestine into the lumen of the jejunum, ileum, and colon. The researchers hypothesized that the hydrocarbons, which are not significantly absorbed, act as a lipophilic compartment in the gut lumen, shifting the equilibrium between gut wall and lumen in favor of the lumen for hydrophilic substances such as hexachlorobenzene. This is consistent with the fat-flush hypothesis of gastrointestinal absorption proposed by Schlummer et al. (1998). After fat-flush enhanced lipid absorption in the duodenum and jejunum is complete, the diffusion gradient is reversed in subsequent portions of the intestines.

In lactating mothers, breast milk is also an important route of excretion for hexachlorobenzene. Hexachlorobenzene has been detected in human breast milk in many studies (Craan and Haines 1998; Czaja et al. 1997; Gladen et al. 1999; Gocmen et al. 1989; Lunden and Noren 1998; Newsome and Ryan 1999; Scheele et al. 1995; Weisenberg 1986; Wickstrom et al. 1983; and many others). Several animal studies have quantified lactational transfer of hexachlorobenzene from mothers to their offspring (Courtney and Andrews 1985; Cripps 1990; Goldey et al. 1990; Nakashima et al. 1997). These studies confirm the importance of breast milk as a route of elimination in the mother and as a source of exposure in neonates.

Studies that monitored elimination of hexachlorobenzene for an extended period of time noted that the rate of elimination decreases over time (Koss et al. 1978, 1983; Sundlof et al. 1982; Yang et al. 1978). In rats treated with hexachlorobenzene every other day for 6 weeks, the elimination half-time was estimated as a relatively rapid 8 days soon after exposure stopped, a much slower 10 weeks 3 months later, and a very slow 12 months after 1.5 years, suggesting that elimination of hexachlorobenzene could continue for years (Koss et al. 1978, 1983). Yang et al. (1978) and Sundlof et al. (1982) both applied 3-compartment pharmacokinetic models to their data on dogs and monkeys, respectively. Sundlof et al. (1982) obtained elimination half-time estimates ranging from 6 weeks to 3 years in the three dogs modeled. Yang et al. (1978) calculated elimination rate constants corresponding to half-times of 91–114 days in two monkeys, but also performed additional modeling exercises that suggested elimination half times as long as 250 years. Freeman et al. (1989) used a physiologically based pharmacokinetic (PBPK) model of hexachlorobenzene in the rat to show that approximately 75% of the decline in fat concentrations over time is due to growth (i.e., dilution), with only 25% due to excretion. Thus, the growth of animals during experiments may affect the apparent half-life of hexachlorobenzene. A PBPK model developed by Yesair et al. (1986) predicted a half-life of 215 days for hexachlorobenzene in a growing human female exposed to doses of 0.5–32 mg/kg/day for 15 weeks at 15 years of age.

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**3.4.4.3 Dermal Exposure**

No studies were located regarding excretion in humans or animals after dermal exposure to hexachlorobenzene.

**3.4.4.4 Other Routes of Exposure**

No studies were located regarding excretion in humans after other routes of exposure to hexachlorobenzene.

The major portion of injected hexachlorobenzene is eliminated unchanged in feces, while a smaller fraction, composed of metabolites, is eliminated in urine. Yang et al. (1978) administered a single intravenous dose of hexachlorobenzene to monkeys; 1 year after intravenous injection, only 28.2% of the administered dose had been excreted in the feces, 90% unchanged, and in urine, 1.6% of the total dose was excreted as metabolites (no unchanged compound detected). The researchers attributed slow elimination of hexachlorobenzene to long-term storage of the chemical in the fat. Unchanged hexachlorobenzene and metabolites were detected in bile. Yang et al. (1978) administered a single intravenous dose of hexachlorobenzene to rats; within 48 hours, only 1% appeared in the feces, and 0.2% in the urine. Following a single intraperitoneal injection of hexachlorobenzene, rats excreted 34% of the total dose in feces over 14 days, 80% of which was unchanged parent compound; only 5% was excreted in urine over 14 days and only 4% was unchanged parent compound (Koss and Koransky 1975). Neither Koss and Koransky (1975) nor Yang et al. (1978) detected hexachlorobenzene elimination in air expired by treated animals. Yang et al. (1978) calculated an initial half-life of 91–114 days, and subsequent half-lives as long as 250 years.

**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

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pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

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

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

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is 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

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sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-4 shows a conceptualized representation of a PBPK model.

#### **3.4.5.1 Summary of PBPK Models**

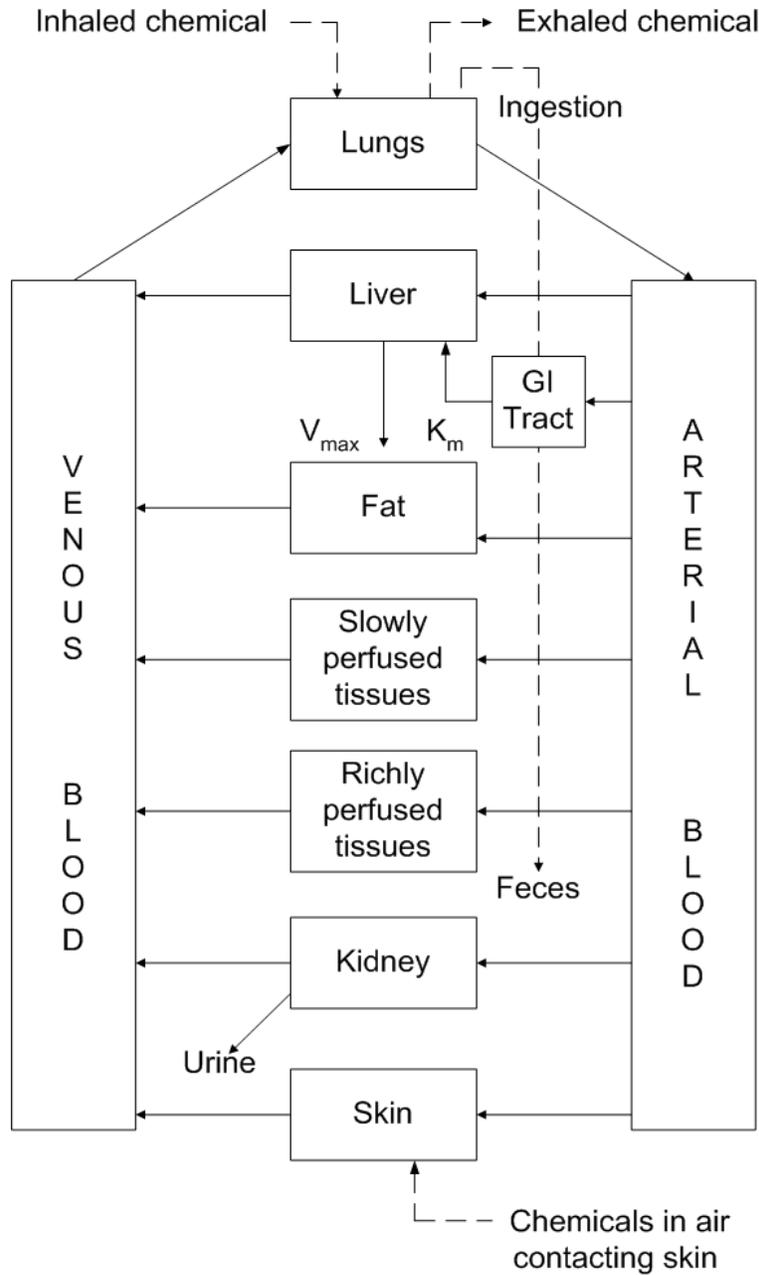
PBPK models for hexachlorobenzene have been developed by Yesair et al. (1986) and Freeman et al. (1989). The Yesair et al. (1986) model describes the absorption, distribution, and elimination of ingested hexachlorobenzene in growing rats and humans. The Freeman et al. (1989) model describes distribution and excretion of intravenously injected hexachlorobenzene in growing rats.

#### **3.4.5.2 Hexachlorobenzene PBPK Model Comparison**

The Yesair et al. (1986) and Freeman et al. (1989) models are similar attempts to describe distribution and clearance of hexachlorobenzene. Both models included numerous tissue compartments and allowed for growth over time. The Yesair et al. (1986) model went further than the Freeman et al. (1989) model by including oral exposure, fetal and breast milk compartments, and metabolism and tissue sequestration of hexachlorobenzene, and by modeling humans as well as rats. Both rat models were validated using experimental data.

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**Figure 3-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance**



Source: adapted from Krishnan et al. 1994

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

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**3.4.5.3 Discussion of Models****The Yesair Model.**

**Risk assessment.** The Yesair model was not used for risk assessment.

**Description of the model.** The Yesair model was initially developed to simulate oral exposure to hexachlorobenzene in growing male and female rats, and was then expanded to include pregnancy and offspring in the female model. A human model was produced by using the same model structure with human physiological parameter values. The model includes compartments for intestinal lumen, systemic circulation, feces, liver, metabolites, kidney, urine, brain, richly perfused tissues, poorly perfused tissues, breast milk, fetus, and lactating offspring. Parameters used in the model included body and organ weights and growth rates, blood-flow rates, empirical clearance factors, reaction-rate constants, distribution ratios, and capacity limits. The forms of the growth characteristics and the parameter values were obtained from the literature, experimental data from Kuiper-Goodman et al. (1977), and empirical considerations. Both free and sequestered forms of hexachlorobenzene were estimated in each compartment, and only freely available material was allowed to leave the compartment (except for the systemic circulation and breast milk compartments). When the rat models were adapted for humans, the appropriate human physiological values were substituted for the rat values.

**Validation of the model.** The rat model was compared to data from Courtney et al. (1979), Iatropoulos et al. (1975), Koss and Koransky (1975), Koss et al. (1978), and Kuiper-Goodman et al. (1977). In general, the model approximated the observed results reasonably well in all tissues. The human model was not validated.

**Target tissues.** Using the rat model, correlations were obtained between predicted yield of metabolites and experimentally observed liver toxicity (porphyria and increased liver weight reported by Koss et al. 1978 and Kuiper-Goodman et al. 1977), between estimated concentrations of hexachlorobenzene in the brain and observed central nervous system effects (tremors and other signs reported by Koss et al. 1978 and Kuiper-Goodman et al. 1977), and between estimated extent of lactational transfer of hexachlorobenzene and observed offspring mortality (data from Kitchen et al. 1982). The model predicts little transfer of hexachlorobenzene to the fetus during gestation and extensive mobilization of hexachlorobenzene to the offspring during lactation. The data are consistent with this model. A half-life of 215 days was predicted for hexachlorobenzene in a growing human female exposed to doses of

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0.5–32 mg/kg/day for 15 weeks at 15 years of age, suggesting that approximately 4 years (7 half-lives) are required to establish equilibrium between intake and excretion. Further simulations showed that doubling or halving the administered dose resulted in doubling or halving, respectively, of the tissue concentrations after 3–5 years.

**Species extrapolation.** Species extrapolation was not attempted in this model.

**Interroute extrapolation.** Interroute extrapolation was not attempted in this model.

### **The Freeman Model.**

**Risk assessment.** The Freeman model was not used for risk assessment.

**Description of the model.** The Freeman model was developed to simulate intravenous injection of hexachlorobenzene in growing rats. The model includes compartments for plasma, gastrointestinal tract, colon, feces, liver, lung, kidney, urine, brain, heart, spleen, skin, muscle, and fat. Parameters used in the model include organ weights and blood flow fractions obtained from the literature and tissue:serum partition coefficients derived from experimental studies by Scheufler and Rozman (1984a, 1984b). The model was designed to accommodate differential growth of tissue/organ weights as a function of total body weight. Metabolism was assumed to be zero based on experimental data (attributed to Rozman and colleagues) suggesting little metabolism of hexachlorobenzene in the rat.

**Validation of the model.** The model predictions were compared to data from Scheufler and Rozman (1984a, 1984b). In general, the model approximated the observed results reasonably well in the compartments examined: blood, liver, fat, urine, and feces.

**Target tissues.** Levels in liver and fat were well-predicted by this model. An interesting prediction is that approximately 75% of the decline in fat concentrations over time is due to growth (i.e., dilution), with only 25% due to excretion. Thus, the growth of animals during experiments may affect the apparent half-life of hexachlorobenzene.

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**Species extrapolation.** Species extrapolation was not attempted in this model.

**Interroute extrapolation.** Interroute extrapolation was not attempted in this model.

### 3.5 MECHANISMS OF ACTION

#### 3.5.1 Pharmacokinetic Mechanisms

**Absorption.** Schlummer et al. (1998) found that absorption following oral exposure to hexachlorobenzene decreased with increasing hexachlorobenzene blood levels in volunteers. Data was fit to a linear regression. The calculated regression equation was:

$$\text{percent absorption hexachlorobenzene} = 0.8538 - 0.0021 \times (\text{ng hexachlorobenzene/g blood lipid})$$

This equation indicates that 85.4% of ingested hexachlorobenzene will be absorbed when the blood contains no hexachlorobenzene, and that this percentage will be reduced by 0.2% for each ng of hexachlorobenzene per g lipid in blood. This regression equation provided an excellent fit to the data ( $R^2=0.98$ ), leading to the conclusion that concentration of hexachlorobenzene in the blood is a major factor influencing absorption of hexachlorobenzene from the gut. Although absorption of lipophilic compounds such as hexachlorobenzene is thought to occur by simple passive diffusion, analysis of the entire data set in this study, which included 17 polychlorinated dibenzo-*p*-dioxins/furan congeners and 10 PCBs in addition to hexachlorobenzene, showed that absorption of these compounds could not be explained by simple gradients between lipid-based food and blood concentrations or between gut contents and gut tissue. The researchers offered a “fat-flush” hypothesis of absorption for hexachlorobenzene and related compounds whereby lipid absorbed into gut tissue would temporarily increase lipid content of the tissue, diluting contaminant concentration in the gut tissue (on a lipid basis) and increasing the diffusion gradient for the contaminant from the gut contents, before being transported from the gut tissue to the lymph and blood.

Animal studies have demonstrated that hexachlorobenzene is absorbed more rapidly from oil than from aqueous suspension (Albro and Thomas 1974; Iatropoulos et al. 1975; Ingebrigtsen and Nafstad 1983; Ingebrigtsen et al. 1981; Koss and Koransky 1975; Sundlof et al. 1982; Zabick and Schemmel 1980; and others). Nakashima et al. (1999) observed that lactational transfer of hexachlorobenzene was increased by feeding nursing rats high fat diets. Zabick and Schemmel (1980) demonstrated that a high fat diet also

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enhances absorption of hexachlorobenzene, in comparison to a high carbohydrate diet. Groups of six female Osborne-Mendel rats were fed either a high fat diet or one of two high carbohydrate diets supplemented with 32 mg/kg/day of hexachlorobenzene for 6–18 days. The high fat diet resulted in higher carcass fat content and greatly increased concentrations of hexachlorobenzene in perirenal fat, liver, and gastrocnemius. At the same time, concentrations of hexachlorobenzene in the feces were much lower with the high fat diet, suggesting that the high fat diet facilitated absorption of hexachlorobenzene from the gut, thereby leading to increased tissue levels. These data showing enhanced absorption of hexachlorobenzene when administered in oil or a high fat diet are consistent with the “fat-flush” hypothesis for hexachlorobenzene absorption proposed by Schlummer et al. (1998).

Iatropoulos et al. (1975) measured absorption in Sprague-Dawley rats following oral gavage of hexachlorobenzene in aqueous methylcellulose suspension, and observed that hexachlorobenzene was absorbed through the walls of the stomach, duodenum, jejunum, and ileum. Based on their data, the authors concluded that the majority of ingested hexachlorobenzene was absorbed from the small intestine by the lymphatic system and deposited in the fat, bypassing portal circulation (to the liver), systemic circulation, and the excretory organs.

**Distribution.** Hexachlorobenzene has been detected in human and animal blood, and circulation is the primary mechanism of inter-tissue distribution. Due to its lipophilic nature, hexachlorobenzene distributes preferentially to fat, and to a lesser extent, other lipid-rich tissues (Foster et al. 1995a, 1995b; Iatropoulos et al. 1975; Ingebrigtsen and Nafstad 1983; Jarrell et al. 1993; Knauf and Hobson 1979; Koss and Koransky 1975; Koss et al. 1978; Lecavalier et al. 1994; Sundlof et al. 1982). Although distribution studies have produced somewhat conflicting results, a rough approximation of hexachlorobenzene distribution is: fat > lymph nodes, adrenal and thyroid glands > skin > bone marrow, Harderian gland, nasal mucosa, preputial gland, and intestinal tract > liver, lung > kidney, brain, blood, heart, muscle, spleen, pancreas, ovary.

Human and animal studies suggest that breast milk is enriched with hexachlorobenzene, relative to blood, and that blood levels actually drop in lactating mothers (Greizerstein et al. 1999; Petzold et al. 1999; Nakashima et al. 1997, 1999; Nakashima and Ikegari 2000; Waliszewski et al. 1999a, 1999b). This is probably due to the lipophilicity of hexachlorobenzene.

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**Metabolism.** Hexachlorobenzene is slowly metabolized by hepatic cytochrome P-450 system (CYP3A1, CYP3A2, CYP3A4 isoforms) (Den Besten et al. 1994; Mehmood et al. 1996; Schielen et al. 1995a); by conjugation with glutathione, glucuonide, and sulfate; and by reductive dechlorination (Ingebrigtsen et al. 1986; Koss et al. 1979; Renner 1988).

Two alternatives have been proposed for the mechanism of conversion of hexachlorobenzene to PCP: formation of an epoxide or free radical attack on the carbon-chlorine bond. Substitution of adjacent carbons with chlorine argues against a mechanism involving an epoxide; either cleavage of the bond by free radical attack followed by hydroxylation, or conjugation with glutathione seems more plausible. However, if the presence of o- and p-hydroxy derivatives of PCP could be confirmed, there would be a strong possibility that epoxides are intermediates in the dechlorination or hydroxylation of hexachlorobenzene or both (Lui et al. 1976).

**Excretion.** Following metabolism to more polar metabolites, hexachlorobenzene is excreted in urine (Ingebrigtsen et al. 1981, 1986; Koss and Koransky 1975; Koss et al. 1986; Lui and Sweeney 1975; Rozman et al. 1977a; Scheufler and Rozman 1984a, 1984b; To-Figueras et al. 1992; van Ommen et al. 1985; Yang et al. 1978).

Hexachlorobenzene eliminated in the feces is predominantly unchanged parent compound, although small amounts of various metabolites have also been found (Koss and Koransky 1975; Yang et al. 1978). Fecal elimination is primarily the product of fecal excretion, although biliary excretion (from the liver) is also important (Ingebrigtsen et al. 1981; Richter and Schafer 1981; Rozman et al. 1981; Yang et al. 1978).

For nursing mothers, excretion of unchanged hexachlorobenzene into milk may represent a significant, and even the primary, route of excretion (Courtney and Andrews 1985; Craan and Haines 1998; Cripps 1990; Czaja et al. 1997; Gladen et al. 1999; Gocmen et al. 1989; Goldey et al. 1990; Lunden and Noren 1998; Nakashima et al. 1997; Newsome and Ryan 1999; Scheele et al. 1995; Weisenberg 1986; Wickstrom et al. 1983; and many others).

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**3.5.2 Mechanisms of Toxicity**

Hexachlorobenzene induces porphyria characterized by increased d-ALA synthase (the enzyme that controls the rate of porphyrin production) activity and decreased uroporphyrinogen decarboxylase (the enzyme that converts uroporphyrinogen III to coproporphyrinogen III) activity (Dowdele et al. 1967; Rajamanickam et al. 1972; Smith and de Matteis 1990; Strand et al. 1971). Uroporphyrinogen III is the first cyclic tetrapyrrole in the pathway of heme biosynthesis. This is the reduced colorless precursor of uroporphyrin III (hexahydro-uroporphyrin) and will give rise to the corresponding porphyrin on reoxidation. Uroporphyrinogen decarboxylase (a cytosolic enzyme) converts uroporphyrinogen III to coproporphyrinogen III by the stepwise decarboxylation of the four acetic acid side chains to leave methyl residues, but the corresponding porphyrin (uroporphyrin III) cannot be decarboxylated and will not be metabolized further. Thus, the accumulation of uroporphyrins in the liver may be due to a deficiency of the decarboxylation of uroporphyrinogen III catalyzed by uroporphyrinogen decarboxylase. This hypothesis led to the proposal that in certain porphyria where uroporphyrin accumulates (uroporphyrurias), the mechanism responsible may be an accelerated oxidation of uroporphyrinogen, causing an "oxidative escape" of this intermediate from the pathway of heme biosynthesis (Meola and Lim 1993; Smith and de Matteis 1990). A marked inhibition of uroporphyrinogen decarboxylase has been widely reported to occur prior to the manifestation of the typical porphyrinogenic effects of hexachlorobenzene (Bleckenherst et al. 1976; Elder et al. 1976; Smith and Francis 1987; Smith et al. 1986a). A study conducted with Osteogenic Disorder Shionogi (ODS) rats provided evidence that chemically-induced porphyria seems to be mediated by inhibition of CYP1A2-catalyzed uroporphyrinogen oxidation (Sinclair et al. 1995).

*In vitro* studies with hexachlorobenzene have demonstrated that this chemical does not exert a direct action on uroporphyrinogen decarboxylase (Rios de Molina et al. 1980). The major hexachlorobenzene metabolites (TCHQ, PCP, pentachlorothiophenol, pentachlorothioanisole) had no influence on the porphyrin pathway as indicated by alteration in total hepatic porphyrin levels and urinary levels of d-ALA, porphobilinogen, or uroporphyrins (Goldstein et al. 1977, 1978; Kimbrough and Linder 1978; Lui et al. 1976; Smith and Francis 1987; Wainstok de Calmanovici and San Martin de Viale 1980). However, PCP and TCHQ appear to be capable of altering porphyrin metabolism in *in vitro* systems containing d-ALA (Goerz et al. 1978; Goldstein et al. 1977). Furthermore, co-administration of PCP and TCHQ with hexachlorobenzene increased the severity of the resultant porphyria (Debets et al. 1980a), indicating a probable role for these metabolites in porphyria induction. It has been suggested that changes in K<sup>+</sup> permeability mediated by lipid peroxidation and mitochondrial dysfunction may be contributing

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factors in hexachlorobenzene-induced hepatotoxicity. This was based on the results of a study in rats in which mitochondrial lipid peroxidation was found to have increased proportionally with a 100-fold increase in hepatic porphyrin content (Feldman and Bacon 1989; Masini et al. 1988). Porphyrin uptake in the mitochondria of iron-supplemented rats was inhibited by PCP (hexachlorobenzene metabolite), indicating that peroxidative reactions in the mitochondrial membranes may be responsible for changes in membrane permeability (Masini et al. 1988).

It is unlikely, however, that the hexachlorobenzene metabolites, pentachlorobenzene and PCP, are by themselves porphyrinogenic agents, and P-450 induction may not correlate with porphyria development. In one study, rats fed diets containing hexachlorobenzene or its metabolites (pentachlorobenzene and PCP) exhibited increases in hepatic cytochrome P-450, but the metabolites had no effect on urinary porphyrin excretion, while hexachlorobenzene produced a high level of urinary porphyrins (Vos et al. 1988). In other studies, the major hexachlorobenzene metabolites (TCHQ, PCP, pentachlorothiophenol, pentachlorothioanisole) had no influence on the porphyrin pathway as indicated by alteration in total hepatic porphyrin levels and urinary levels of d-ALA, porphobilinogen, or uroporphyrins (Goldstein et al. 1977, 1978; Kimbrough and Linder 1978; Smith and Francis 1987; Wainstok de Calmanovici and San Martin de Viale 1980). However, PCP and TCHQ appear to be capable of altering porphyrin metabolism in *in vitro* systems containing d-ALA (Goerz et al. 1978; Goldstein et al. 1977). Furthermore, co-administration of PCP and TCHQ with hexachlorobenzene increased the severity of hexachlorobenzene-induced porphyria (Debets et al. 1980a).

In a study with rats, it was proposed that the involvement of the histidine residue of the enzyme in substrate (hexachlorobenzene) binding may be the mechanism by which hexachlorobenzene exerts its porphyrinogenic action *in vivo* (Billi de Catabbi et al. 1991). Another study in rats and mice concluded that hexachlorobenzene induces chronic porphyria by modifying sulfhydryl groups in porphyrinogen decarboxylase, the action restricted to the catalytic or substrate-binding sites (Elder and Urquhart 1986).

Iron (as iron dextran) alone has been shown to induce porphyria; therefore, iron may have a role in the pathogenesis of hexachlorobenzene-induced porphyria (Siersema et al. 1991; Smith and Francis 1983; Smith et al. 1986a) and hepatocarcinogenesis (Smith 1989), although co-administration of carbonyl iron did not have a significant effect on elevated hepatic and mitochondrial fraction porphyrin contents in rats following hexachlorobenzene treatment (Masini et al. 1988), but in other animal studies, exposure of mice to hexachlorobenzene and iron produced a dramatic increase (nearly 1,000-fold) in hepatic uroporphyrin levels (Vincent et al. 1989). The small number of animals used in this study limits the reliability of the

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conclusions of this study. Another investigator concluded that liver mitochondrial porphyrin uptake may involve the  $K^+$  transmembrane gradient and further suggested that peroxidative reactions in the mitochondrial membranes may be responsible for changes in membrane permeability that affects  $K^+$  permeability (Masini et al. 1988). Liver malonaldehyde levels increased while glucose-6-phosphate activity decreased in rats administered intraperitoneal injections of 50 mg of hexachlorobenzene per day (total dose=300 mg) during a 42-day test period followed by treatment with intraperitoneal doses of iron (as ferrihydroxide-dextran complex), suggesting a close relationship between accumulation of porphyrins, iron overload, and free radical formation or lipid peroxidation (Visser et al. 1989).

Experiments with rats and iron-loaded mice indicate that there may also be an association between the induction of uroporphyrin and the development of liver tumors after the administration of poly-halogenated aromatic chemicals (Smith and De Matteis 1990). Hyperplastic nodules were observed in the liver lobes of 80% of female Fischer 344 rats pretreated with Imferon (iron-dextran) and then given dietary hexachlorobenzene in arachis oil for 65 weeks resulting in a dose of 5 or 10 mg/kg/day. There was a high incidence of fibrin throughout the liver with sinusoidal telangiectasis, and nodular peliosis hepatitis and hepatocellular necrosis. The study proposed a nongenotoxic mechanism for tumor induction by hexachlorobenzene, concluding that the formation of hepatomas and hemangiomas with elements of peliosis could be explained by the compensatory hyperplastic responses to hepatocellular injury or necrosis and by the simultaneous loss of hepatocellular cords. The study further concluded that the accumulation of iron in the liver would strongly potentiate the development of hepatic tumors (Carthew and Smith 1994).

Iron overload also greatly sensitized mice to the development of liver tumors. Mice given oral hexachlorobenzene doses preceded by subcutaneous administration of iron developed iron-excluded hyperplastic nodules (all treated animals) and hepatocellular carcinoma (most animals). Based on the results of this investigation, an alternate mechanism has been suggested for the hepatic toxicity of hexachlorobenzene that may involve the uncoupling of an induced cytochrome P-450 system releasing active oxygen species. Iron is seen as catalyzing the formation of the hydroxyl radical or perhaps forming reactive iron-oxygen complexes (Smith 1989).

Data from a study in male Long Evans rats suggested that the metabolism of hexachlorobenzene to pentachlorobenzene and other more polar metabolites proceed either through a free-radical mechanism or by initial formation of an arene oxide. These reactive intermediates may form covalent bonds with cellular constituents (such as protein amino acids or DNA nucleic acids) leading to irreversible cell damage (Lui

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and Sweeney 1975). Several other studies have also found evidence of binding to cellular proteins by reactive electrophilic metabolites of hexachlorobenzene formed by cytochrome P-450 system (Gopaldaswamy and Nair 1992; Rajamanickam and Padmanaban 1974; van Ommen et al. 1985).

### 3.5.3 Animal-to-Human Extrapolations

Studies have investigated the adverse effects of hexachlorobenzene in rats, mice, hamsters, dogs, pigs, and monkeys following subchronic exposure and in rats, mice, and hamsters following chronic exposure. Substantial bodies of both of human data and animal data are available that demonstrate qualitative similarities between animals and humans for such end points as porphyria and dermal lesions. Overall, data in animal studies do not suggest species variations in the toxicokinetics of hexachlorobenzene except in carcinogenic responses. The cancer toxicity data suggest that species differences exist, as demonstrated by multi-tumor-type responses evident in hamsters and single-tumor-type responses observed in mice (Cabral et al. 1977, 1979; EPA 1980b; Ertürk et al. 1986; Lambrecht et al. 1983a; Smith 1989; Smith et al. 1985).

## 3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Colborn and Clement (1992), was also used in 1996 when Congress mandated the Environmental Protection Agency (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), which in 1998 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

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natural hormone mimics are the isoflavonoid 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 1997c). 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).

Hexachlorobenzene mediates multiple adverse effects through the neuroendocrine axis. Hormonal changes associated with exposure to hexachlorobenzene include decreased serum thyroxine (hypothyroidism), increased serum parathyroid hormone (hyperparathyroidism), decreased corticosterone released from the adrenal gland, and changes in estradiol and progesterone levels in females at certain times in the menstrual cycle. The female hormone changes are coincident with ovarian lesions and changes in female reproductive cycles in the same studies. Reduced fertility in breeding trials with hexachlorobenzene may be secondary to the ovarian effects. These alterations are described in more detail in Section 3.2. The effect of hexachlorobenzene on thyroxine appears to involve stimulation of dehalogenation of the hormone in the liver, rather than an effect on synthesis of the hormone in the thyroid (Kleiman de Pisarev et al. 1989, 1990). There is also some evidence that hexachlorobenzene may competitively inhibit binding of thyroxine to serum carrier proteins, further depressing circulating levels of the hormone (Foster et al. 1993; Van Den Berg 1990). The effects on ovarian and adrenal hormones have been hypothesized to reflect alterations in steroidogenesis in these tissues, possibly as a consequence of lipid peroxidation of mitochondrial membranes (Foster et al. 1995a, 1995b). Ultrastructural lesions consistent with lipid peroxidation have been observed in mitochondria from the ovaries of monkeys treated with hexachlorobenzene (Bourque et al. 1995); similar lesions have also been observed in rats (Alvarez et al. 2000). Breast cancer is another end point believed to be influenced through the neuroendocrine axis. Studies available to date have found little or no evidence for an association between hexachlorobenzene and breast cancer in humans (Dorgan et al. 1999; Guttus et al. 1998; Liljegren et al. 1998; Mendonca et al. 1999; Moysich et al. 1998; Zheng et al. 1999). Adipose hexachlorobenzene levels were increased in males with undescended testis compared to controls (Hosie et al. 2000); this adverse effect may be related to *in utero* changes in hormone levels.

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**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

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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).

Infants and young children appeared to be especially sensitive to the effects of hexachlorobenzene in the Turkish grain poisoning epidemic. During the epidemic, there was an extremely high rate of mortality (close to 100% in some villages) in breast fed infants (under 2 years of age) of mothers known to have ingested the contaminated bread (Gocmen et al. 1989; Peters et al. 1982). This is in contrast to a 10% rate of mortality in exposed adults (Peters et al. 1982, 1987). Poisoned infants displayed a condition known as *pembe yara* or "pink sore" because of the associated skin lesions (blistering and epidermolysis and annular erythema) (Cripps et al. 1984; Peters et al. 1982, 1987). The infant deaths were caused by respiratory and cardiovascular failure resulting from the disease, and sometimes followed tremors and convulsions (Peters et al. 1982). Pink sore was not seen in exposed adults. Infants in this study were likely exposed *in utero* via transplacental transfer and postnatally by lactational transfer (Cripps et al. 1984; Peters et al. 1982, 1987). No quantitation of exposure (dose and duration) was presented in any of these clinical reports. However, an estimated dose of 0.05–0.2 g/day (0.7–2.9 mg/kg/day for a 70-kg person) is considered to be reliable by the original investigators of the Turkey epidemic (Cam and Nigogosyan 1963). Analysis of human milk from exposed women and unexposed controls in this epidemic showed hexachlorobenzene concentrations of 0.51 and 0.07 ppm, respectively (Cripps et al. 1984; Gocmen et al. 1989; Peters et al. 1982, 1987).

Based on 20–30-year follow-up studies (Cripps et al. 1984; Peters et al. 1982), patients who were young children (average age 7 years) during this exposure later developed numerous dermatologic, neurologic, and orthopedic abnormalities associated with the developmental toxicity of hexachlorobenzene. The reproductive histories of 42 females exposed to hexachlorobenzene as children or young adults were also studied. Of the 188 pregnancies in the 42 women that occurred in a 4-year period (1977–1981), there were 15 fetal deaths (13 miscarriages and 2 stillbirths) and 173 live births (Peters et al. 1982, 1987);

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however, the relevance of this study is limited because the numbers of expected miscarriages and stillbirths were not provided. These mothers had 0.51 ppm hexachlorobenzene in their breast milk compared to 0.07 ppm in unexposed controls (Gocmen et al. 1989). The fetal mortalities may be related to the mobilization of hexachlorobenzene from the maternal fat pool and its subsequent exposure to the fetus through the placenta.

Based on partial evaluation of 63 of a planned 100 cases, Sala et al. (1999b) published a preliminary study, reporting that a significant association between prenatal hexachlorobenzene exposure and impaired development of locomotor skills had been detected in newborn babies in Flix, compared with those of nearby villages. A study of a less-exposed population in New York was unable to correlate hexachlorobenzene levels in umbilical blood or breast milk with infant intelligence test results (Darvill et al. 2000).

A German case-control study found that adipose hexachlorobenzene levels in 18 male patients who underwent orchidopexy to correct unilateral or bilateral undescended testis (mean age 4.2 years) were 3-fold higher compared to a group of 30 male control patients (mean age 3.5 years); this difference was highly significant (Hosie et al. 2000). A similar correlation was also observed for heptachloroepoxide (HCE), but not for other organochlorines. The weaknesses of this study are the small study size, the lack of age-adjustment between groups, and the potentially confounding effect of HCE.

Although there is only limited direct evidence that hexachlorobenzene crosses the placenta in humans (Ando et al. 1985), animal studies have shown that hexachlorobenzene crosses the placenta readily and accumulates in fetal tissues (Courtney and Andrews 1985; Courtney et al. 1979; Cripps 1990; Villeneuve and Hierlihy 1975; Villeneuve et al. 1974a). While numerous human studies have demonstrated the presence of hexachlorobenzene in breast milk, animal studies have shown in addition that hexachlorobenzene concentrates in the breast milk and is transferred to the suckling neonate in considerable amounts (Bailey et al. 1980; Cripps 1990; Goldey et al. 1990).

Animal studies have also confirmed that the developing organism is an especially sensitive target for hexachlorobenzene. Findings from laboratory animal single- and multi-generation reproductive toxicity studies conducted in rats exposed to hexachlorobenzene indicate that fertility, gestational viability, and lactational indices may be affected by hexachlorobenzene exposure (Grant et al. 1977; Kitchin et al. 1982). Studies on prenatally exposed animals have shown immune and neurological effects at lower doses in the young developing animals than in adults (Goldey and Taylor 1992; Vos et al. 1979a). The

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most sensitive end point in any study, and the basis for the chronic MRL, was liver lesions that developed during adulthood in rats treated with combined pre- and postnatal lifetime exposure (Arnold et al. 1985).

Animal studies have also shown that hexachlorobenzene mediates toxicity through the neuroendocrine axis, with multiple effects on the thyroid gland (hypothyroidism), parathyroid gland (hyperparathyroidism), adrenal gland, and ovaries (Alvarez et al. 2000; Andrews et al. 1988, 1990; Den Besten et al. 1993; Den Tonkelaar et al. 1978; Foster et al. 1992b, 1993, 1995a, 1995b; Kimbrough and Linder 1974; Kleiman de Pisarev et al. 1989, 1990). Because the hormones produced by these endocrine organs play a crucial role in growth and development of the organism, it is not surprising that hexachlorobenzene interferes with these processes. Neuroendocrine end points have not been studied in developing organisms.

#### 3.8 BIOMARKERS OF EXPOSURE AND EFFECT

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

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to hexachlorobenzene are discussed in Section 3.8.1.

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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 hexachlorobenzene 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 Hexachlorobenzene**

Human tissues and body fluids that have been analyzed for hexachlorobenzene to identify and quantify exposure include blood and serum (Ataniyazova et al. 2001; Glynn et al. 2000; Hagmar et al. 2001; Karmaus et al. 2001; Rutten et al. 1988; Sala et al. 1999b, 2001b; Schlummer et al. 1998; Siyali 1972; Waliszewski et al. 2001; Weiderpass et al. 2000; and many others), liver (Dewailly et al. 1999; Westrand and Noren 1998), bone marrow (Bucholski et al. 1996; Scheele et al. 1995), brain (Dewailly et al. 1999), fat (Ansari et al. 1986; Dewailly et al. 1999; Lordo et al. 1996; Robinson et al. 1990; Scheele et al. 1995; Siyali 1972; Szymczynski and Waliszewski 1981; Teufel et al. 1990; Westrand and Noren 1998), semen (Szymczynski and Waliszewski 1981), the placenta (Poli et al. 1999), the umbilical cord (Burse et al. 2000; Darvill et al. 2000), and breast milk (Ataniyazova et al. 2001; Craan and Haines 1998; Czaja et al. 1997; Darvill et al. 2000; Dewailly et al. 2000; Fitzgerald et al. 2001; Gladen et al. 1999; Gocmen et al. 1989; Huang et al. 1989; Lunden and Noren 1998; Newsome and Ryan 1999; Scheele et al. 1995; Weisenberg 1986; Wickstrom et al. 1983; and others).

Reliable methods are also available to measure hexachlorobenzene in feces (Albro and Thomas 1974; Koss and Koransky 1975; Schlummer et al. 1998) and urine. Trace amounts of unchanged hexachlorobenzene have been detected in urine; however, urinary metabolites are more easily detected and quantified (Ingebrigtsen et al. 1981, 1986; Koss et al. 1976; Lui and Sweeney 1975; Rozman et al. 1977a;

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To-Figueras et al. 1992; van Ommen et al. 1985; Yang et al. 1978) as biomarkers for hexachlorobenzene exposure. Although urinary PCP and tissue hexachlorobenzene correlated in 60 patients studied, it is possible that the urinary PCP originated from other chlorinated hydrocarbons such as pentachlorobenzene, alpha-hexachlorocyclohexane, or pentachloronitrobenzene (Burton and Bennett 1987; Currier et al. 1980; Koss et al. 1986; To-Figueras et al. 1992).

Indirect biomarkers of hexachlorobenzene exposure include measurement of *gamma*-glutamyl transferase in blood, uroporphyrin and d-ALA in urine, and coproporphyrin in feces (Koss et al. 1986; To-Figueras et al. 1992). Because these biomarkers are not specific for hexachlorobenzene, their usefulness in monitoring exposed populations is limited.

Several studies have correlated hexachlorobenzene levels with different end points. In humans, hexachlorobenzene levels are correlated between feces and serum (To-Figueras et al. 2000), maternal and umbilical cord blood levels (Ataniyazova et al. 2001; Sala et al. 2001a; Waliszewski et al. 2000), length of breast-feeding and infant serum levels (Abraham et al. 2000), and the presence of other organochlorines in serum (Burse et al. 2000; Glynn et al. 2000; Hoppin et al. 2000; and others).

Sufficient data of air levels of hexachlorobenzene have not been available to determine quantitative biomarkers of inhalation exposure. However, hexachlorobenzene levels have been assayed in people of Flix, Spain, who were exposed to hexachlorobenzene from an nearby electrochemical plant that produced organochlorines (Ballester et al. 2000; Grimalt et al. 1994; Herrero et al. 1999; Sala et al. 1999a, 1999b; To-Figueras et al. 1997). These studies found higher serum levels in factory workers compared to nonworkers, in male workers compared to females (presumably due to increased work-related exposure), in nonworkers who lived with factory workers compared to nonworkers who did not live with factory workers, and in people living near the factory compared to people living further away.

#### **3.8.2 Biomarkers Used to Characterize Effects Caused by Hexachlorobenzene**

Although not specific to hexachlorobenzene, porphyria is the primary biomarker of effect from human exposure to hexachlorobenzene. Disturbance of the heme biosynthesis pathway of the body's porphyrin metabolism in the liver is the major action of hexachlorobenzene in short- or long-term exposure. Due to this disturbance, abnormal levels of porphyrin precursors are found in exposed individuals. In some cases, porphyria cutanea tarda, displayed as scarring or cutaneous annular erythema (a condition termed *pembe yara*, or pink sore), is present. Such exposed people also exhibited painless arthritis, osteoporosis,

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and small distinctive hands (Cripps et al. 1984; Peters et al. 1982, 1987). Increases in serum *gamma*-glutamyl transferase, uroporphyrin (red-tinged urine), and d-ALA in the urine, and uroporphyrin and coproporphyrin in the stool are also indicative of the effect of hexachlorobenzene. While low levels of hexachlorobenzene have been found in human tissues and body fluids, such reported low levels have not generally been associated with adverse health effects (Booth and McDowell 1975). Recently, associations have been found between increased hexachlorobenzene levels and decreased interferon- $\gamma$  (Daniel et al. 2001), decreased lymphocyte IL-10 secretion (Belles-Isles et al. 2000), ear infections in infants (Dewailly et al. 2000), undescended testis (Hosie et al. 2000), and locomotor skill impairment in newborns (Sala et al. 1999b).

For more information on biomarkers for renal and hepatic effects of chemicals see Agency for Toxic Substances and Disease Registry/Centers for Disease Control and Prevention Subcommittee Report on Biological Indicators of Organ Damage (1990) and for information on biomarkers for neurological effects see OTA (1990).

### 3.9 INTERACTIONS WITH OTHER CHEMICALS

Certain chemicals may interfere with the toxicity of hexachlorobenzene indirectly by influencing its metabolism through their actions on drug metabolizing enzymes. The duration and intensity of action of hexachlorobenzene are largely determined by the speed at which it is metabolized in the body by the liver microsomal cytochrome P-450 system. More than 200 drugs, insecticides, and other chemicals are known to induce the activity of liver microsomal drug-metabolizing enzymes. The characteristic biological actions of these chemicals are highly varied. Although there is no clear relationship between their actions and structures and their ability to induce enzymes, most of the inducers are lipid soluble at physiological pH. These inducers of the P-450 system include the following classes of drugs: hypnotics and sedatives (barbiturates, ethanol); anesthetic gases (methoxyflurane, halothane); central nervous system stimulants (amphetamine); anticonvulsants (diphenylhydantoin); tranquilizers (meprobamate); antipsychotics (trifluromazine); hypoglycemic agents (carbutamide); anti-inflammatory agents (phenylbutazone); muscle relaxants (orphenadrine); analgesics (aspirin, morphine); antihistaminics (diphenhydramine); alkaloids (nicotine); insecticides (chlordane, DDT, BHC, aldrin, dieldrin, heptachlorepoxyde, pyrethrins); steroid hormones (testosterone, progesterone, cortisone); and carcinogenic polycyclic aromatic hydrocarbons (3-methylcholanthrene, 3,4-benzpyrene) (Klaassen et al. 1995; Williams and Burson 1985).

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Hexachlorobenzene has been reported to increase the activity of aryl hydrocarbon hydroxylase and other enzymes associated with both the 3-MC and phenobarbital-inducible isozymes of cytochrome P-450 in the rat (Goldstein et al. 1986). Thus, exposure to any of these enzyme inducers prior to, concurrent with, or after exposure to hexachlorobenzene may result in accelerated biotransformation to the more toxic PCP. The extent of toxicity mediated by this phenomenon is dependent on how rapidly the PCP is hydrolyzed or conjugated to the less chlorinated benzenes which are much less toxic. In animal studies, pretreatment of rats with 3-methylcholanthrene or phenobarbital increased the metabolism and toxicity of hexachlorobenzene (Gopaldaswamy and Nair 1992; Rajamanickam and Padmanaban 1974; van Ommen et al. 1985; Vos et al. 1988). PCP (500 ppm) accelerated the onset of hexachlorobenzene-induced porphyria, indicated by an increase in urinary excretion of uroporphyrin and a decrease of porphyrin with 2 and 3 carboxylic groups in female rats fed diets containing 1,000 ppm hexachlorobenzene (Debets et al. 1980a). This increase occurred 3 weeks earlier in the hexachlorobenzene plus PCP-treated animals than in animals treated with hexachlorobenzene alone. Intraperitoneal pretreatment with diethylstilbestrol followed by oral administration of hexachlorobenzene to male and female rats stimulated the excretion of hexachlorobenzene metabolites via urine and feces (Rizzardini and Smith 1982). A 2-fold increase in the accumulation of hexachlorobenzene in tissues also occurred (Villeneuve et al. 1977). An exacerbation in the increase of hepatic accumulation and urinary excretion of uroporphyrin occurred in rats given doses of hexachlorobenzene (25 mg/kg/day for 12 consecutive days) when hexachlorobenzene was co-administered with methyl isobutyl ketone. The authors speculated on the involvement of hepatic isozyme inhibition and porphyria induction by methyl isobutyl ketone in hexachlorobenzene porphyrinogenic action (Krishnan et al. 1992).

Similarly, prior or concurrent exposure to hexachlorobenzene and MFO enzyme-inhibiting substances (e.g., carbon monoxide; ethylisocyanide; SKF 525A, halogenated alkanes, such as  $\text{CCl}_4$ ; alkenes, such as vinyl chloride; and allelic and acetylenic derivatives) may decrease the toxicity of hexachlorobenzene by decreasing the rate of the hydrolytic dealkylation and hydrolysis of both parent hexachlorobenzene (Williams and Burson 1985). Rats treated with hexachlorobenzene in combination with the cytochrome P450III A1 (CYP3A1) inhibitor, TAO, showed a marked reduction in hexachlorobenzene-induced immunomodulatory effects. These results suggest that the oxidative metabolites, PCP and TCHQ, are not likely to be implicated in the immunostimulatory effects of hexachlorobenzene (Schielen et al. 1995a). Similar conclusions were reached by the investigators of a 13-week rat study to assess the role of oxidative metabolism in hexachlorobenzene-induced porphyria and thyroid hormone homeostasis (Den Besten et al. 1993) as well as in other animal studies in which pretreatment of rats with TAO decreased

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the metabolism of hexachlorobenzene (Gopaldaswamy and Nair 1992; Rajamanickam and Padmanaban 1974; van Ommen et al. 1985; Vos et al. 1988).

Food deprivation has also been shown to increase susceptibility of animals to the toxicity of hexachlorobenzene. During 4 weeks of exposure to hexachlorobenzene at 40 and 200 mg/kg, food deprivation (50%) increased the ability of hexachlorobenzene to cause liver hypertrophy and induce microsomal enzyme activity. A 2-fold increase in the accumulation of hexachlorobenzene in tissues also occurred (Villeneuve et al. 1977). Since absorption was not measured, it is not clear whether these observations are due to metabolic changes in fat metabolism and release of hexachlorobenzene to target organs or to increased fractional absorption of hexachlorobenzene. These findings were validated by Kishima et al. (2000); 50 ppm hexachlorobenzene did not induce liver toxicity in liver-initiated Wistar rats when administered in a normal diet, but caused liver damage (decreased weight, foci of altered enzyme expression, hypertrophy) when administered in an energy-restricted diet which provided only 50% of the calories in the normal diet.

Results from other studies indicate that hexachlorobenzene has the potential to alter the toxicity of other chemicals. Co-treatment of hexachlorobenzene (400  $\mu\text{mol/kg}$ ) and 2,3,7,8-TCDD (10 or 30  $\mu\text{g/kg}$ ) in rats exacerbated both body weight loss and thymic atrophy caused by 2,3,7,8-TCDD, while hexachlorobenzene administered at doses as high as 3,000  $\mu\text{mol/kg}$  did not cause any significant effects on these parameters (Li et al. 1989). Exposure to 4 mg/kg/day of hexachlorobenzene from 2 weeks prior to mating through lactation and partially through the placenta increased the  $\text{LD}_{50}$  value for malathion in 17–18-day-old Wistar rat pups by more than a factor of 2. In general, the inhibitory effect of malathion on cholinesterase activities was decreased by pretreatment with hexachlorobenzene. The authors attributed the increased resistance to intoxication by malathion and reduction of esterase inhibition in the pups to an increase in tissue carboxylesterase activity, presumably malathionase, and a decrease in malaxon formation (Mendoza and Shields 1976). In a study with female Sprague-Dawley rats administered single gavage doses of 400 or 600 mg/kg hexachlorobenzene in corn oil, or 10 or 12.5 mg/kg mercuric chloride, or a combination of 400 or 600 mg/kg hexachlorobenzene and 10 or 12.5 mg/kg mercuric chloride, hexachlorobenzene and mercuric chloride interacted additively with respect to lethality and endocrine, kidney, and liver toxicity. Although no deaths were reported in the 400 mg/kg hexachlorobenzene or 10 mg/kg mercuric chloride dose group animals, one death each was reported in the combined 400 mg/kg hexachlorobenzene plus 10 mg/kg mercuric chloride, and 600 mg/kg hexachlorobenzene plus 10 mg/kg mercuric chloride dose group animals; and two animals died in the 600 mg/kg hexachlorobenzene plus 12.5 mg/kg mercuric chloride dose group animals. Similarly, mild to

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moderate morphological changes observed in the liver, thyroid, thymus, and bone marrow of rats exposed to hexachlorobenzene or hexachlorobenzene plus mercuric chloride; and in the kidneys of mercuric chloride- or mercuric chloride plus hexachlorobenzene-exposed rats were more severe in animals that received a combination of hexachlorobenzene and mercuric chloride (Lecavalier et al. 1994). The mechanism of these interactive effects are not known.

Iron overload aggravates hexachlorobenzene-induced porphyria and related hepatopathology. There was increased porphyrin excretion in female C57BL/6J mice (strains B6-Ah<sup>b</sup> and B6-Ah<sup>d</sup>) pretreated with iron and then fed diets containing 26 mg/kg/day of hexachlorobenzene for 9, 15, or 17 weeks as compared to rats given hexachlorobenzene alone. This is consistent with the proposition that the sustained induction of either P3-450 (the mouse CYP1A2 ortholog), or P1-450 (CYP1A1), or both may be a causative factor in the development of this disease. Furthermore, differential induction of the P3-450 (the mouse CYP1A2 ortholog) and P1-450 (CYP1A1) isozymes in B6-Ah<sup>b</sup> responsive versus B6-Ah<sup>d</sup> nonresponsive mice suggests that hexachlorobenzene may act through the Ah receptor (Hahn et al. 1988). Iron overload also caused a significantly depressed EROD (an estimate of CYP1A1 activity), in the livers of hexachlorobenzene-fed rats for 5 or 15 weeks while PROD (an estimate of CYP2B1 activity) and BROD (an estimate of CYP2B1 and other P-450 isozymes activity) were depressed in female Fischer 344 rats that received iron-dextran solution (50 mg/mL) by subcutaneous injection for 1 week and then were administered dietary hexachlorobenzene at a dose of 10 mg/kg/day in corn oil for 65 weeks (Smith et al. 1993).

The interactive effect of hexachlorobenzene with other substances in cancer induction has also been studied in animals. The toxicological effects of hexachlorobenzene exposure as a consequence of varying the dietary levels of vitamin A were evaluated in a single-generation lifetime study. There were no significant differences in hematological and pathological lesions in rats fed basal diets with either 0.1 or 10 times the vitamin A content of the control diet and animals fed similar diets which also included hexachlorobenzene (Arnold et al. 1985). Hyperplastic nodules were observed in the liver lobes of 80% of female Fischer 344 rats pretreated with Imferon (iron-dextran) then given dietary hexachlorobenzene at doses of 5 or 10 mg/kg/day in arachis oil for 65 weeks. There was a high incidence of fibrin throughout the liver with sinusoidal telangiectasis, and nodular peliosis hepatitis and hepatocellular necrosis. The study proposed a nongenotoxic mechanism for tumor induction by hexachlorobenzene, concluding that the formation of hepatomas and hemangiomas with elements of peliosis could be explained by the compensatory hyperplastic responses to hepatocellular injury or necrosis and by the simultaneous loss of

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hepatocellular cords. The study further concluded that the accumulation of iron in the liver would strongly potentiate the development of hepatic tumors (Carthew and Smith 1994).

**3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE**

A susceptible population will exhibit a different or enhanced response to hexachlorobenzene than will most persons exposed to the same level of hexachlorobenzene 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 hexachlorobenzene, or compromised function of organs affected by hexachlorobenzene. Populations who are at greater risk due to their unusually high exposure to hexachlorobenzene are discussed in Section 6.7, Populations With Potentially High Exposures.

Hexachlorobenzene has been shown to elevate porphyrin levels in humans following inhalation exposure (Herrero et al. 1999; Sala et al. 1999b; Seldon et al. 1999) and to cause porphyria cutanea tarda (a specific disease resulting from elevated porphyrin levels) following oral exposure (Cam and Nigogosyan 1963; Cripps et al. 1984; Dogramaci 1964; Gocmen et al. 1989; Peters et al. 1982, 1987). Studies unrelated to hexachlorobenzene-exposure have associated the diagnosis of porphyria cutanea tarda with infections of HIV and hepatitis C virus (Drobacheff et al. 1998; Egger et al. 2002; Meola and Lim 1993). It is not known if, or the degree to which, these diseases contribute to or exacerbate one another; however, HIV and hepatitis C-infected individuals may have increased susceptibility to porphyria cutanea tarda following hexachlorobenzene exposure.

Case studies of hexachlorobenzene poisoning in humans indicate that young children are more sensitive to hexachlorobenzene intoxication. Children (average age, 7 years) who had ingested hexachlorobenzene-contaminated bread during the epidemic of hexachlorobenzene poisoning in Turkey between 1955 and 1959 developed short stature, pinched faces, osteoporosis of bones of the hand, and painless arthritic changes. Some of the young children in this study were presumed to have been exposed *in utero* via transplacental transfer and postnatally by lactational transfer. The children who died were between the ages of 1 and 2 years, and died from a disease known as *pembe yara* or “pink sore” (Cripps et al. 1984; Peters et al. 1982, 1987). Analysis of human milk from exposed women and unexposed controls in this epidemic showed hexachlorobenzene concentrations of 0.51 and 0.07 ppm, respectively (Cripps et al. 1984; Gocmen et al. 1989; Peters et al. 1982, 1987).

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In laboratory animals, reduced survival of suckling offspring of lactating mothers and fetuses of mothers exposed to hexachlorobenzene was also reported in several studies (Arnold et al. 1985; Grant et al. 1977; Kitchin et al. 1982). There is evidence that hexachlorobenzene is concentrated in milk of lactating monkeys exposed to hexachlorobenzene, suggesting that the risk of exposure to nursing infants may be greater than the risk to their mothers. Blood and tissue levels in the infants were higher than in mothers, and infants exhibited clinical symptoms of toxicity sooner than their mothers (Bailey et al. 1980).

#### 3.11 METHODS FOR REDUCING TOXIC EFFECTS

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

Tintinalli JE, Ruiz E, and Krone RL, eds. 1996. Emergency medicine. A comprehensive study. American College of Emergency Physicians. 4<sup>th</sup> ed. The McGraw-Hill Companies, Inc.

Goldfrank RL, et al. 1994. Goldfrank's toxicologic emergencies. 5<sup>th</sup> ed. Appleton and Lange 5th Edition.

Ellenhorn MJ and Barceloux DG. 1988. Medical toxicology: Diagnosis and treatment of human poisoning. New York, NY: Elsevier Science Publishing Company, Inc.

##### 3.11.1 Reducing Peak Absorption Following Exposure

For inhalation exposure, management commonly includes moving the exposed individual to fresh air, and then monitoring for respiratory distress. Injuries to the lungs are more likely when there is severe respiratory irritation and persistent cough. Emergency airway support and 100% humidified supplemental oxygen with assisted ventilation may be needed (Dreisbach 1983; Ellenhorn and Barceloux 1988; Haddad and Winchester 1990; Rumack and Lovejoy 1991).

Emesis may be indicated in acute ingestion unless the patient is obtunded, comatose, or convulsing, has lost the gag reflex, or if hexachlorobenzene was suspended in petroleum distillates, so that there is danger that emesis would result in aspiration. It is most effective if initiated within 30 minutes of exposure. Administration of mineral oil or castor oil-based cathartics are contraindicated because they tend to

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increase intestinal absorption of lipophilic toxicants like hexachlorobenzene. Adrenergic amines (decongestants, bronchodilators, or caffeine) and sympathomimetics (e.g., epinephrine) are not recommended because they may increase myocardial irritability and produce refractory ventricular arrhythmias or dysrhythmias. Cholestyramine or other agents that may bind to hexachlorobenzene may be useful in limiting absorption (Bryson 1989; Dreisbach 1983; Ellenhorn and Barceloux 1988; Haddad and Winchester 1990; Rumack and Lovejoy 1991). Gastric lavage with subsequent administration of activated charcoal and sorbitol cathartic have been recommended in acute management to reduce gastrointestinal absorption. Repeated dosing with activated charcoal or cholestyramine resin may be administered to enhance elimination by interrupting enterohepatic circulation, as has been demonstrated for chlordane and kepone (Cohn et al. 1978; Ellenhorn and Barceloux 1988).

Decontamination is the first step in reducing dermal absorption. It is recommended that decontamination begin immediately after the exposure; that contaminated clothing be removed; and that the skin, hair, and nails be washed copiously with soap and water. Leather clothing absorbs hexachlorobenzene and should be discarded. The use of oils could facilitate dermal absorption and their use is not recommended. If the material enters the eyes, thorough rinsing with sterile physiological saline is suggested (Ellenhorn and Barceloux 1988; Haddad and Winchester 1990; Rumack and Lovejoy 1991). If irritation, lacrimation, or especially pain, swelling, and photophobia persist after 15 minutes of irrigation, then ophthalmologic consultation to evaluate potential ocular damage is recommended (Haddad and Winchester 1990).

#### **3.11.2 Reducing Body Burden**

Little can be done to reduce the body burden of absorbed hexachlorobenzene (Ellenhorn and Barceloux 1988; Haddad and Winchester 1990; Rumack and Lovejoy 1991). Diuresis is not likely to be effective because of the high lipophilic nature of hexachlorobenzene. Exchange transfusion, peritoneal dialysis, hemodialysis, and hemoperfusion are not likely to be beneficial because of the rapidity with which hexachlorobenzene leaves the blood and locates in peripheral compartments, since this substance has an initial large volume of distribution. However, continued treatment with charcoal and cholestyramine may be useful to reduce enterohepatic recirculation (Cohn et al. 1978; Ellenhorn and Barceloux 1988), although no differences in fecal excretion of hexachlorobenzene were observed when cholestyramine or sesame oil was administered orally to rats and Rhesus monkeys following ingestion of hexachlorobenzene. When mineral oil was added to the diet of Rhesus monkeys treated with hexachlorobenzene, a 6–9-fold increase in fecal excretion of hexachlorobenzene and its metabolites was observed. Continuous administration of mineral oil led to increased depletion of hexachlorobenzene from both the blood and adipose tissues.

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Administration of n-hexadecane enhanced fecal excretion of hexachlorobenzene about 5-fold in rats (Rozman et al. 1981). The barbiturates, which have been used to control poison-induced convulsions, may hasten metabolism and elimination of hexachlorobenzene (Smith 1991).

Hexachlorobenzene is known to be toxic to developing perinatal animals. The particularly potent effects seen in nursing infants following maternal exposure to hexachlorobenzene must be recognized when counseling hexachlorobenzene-exposed women of childbearing age. It is recommended that plans for pregnancy and contraception be included in the physician's clinical assessment, with consideration to specialty evaluation of residual hexachlorobenzene contamination.

#### **3.11.3 Interfering with the Mechanism of Action for Toxic Effects**

The most serious acute toxicological effect of exposure to chlorinated hydrocarbon pesticides appears to be central nervous system toxicity. These organochlorine compounds interfere with the normal flux of sodium and potassium ions across the neuronal membrane and disrupting the normal repolarization of neurons, resulting in hyperexcitation and seizures. Organochlorines also inhibit the ability of calmodulin, a calcium mediator in the nerves, to transport calcium ions essential for the intraneuronal release of neurotransmitters, thereby further inhibiting repolarization and increasing neuronal sensitivity to subsequent stimuli resulting in hyperexcitation and seizures (Klaassen et al. 1995). Hexachlorobenzene appears to produce little central nervous system toxicity at low doses. At high doses, central nervous system depression can dominate the clinical profile (de Matteis et al. 1961). Thus, management of seizures with anticonvulsants is much less likely to be needed except in acute intoxication management. The number of acute hexachlorobenzene-intoxication patients with seizures, however, was negligible (de Matteis et al. 1961). Diazepam or phenobarbital is recommended for use to reduce seizures, if seizures occur (Bryson 1989).

In Turkey, in 1956, prolonged oral exposure to hexachlorobenzene was associated with an outbreak of acquired porphyria cutanea tarda characterized by neurological, visceral, arthritic, cutaneous, and hepatic symptoms. The victims also exhibited bulbous, erythematous skin lesions, which progressed to atrophy, hyperpigmentation, hypertrichosis (increased body hair), and ulcerations. Treatment for these conditions was primarily supportive. Anecdotal reports from Turkey indicated that chelating agents (disodium ethylenediaminetetraacetic acid [EDTA] and dimercaptopropanol [BAL]) administration over 3 months (1.5 g daily for 5 days intravenously followed by daily oral doses of 1–2 g) successfully reduced the symptoms of patients with hexachlorobenzene-induced porphyria (Ellenhorn and Barceloux 1988; Peters

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1956, 1993; Peters and Cripps 1985; Peters et al. 1957, 1966, 1986b). However, this method of treating acute porphyria has not been validated.

The role of iron overload in the pathogenesis of hexachlorobenzene-induced porphyria has also been examined based on observations that 80% of patients with porphyria cutanea tarda have increased liver stores of iron and increased levels of uroporphyrin 1 (Smith and de Matteis 1990; Wainstok de Calmanovici et al. 1991). In these patients, phlebotomy often induces disease remission and a decrease in urinary porphyrin 1 excretion. It remains to be seen whether iron overload plays a permissive or etiologic role in patients exposed to porphyria-producing toxins, and whether phlebotomy has any role in the treatment of these patients.

In other reports, co-administration of S-adenosyl-L-methionine (SAM) via subcutaneous injection for the last 15 days of treatment with an oral dose of hexachlorobenzene (100 mg/kg/day) reversed some of the effects of hexachlorobenzene exposure (elevation of liver porphyrin content and liver weight). It has been suggested that the beneficial effects of SAM on hexachlorobenzene-induced toxicity may be related to effects on adenosine triphosphate availability (Cantoni et al. 1990; Cuomo et al. 1991).

A study conducted with Osteogenic Disorder Shionogi (ODS) rats provided evidence that large doses of ascorbic acid may inhibit chemically-induced uroporphyrin in humans. This effect seems to be mediated by inhibition of CYP1A2-catalyzed uroporphyrinogen oxidation. However, a significant depletion of hepatic ascorbic acid may be required for any beneficial effect of ascorbic acid to be observed (Sinclair et al. 1995).

#### **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 hexachlorobenzene 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 hexachlorobenzene.

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

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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 Hexachlorobenzene

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to hexachlorobenzene are summarized in Figure 3-5. The purpose of this figure is to illustrate the existing information concerning the health effects of hexachlorobenzene. 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.

As shown in Figure 3-5, there are data available regarding a number of toxic end points in humans exposed to hexachlorobenzene by inhalation and ingestion, including death, chronic systemic toxicity, immunological, neurological, reproductive and developmental effects, and cancer. However, the extent of the data available is limited, particularly for inhalation exposure. No data were located regarding the toxicity of hexachlorobenzene by dermal exposure in humans. Hexachlorobenzene has been well studied in animals following oral exposure; the full range of end points have been assessed. However, only immunological effects have been studied in animals following inhalation exposure and no studies at all were located regarding toxicity of hexachlorobenzene in animals following dermal exposure.

#### 3.12.2 Identification of Data Needs

**Acute-Duration Exposure.** No information was located regarding health effects in humans following acute-duration exposure to hexachlorobenzene by any route. The available animal data were sufficient to identify target organs of acute oral exposure. Extensive study of animals exposed by the oral route for acute durations has identified doses producing a wide range of health effects, including porphyria and other hepatic effects, renal tubular lesions, changes in thyroid and reproductive hormone levels, impaired male reproductive performance, developmental effects ranging from subtle

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neurobehavioral effects in neonates to fetotoxic and teratogenic effects, overt neurological effects, and lethality (Bouthillier et al. 1991; Courtney et al. 1976; De Matteis et al. 1961; Foster et al. 1993; Goldey

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Figure 3-5. Existing Information on Health Effects of Hexachlorobenzene

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation			•	•	•		•		•	
Oral	•		•		•	•	•		•	
Dermal										

Human

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation				•						
Oral	•	•	•	•	•	•	•	•	•	•
Dermal										

Animal

- Existing Studies

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and Taylor 1992; Goldstein et al. 1978; Kennedy and Wigfield 1990; Khera 1974a; Mehendale et al. 1975; Simon et al. 1979). Most of the existing acute studies were conducted in rats, but mice and guinea pigs were also studied. Pharmacokinetic models for oral exposure in rats and humans are available (Freeman et al. 1989; Yesair et al. 1986), and provided good correlations between predicted yield of metabolites and experimentally observed liver toxicity (porphyria and increased liver weight reported by Koss et al. 1978 and Kuiper-Goodman et al. 1977), between estimated concentrations of hexachlorobenzene in the brain and observed central nervous system effects (tremors and other signs reported by Koss et al. 1978 and Kuiper-Goodman et al. 1977), and between estimated extent of lactational transfer of hexachlorobenzene and observed offspring mortality (data from Kitchen et al. 1982). The database was sufficient to support derivation of an acute oral MRL for hexachlorobenzene. Acute studies by inhalation exposure in animals were limited to a single study of immunological effects (Sherwood et al. 1989). No acute dermal studies in animals were located. Although an acute study in rats suggested that hexachlorobenzene can be absorbed across the skin (Koizumi 1991), pharmacokinetic models for inter-route extrapolation are not available. Additional acute studies by the inhalation and dermal routes would identify acute effect levels for these routes of exposure.

**Intermediate-Duration Exposure.** A few case-control studies have found evidence of developmental toxicity in newborn humans (Belles-Isles et al. 2000; Hosie et al. 2000); no information was located regarding health effects in humans following intermediate-duration exposure to hexachlorobenzene by any route. Extensive study of animals exposed by the oral route for intermediate durations has identified doses producing a broad spectrum of health effects, including porphyria and other hepatic effects, renal tubular lesions, pulmonary lesions, cardiac lesions, anemia and leukocytosis, osteosclerotic changes in bone, necrotic lesions in muscle, skin lesions, thymic atrophy, splenomegaly and altered spleen morphology, lymph node histopathology, altered immunoglobulin levels, suppression of immune function, changes in the thyroid, parathyroid, and adrenal glands and associated hormone levels, ovarian and testicular lesions, alterations in female menstrual cycling and reproductive hormone levels, reduced fertility, developmental effects ranging from subtle neurobehavioral effects in neonates to fetotoxic effects and pup death, overt neurological effects, and lethality (Andrews et al. 1988, 1989, 1990; Babineau et al. 1991; Bourque et al. 1995; Bouthillier et al. 1991; Den Besten et al. 1993; Den Tonkelaar et al. 1978; Foster et al. 1992a, 1992b; Iatropoulos et al. 1976; Jarrell et al. 1993; Kennedy and Wigfield 1990; Kimbrough and Linder 1974; Knauf and Hobson 1979; Koss et al. 1978; Kuiper-Goodman et al. 1977; Lilienthal et al. 1996; Loose et al. 1978, 1981; Ockner and Schmid 1961; Schielen et al. 1995a, 1995b; Smith et al. 1985; Vos et al. 1979a, 1979b, 1983; others). Most of the existing intermediate-duration studies were conducted in rats, but monkeys, mice, rabbits, dogs, and pigs were also studied.

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Pharmacokinetic models for oral exposure in rats and humans are available (Freeman et al. 1989; Yesair et al. 1986), and provided good correlations between predicted yield of metabolites and experimentally observed liver toxicity (porphyria and increased liver weight reported by Koss et al. 1978 and Kuiper-Goodman et al. 1977), between estimated concentrations of hexachlorobenzene in the brain and observed central nervous system effects (tremors and other signs reported by Koss et al. 1978 and Kuiper-Goodman et al. 1977), and between estimated extent of lactational transfer of hexachlorobenzene and observed offspring mortality (data from Kitchen et al. 1982). The database was sufficient to support derivation of an intermediate-duration oral MRL for hexachlorobenzene. Intermediate-duration studies by inhalation exposure in animals were limited to a single study of immunological effects (Sherwood et al. 1989). No intermediate-duration dermal studies in animals were located. Pharmacokinetic models for inter-route extrapolation are not available. Additional intermediate-duration studies by the inhalation and dermal routes would identify intermediate-duration effect levels for these routes of exposure.

**Chronic-Duration Exposure and Cancer.** There are data available on humans chronically exposed to hexachlorobenzene by the inhalation and oral routes, but no quantitative exposure information. The inhalation data are very limited, but tentatively found effects on the liver and immune system of exposed individuals (Queiroz et al. 1997, 1998a, 1998b; Richter et al. 1994; Selden et al. 1999). The oral data much more clearly identified the liver, skin, bone, thyroid, and central nervous system as target tissues for hexachlorobenzene in chronically exposed people (Cam and Nigogosyan 1963; Cripps et al. 1984; Peters et al. 1982, 1987). Based on very limited data, the original investigators of the Turkey epidemic estimated that the daily average oral dose was 0.05–0.2 g/day (0.7–2.9 mg/kg/day for a 70-kg person) (Cam and Nigogosyan 1963). No information regarding chronic dermal exposure in humans was located. Chronic oral animal studies identified dose levels associated with systemic (cardiovascular, gastrointestinal, hematological, hepatic, renal, and dermal), immunological, overt neurological, and developmental effects, as well as death (Arnold et al. 1985; Cabral et al. 1977, 1979; Gralla et al. 1977a; Mollenhauer et al. 1975; Smith and Cabral 1980; Smith et al. 1985, 1989, 1993; others). The database was sufficient to support derivation of a chronic oral MRL for hexachlorobenzene. No chronic animal studies were located using inhalation or dermal exposure. Pharmacokinetic models for inter-route extrapolation are not available. Additional chronic studies by the inhalation and dermal routes would identify chronic effect levels for these routes of exposure.

Data from people exposed to hexachlorobenzene by inhalation provide weak evidence for an association between exposure to hexachlorobenzene and cancer of the thyroid, brain, and liver (Grimalt et al. 1994; Selden et al. 1989), while very limited data from orally exposed people showed no increase in cancer risk

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(Cripps et al. 1984; Peters et al. 1982). One case-control study associated elevated adipose levels of hexachlorobenzene with increased risk of breast cancer (Dewailly et al. 1994), but other case-control studies have not found any relationship between body burdens of hexachlorobenzene and breast cancer (Dorgan et al. 1999; Falck et al. 1992; Guttus et al. 1998; Liljegren et al. 1998; Mendonca et al. 1999; Moysich et al. 1998; Mussalo-Rauhamaa et al. 1990; Zheng et al. 1999), bone sarcoma, or leukemia (Hardell et al. 1997; Scheele et al. 1996). The available epidemiology reports taken together do not support an association between hexachlorobenzene exposure and increased cancer incidence, but their limitations (including small study sizes and potentially confounding effects of other organochlorines) preclude considering them evidence of noncarcinogenicity. Because hexachlorobenzene produces porphyria, it is noteworthy that several human studies have associated porphyria with increased incidence of liver cancer (Axelson 1986; Fracanzani et al. 2001).

Several animal studies have demonstrated that oral exposure to hexachlorobenzene increases the incidence of tumor formation. The evidence of carcinogenicity is strongest in the liver; hexachlorobenzene has been shown to induce hyperplasia (in rats, mice, pigs, dogs, and monkeys), metaplasia (in rats), benign tumors (hepatoma in mice and rats; hemangiohepatoma and bile duct adenoma in rats), and malignant tumors (hepatocarcinoma in rats, mice, and hamsters; bile duct adenocarcinoma in rats) (Arnold et al. 1985; Cabral et al. 1979; Ertürk et al. 1986; Pereira et al. 1982; Smith and Cabral 1980; Smith et al. 1985). Additionally, exposure to hexachlorobenzene has been shown to induce renal metaplasia, adenomas, and renal cell carcinomas (in rats, mice, and hamsters); lymphosarcomas (in rats, mice, and hamsters); adrenal hyperplasia and pheochromocytoma (in rats); parathyroid adenomas (in rats); and hemangioendothelioma and thyroid tumors (in hamsters) (Arnold et al. 1985; Den Besten et al. 1993; Ertürk et al. 1986; Kimbrough and Linder 1974). No animal cancer bioassays by inhalation or dermal exposure were located. Pharmacokinetic models for inter-route extrapolation are not available. Based on these findings in animals, hexachlorobenzene is considered a probable human carcinogen. Additional epidemiological studies of people with known hexachlorobenzene exposure would enable better assessment of the carcinogenic risk of this chemical to humans.

**Genotoxicity.** Human genotoxicity data for hexachlorobenzene are limited to a case study (route of exposure unknown) and *in vitro* studies in human cell lines. The frequency of micronuclei in peripheral lymphocyte was increased in 41 workers exposed to a mixture of chlorinated solvents that included hexachlorobenzene (da Silva Augusto et al. 1997). Hexachlorobenzene did not produce chromosomal aberrations in human peripheral lymphocytes *in vitro* (Siekel et al. 1991), but did produce weak positive results in assays for DNA fragmentation and micronuclei formation in primary cultures of human

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hepatocytes (Canonero et al. 1997) and minimal formation of DNA adducts in cultured human Hep G2 hepatoma cells (Dubois et al. 1997). No information on the genotoxicity of hexachlorobenzene in animals by inhalation or dermal exposure was located. Hexachlorobenzene did not cause gene mutations or unscheduled DNA repair in microbial assays (Gopaldaswamy and Nair 1992; Haworth et al. 1983; Siekel et al. 1991), and did not produce dominant lethal mutations in orally-exposed rats (Khera 1974a; Simon et al. 1979), or bind strongly to rat DNA *in vitro* or *in vivo* (Gopaldaswamy and Nair 1992). However, hexachlorobenzene did produce DNA fragmentation in cultured rat hepatocytes (Canonero et al. 1997) and DNA adducts in fetal hepatocytes from rats and quail (Dubois et al. 1997). Additional studies employing other *in vivo* and *in vitro* assays would be useful to determine the genotoxic potential of hexachlorobenzene.

**Reproductive Toxicity.** No data were located regarding reproductive effects in humans or animals with inhalation or dermal exposure. Several miscarriages and stillbirths were reported among people with previous oral exposure to hexachlorobenzene (Peters et al. 1982, 1987), but it is not clear that the rate of miscarriages was significantly higher than normal for this population. One study associated elevated hexachlorobenzene blood levels with increased risk for spontaneous abortion (Jarrell et al. 1998), but other studies did not (Gerhard et al. 1998; Leoni et al. 1986, 1989). The cessation of agricultural uses of hexachlorobenzene in Xixin did not affect reproductive outcomes there (Huang et al. 1989). Animal studies using oral exposure have identified doses associated with reproductive effects, including ovarian lesions and hormonal and menstrual changes, in female rats and monkeys (Alvarez et al. 2000; Babineau et al. 1991; Bourque et al. 1995; Foster et al. 1992a, 1992b, 1993, 1995a; Iatropoulos et al. 1976; Jarrell et al. 1993; Muller et al. 1978; Sims et al. 1991), reduced fertility in rats (Grant et al. 1977), reduced mating index in male rats (Simon et al. 1979), and testicular effects in rats and pigs (including increased weight, degenerative lesions, and retarded maturation) (Den Tonkelaar et al. 1978; Gralla et al. 1977a; Smith et al. 1985). The intermediate-duration MRL for oral exposure is based on ovarian effects in monkeys. Reproductive effects have not been studied in animals by inhalation or dermal exposure, and pharmacokinetic models for inter-route extrapolation are not available. Epidemiological studies of people with known hexachlorobenzene exposure would be useful to establish whether these effects are also seen in people. Additional mechanistic studies to better understand the ovarian and hormonal changes might also help establish the relevance of these findings to humans.

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**Developmental Toxicity.** No studies on the developmental effects of hexachlorobenzene in humans following dermal exposure or in laboratory animals following inhalation or dermal exposure were identified, and pharmacokinetic models for inter-route extrapolation are not available. Dramatic developmental toxicity (high mortality, skin lesions) was seen in infants whose mothers consumed bread contaminated with hexachlorobenzene (Cripps et al. 1984; Gocmen et al. 1989; Peters et al. 1982); this study clearly established hexachlorobenzene as a developmental toxicant. Other human studies have found suggestive evidence linking hexachlorobenzene exposure with developmental toxicity, e.g., locomotor skill impairment associated with inhalation exposure (Sala et al. 1999b) and increased risk of undescended testis (route of exposure unknown) (Hosie et al. 2000), although an additional study found no correlation between hexachlorobenzene levels (in blood and milk) and infant intelligence test results (Darvill et al. 2000). Studies in orally exposed rats have demonstrated neurodevelopmental (Goldey and Taylor 1992; Lilienthal et al. 1996) and immunodevelopmental effects (Barnett et al. 1987; Vos et al. 1979a, 1983), reduced neonatal viability and growth (Grant et al. 1977; Kitchin et al. 1982; Vos et al. 1979a, 1983), and some evidence of teratogenic abnormalities (Courtney et al. 1976; Khera 1974a). Hexachlorobenzene caused neurological, hepatic, and cardiovascular effects, as well as death, in lactationally exposed Rhesus monkey infants (Bailey et al. 1980; Iatropoulos et al. 1978). Additional studies that included an assessment of more sensitive end points, such as endocrine changes and neurological or immunological effects, and an investigation of different periods of developmental sensitivity (such as prenatal versus postnatal exposures) would contribute to a clearer understanding of the developmental toxicity of hexachlorobenzene.

**Immunotoxicity.** Studies on the immunotoxicity of hexachlorobenzene in humans following oral or dermal exposure are lacking. Occupational studies have associated inhalation exposure to hexachlorobenzene with effects on immunological parameters (neutrophil chemotaxis and cytolytic activity, serum immunoglobulin and IFN- $\gamma$  levels) (Daniel et al. 2001; Queiroz et al. 1997, 1998a, 1998b; Richter et al. 1994). Case-control studies have associated increased body burdens of hexachlorobenzene (putatively resulting from consumption of contaminated food) with alterations in markers of immune function and susceptibility to infection (Belles-Isles et al. 2000; Dewailly et al. 2000). No studies on the immunotoxicity of hexachlorobenzene in animals after dermal exposure were located. An intermediate-duration study found slight decreases in humoral and pulmonary cellular defenses of rats exposed to hexachlorobenzene via inhalation (Sherwood et al. 1989). Following oral exposure, immunosuppression has been observed in rats, mice, monkeys, and bears (Bernhoft et al. 2000; Carthew et al. 1990; Iatropoulos et al. 1976; Loose et al. 1977, 1981; Michielsen et al. 1997; Silkworth and Loose 1981; Van Loveren et al. 1990) and at least a partial stimulation of the immune system in rats and dogs (Gralla et al.

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1977a; Kennedy and Wigfield 1990; Koss et al. 1978; Schielen et al. 1993, 1995b; Vos et al. 1979a, 1979b). Additionally, a number of animal studies have observed inflammation and immune cell infiltration in tissues such as the liver (Arnold et al. 1985; Ertürk et al. 1986), respiratory tract (Goldstein et al. 1978; Kimbrough and Linder 1974; Kitchin et al. 1982; Michielsen et al. 1997, 1999, 2001; Vos et al. 1979a, 1983), and skin (Koss et al. 1978; Michielsen et al. 1997, 2000; Schielen et al. 1993, 1995b; Torinuki et al. 1981) following oral exposure to hexachlorobenzene. Additional chronic-duration studies in humans in the workplace would identify effect levels for immunotoxicity.

**Neurotoxicity.** No information regarding neurotoxicity in humans following dermal exposure was located. Following ingestion of bread contaminated with hexachlorobenzene, observed neurological effects included profound weakness, loss of muscle control (inability to handle utensils, myotonia [delayed muscle relaxation after an initial contraction], and cogwheeling [irregular jerkiness of movement due to increased muscle tone as seen in Parkinson's disease]), paresthesia (spontaneous tingling or burning sensations), and sensory shading (graded sensory loss indicative of polyneuropathy) (Cam and Nigogosyan 1963; Gocmen et al. 1989; Peters et al. 1982, 1987). Inhalation data are limited to suggestive evidence linking inhalation exposure to hexachlorobenzene with impaired development of locomotor skills in newborn babies (Sala et al. 1999a). A case-control study did not associate umbilical blood or breast milk hexachlorobenzene levels with infant intelligence test results (Darvill et al. 2000). No studies on the neurotoxicity of hexachlorobenzene in animals after inhalation or dermal exposure were located. Oral studies, primarily in rats but also in mice, rabbits, pigs, monkeys, and quail, have demonstrated serious neurological effects such as convulsions, tremors (intermittent and constant), lethargy, and progressive weakness (Cabral et al. 1979; Cripps 1990; De Matteis et al. 1961; Den Besten et al. 1993; Den Tonkelaar et al. 1978; Grant et al. 1977; Hahn et al. 1988; Kennedy and Wigfield 1990; Kimbrough and Linder 1974; Khera 1974a; Knauf and Hobson 1979; Ockner and Schmid 1961; others) as well as neurobehavioral effects in rats following developmental exposure (Goldey and Taylor 1992; Lilienthal et al. 1996; Taylor and Goldey 1990), changes in adult rat brain chemistry (Billi de Catabbi et al. 2000b; Cochon et al. 2001), and electrophysiological changes in the brains of adult dogs (Sufit et al. 1986; Sundlof et al. 1981). The acute-duration MRL for oral exposure is based on neurobehavioral changes in rats following developmental exposure (Goldey and Taylor 1992). Additional inhalation and dermal studies would identify the potential neurotoxicity of hexachlorobenzene by these routes of exposure.

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**Epidemiological and Human Dosimetry Studies.** No information regarding the adverse effects of hexachlorobenzene in humans following dermal exposure is available, and no human dosimetry data are available. Health effects (death, systemic [e.g. liver, skin, bone, and thyroid], neurological, developmental, and endocrine) were identified in cohorts from a group of approximately 4,000 people orally exposed in Turkey to hexachlorobenzene (in contaminated bread) between 1955 and 1959 (Booth and McDowell 1975; Cam and Nigogosyan 1963; Cripps et al. 1984; Gocmen et al. 1989; Peters et al. 1982, 1987; Selden et al. 1989). Related to inhalation exposure, health effects (systemic [hepatic, renal, and endocrine] and neurological) have been identified in residents of a rural town (Flix, Spain) with airborne hexachlorobenzene pollution attributed to a nearby organochlorine factory, workers from that factory, and other people with occupational exposure (Grimalt et al. 1994; Herrero et al. 1999; Queiroz et al. 1997, 1998a, 1998b; Richter et al. 1994; Sala et al. 1999a, 1999b, 2001a; To-Figueras et al. 1997). Multiple case-studies have investigated possible associations between body burdens of hexachlorobenzene levels (in blood, fat, urine, and feces) with multiple health effects (Belles-Isles et al. 2000; Darvill et al. 2000; Dewailly et al. 1994, 2000; Dorgan et al. 1999; Falck et al. 1992; Gerhard et al. 1998; Guttes et al. 1998; Hagmar et al. 2001; Hosie et al. 2000; Leoni et al. 1986, 1989; Liljegren et al. 1998; Mendonca et al. 1999; Moysich et al. 1998; Mussalo-Rauhamaa et al. 1990; Zheng et al. 1999; others). None of these human studies have provided reliable direct exposure data (dose and duration); therefore, no evidence of an exposure-response relationship has been possible. Further studies of populations with elevated exposures to hexachlorobenzene (e.g., occupational, consumption of fish from contaminated areas) would provide additional information useful in assessing dosimetry and health effects such as reproductive and developmental toxicity.

**Biomarkers of Exposure and Effect.**

**Exposure.** Hexachlorobenzene has been measured in human blood and serum, liver, bone marrow, brain, fat, semen, placenta, umbilical cord (and cord blood), breast milk, feces, and urine (Ataniyazova et al. 2001; Bucholski et al. 1996; Burse et al. 2000; Dewailly et al. 1999; Poli et al. 1999; Schlummer et al. 1998; Szymczynski and Waliszewski 1981; many others). Metabolites of hexachlorobenzene (including chlorophenols, pentachlorobenzene, alpha-hexachlorocyclohexane, or pentachloronitrobenzene) have been measured in blood, urine, and feces (Ingebrigtsen et al. 1981, 1986; Koss et al. 1976; Lui and Sweeney 1975; Rozman et al. 1977a; To-Figueras et al. 1992; van Ommen et al. 1985; Yang et al. 1978). Indirect biomarkers used to detect intermediate- and chronic-exposure to hexachlorobenzene exposure include measurement of *gamma*-glutamyl transferase in blood, uroporphyrin and d-ALA in urine, and coproporphyrin in feces (Koss et al. 1986; To-Figueras et al. 1992); because of their lack of specificity,

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the usefulness of these biomarkers is limited. Further studies to develop additional, more sensitive biomarkers of exposure that are specific for hexachlorobenzene exposure would be especially useful in the monitoring of people living near hazardous waste sites.

**Effect.** Porphyrin is the primary biomarker of effect from human acute, intermediate, and chronic exposure to hexachlorobenzene. Studies of an orally exposed population have diagnosed several unusual disease states of porphyria cutanea tarda, including dermal lesions (*pembe yara* or “pink sore” and *kara yara* or “black sore,” associated with photosensitivity, dermal fragility and scarring, hyperpigmentation and hirsutism) and small distinctive hands (shortened and spindled fingers with painless swelling and osteoporosis) (Cripps et al. 1984; Gocmen et al. 1989; Peters et al. 1982, 1987). Increases in serum *gamma*-glutamyl transferase, uroporphyrin and d-ALA in the urine (red-tinged urine), and uroporphyrin and coproporphyrin in the stool are also indicative of the effect of hexachlorobenzene (Booth and McDowell 1975; others). Additional studies that identified alternative biomarkers would complement these existing biomarkers. Moreover, direct assessments of exposure would facilitate the identification of effect levels.

**Absorption, Distribution, Metabolism, and Excretion.** One study was located in which gastrointestinal absorption of hexachlorobenzene in humans was quantified (Schlummer et al. 1998). Information regarding absorption in humans following inhalation exposure is based on observations of toxicity (Grimalt et al. 1994; Herrero et al. 1999; Queiroz et al. 1997, 1998a, 1998b; Richter et al. 1994; Sala et al. 1999b; Selden et al. 1997; To-Figueras et al. 1997). No experimental information regarding absorption in humans by dermal exposures was located; dermal data from a rat study were used to develop a compartment model for application to a 70-kg worker (Koizumi 1991). Only one dermal absorption study (Koizumi 1991) and no inhalation absorption studies in animals are available. Animal data suggest that oral absorption is rapid if dissolved in a lipid, but absorption from aqueous solution is low (Ingebrigtsen and Nafstad 1983; Koss and Koransky 1975). Additional information on the absorption of hexachlorobenzene, especially by the inhalation route, as well as data regarding enterohepatic circulation and gastrointestinal reabsorption would allow more accurate estimations of exposure and evaluation of route-specific differences in hexachlorobenzene toxicity.

No data on distribution in humans following inhalation or dermal exposure or in animals following inhalation exposure were available, but limited information on the distribution of hexachlorobenzene following oral exposure was located. Available data suggest that hexachlorobenzene is preferentially and rapidly distributed to tissues with high lipid content (Cripps 1990; Ingebrigtsen and Nafstad 1983; Jarrell

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et al. 1993; Mehendale et al. 1975; Verschueren 1983). Additional distribution studies would provide information regarding the tissue doses associated with adverse effects.

The metabolism of hexachlorobenzene has not been studied in humans. Studies in monkeys and rats indicate that hexachlorobenzene is metabolized to less chlorinated benzenes, chlorinated phenols, other minor metabolites, and glucuronide and glutathione conjugates (Ingebrigtsen and Nafstad 1983; Ingebrigtsen et al. 1981, 1986; Jansson and Bergman 1978; Koss et al. 1986; Rozman et al. 1977a). Because differences in metabolism may occur with differences in the route of exposure, it would be useful to have more data on inhalation and dermal metabolic studies as a comparison with the available oral studies.

No studies were located regarding excretion of hexachlorobenzene in animals or humans following inhalation or dermal exposure. Oral studies in animals indicate that the parent hexachlorobenzene is excreted primarily in feces, while metabolites were detected in urine (Albro and Thomas 1974; Ingebrigtsen et al. 1981; Mehendale et al. 1975; Rozman et al. 1977a, 1981; To-Figueras et al. 1991). Studies on excretion following inhalation and dermal exposure to hexachlorobenzene would be useful to determine if excretion patterns vary with different routes.

PBPK models for hexachlorobenzene have been developed by Yesair et al. (1986) and Freeman et al. (1989). The Yesair et al. (1986) model describes the absorption, distribution, and elimination of ingested hexachlorobenzene in growing rats and humans. The Freeman et al. (1989) model describes distribution and excretion of intravenously injected hexachlorobenzene in growing rats. Additional PBPK models to extrapolate from high- to low-exposure and between routes of exposure would aid in risk analysis.

**Comparative Toxicokinetics.** Although no toxicokinetic information is available for humans following dermal or inhalation exposure, data from a rat study were used to develop a compartment model for application to a 70-kg worker (Koizumi 1991).

Overall, data in animal studies do not indicate the toxicokinetics of hexachlorobenzene are similar among species (Albro and Thomas 1974; Cripps 1990; Goldey et al. 1990; Iatropoulos et al. 1975; Koizumi 1991; Koss et al. 1986; Rozman et al. 1977a; others). Differences observed in absorption may be related to vehicle and route of administration (Iatropoulos et al. 1975; Ingebrigtsen and Nafstad 1983; Koss and Koransky 1975; Lecavalier et al. 1994; Sundlof et al. 1982; others), and no remarkable differences have

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been seen for distribution, metabolism, or excretion (Cripps 1990; Ingebrigtsen and Nafstad 1983; Jarrell et al. 1993; Mehendale et al. 1975; Verschueren 1983; others).

PBPK models for hexachlorobenzene have been developed for rats to describe the absorption, distribution, and elimination of ingested hexachlorobenzene, but were not considered appropriate for inter-species extrapolations (Freeman et al. 1989; Yesair et al. 1986). One of the models was adapted for human modeling by using the same model structure with human physiological parameter values (Yesair et al. 1986). Although no empirical data are available on the dermal absorption of hexachlorobenzene in humans, dermal data from a rat study were used to develop a compartment model for application to a 70-kg worker (Koizumi 1991).

Further development of a human toxicokinetic model would be valuable in assessing risks to human health from hexachlorobenzene exposure.

**Methods for Reducing Toxic Effects.** Although available poison-treatment recommendations provide some guidance for reducing the toxic effects of absorbed hexachlorobenzene through inhalation, oral, or dermal exposures, these recommendations are not specific to hexachlorobenzene.

Recommendations to reduce peak absorption following exposure include such general procedures as moving the individual to fresh air following inhalation exposure, emesis and gastric lavage with activated charcoal following oral exposure, and removal of contaminated clothing and washing of the skin following dermal exposure. Little can be done to reduce body burden of hexachlorobenzene. Treatments that interfere with the mechanism of action for toxicity or repair tissue damage have not been developed specifically for hexachlorobenzene. However, some general recommendations are available, such as use of diazepam or phenobarbital to control convulsions related to hexachlorobenzene exposure.

Development of methods for reducing toxic effects targeted specifically to hexachlorobenzene would be useful, and additional studies into the mechanisms of action would support this goal.

**Children's Susceptibility.** No data regarding children's susceptibility following dermal or inhalation exposure to hexachlorobenzene were identified. The available human data suggest that infants and young children are at increased risk from exposure to hexachlorobenzene compared to adults (Cripps et al. 1984; Gocmen et al. 1989; Peters et al. 1982, 1987). Studies of an orally exposed population reported 95% mortality in exposed infants (under 2 years of age) associated with dermal lesions; adolescents (between the ages of 6 and 15 years) exhibited health effects (including 10% mortality and dermal lesions) more frequently than adults (Cripps et al. 1984; Gocmen et al. 1989; Peters et al. 1982,

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1987). Other studies focused on children's health found suggestive evidence of neurological and immunological effects, but did not assess exposure (Belles-Isles et al. 2000; Darvill et al. 2000; Dewailly et al. 2000; Hosie et al. 2000; Sala et al. 1999). Although immunological effects have been seen in humans exposed as adults (Richter et al. 1994; Queiroz et al. 1997, 1998a, 1998b), neurological effects have not; therefore, children may be more susceptible than adults to the neurotoxicity of hexachlorobenzene.

No animal studies relevant to children's susceptibility following dermal or inhalation exposure were identified. Animal studies have confirmed that hexachlorobenzene is transferred to the developing organism through the placenta *in utero* and via lactation after birth, and that the developing animals exhibited signs of toxicity (such as reduced survival and anatomical abnormalities) not seen in parental animals at the same exposure levels (Arnold et al. 1985; Bailey et al. 1980; Courtney et al. 1979; Grant et al. 1977; Iatropoulos et al. 1978; Khera 1974a; Kitchin et al. 1982; others). These experiments suggest that the ability of hexachlorobenzene to sensitively affect the developing organism may be related to its demonstrated capabilities to mediate toxicity through the neuroendocrine axis (Alvarez et al. 2000; Andrews et al. 1988, 1990; Den Besten et al. 1993; Den Tonkelaar et al. 1978; Foster et al. 1992b, 1993, 1995a, 1995b; Kimbrough and Linder 1974; Kleiman de Pisarev et al. 1989, 1990). However, endocrine end points have not been monitored in developing organisms. A developmental study that included assessment of endocrine end points along with other sensitive end points such as neurobehavioral and immune function would be useful to determine the role of endocrine changes with regard to these effects, and would identify critical levels of effect.

No data were located concerning whether pharmacokinetics of hexachlorobenzene in children are different from adults. A PBPK model (Yesair et al. 1986) has modeled fetal and breast milk compartments, in humans as well as rats, for oral exposure to hexachlorobenzene. Two PBPK models (Freeman et al. 1989; Yesair et al. 1986) have characterized the pharmacokinetics of hexachlorobenzene in growing rats, and have been validated using experimental data. No information regarding biomarkers of exposure and effect or potential interactions of hexachlorobenzene with other chemicals pertinent to children's susceptibility were identified. There are no pediatric-specific methods to reduce peak absorption of hexachlorobenzene following exposure, or to reduce body burden, or to interfere with mechanisms of action for hexachlorobenzene.

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.

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

**3.12.3 Ongoing Studies**

Ongoing studies pertaining to hexachlorobenzene were located in FEDRIP 2001.

The Toxic Substances Research Initiative of the Government of Canada is sponsoring a study titled *Risk assessment for hexachlorobenzene: mechanism of gender related tumor promotion* for fiscal years 1999–2002 by researchers Michel Charbonneau and Daniel Cyr at the Universite du Quebec.

National Institute of Environmental Science (NIEHS) is sponsoring a study for fiscal years 1996–2002 by researcher Gayle Windham at the Public Health Institute in Berkeley, California to investigate whether there is a relationship between exposure to chlorinated chemicals, which mediate toxicity through the neuroendocrine axis in animals, and menstrual cycle disturbances in women in a Laotian immigrant population in the San Francisco Bay area.

NIEHS is sponsoring a study for fiscal years 1996–2002 by researcher Stephen Schwartz at the Fred Hutchinson Cancer Research Center in Seattle, Washington to examine the potential relationship between exposure to organochlorine compounds and development of uterine fibroids in a case-control study.

NIEHS is also sponsoring a study for fiscal years 2001–2005 by researcher Stephen Schwartz to investigate the potential relationship between exposure to organochlorine compounds and the development of testicular germ cell carcinoma in a case-control study.

NIEHS is sponsoring a program for fiscal year 2001 by researcher Maria Schymura at the State University of New York in Albany to monitor organochlorine exposure in a Native American population in the state of New York.

NIEHS is sponsoring a study for fiscal years 2000–2005 by researcher Lawrence Schell at the State University of New York at Albany in Albany, New York, to investigate whether there is a relationship among exposure to environmental pollutants, thyroid function, and psychosocial outcomes in a Native American population in the state of New York.

## 4. CHEMICAL AND PHYSICAL INFORMATION

### 4.1 CHEMICAL IDENTITY

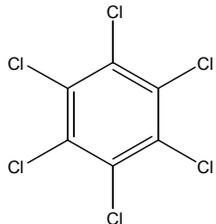
Hexachlorobenzene is a chlorinated hydrocarbon industrial chemical. Although hexachlorobenzene is not currently manufactured as a commercial end product in the United States, it is formed as a waste product in the production of several chlorinated hydrocarbons such as tetrachloroethylene, trichloroethylene, and carbon tetrachloride, and is a contaminant in some pesticides such as pentachloronitrobenzene and pentachlorophenol. Its presence in the environment is also due to its previous use as a fungicide. Hexachlorobenzene is a very persistent environmental chemical due to its chemical stability and resistance to biodegradation. Information regarding the chemical identity of hexachlorobenzene is located in Table 4-1.

### 4.2 PHYSICAL AND CHEMICAL PROPERTIES

Hexachlorobenzene is a white, crystalline solid (Verschueren 1996) that is practically insoluble in water (Lide 1998). When heated to decomposition, it emits toxic fumes of chlorides (Sax 1984). Dimethyl formamide and hexachlorobenzene react violently above 65 EC (NFPA 1986). Information regarding the physical and chemical properties of hexachlorobenzene is located in Table 4-2.

## 4. CHEMICAL AND PHYSICAL INFORMATION

**Table 4-1. Chemical Identity of Hexachlorobenzene**

Characteristics	Information	Reference
Chemical name	Hexachlorobenzene	Budavari 1996
Synonyms	Perchlorobenzene; HCB; pentachlorophenyl chloride	Budavari 1996 Farm Chemicals Handbook 2001 HSDB 2001
Trade names	AntiCarie; Ceku C. B.; No Bunt	Farm Chemicals Handbook 2001
Chemical formula	C <sub>6</sub> Cl <sub>6</sub>	Budavari 1996
Chemical structure		
Identification numbers:		
CAS Registry	118-74-1	Farm Chemicals Handbook 2001
NIOSH RTECs	DA2975000	HSDB 2001
EPA Hazardous Waste	U127	EPA 1999e (40 CFR 261.33)
OHM/TADS	8100010	HSDB 2001
DOT/UN/NA/IMCO	UN2729	HSDB 2001
Shipping		
HSDB	1724	NLM 2001
NCI	No data	

CAS = Chemical Abstracts Service; DOT/UN/NA/IMO = 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

## 4. CHEMICAL AND PHYSICAL INFORMATION

**Table 4-2. Physical and Chemical Properties of Hexachlorobenzene**

Property	Information	Reference
Molecular weight	284.78	Budavari 1996
Color	White	Verschueren 1996
Physical state	Crystalline solid	Verschueren 1996
Melting point	231 EC	Budavari 1996
Boiling point	325 EC 323–326 EC	Lide 1998 Budavari 1996
Density at 23 EC	2.044	Budavari 1996
Odor	No data	
Odor threshold: Water	No data	
Air	No data	
Solubility: Water at 25 EC	0.006 mg/L	Farmer et al. 1976
Water at 20 EC	0.005815 mg/L	Yalkowsky 1992
	0.006 mg/L	Verschueren 1996
Organic solvents	Insoluble in water, slightly soluble in ethanol, soluble in ethyl ether, and very soluble in benzene	Lide 1998
Partition coefficients: Log octanol/water	5.73	Hansch et al. 1995
Log $K_{oc}$	6.08 5.22 3.59	EPA 1981a Kenaga and Goring 1978
Vapor pressure at 20 EC	$1.09 \times 10^{-5}$ mmHg	Budavari 1996
Henry's law constant	$5.8 \times 10^{-4}$ atm·m <sup>3</sup> /mol	Ten Hulscher et al. 1992
Hydroxyl radical constant at 25 EC	$2.7 \times 10^{-14}$ cm <sup>3</sup> /molecule-second	Brubaker and Hites 1998
Autoignition temperature	No data	
Flashpoint	242 EC	Budavari 1996
Flammability limits	No data	
Conversion factors	1 ppm = 11.8 mg/m <sup>3</sup> 1 mg/m <sup>3</sup> = 0.08 ppm	Verschueren 1996
Explosive limits	No data	



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

### 5.1 PRODUCTION

Hexachlorobenzene is not currently manufactured as a commercial end product in the United States, and evidence indicates that it has not been commercially produced since the late 1970s (Beyer 1996; EPA 1986e). However, limited amounts of hexachlorobenzene are produced for laboratory use. The compound can be produced commercially by reacting benzene with excess chlorine in the presence of ferric chloride at 150–200 EC. In addition, at least one former producer isolated hexachlorobenzene from distillation residues obtained as a by-product in the manufacture of tetrachloroethylene (IARC 1979). Hexachlorobenzene is currently produced as a by-product or impurity in the manufacture of several chlorinated solvents (e.g., tetrachloroethylene, trichloroethylene, carbon tetrachloride); other chlorinated compounds (e.g., vinyl chloride); and several pesticides, including pentachloronitrobenzene (PCNB), tetrachloroisophthalonitrile (chlorothalonil), 4-amino-3,5,6-trichloropicolinic acid (picloram), pentachlorophenol (PCP) (only in Europe) (EPA 1986e; Tobin 1985), and dimethyltetrachloroterephthalate (DCPA or Dacthal<sup>®</sup>) (Verschuere 1996); and was also produced as a by-product during the production of atrazine, propazine, simazine, and mirex (IARC 1979). Hexachlorobenzene is also released in the environment due to ongoing use in developing countries and improper storage or disposal in developed countries (Dewailly et al. 1999).

Currently, hexachlorobenzene is produced for on-site use and processing, as a by-product, or as an impurity by the following facilities: Albemarle Corporation of Baton Rouge, Louisiana; AMVAC Chemical Corporation of Los Angeles, California; Dow Chemical Co. of Freeport, Texas; Dow Chemical Co. of Plaquemine, Louisiana; GB Biosciences Corporation of Houston, Texas; Oxy Vinyls LP of La Porte, Louisiana; PPG Industries, Inc. of Lake Charles, Louisiana; Vonroll America Inc. of East Liverpool, Ohio; Vulcan Materials Co. of Geismar, Louisiana (TRI99 2001). Hexachlorobenzene is also processed by the following waste disposal facilities: Chemical Waste Management of Lake Charles, Louisiana; Safety-Kleen of Bridgeport, New Jersey; Safety-Kleen of Deer Park, Texas; Clean Harbors Environmental Services of Kimbal, Nebraska; and U.S. Filter Recovery Services of Los Angeles, California (TRI99 2001).

In 1972, hexachlorobenzene produced as a by-product during the production of many other chlorinated chemicals was estimated to range from 1,123,500 kg (2,476,868 pounds) to 2,224,900 kg (4,905,015 pounds) (IARC 1979). Limited data indicate that hexachlorobenzene was produced at the

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

Dover Chemical Company, Dover, Ohio and Hummel Chemical Company, South Plainfield, New Jersey, until 1977. It is estimated that 1,450 kg (3,200 pounds) of hexachlorobenzene (as an end-product) were produced in the United States in 1975, and that 3,500–11,500 kg (7,700–25,350 pounds) of hexachlorobenzene were inadvertently produced in the manufacture of chlorinated solvents in 1984 (EPA 1986e). No current estimates of hexachlorobenzene production are available (SRI 2001).

Table 5-1 lists the facilities in each state that manufacture or process hexachlorobenzene, the intended use, and the range of maximum amounts of hexachlorobenzene that are stored on-site. There are 20 facilities that produce or process hexachlorobenzene in the United States. Current estimates for the amounts of hexachlorobenzene stored on-site as a by-product or impurity range from 0 to 999,999 pounds per year (0–453,951 kg/year) (TRI99 2001). The data from the Toxics Release Inventory (TRI) listed in Table 5-1 should be used with caution, however, since only certain types of facilities were required to report (EPA 1995c). This is not an exhaustive list.

There are some indications that any process that produces dioxins or dibenzofurans (e.g., pulp and paper mills using chlorine for bleaching) will also yield other chlorinated organic compounds such as hexachlorobenzene (EPA 1992b). In addition, hexachlorobenzene may be produced as a by-product in waste streams of chlor-alkali plants and wood preserving plants (Leger 1992), and in fly ash (Eicman et al. 1981) and flue gas effluents from municipal incineration (Oberg and Bergstrom 1985; Oehme et al. 1987; Tiernan et al. 1985). No estimates for the amount of hexachlorobenzene produced as a by-product via these sources was available.

## 5.2 IMPORT/EXPORT

Hexachlorobenzene imports of 2,440 kg (5,400 pounds) in 1977 and 17,300 kg (38,100 pounds) in 1982 were reported (HSDB 1995). No other recent data for import or export in the United States was located. However, the United Nations Environment Program conducted a survey of import/export data for persistent organic pollutants worldwide. Although this report contained no production data, it did contain worldwide import/export data. From 1990–1994, 158.45 tons of hexachlorobenzene were exported worldwide, while 2,258 tons of hexachlorobenzene were imported worldwide (UNEP 1996). It should be noted that U. S. import/export data are not included in this study.

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

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

State <sup>a</sup>	Number of facilities	Minimum amount on site in pounds <sup>b</sup>	Maximum amount on site in pounds <sup>b</sup>	Activities and uses <sup>c</sup>
CA	4	100	99,999	1, 2, 3, 5, 6, 13
KY	2	1,000	99,999	1, 3, 7, 13
LA	5	0	999,999	1, 3, 5, 7, 8, 13
NE	1	10,000	99,999	13
NJ	1	1,000	9,999	13
OH	1	1,000	9,999	13
TN	1	1,000	9,999	1, 6
TX	5	1,000	999,999	1, 3, 5, 6, 13

Source: TRI99 2001

<sup>a</sup>Post office state abbreviations used

<sup>b</sup>Amounts on site reported by facilities in each state

<sup>c</sup>Activities/Uses:

- |                          |                      |                             |
|--------------------------|----------------------|-----------------------------|
| 1. Produce               | 6. Impurity          | 10. Repackaging             |
| 2. Import                | 7. Reactant          | 11. Chemical processing aid |
| 3. Onsite use/processing | 8. Formulation       | 12. Manufacturing aid       |
| 4. Sale/Distribution     | component            | 13. Ancillary/other uses    |
| 5. Byproduct             | 9. Article component |                             |

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

**5.3 USE**

There are no current commercial uses of hexachlorobenzene as an end-product in the United States. However, hexachlorobenzene was used as a fungicide on the seeds of onions, sorghum, wheat, and other grains (IARC 1979) until 1984, when the last registered use of the compound as a pesticide was voluntarily cancelled. Hexachlorobenzene was also used in the production of pyrotechnic and ordinance materials for the military, the production of synthetic rubber (EPA 1986e), as a porosity controller in the manufacture of electrodes, a chemical intermediate in dye manufacturing, and a wood preservative (IARC 1979).

**5.4 DISPOSAL**

Hexachlorobenzene is listed as a toxic substance under Section 313 of the Emergency Planning and Community Right-to-Know Act (EPCRA) under Title III of the Superfund Amendments and Reauthorization Act (SARA) (EPA 1995c). Disposal of wastes containing hexachlorobenzene is controlled by a number of federal regulations. Land disposal restrictions (e.g., treatment standards) apply to wastes containing hexachlorobenzene. Incineration at high temperatures is a proposed disposal method, but incineration can lead to chlorinated products as toxic as hexachlorobenzene. Past disposal methods for industrial wastes containing hexachlorobenzene included incineration, disposal in landfills, discharge to municipal sewage treatment plants, and emission to the atmosphere (Clayton and Clayton 1981; EPA 1988a, 1989a). High temperature incineration (around 1,300 EC) with a retention time of approximately 0.25 seconds is the recommended disposal technique because it is reported to destroy more than 99% of the chemical (IRPTC 1985). Lamb et al. (1994) reported that organic waste compounds including hexachlorobenzene are used to co-fire cement kilns. These authors reported that the destruction efficiency of hexachlorobenzene fed to a rotary kiln/afterburner incinerator was greater than 99.9999%. Landfill disposal of hexachlorobenzene can lead to migration of the compound via water and sublimation of the compound into the air. Calaminus et al. (1993) conducted pyrolysis experiments with hexachlorobenzene in an inert atmosphere of argon. These authors reported hexachlorobenzene was substantially pyrolyzed (70%) at temperatures of 1,100 EC for 20 seconds into elemental carbon (soot) and chlorine (Cl<sub>2</sub>), but that other polychlorinated compounds (e.g., hexachlorohexane, hexachloro-1,3-cyclopentadiene, octachlorostyrene, octachloronaphthalene, octochloroacenaphthalene, and decachloronaphthoacenaphthalene) were also produced. Process wastes containing hexachlorobenzene from the production of chlorinated aliphatic hydrocarbons has an EPA-prescribed treatment standard before land

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

disposal. These wastes must be treated to specified concentrations prior to land disposal at a hazardous waste facility (EPA 1995c). Deep well injection of HCB is also not recommended (IRPTC 1985).

The waste water treatment technology that most closely resembles incineration is wet air oxidation. It is specifically designed to destroy organics in waste waters and efficiently oxidizes organics in aqueous media by operating at relatively high temperatures and pressures. Furthermore, wet air oxidation is typically performed on waste waters that contain relatively high concentrations of organics (i.e., those that are at or near the 1% total organic carbon cutoff for waste water). Carbon adsorption has been specified as part of the treatment train because hexachlorobenzene is believed to be adsorbable when present in low concentrations as might be expected in an effluent from either wet air or chemical oxidation (EPA 1985c).

No other information was located on the past or present volumes of hexachlorobenzene disposed of by each disposal method.



## 6. POTENTIAL FOR HUMAN EXPOSURE

### 6.1 OVERVIEW

Hexachlorobenzene has been identified in at least 107 of the 1,613 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2002). However, the number of sites evaluated for hexachlorobenzene is not known. The frequency of these sites can be seen in Figure 6-1. All of these sites are located within the United States and none are located in the Commonwealth of Puerto Rico (not shown).

Hexachlorobenzene has not been sold in the United States (as an end-product) since its last registered use as a pesticide was voluntarily canceled in 1984. Hexachlorobenzene is released to the environment almost entirely by industrial activities. Currently, it is released as a by-product during the manufacture of several chlorinated solvents (carbon tetrachloride, perchloroethylene, trichloroethylene, and chlorinated benzenes) or as an impurity in several currently registered pesticides. Additional amounts of hexachlorobenzene are also formed during combustion processes such as incineration of municipal refuse (EPA 1986e) or through use of pyrotechnic mixtures (Karlsson et al. 1991).

Hexachlorobenzene may enter the environment through air emissions and in waste water from facilities involved in the production of solvents or pesticides, combustion products (i.e., flue gases and fly ash) from municipal incinerators, and air emissions released from the use of pyrotechnic mixtures. Nonpoint source dispersal of hexachlorobenzene in both agricultural and urban settings results from its presence as a contaminant in several widely used pesticides. These sources, in addition to hazardous waste site sources, account for the majority of human exposures to hexachlorobenzene.

Hexachlorobenzene is among the most persistent environmental pollutants because of its chemical stability and resistance to degradation. If released to the atmosphere, hexachlorobenzene exists primarily in the vapor phase and degradation is extremely slow. Half-life estimations for hexachlorobenzene in the atmosphere are highly variable, ranging from 0.63 years in tropical/subtropical regions, to 1.94 years in temperate/boreal regions, to 6.28 years in polar regions. A calculated half-life of 1.69 years was attained from a measured hydroxyl rate constant ( $2.7 \times 10^{-14}$  cm<sup>3</sup>/molecule-second). Long-range global transport is possible from the temperate to the polar regions. Physical removal of hexachlorobenzene from the air

**Figure 6-1. Frequency of NPL Sites with Hexachlorobenzene Contamination**



## 6. POTENTIAL FOR HUMAN EXPOSURE

may occur via washout by rainfall or snowfall, or via dry deposition. If released to water, hexachlorobenzene will partition from the water column into sediment and suspended particulate matter.

In water, it is a persistent chemical not readily degraded by either abiotic or biotic processes. The half-life value of hexachlorobenzene is estimated to range from 2.7 to 5.7 years in surface water and from 5.3 to 11.4 years in groundwater. Volatilization from the water column is moderately rapid; however, the compound's strong adsorption to particulates and organic matter in water can result in lengthy persistence in the sediment. If released to soil, hexachlorobenzene can volatilize from the soil surface relatively quickly, but will be strongly adsorbed to organic matter and is generally considered immobile with respect to leaching. Its half-life value in soils is estimated to range from 3 to 6 years. Hexachlorobenzene bioaccumulates significantly in both terrestrial and aquatic food chains. Bioconcentration factors (BCFs) as high as 17,000,000 and 21,900 have been reported for lichens and fish, respectively.

Monitoring for hexachlorobenzene has focused primarily in the Great Lakes region where production of chlorobenzenes was historically high. Atmospheric monitoring detected the compound at mean and median concentrations of 36.68 (0.03668 ng/m<sup>3</sup>) and 30.94 (0.03094 ng/m<sup>3</sup>) pg/m<sup>3</sup>, respectively, from 56 air samples in Villeroy, Quebec in 1992 (Poissant et al. 1997). Hexachlorobenzene has also been detected in minute amounts (up to 0.174 ng/L [ppt]) in precipitation samples from the Great Lakes region (Chan et al. 1994) and in precipitation samples collected from Villeroy, Quebec in 1992 (0.04 ng/L) (Poissant et al. 1997). It was also detected in drinking water in three cities on Lake Ontario at a mean concentration of 0.1 ppt (Oliver and Nichol 1982a). Hexachlorobenzene has also been detected in soil and sediment samples in both agricultural areas where it was used as a fungicide on seed grains and in urban soils near production and waste disposal sites (EPA 1985g). Sediment samples (2 cm depth) collected from lakes (Allen-Gil et al. 1997a) and landfills have also been contaminated with hexachlorobenzene (Yasuhara et al. 1999).

Concentrations of hexachlorobenzene have been reported for a variety of commercial fish species in the Great Lakes (Allen-Gil et al. 1997a; Kuchlick and Baker 1998) with concentrations up to 17 ppb in raw fish fillets (Newsome and Andrews 1993; Zabik et al. 1995). In the National Pesticide Monitoring Program, concentrations as high as 700 ppb were reported in whole fish samples collected from contaminated areas (Schmitt et al. 1990). This chemical has also been detected in the fatty tissues and muscle of a wide variety of waterfowl (Foley 1992; Gebauer and Weseloh 1993; Swift et al. 1993), marine mammals (Becker et al. 1997; Langlois and Langis 1995), and mammals (Corsolini et al. 1999). In terrestrial ecosystems, hexachlorobenzene has been detected in lichens (Muir et al. 1993) and in

## 6. POTENTIAL FOR HUMAN EXPOSURE

caribou that graze primarily on lichens (Elkin and Bethke 1995). Concentrations of hexachlorobenzene in these fish and wild game species can be a source of hexachlorobenzene exposure to man.

Hexachlorobenzene residues have been detected in 76% of samples analyzed as part of the National Human Adipose Tissue Survey (FY82) (EPA 1986f). These hexachlorobenzene residues are most likely the result of consumption of low levels of hexachlorobenzene in food, with a calculated yearly intake of 68, 22, and 5 µg for adults, toddlers, and infants, respectively (EPA 1986e). Compared to this, exposure to hexachlorobenzene via inhalation or through drinking water is relatively low. Human exposure may also occur via dermal contact with contaminated soil or sediment or via ingestion of contaminated soil by children. In occupational settings, exposure occurs primarily via inhalation or dermal contact.

Hexachlorobenzene has been identified in at least 107 of 1,613 current or former NPL hazardous waste sites (HazDat 2002). However, the number of sites evaluated for hexachlorobenzene is not known. The frequency of these sites within the United States can be seen in Figure 6-1.

Due to extensive research conducted on hexachlorobenzene, the data reported herein do not encompass complete and thorough research for this chemical.

## 6.2 RELEASES TO THE ENVIRONMENT

Releases of hexachlorobenzene are required to be reported under SARA Section 313; consequently, data are available for this compound in the Toxics Release Inventory (TRI) (EPA 1995c). According to the TRI, a total of 13,818 pounds (6,267 kg) of hexachlorobenzene was released to the environment in 1998. In addition, an estimated 490 pounds (222 kg) were released by manufacturing and processing facilities to publicly owned treatment works (POTWs) and an estimated 13,328 pounds (6,045 kg) were transferred off-site (TRI98 2000). The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

Hexachlorobenzene has been identified in a variety of environmental media (air, surface water, leachate, groundwater, soil, and sediment) collected at 107 of 1,613 current or former NPL hazardous waste sites (HazDat 2002).

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**6.2.1 Air**

Releases to the air from the production of chlorinated solvents, where hexachlorobenzene is a minor by-product, have been estimated at 0.3 kg (0.7 pounds) annually and emissions from municipal refuse incineration have been estimated at 85–8,512 kg (187–1,870 pounds) annually (Bailey 2001).

Table 6-1 Part B summarizes U.S. hexachlorobenzene emissions in the mid 1990s. As incineration has emerged as a prevalent technology for reducing the bulk of hazardous and nonhazardous wastes, investigations have shown that even with careful controls it is virtually impossible to eliminate unwanted by-products (Products of Incomplete Combustion [PICs]) (Martens et al. 1998). Slight temperature differences on the surfaces of incinerator kiln and reactor components, or other reactions in flues, can lead to the formation of numerous chemical compounds. Where the original wastes contain organochlorines, one type of toxicant may be transformed into another (Dellinger et al. 1989). Hexachlorobenzene, for example, has been detected at concentrations ranging from 20 to 70 ppm in gases emitted by the thermal degradation of toxaphene (Lahaniatis et al. 1992). Since incineration of wastes is a growing global phenomenon, there are concerns that inadequate management attention is given to minimizing PICs. For hexachlorobenzene, and many other organochlorines that can be dispersed widely through atmospheric transport pathways, the virtual absence of data on PICs can lead to complications in estimating environmental releases and mass balances of hexachlorobenzene for regional areas or on a global scale (Lahaniatis et al. 1992).

Nonpoint source dispersal of hexachlorobenzene historically has resulted from its use as a seed fungicide (Beyer 1996) and results from the use of a number of registered pesticides in which it is a contaminant. Eight major pesticides (chlorothalonil, DCPA or Dacthal<sup>®</sup>, pentachlorophenol or PCP, picloram, PNCB or quintozone, atrazine, simazine, and lindane) in current use contain up to 0.3% hexachlorobenzene as an impurity (see Section 6.2.3 and Table 6-1 Part A). When these pesticides are applied in sprays, they have the greatest potential for release into the air. Most of the pesticide, and the hexachlorobenzene impurities, end up on the top layer of the soil and can become airborne through volatilization of the vapor or adsorbed onto soil particles. The hexachlorobenzene agriculturally applied through the use of these eight pesticides amounts to an estimated 1,270 kg/year (2,790 pounds/year); however, the total amount of hexachlorobenzene actually released into the air could not be estimated (Bailey 2001).

Another minor source of hexachlorobenzene releases to the air comes from the use of pyrotechnic mixtures that produce white obscurant screening smokes (Karlsson et al. 1991). These screening smokes

Table 6-1. U.S. Hexachlorobenzene Emissions Summary, Mid 1990s, Part A

	HCB concentration	Average annual U.S. use (kg/year)	HCB emissions (kg/year)
<i>Products containing HCB</i>			
<i>Pesticides</i>			
DCPA (dacthal)	1,000 ppm	677,791	677.8
Atrazine	1 ppm	32,233,523	32.2
Simazine	1 ppm	1,825,391	1.8
Picloram	50 ppm	655,922	32.8
PCNB	500 ppm	627,338	313.7
Chlorothalonil	40 ppm	4,928,591	197.1
Lindane	50 ppm	51,345	2.6
Pentachlorophenol	50 ppm	4,000,000	12.0 <sup>a</sup>
<b>Pesticides subtotal</b>			<b>1,270.0</b>
Chlorinated solvent usage	1 ppb	282,600,000	0.3
<i>Manufacturing</i>			
U.S. Chemical manufacturing			<b>399</b>

**Table 6-1. U.S. Hexachlorobenzene Emissions Summary, Mid 1990s, Part B**

	Emissions factors (kg HCB/kg)			Product (kg/year)	Calculated emissions (kg/year)		
	Low	Mean	High		Using low factors	Using mean factors	Using high factors
<i>Metals</i>							
Aluminum casting	86	2.2x10 <sup>-3</sup>	4.3x10 <sup>-3</sup>	HCE 5.88x10 <sup>4</sup>	51	129	253
Secondary copper	3.9x10 <sup>-9</sup>	3.9x10 <sup>-8</sup>	3.9x10 <sup>-7</sup>	6.95x10 <sup>8</sup>	3	27	271
<b>Metals subtotals</b>					<b>53</b>	<b>156</b>	<b>524</b>
<i>Combustion</i>							
Municipal	2.9x10 <sup>-9</sup>	2.9x10 <sup>-8</sup>	2.9x10 <sup>-7</sup>	2.93x10 <sup>9</sup>	85	851	8,512
Hazardous wastes	1.9x10 <sup>-9</sup>	1.9x10 <sup>-8</sup>	1.9x10 <sup>-7</sup>	1.5x10 <sup>6</sup>	3	29	285
Medical	2.9x10 <sup>-9</sup>	2.9x10 <sup>-9</sup>	2.9x10 <sup>-9</sup>	7.7x10 <sup>8</sup>	2	22	223
Coal	1.3x10 <sup>-12</sup>	1.3x10 <sup>-11</sup>	1.3x10 <sup>-10</sup>	7.91x10 <sup>11</sup>	1	10	103
Cement	1.7x10 <sup>-11</sup>	1.7x10 <sup>-10</sup>	1.7x10 <sup>-9</sup>	6.76x10 <sup>10</sup>	1	11	115
Iron sintering	1.5x10 <sup>-10</sup>	1.5x10 <sup>-9</sup>	1.5x10 <sup>-8</sup>	1.22x10 <sup>10</sup>	2	18	183
Sewage sludge	4.7x10 <sup>-10</sup>	4.7x10 <sup>-9</sup>	4.7x10 <sup>-8</sup>	8.65x10 <sup>8</sup>	0	4	41
Biomass	6.0x10 <sup>-12</sup>	6.0x10 <sup>-11</sup>	6.0x10 <sup>-10</sup>	2.28x10 <sup>11</sup>	1	14	137
<b>Combustion subtotals</b>					<b>96</b>	<b>960</b>	<b>9,598</b>
<b>Total U.S. HCB emissions (kg/year)</b>					<b>1,818</b>	<b>2,785</b>	<b>11,791</b>

<sup>a</sup>Based on 6% volatilization of HCB from pentachlorophenol-treated wood.

Source: Bailey 2001

## 6. POTENTIAL FOR HUMAN EXPOSURE

are used by the military to obscure vision and hide targets, and are used by civilian firefighters during fire training sessions.

The estimated release of 1,535 pounds (698 kg) of hexachlorobenzene to the atmosphere from 12 manufacturing, processing, and waste disposal facilities in 1999 accounted for about 10.5% of the estimated total environmental releases (TRI99 2001). These releases are summarized in Table 6-2. The data from the TRI listed in Table 6-2 should be used with caution, however, since only certain types of facilities are required to report (EPA 1995c). This is not a comprehensive list.

Hexachlorobenzene has been identified in air samples at 7 sites, collected from 1,613 NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2002).

### 6.2.2 Water

The principal release of hexachlorobenzene into water in the past has been through direct discharges from chemical solvent manufacturing facilities. Total production of chlorobenzenes in the United States has declined from more than 300,000 metric tons (300 million kg or 661 million pounds) in 1970 to about 200,000 metric tons (200 million kg or 441 million pounds) in 1980. The total amount of hexachlorobenzene released as a by-product in production of all chlorinated solvents has been estimated to range from 70,343 to 241,311 kg/year (154,000–532,000 pounds/year) (EPA 1986e). Estimated hexachlorobenzene releases into water from these sources, however, were only 70 kg/year (154 pounds/year) (EPA 1986e).

The estimated release of 8 pounds (4 kg) of hexachlorobenzene to water from two domestic manufacturing and processing facilities in 1999 accounted for about 0.055% of the estimated total environmental releases (TRI99 2001). An additional 13,559 pounds (6,045 kg) were transferred off-site, including to POTWs (TRI99 2001). These releases are summarized in Table 6-2. The data from the TRI listed in Table 6-2 should be used with caution, however, since only certain types of facilities are required to report (EPA 1995c). This is not a comprehensive list.

Hexachlorobenzene has been identified in surface and groundwater samples at 10 and 42 sites, respectively, collected from 1,613 NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2002).

**Table 6-2. Releases to the Environment From Facilities That Produce, Process, or Use Hexachlorobenzene**

State <sup>b</sup>	Number of facilities	Reported amounts released in pounds per year <sup>a</sup>						
		Air <sup>c</sup>	Water	Underground injection	Land	Total on-site release <sup>d</sup>	Total off-site release <sup>e</sup>	Total on and off-site release
CA	4	7	0	No data	0	7	No data	7
KY	2	0	No data	No data	No data	0	No data	0
LA	5	1,387	7	No data	13,003	14,397	1	14,398
NE	1	5	No data	No data	0	5	No data	5
NJ	1	3	0	No data	0	3	4	7
OH	1	2	1	No data	No data	3	5	8
TN	1	0	No data	No data	No data	0	No data	0
TX	5	131	0	No data	20	151	13,549	13,700
Total	21	1,535	8	0	13,023	14,566	13,559	28,125

Source: TRI99 2001

<sup>a</sup>Data in TRI are maximum amounts released by each facility.

<sup>b</sup>Post office state abbreviations are used.

<sup>c</sup>The sum of fugitive and stack releases are included in releases to air by a given facility.

<sup>d</sup>The sum of all releases of the chemical to air, land, water, and underground injection wells.

<sup>e</sup>Total amount of chemical transferred off-site, including to publicly owned treatment works (POTW).

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**6.2.3 Soil**

Historically, hexachlorobenzene was released to soils directly through its application as a fungicide on seed grains. Even after use of hexachlorobenzene as a pesticide ceased, an estimated 95% of hexachlorobenzene produced in the manufacture of chemical solvents was disposed of in land applications (EPA 1986e). Current releases to soils may occur through land disposal of hexachlorobenzene-containing wastes, from discharges from manufactured facilities, and from use of currently registered pesticides containing small amounts of hexachlorobenzene. Contamination of soil and sediment with hexachlorobenzene is frequently secondary to the discharge of contaminated water, from which the hexachlorobenzene is then adsorbed by the soil or sediment. Sediment samples (2 cm depth) were collected from four lakes (Feniak, Desperation, Schrader, and Elusive) from the foothills of the Brooks Range, Alaska. All lakes were oligotrophic, and the pH was neutral to slightly alkaline. The mean concentration among the six samples was 0.17 ng/g dry weight, derived from the concentrations of the sediments from Lakes Feniak (0.27 ng/g dry weight), Desperation (0.08 ng/g dry weight), Schrader (0.11 ng/g dry weight), and Elusive (0.21 ng/g dry weight) (Allen-Gil et al. 1997a). Substantial levels of hexachlorobenzene, ranging from 0.5 to 460 ppb, have been detected in sediment cores sampled at 1 cm intervals to a sediment depth of 8 cm in Lake Ontario. The highest sediment contamination in Lake Ontario was found in sediments 1–2 cm in depth which correspond to sediments laid down from 1971 to 1976 during a period of high U.S. production of chlorobenzenes (Oliver and Nichol 1982a). Although no studies concerning the release of hexachlorobenzene from landfills have been located for the United States, Yasuhara et al. (1999) sampled leachates from 11 landfills in Japan. Leachates were sampled at the outlet of the leachate collecting pipe from open and controlled landfills. Hexachlorobenzene concentrations in the 11 leachate samples from 11 landfills ranged from not detected to 0.054 ng/L. Of the 11 sites, 6 are currently under reclamation and at least 3 sites were sampled 12–17 years after completion of reclamation. Site 2, which was sampled after 14 years of reclamation, had no detectable levels of hexachlorobenzene. Leachates from sites 3 and 4, which were sampled after 17 and 12 years of reclamation, had hexachlorobenzene concentrations of 0.033 and 0.054 ng/L, respectively. Site 4 had the highest detection of hexachlorobenzene concentration. The median concentration among these sites was 0.03 ng/L.

The presence of hexachlorobenzene as an impurity in several currently registered pesticides appears to be a continuing source of exposure for the general population. The pesticides containing impurities of hexachlorobenzene include: picloram, PCNB or quintozone, chlorothalonil, DCPA or Dacthal<sup>®</sup>, pentachlorophenol or PCP, atrazine, simazine, and lindane (Bailey 2001; Kutz et al. 1991). Estimated emissions of these eight pesticides is summarized in Table 6-1 Part A. Picloram is a herbicide used in agriculture and

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silviculture to control broad-leaf weeds and conifers in grasses (Tomlin 1997). PCNB is used as a fungicide, herbicide, disinfectant, and antifouling ingredient in paint and wood preservatives. It is also a seed dressing agent widely used on turf and ornamental plants (EPA 1986e). PCNB, or quintozene, is used as a soil fungicide on lawns and ornamental crops, as a seed treatment of field crops and vegetables (e.g., barley, corn, cotton, oats, rice, and wheat), and as a slime inhibitor in industrial waters (Budavari 1996; IARC 1974). Chlorothalonil, and Dacthal<sup>®</sup> are used widely in agriculture, but also are used in home gardens, lawn care, or other applications around residences or in urban areas (Farm Chemicals Handbook 1993). Chlorothalonil (sold under the trade name Bravo<sup>®</sup>) is a fungicide used on horticultural crops, golf courses, and residential turf, and as a biocide in paints and wood preservatives. Dacthal<sup>®</sup> is a pre-emergent herbicide widely used on lawns and turf grass (EPA 1986e). Pentachlorophenol (PCP) is an insecticide and fungicide used to protect timber from fungal rot and wood-boring insects (Tomlin 1997). Atrazine and simazine are selective herbicides used to control broadleaf and grassy weeds in corn and other crops (Tomlin 1997). Lindane is an insecticide and fumigant that has been used on a wide range of soil-dwelling and plant-eating insects. It is commonly used on a wide variety of crops, in warehouses, in public health to control insect-borne diseases, and (with fungicides) as a seed treatment (Tomlin 1997).

Although hexachlorobenzene impurities in Dacthal<sup>®</sup> were as much as 10% in the early 1970s, current levels of hexachlorobenzene contamination in all five pesticides are much lower. A registration standard was issued for picloram in 1985 that specified a maximum hexachlorobenzene content of 0.02%. By the terms of an EPA PCNB rebuttal presumption against registration in 1982, PCNB registrants agreed to reduce hexachlorobenzene contamination levels in PCNB to 0.5% by 1983 and to 0.1% by April 1988. A registration standard was issued by EPA for chlorothalonil in 1984 requiring that hexachlorobenzene contamination not exceed 0.05%. Since 1973, the maximum allowable hexachlorobenzene content of technical grade DCPA (Dacthal<sup>®</sup>) has been 0.3% (EPA 1986e). As a result of a settlement agreement between the EPA and chemical producers of PCP, the producers agreed to reduce hexachlorobenzene contamination in PCP to no more than 75 ppm (0.0075%). Recent surveillance monitoring by EPA has generally detected <50 ppm (0.005%) hexachlorobenzene contamination in PCP samples (EPA 1994c).

In 1999, 13,023 pounds of hexachlorobenzene were released to land from 21 domestic manufacturing, processing, and waste disposal facilities reporting releases of the compound to the environment (TRI99 2001). No releases (0 pounds) of hexachlorobenzene occurred via underground injection (TRI99 2001). Releases to the environment from facilities that produce, process, or use hexachlorobenzene are summarized in Table 6-2. The data from the TRI should be used with caution since only certain types of facilities are required to report (EPA 1995c). This is not a comprehensive list.

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The annual total emissions of hexachlorobenzene in the United States was estimated to be on average 2,785 kg (Bailey 2001). This estimated total was calculated using emission subtotals of 1,270 kg for pesticide use, 0.3 kg for chlorinated solvent use, 399 kg from manufacturing processes, 156 kg from metal industries (using mean emission factors), and 960 kg from combustion sources (using mean emission factors). These data are summarized in Table 6-1.

Hexachlorobenzene has been identified in soil and sediment samples at 76 and 33 sites, respectively, collected from 1,613 NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2002).

### 6.3 ENVIRONMENTAL FATE

#### 6.3.1 Transport and Partitioning

Hexachlorobenzene has a moderate vapor pressure ( $1.09 \times 10^{-5}$  mmHg) (Budavari 1996) and has a very low solubility (0.005815 mg/L) (Yalkowsky 1992) in water (see Table 4-2). If released to the atmosphere, hexachlorobenzene can exist in both the vapor phase in association with particulates (Eisenreich et al. 1981); however, monitoring studies have demonstrated that the vapor phase generally predominates (Ballschmiter and Wittlinger 1991; Bidleman et al. 1989; Lane et al. 1992). Hexachlorobenzene concentrations in the vapor phase represented 92–100% of the total hexachlorobenzene concentration in air samples collected in a monitoring study conducted in Ontario, Canada (Lane et al. 1992). Although physical removal of hexachlorobenzene from the atmosphere is possible via both wet and dry deposition (Howard 1990), the compound is hydrophobic, and somewhat resistant to wet deposition scouring unless it becomes sorbed to airborne dust or cloud condensation nuclei. Its resistance to wet deposition tends to slow down its transfer across the equatorial areas between the northern and southern hemispheres. At high latitudes, the typically cold air conditions encourage dry deposition of aerosols (Ballschmiter and Wittlinger 1991; Lane et al. 1992; Wania and Mackay 1993). These factors lead to atmospheric pathways as a major transport mechanism for hexachlorobenzene. The net residence time of hexachlorobenzene in the atmosphere is significantly less than 1 year, and is based on physical translocation and not on chemical transformation (Ballschmiter and Wittlinger 1991). The atmospheric mechanisms can operate over large distances, perhaps on a hemispheric scale (Kelly et al. 1991). At higher latitudes, transfers and partitioning back to aqueous systems may be accentuated by the cold, dry air. Since these areas are not zones of hexachlorobenzene production or use, the presence of such contaminants has attracted considerable attention in research studies (Ballschmiter and Wittlinger 1991).

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The Henry's law constant value for this compound ( $5.8 \times 10^{-4}$  atm-m<sup>3</sup>/mol) (Ten Hulscher et al. 1992) suggests that releases of hexachlorobenzene to surface water will volatilize at a moderate rate, and that volatilization can be a significant transfer mechanism (Thomas 1990). If released to water, adsorption of hexachlorobenzene to sediment or soil particulates is also expected to be significant on the basis of the high organic carbon partition coefficient ( $K_{oc}$ ) value (EPA 1981a) (see Table 4-2). Since hexachlorobenzene will adsorb strongly to soil particles and sediments, it may build up in the bottom sediments of large aquatic systems such as the Great Lakes. The concentration of hexachlorobenzene in Lake Ontario sediment is about 1 million times higher than in Lake Ontario water (Oliver and Nichols 1982a). In Lakes Superior, Michigan, and Huron, the very large sizes, considerable depths, and appreciable retention times have allowed much of the historical organochlorine burden to become immobilized in bottom sediments, with a concomitant reduction in the levels of hexachlorobenzene found in surface waters. In the upper Great Lakes, the vast majority of the ongoing mass balance inputs seem related to atmospheric deposition (Eisenreich et al. 1981). For other parts of the Great Lakes system, and especially the connecting waters and Lakes Erie and Ontario, mass balance studies can give different impressions. Detailed studies on Lake Erie suggest that well over half of the hexachlorobenzene inputs come from wet or dry atmospheric deposition processes (270 kg/year or 600 pounds/year) (Kelly et al. 1991). However, a significant portion (110 kg/year or 240 pounds/year) also comes from river pathways such as the highly polluted Detroit River via surface runoff and contaminated sediments resuspended during their passage through the connecting waters. Because of its strong adsorption to sediment, most of the hexachlorobenzene is transported with silt and sediment particles during floods, and very little is dissolved in the water. Quemerais et al. (1994) reported that 23% of the hexachlorobenzene in whole water samples collected from the St. Lawrence River was associated with the dissolved phase, while 77% was associated with the particulate phase. Although Rostad et al. (1988) did not quantify the percentage of hexachlorobenzene found in the dissolved versus the particulate phase, they reported that hexachlorobenzene was one of the organic compounds associated with suspended sediment particles in several river systems within the Mississippi River drainage area. In a 1999 study, Rostad et al. (1999) measured hexachlorobenzene concentrations in suspended sediment particles within the Mississippi River in the spring and summer of 1989 and 1990. Concentrations of hexachlorobenzene fluctuated between Winfield, Missouri and Belle Chasse, Louisiana during the spring and the summer; however, in both seasons, the concentration was higher at Chasse, Louisiana (1.9 ng/g in the spring; 2.1 ng/g in the summer) than at Winfield, Missouri (1.2 ng/g in the spring; 0.13 ng/g in the summer). Furthermore, Rostad et al. (1999) estimated annual transport of hexachlorobenzene via suspended sediments to the Gulf of Mexico by averaging the St. Francisville, Louisiana and Belle Chasse, Louisiana daily loads, averaging the spring and summer values for hexachlorobenzene, and projecting annual transport. The Gulf of Mexico receives

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an estimated 145 kg/year hexachlorobenzene via suspended sediment particles of the Mississippi River (Rostad et al. 1999).

Because of its high sorption characteristics, hexachlorobenzene is expected to be immobile in soil and unlikely to leach into groundwater (Swann et al. 1983). At waste disposal sites, where bioremediation techniques are proposed to reduce the mass of carbon-containing contaminants, there is the potential for augmenting the leaching properties of hexachlorobenzene and other organochlorines. The lipid materials in bacterial cell membranes may lead to a repartitioning of hexachlorobenzene sorbed to soil colloids. This can lead to a phenomenon called facilitated transport where the mobility of hydrophobic pollutants such as hexachlorobenzene adsorbed to soils may be enhanced by biosorption on bacteria and move into aquifers along with the bioremedial bacterial cultures (Lindqvist and Enfield 1992). Except at NPL sites, however, this potential source of groundwater pollution would seem to be remote.

The Henry's law constant value ( $5.8 \times 10^{-4}$  atm-m<sup>3</sup>/mol) (Ten Hulscher et al. 1992) suggests that hexachlorobenzene released to moist soil will volatilize at a moderate rate. Several studies have indicated that volatilization may be a significant mechanism for loss of hexachlorobenzene released to soils. Beall (1976) studied the persistence of aerially applied hexachlorobenzene (equivalent to 10 ppm in the top 5 cm of soil) in a simulated pasture maintained for 19 months in a greenhouse. Twenty hours post-application, the top 2 cm of soil contained 5.6 ppm (air-dry basis). Hexachlorobenzene concentrations in the top 2 cm of soil found after 0.5, 1, 6.5, 12, and 19 months were 45.2, 24.4, 7.9, 4.7, and 3.4% of day 1 values, respectively. However, no significant change in the deeper 2–4 cm layer of soil which averaged hexachlorobenzene residues of 0.11 ppm was observed over the 19-month study.

Concentrations of hexachlorobenzene in pasture grass on day 1 were 1,060 ppm, but 2 weeks postapplication only 15.6 ppm (1.5% of day 1 residues) were detected. Although hexachlorobenzene volatilized fairly rapidly from plant and soil surfaces, it could be persistent within the soil if treated surface soil were mixed into deeper soil layers by plowing. Nash and Gish (1989) studied the volatilization and dissipation of several halogenated pesticides from moist sandy loam soil under controlled conditions in micro-agroecosystem chambers maintained in a greenhouse for 154 days. As soil temperature increased from 5 to 35 EC, the percentage of originally applied hexachlorobenzene that was detected in the soil compartment decreased, while the percentage detected in the air increased suggesting that hexachlorobenzene volatilizes more rapidly with increased soil temperature.

The high octanol/water partition coefficient ( $K_{ow}$ ) value (Hansch et al. 1995) for hexachlorobenzene (see Table 4-2) suggests that bioconcentration and biomagnification of hexachlorobenzene are likely to occur

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to a significant degree. Veith et al. (1979) measured biological concentration factor (BCF) values of 16,200 for fathead minnows, 21,900 for green sunfish, and 5,500 for rainbow trout exposed to hexachlorobenzene at 15 EC for 32 days. Oliver and Niimi (1983) studied bioconcentration in rainbow trout exposed to water containing 2 concentrations of hexachlorobenzene (0.32 and 8 ng/g [ppb]) for 119 and 105 days, respectively. The BCF values were 12,000 and 20,000 at the 0.32 and 8 ng/g (ppb) exposure levels, respectively. Chaisuksant et al. (1997) conducted a bioconcentration experiment using mosquito fish (*Gambusia affinis*) as well. The fish were exposed to three concentrations of eight chemicals, and the highest concentration used consisted of a mixture with each chemical present in a concentration equal to 1/20 of the LC<sub>50</sub>. After 96 hours of exposure, the BCF of hexachlorobenzene in mosquito fish was 3,730. In 1992, the Chemicals Inspection and Testing Institute (1992) conducted a bioconcentration experiment using carp (*Cyprinus carpio*). After an 8-week exposure period to concentrations of 0.5 and 0.05 µg/L of hexachlorobenzene, the BCFs in carp were 11,000–27,000 and 6,000–30,000, respectively.

In a model aquatic ecosystem to which hexachlorobenzene was introduced, the BCF averaged 740 for algae (*Oedogonium cardiacum*), 1,500 for the snail (*Helisoma sp.*), 910 for the daphnid (*Daphnia magna*), 1,610 for the mosquitofish (*G. affinis*), and 10,610 for the catfish (*Ictalurus punctatus*) (Isensee et al. 1976). The authors concluded that biomagnification was also occurring within the food chain because the catfish (highest trophic level species) accumulated over 10 times more hexachlorobenzene than the next highest trophic level (snails and mosquitofish), and these species accumulated 1.5–2 times more than the lowest food chain species, the daphnids (primary consumers) and the algae (primary producers). In studies of natural populations of white bass in Lake Erie, Russell et al. (1995) concluded that biomagnification of hexachlorobenzene did not occur. These authors did report biomagnification in Lake Erie fish populations was occurring for several other organic chemicals with log K<sub>ow</sub> values greater than 6.1. Hexachlorobenzene bioaccumulation factors (BAFs) in aquatic fish species has been measured by Burkhard et al. (1997) in the Bayou d'Inde of the Calcasieu River system near Lake Charles, Louisiana. This field study resulted in log BAF values of 5.80 for blue crab (*Callinectes Sapidus*), 6.03 for mummichog fish (*Fundulus Heteroclitus*), 6.30 for Atlantic croaker (*Micropogonias undulatus*), and 6.68 for gulf menhaden (*Brevoortia Patronus*). The author further compared the measured values obtained to previously reported and predicted BAF values. A comparison of these data with that of Pereria et al. (1988) reveals a difference that was not considered significant by the author. Pereria et al. (1988) determined log BAF values of 4.03 for blue crab, 4.56 for Atlantic croaker, 4.12 for spotted sea trout (*Cynoscion nebulosis*), and 4.61 for blue catfish (*Ictalurus furcatus*).

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Connell et al. (1988), using data derived from terrestrial laboratory microcosm studies with two oligochaete worms (*Limnodrilus hoffmeisteri* and *Tubifex*), suggest that interstitial water may be the source from which lipophilic compounds such as hexachlorobenzene in sediment are bioconcentrated by oligochaetes. The concentration factor was 0.54 for hexachlorobenzene during a 110-day exposure test. In a similar study of the earthworm (*Eisenia andrei*) raised in field-contaminated soil, Belfroid (1995) reported a biota-to-soil accumulation factor of 0.507 for hexachlorobenzene. These authors also noted an initial elimination half-life of 1.9 days followed by a period of slower elimination with a half-life of 47 days. In a terrestrial food web study conducted on the Niagara Peninsula of Ontario, Canada from 1987 to 1989, Hebert et al. (1994) reported concentrations of hexachlorobenzene increased from the lower trophic level species to higher trophic level predator species. Concentrations of hexachlorobenzene were not detected in soil or plant material; however, concentration ranges were 0.2–0.3 µg/kg (ppb) (wet weight) in earthworms, not detected to 1.0 µg/kg (ppb) in mammals, 2.0–2.4 µg/kg (ppb) in starlings, 1.8–2.5 µg/kg (ppb) in robins, and 2.1–5.1 µg/kg (ppb) in kestrels at the top of the food web.

Several agricultural species of plants have been shown to bioaccumulate hexachlorobenzene in their roots and in portions of the plant growing closest to the soil (Scheunert et al. 1983; Smelt and Leistra 1974). There were marked differences in the BCFs among the various plant species with higher residues associated with those species with the higher lipid content (Schroll et al. 1994; Smelt and Leistra 1974). The roots of the plants generally accumulate higher concentrations of soil-applied hexachlorobenzene than do the aerial parts of the plants. This has been demonstrated for hexachlorobenzene in sugar beets, carrots, turnips, wheat, and pasture grass (Scheunert et al. 1983; Smelt and Leistra 1974). The edible root portion of carrots accumulated the highest concentration of hexachlorobenzene (1,250 ppb with a plant/soil BCF of 19) for a human food source. The measured BCF for hexachlorobenzene was 210 and 470 in soy bean plants via root uptake from water containing 0.2 and 0.4 µg/L hexachlorobenzene, respectively (Kraaij and Connell 1997). Concentrations of hexachlorobenzene were also high in grass roots (810 ppb) and the lower (0–5 cm) part of the blade (220 ppb) (Smelt and Leistra 1974). It is assumed that hexachlorobenzene in soil is mobile mainly in the gas phase. Gaseous hexachlorobenzene can diffuse directly into the plant root or evaporated hexachlorobenzene can be taken up by plant foliage (Ecker and Horak 1994). Some studies have reported no marked translocation of the hexachlorobenzene from roots to shoots or vice versa (Schroll et al. 1994). Residues in the roots were associated only with root uptake from the soil; those residues in the shoots were only from foliar uptake from the air. Recent studies by Ecker and Horak (1994), however, suggest that root uptake of hexachlorobenzene by oil pumpkins occurred and that the hexachlorobenzene was translocated into the shoots. These authors believe that uptake of dissolved hexachlorobenzene from soil solution into the roots may not have been

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considered earlier as a source for the translocated compound. Pollutants entering the plant from contaminated soil via roots would be translocated in the plant by the xylem while gas- and particle-phase deposition onto leaves or uptake by the stomata would be translocated by the phloem (Simonich and Hites 1995). Concentrations of hexachlorobenzene in agricultural crops can be directly transferred to humans via direct consumption, while concentrations in grass and other forage crops can be indirectly transferred to humans via consumption of dairy products or meat from cattle grazing on contaminated pastures.

Lichen from Northwestern Ontario and South Central Ontario exhibited BCF values of  $1.7 \times 10^7$  and  $8.8 \times 10^6$ , respectively, for hexachlorobenzene. These BCF values were calculated as the concentration of hexachlorobenzene in the lichen ( $\text{ng}/\text{m}^3$  wet weight) compared to the concentration in the air ( $\text{ng}/\text{m}^3$ ) (Muir et al. 1993). Furthermore, bioconcentration of hexachlorobenzene by lichen, a major forage food for caribou can transfer hexachlorobenzene to recreational hunters and natives peoples that consume caribou in their diets (Elkin and Bethke 1995).

### 6.3.2 Transformation and Degradation

#### 6.3.2.1 Air

Few studies regarding atmospheric degradation of hexachlorobenzene have been located. Photodegradation of hexachlorobenzene in its vapor phase, or as an adsorbable on silica gel, has been reported as not occurring when hexachlorobenzene was irradiated with ultraviolet radiation of wavelength 290 nm for 6 days (Parlar 1978); however, production of HCl and  $\text{CO}_2$  was observed when hexachlorobenzene was irradiated at 230 nm (Parlar 1978). In the troposphere, hexachlorobenzene is probably photochemically stable, but degradation in the stratosphere by photo-dissociation by shorter-wavelength, higher energy-ultraviolet light may be a mechanism for atmospheric degradation in the stratosphere.

The photo-oxidation half-life (first-order kinetics) of hexachlorobenzene based on the vapor phase reaction with hydroxyl radicals in air was estimated to range from 156.4 days to 4.2 years by Howard et al. (1991) and from 158 days to 4.3 years by Kwok and Atkinson (1995). Wania and Mackay (1995) estimated the degradation half-life (first-order kinetics) of hexachlorobenzene to be 0.63 years (230 days), 1.94 years (708 days), and 6.28 years (2,292 days) in air in tropical/subtropical regions, temperate/boreal regions, and polar regions, respectively. Brubaker and Hites (1998) measured a hydroxyl rate constant of  $2.7 \times 10^{-14} \text{ cm}^3/\text{molecule-second}$  at 25 EC, corresponding to a calculated half-life of 1.69 years. Thus, atmospheric degradation is extremely slow and is not an efficient method of hexachlorobenzene removal.

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**6.3.2.2 Water**

Hexachlorobenzene is a persistent compound and is not significantly degraded by either abiotic or biodegradation processes in water. It is resistant to the types of hydrolysis reactions that can help degrade other organochlorines or organophosphates, and it is not markedly subject to photolytic decay (Mill and Haag 1986). Biodegradation of organic priority pollutants in a waste water inoculum system was studied by Tabak et al. (1981). Among the 57 environmental pollutants tested, hexachlorobenzene at concentrations of 5 and 10 ppm was among the more slowly biodegraded compounds tested, with only 21–56% degradation in 1 week. Further biodegradation after the first week was minimal in three subsequent 7-day subcultures with settled domestic waste water as microbial inoculum. Biodegradation of hexachlorobenzene in waste water treatment systems is expected to be slow.

An aquatic ecosystem study conducted by Schauerte et al. (1982) shows that hexachlorobenzene will mainly absorb onto particulate matter in the water and then be transported to the bottom sediment. After 145 weeks, the study found a significant amount (10–20%) of hexachlorobenzene remaining in the upper sediment layers (0–10 cm). The half-life (first-order kinetics) of hexachlorobenzene was estimated to range from 2.7 to 5.7 years in surface water and from 5.3 to 11.4 years in groundwater based on unacclimated aqueous aerobic biodegradation (Howard et al. 1991).

Hirsch and Hutzinger (1989) conducted surface water photolysis test with hexachlorobenzene in a laboratory setting and found that this process may occur. A first order rate constant ( $1.3 \times 10^{-6}/\text{sec}$ ) corresponding to a half-life of 6.17 days for the photolysis of hexachlorobenzene in distilled water in a photochemical reactor equipped with mercury arc lamps was reported. Hexachlorobenzene in an acetonitrile:water mixture exposed to wavelengths of 290 nm for 8 hours resulted in a 33.5% loss of hexachlorobenzene. 1,2,3,4,5-Pentachlorobenzene (76.8%), 1,2,3,5-tetrachlorobenzene (1.2%), 1,2,4,5-tetrachlorobenzene (1.7%), and 1,2,4-trichlorobenzene (0.2%) were found as hexachlorobenzene transformation products (Choudhry et al. 1986). In another experiment, hexachlorobenzene in a water:acetonitrile solution was exposed to sunlight and resulted in a half-life of 70 days (Mill and Haag 1986). The studies above found photolysis of hexachlorobenzene a feasible loss process with half-lives ranging from 6.17 to 70 days.

Hydrolysis is not expected to be an important fate process. EPA (1987g) observed zero hydrolysis after 13 days for pH values of 3, 7, and 11 at 85 EC.

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Hexachlorobenzene can also be eliminated by ozone reactions. Roche and Prados (1995) conducted a study and compared the efficiencies of ozone and ozone-hydrogen peroxide systems in removing hexachlorobenzene from water treatment processes. The concentration of ozone during the experiments was 70 mg O<sub>3</sub>/L. When ozone was applied, 11–14% of an initial concentration of 1.0 µg/L hexachlorobenzene was removed. This removal increased to 15–48% when hydrogen peroxide and ozone were applied together.

**6.3.2.3 Sediment and Soil**

Hexachlorobenzene is a persistent compound and is not significantly degraded in soils by either abiotic or biodegradation processes. In a year-long laboratory study, soil treated with 0.1, 1.0, and 10 ppm of hexachlorobenzene was stored under aerobic (sterile and nonsterile) conditions and under anaerobic nonsterile conditions in covered containers to retard hexachlorobenzene volatilization (Isensee et al. 1976). No loss in the soil-incorporated hexachlorobenzene was observed at any treatment concentration or under any storage condition. Beck and Hansen (1974) measured a half-life (first-order kinetics) of 3–6 years for hexachlorobenzene in soils. Anaerobic biological dechlorination of hexachlorobenzene has also been demonstrated in anaerobic sewage sludge (Fathepure et al. 1988). These authors reported that hexachlorobenzene was dechlorinated to tri- and dichlorobenzenes under anaerobic conditions when sewage sludge was maintained in serum bottles and incubated in the laboratory. Complete biotransformation of a 50 ppm inoculum occurred within 3 weeks. Two routes of dechlorination were observed. The major route was hexachlorobenzene → pentachlorobenzene → 1,2,3,5-tetrachlorobenzene → 1,3,5-trichlorobenzene; the minor route was hexachlorobenzene → pentachlorobenzene → 1,2,4,5-tetrachlorobenzene → 1,2,4-trichlorobenzene → dichlorobenzenes (i.e., 1,2-, 1,3-, and 1,4-dichlorobenzene). Yuan et al. (1999) also conducted an anaerobic biological dechlorination study using sewage sludge obtained from the Di-Hua Municipal Sewage Treatment Plant in Taipei, Japan. All experiments were performed using 25 mL serum bottles containing 9 mL of sewage sludge and various concentrations of hexachlorobenzene. After a 20-day incubation period, 98% of the 2 mg/L hexachlorobenzene remained, while addition of 1,2,3-trichlorobenzene adapted consortium accelerated dechlorination which occurred at a calculated rate of 0.29 mg/L/day. At hexachlorobenzene concentrations of 2, 5, and 10 mg/L, complete dechlorination occurred within 6 days and at the 50 mg/L concentration, dechlorination occurred in 8 days. Optimal dechlorination occurred at a rate of 0.29 mg/L/day, pH of 7.0, and 30 EC. According to Yuan et al. (1999), dechlorination occurred via the following path: hexachlorobenzene → pentachlorobenzene → 1,2,3,4-tetrachlorobenzene + 1,2,3,5-tetrachlorobenzene → 1,2,4-trichlorobenzene + 1,2,3-trichlorobenzene + 1,3,5-trichlorobenzene → 1,2-dichlorobenzene + 1,4-dichlorobenzene. From this and other

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studies, it is clear that in a time frame of days to years, anaerobic biodegradation may remove hexachlorobenzene from soils.

The Chemicals Inspection and Testing Institute (1992) of Japan conducted an aerobic sludge study to test hexachlorobenzene biodegradation. Hexachlorobenzene, present at 100 mg/L, reached 0% of its theoretical biological oxygen demand (BOD) in 2 weeks using an activated sludge inoculum at 30 mg/L and the Japanese Ministry of International Trade and Industry (MITI) test; thus, aerobic degradation is not an important fate process.

Likewise, in areas of the Great Lakes region with a long history of hexachlorobenzene contaminated waste water discharges affecting aquatic sediments, the concentrations of hexachlorobenzene in the sediments can be significant (see Section 6.4.2). Susarla et al. (1997) examined the transformation of hexachlorobenzene in fresh water lake (Lake Kasumigaura, Japan) sediments under anaerobic conditions. Dechlorination occurred after a 4-day lag phase and was complete in 32 days. The calculated rate of dechlorination was 0.110/day. Hexachlorobenzene transformation pathway under sulfidogenic conditions resulted in hexachlorobenzene  $\rightarrow$  pentachlorobenzene  $\rightarrow$  1,2,3,5-tetrachlorobenzene  $\rightarrow$  1,3,5-trichlorobenzene  $\rightarrow$  1,3-dichlorobenzene. Under methanogenic conditions the pathway was as follows: hexachlorobenzene  $\rightarrow$  pentachlorobenzene  $\rightarrow$  1,2,3,4-tetrachlorobenzene  $\rightarrow$  1,2,4-trichlorobenzene  $\rightarrow$  1,4-dichlorobenzene. After almost a year, 98% of the hexachlorobenzene was dechlorinated to 1,3- and 1,4-dichlorobenzene (Susarla et al. 1997). In another experiment, dechlorination of hexachlorobenzene in an estuary sediment collected from the mouth of Tsurumi river occurred at a rate of 0.0256/day with a half-life of 27.1 days (Masunaga et al. 1996). Thus, aquatic sediment degradation of hexachlorobenzene occurs in a month to a year.

#### 6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to hexachlorobenzene depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. In reviewing data on hexachlorobenzene levels monitored 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.

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**6.4.1 Air**

Hexachlorobenzene is moderately volatile, but is usually not detected in ambient air samples except at very low concentrations. Ambient air sampling was conducted by the EPA at selected locations in the United States from 1976 to 1979. In 1976, 49% of the 43 composite samples collected in four locations contained detectable concentrations of hexachlorobenzene, with a mean value of 0.1 ng/m<sup>3</sup>. In 1977, 12% of the 34 samples collected in three locations contained hexachlorobenzene, with a mean concentration of 1.5 ng/m<sup>3</sup>. In 1978, the compound was not detected in any of the 33 samples collected at three locations and in 1979, hexachlorobenzene was detected in 31% of the 89 samples collected in eight locations, with a mean of 0.5 ng/m<sup>3</sup> (detection limit: 0.1 ng/m<sup>3</sup>) (EPA 1985g). Eisenreich et al. (1981) reported atmospheric concentrations of hexachlorobenzene in the Great Lakes region ranging from 0.09 to 0.28 ng/m<sup>3</sup>. Results of airborne samples collected between 1990 and 1993 from the Great Lakes region by the Integrated Atmospheric Deposition Network are provided by Hoff et al. (1996). The annual mean gas-phase and particulate-phase concentrations of hexachlorobenzene were 98 and 0.2 pg/m<sup>3</sup>, respectively, in samples from Lake Superior near Eagle Harbor, Michigan, 120 and 0.1 pg/m<sup>3</sup>, respectively, in samples from Lake Michigan near Sleeping Bear Dunes, Michigan, 80 and 0.2 pg/m<sup>3</sup>, respectively, in samples from Lake Erie near Sturgeon Point, New York, and 130 and <0.1 pg/m<sup>3</sup>, respectively, in samples from Lake Ontario near Point Petre, Ontario. From July 1988 to September 1989, 143 air samples were collected at Egbert, Ontario, Canada and were analyzed for PCB and organochlorine concentrations. Hexachlorobenzene was detected at concentrations ranging from a minimum of 0.04 pg/m<sup>3</sup> (0.00004 ng/m<sup>3</sup>) to a maximum of 640 pg/m<sup>3</sup> (0.64 ng/m<sup>3</sup>) (annual mean >54 pg/m<sup>3</sup> (0.054 ng/m<sup>3</sup>)) (Hoff et al. 1992). Inhalation exposure was estimated to be 0.3 ng/m<sup>3</sup> in urban air (Burton and Bennett 1987). Hexachlorobenzene measured in air in Villeroy, Quebec in 1992 found mean and median concentrations of 36.68 (0.03668) and 30.94 pg/m<sup>3</sup> (0.03094 ng/m<sup>3</sup>), respectively, from 56 air samples (Poissant et al. 1997). A meteorological station located in a semirural area outside Lancaster, England was the site of air samples. Four air samples per day (taken at 6-hour intervals) were taken for 7 days. The minimum, maximum, and mean concentrations of hexachlorobenzene in these samples were <28.8, 76.1, and 39.3 pg/m<sup>3</sup>, respectively. The authors found an absence of a cycle in the concentrations of hexachlorobenzene and concluded that the compound was breaking through the polyurethane foam plugs due to its relatively high vapor pressure (Lee et al. 2000).

Hexachlorobenzene air concentrations have also been measured in urban and rural areas in France. Atmospheric fallout from the urban area, Paris, and the rural area, La Ferté-sous-Jouarre, was collected in raw form as bulk precipitation. Hexachlorobenzene concentration in rural fallout measured in

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February–July 1992 and January –September 1993 ranged from 2.5 to 4.5 ng/L and from 0.3 to 4 ng/L, respectively. For the same time periods, urban fallout measured 1.8–17 and 0.3–5.6 ng/L, respectively (Chevreuil et al. 1996). The mean concentrations of hexachlorobenzene in precipitation samples collected in the Great Lakes region from 1986 to 1991 ranged from 0.145 ng/L (ppt) at Sibley Park on Lake Superior, to 0.108 ng/L (ppt) at Pelee Island in Lake Erie, to 0.174 ng/L (ppt) at Wolfe Island in Lake Ontario (Chan et al. 1994). The mean and median concentrations of hexachlorobenzene from eight precipitation samples collected from Villeroy, Quebec in 1992 were 0.04 and 0.05 ng/L, respectively (Poissant et al. 1997). Precipitation samples collected between 1990 and 1993 from the Great Lakes region by the Integrated Atmospheric Deposition Network were analyzed. The annual mean concentration of hexachlorobenzene in these precipitation samples were 0.1 ng/L in samples from Lake Superior near Eagle Harbor, Michigan, 0.06 ng/L in samples from Lake Michigan near Sleeping Bear Dunes, Michigan, 0.04 ng/L in samples from Lake Erie near Sturgeon Point, New York, and 0.3 ng/L in samples from Lake Ontario near Point Petre, Ontario (Hoff et al. 1996). The concentrations of hexachlorobenzene in air, particulate matter, and rain from Galveston Bay, Texas were  $87.3 \pm 103.3$ ,  $0.4 \pm 0.5$ , and  $42.5 \text{ pg/m}^3$  (not detected– $48.1 \text{ pg/m}^3$ ), respectively, between 1995 and 1996 (Park et al. 2001). The median levels of hexachlorobenzene in ambient air samples collected in Zagreb, Croatia in 1997 were  $29 \text{ pg/m}^3$  (range,  $0.5\text{--}49 \text{ pg/m}^3$ ) in the northern residential region of Ksaverska and  $31 \text{ pg/m}^3$  (range,  $15\text{--}61 \text{ pg/m}^3$ ) in the southern region near a landfill (Romanic and Krauthacker 2000). The average concentration of hexachlorobenzene in air at Lake Malawi, in southeast Africa, from February 1997 to May 1998, was  $11 \pm 7.5 \text{ pg/m}^3$  (Karlsson et al. 2000).

Nonoccupational exposure to hexachlorobenzene for residents of two U.S. cities (Jacksonville, Florida and Springfield, Massachusetts) was studied over three seasons: summer 1986, spring 1987, and winter 1988 (Whitmore et al. 1994). The study focused primarily on inhalation exposures with primary environmental monitoring consisting of 24-hour indoor and outdoor air. For the Jacksonville, Florida, population, the estimated mean hexachlorobenzene concentration ranged from 0.3 to  $1.3 \text{ ng/m}^3$  for indoor air and from not detected to  $0.2 \text{ ng/m}^3$  for outdoor air. For the Springfield, Massachusetts population, mean exposures were much less. The estimated hexachlorobenzene concentrations ranged from not detected to  $0.1 \text{ ng/m}^3$  for indoor air and no detectable concentrations of hexachlorobenzene for outdoor air.

Extremely high concentrations of hexachlorobenzene in air have been detected in areas close to production and disposal sites in both outdoor and indoor air. Mann et al. (1974) measured hexachlorobenzene concentrations ranging from 70 to  $23,296 \text{ ng/m}^3$  near chlorinated solvent and pesticide

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manufacturing facilities; air levels near a chemical waste landfill were as high as 16,000 ng/m<sup>3</sup> (EPA 1975b). Hexachlorobenzene has been detected at 11,000 ng/m<sup>3</sup> in flue gas effluents from a municipal refuse-fired steam boiler in Virginia, and at 9.5 ng/m<sup>3</sup> in flue gas effluents from a refuse-derived fuel fired power plant in Ohio (Tiernan et al. 1985). Air concentrations of hexachlorobenzene inside industrial plants can be as high as 150,000 ng/m<sup>3</sup> (Currier et al. 1980); air concentrations inside a pesticide production facility were measured at 22,000 ng/m<sup>3</sup> (Davis and Morgan 1986).

**6.4.2 Water**

Drinking water in three cities in the Lake Ontario vicinity contained hexachlorobenzene ranging from 0.06 to 0.2 ppt (mean of 0.1 ppb), about the same as water from the lake (Oliver and Nichol 1982a).

Hexachlorobenzene was detected in ambient water samples from two of the Great Lakes and their tributary rivers. Mean concentrations of hexachlorobenzene in Lake Ontario, Lake Huron, and the Grand River were 0.06 ppt (range, 0.02–0.1 ppt), 0.04 ppt (range, 0.02–0.1 ppt), and 0.06 ppt (range, 0.02–0.1 ppt), respectively. In the Niagara River, concentrations of 0.02–17 ppt were detected with the highest value measured downstream of a waste disposal site (Oliver and Nichol 1982a). Widely varying measurements in this river may be attributed to the fact that measurements were near the limit of the analytical detection limits. More recently, hexachlorobenzene was detected in 42% of whole water samples (dissolved plus particulate phases) collected during 1991 in the St. Lawrence River and several of its tributaries. Hexachlorobenzene concentrations detected in the St. Lawrence River ranged from not detected to 0.09 ng/L (mean 0.01 ng/L [ppt]) (Quemerais et al. 1994). Hoff et al. (1996) obtained and presented water concentration data from a 1992 sampling study. Hexachlorobenzene concentrations in Lakes Superior, Michigan, Huron, Erie, and Ontario were 0.01, 0.014, 0.007, 0.014, and 0.045 ng/L, respectively. In remote European mountain lake waters, the concentrations of hexachlorobenzene were 8.4±11 pg/L at Redó, Spain, 4.0±1.8 pg/L at Gossenkölle, Austria, and 6.2±1.0 pg/L at Øvre Neådalsvatn, Norway (Vilanova et al. 2001). The concentrations of hexachlorobenzene in microlayer and subsurface Mediterranean seawater off the coast of Alexandria, Egypt were on average, 27.3±17 and 12±6.9 ng/L, respectively (Abd-Allah 1999).

A study was conducted from 1974 to 1975 to collect and analyze surface water samples from sites of known hexachlorobenzene contamination along the Mississippi River near an industrial area in Geismar, Louisiana (EPA 1976a). The maximum hexachlorobenzene concentration detected in water was

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90.3 ppb. A concentration of 2 ppb has been measured in the Mississippi River near Baton Rouge, Louisiana (Laska et al. 1976).

Industrial waste water samples contained hexachlorobenzene levels as high as 300 ppb (EPA 1976b; Schmitt et al. 1990). Effluent concentrations of hexachlorobenzene from four Canadian plants in the Great Lakes region ranged from 0.001 to 0.002 ppb (0.0015 ppb mean) (Oliver and Nichol 1982a).

Hexachlorobenzene concentrations were measured in water at an uncontrolled hazardous waste site near Bayou Baton Rouge, Louisiana (Davis and Morgan 1986). Surface water samples collected from a containment pond used for disposal of wastes from both rubber production and manufacture of chlorinated organics at the site contained up to 8,100,000 ppb hexachlorobenzene.

### 6.4.3 Sediment and Soil

Mean concentrations of hexachlorobenzene in lake sediments in the Great Lakes ranged from 0.2 to 97 ppb with the highest values measured in Lake Ontario. Deeper sediment layers (1–2 cm) had even higher concentrations of hexachlorobenzene (460 ppb) than surface (0–1 cm) samples (270 ppb), with the peak value corresponding to deposition in the years 1971–1976 declining to 270 ppb in 1976–1980 (Oliver and Nichol 1982a). In 1992, 2 cm deep bed sediment samples were collected from the South Platte River at Henderson, Colorado and Cache La Poudre River near Greeley, Colorado. The sediment contained 1.5 and <1 µg/kg, dry weight, hexachlorobenzene, respectively. The authors concluded that this concentration was correlated to the hexachlorobenzene concentrations found in urban and agricultural lands in the South Platte River Basin (Tate and Heiny 1996). Outside of the United States, 12 sediment samples were collected in June 1993 near known discharges from municipalities and industries from Lake Ladoga, Russia. Hexachlorobenzene concentrations were 3.58 and 14.6 ng/g in 2 out of the 12 samples, and was not detected in the remaining 10 samples (Ristola et al. 1996).

In 1972, hexachlorobenzene levels in soil were detected in 11 of 1,485 agricultural sites (0.7%) in 37 states, ranging from 0.01 to 0.44 mg/kg (10–440 ppb). In 1973, only 1 of 1,470 sites (0.1%) contained hexachlorobenzene at 10 ppb, while in a 1976 study of 11 states, only 2 of 391 sites (0.5%) contained hexachlorobenzene at concentrations ranging from 10 to 20 ppb (EPA 1985g). The majority of these agricultural sites with hexachlorobenzene detections were under cultivation with wheat or other seed grains (e.g., barley, oats, rye), which is consistent with the registered agricultural uses of hexachlorobenzene at that time. The authors concluded that the occurrence of hexachlorobenzene residues in

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agricultural soils was associated with hexachlorobenzene's registered pesticide uses rather than general environmental or industrial contamination.

In a study of 40 urban areas sampled during the 1970s, 7 sites (17.5%) contained detectable hexachlorobenzene concentration in soil ranging from 0.01 to 0.59 mg/kg (10–590 ppb) (EPA 1985g). In the levees of the Mississippi River near Baton Rouge, where the river water contained 2 ppb hexachlorobenzene, the soil contained 167 ppb (Laska et al. 1976). In contrast to agricultural soils, hexachlorobenzene residues in urban soils resulted from releases during the manufacture, use, or disposal of hexachlorobenzene or hexachlorobenzene-containing wastes rather than the use of hexachlorobenzene as a pesticide (EPA 1985g).

Hexachlorobenzene concentrations were measured in soil and sediment at several uncontrolled hazardous waste sites in several states (Davis and Morgan 1986). Hexachlorobenzene concentrations of up to 20,000 ppb were measured in soil at a scenic highway site near Bayou Baton Rouge, Louisiana, while concentrations in sediment of 39,500 ppb were measured from a bayou bank downstream of the site. Soil cores from a monitoring well (25–27 feet deep) were as high as 400,000 ppb, and as high as 90,000 ppb in soils collected at 40–41 feet deep (Davis and Morgan 1986). Soil and sediment collected from a disposal site near Sorrento, Louisiana contained 62,000 and 130,000 ppb hexachlorobenzene, respectively. Soil collected at a Crystal City, Texas pesticide disposal site was found to contain 20,000 ppb hexachlorobenzene. A maximum hexachlorobenzene concentration detected in soil at an industrial site of known contamination near Geismar, Louisiana was 53,130 ppb (Laseter et al. 1976).

Sediment concentrations of hexachlorobenzene vary widely from relatively unpolluted areas to those areas used extensively for disposal of hexachlorobenzene-containing wastes. Sediment hexachlorobenzene concentrations from San Luis Pass, located near industrial areas of West Galveston Bay, Texas ranged from 0.05 to 1.5 ppb (dry weight) with a mean of 0.49 ppb (Murray et al. 1981).

Hexachlorobenzene concentrations in marine sediment samples collected from an industrialized area of the harbor in Portland, Maine ranged from <0.03 to 0.37 ppb (mean 0.14 ppb) (Ray et al. 1983).

Concentrations of hexachlorobenzene in sediment from the Niagara River watershed in the vicinity of several hazardous waste disposal areas ranged from 8,000 to 30,000 ppb (Elder et al. 1981). The average concentration of hexachlorobenzene in surficial sediments of the Kaohsiung coast (southwestern Taiwan), which receives wastewater from the largest industrial city in Taiwan (Kaohsiung City), ranged from 1.7 to 24.7 ng/g (Lee et al. 2000a).

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**6.4.4 Other Environmental Media**

Concentrations of hexachlorobenzene have been detected in several species of fish and shellfish. Hexachlorobenzene concentrations were determined for several species of marine organisms collected from San Luis Pass near Galveston Bay, Texas (Murray et al. 1981). Mean concentrations of hexachlorobenzene at were 0.49 ppb wet weight for flounder (species unspecified), 0.65 ppb for longnose killifish (*Fundulus similis*), 0.88 ppb for brown shrimp (*Penaeus aztecus*), 9.6 ppb for blue crab (*Callinectes sapidus*), and 0.71 ppb for the dwarf squid (*Lollingnucula brevis*). Oysters (*Crassostrea virginica*) collected at the lower end of the Houston Ship Channel were found to contain hexachlorobenzene concentrations ranging from 0.31 to 1.41 ppb with a mean of  $0.63 \pm 0.39$  ppb (Murray et al. 1980). The Sheboygan River in Wisconsin is another area of concern for contamination of organochlorine pesticides in fish due to the existence of wetlands, urban and developed land, woodland, and agricultural land surrounding this river. In addition, the lower segment of the river has a history of shipping, industrial and municipal activities, and dredging, including the existence of a landfill designated as a federal superfund site. Schrank et al. (1997) collected white suckers (*Catostomus commersoni*) from two sites of the Sheboygan River; one site was 1 to 2 km from the mouth of the river and the other was 50 km from the mouth of the river, which served as the reference site. The fish collected from both sites contained less than detectable residues of hexachlorobenzene along with other organochlorine compounds, thus minimizing the risk of exposure to hexachlorobenzene from this river.

DeVault (1985) reported concentrations of hexachlorobenzene in whole fish composites collected from the Great Lakes during 1980 and 1981 ranged from  $<0.002$  to 3.47 mg/kg ( $<2$ –347 ppb). Hexachlorobenzene concentrations in fresh water trout (4–6+ years old) from the Great Lakes region ranged from 8 to 127 ppb with the highest concentration found in a fish collected near the discharge of the Niagara river into Lake Ontario (Oliver and Nichol 1982a). In another study of Great Lakes fish species, Newsome and Andrews (1993) reported hexachlorobenzene concentrations in fish fillet composites ranged from 0.22 ng/g (ppb) in bullhead to 9.05 ng/g (ppb) wet weight in trout in lake areas with open fisheries. Zabik et al. (1995) reported that skin-off processing and selected cooking methods reduced hexachlorobenzene residues in chinook salmon and carp harvested from the Great Lakes. Concentrations of hexachlorobenzene averaged 0.017 ppm (17 ppb) and 0.011 ppm (11 ppb) (wet weight) in raw and cooked salmon fillets, respectively, and averaged 0.005 ppm (5 ppb) and 0.003 ppm (3 ppb) in skin-on and skin-off fillets, respectively. The average percentage loss of hexachlorobenzene from chinook salmon fillets by baking, charbroiling, and canning was 40%. Losses of hexachlorobenzene residues from carp fillets were slightly greater than 40% (Zabik et al. 1995). Walleye, siscowet, carp, and whitefish

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were collected for organochlorine pesticides analysis from Lake Superior along the Apostle Islands region during 1991 and 1992. Walleye and carp had hexachlorobenzene concentrations below the limit of quantification, while siscowet and whitefish measured concentrations of 3.2 and 2.8 ng/g wet weight of tissue, respectively (Gerstenberger et al. 1997). Organisms sampled during the summer of 1994, from the Keweenaw Peninsula of Lake Superior, contained measured hexachlorobenzene concentrations ranging from 0.8 to 1.8 ng/g wet weight in smelts, 3.0–4.3 ng/g wet weight in herrings, 4.7–8.4 ng/g wet weight in bloaters, 1.1–4.1 ng/g wet weight sculpins, <0.1–0.2 ng/g wet weight in mysis, 0.8–1.4 ng/g wet weight in limnocalanus, 0.8 ng/g wet weight in amphipods, and 1.7–3.1 ng/g wet weight in lake trout (Kuchlick and Baker 1998). Grayling and lake trout were collected from four lakes (Feniak, Desperation, Schrader, and Elusive) from the foothills of the Brooks Range, Alaska. All lakes were oligotrophic, and the pH was neutral to slightly alkaline. Fifty-six grayling liver samples and 39 grayling muscle samples were analyzed for hexachlorobenzene concentration, and mean and median values were derived. In the 56 grayling liver samples, the mean and median concentrations were 0.65 and 0.48 ng/g dry weight, respectively. The 39 grayling muscle samples had mean and median concentrations of 0.33 and 0.22 ng/g dry weight, respectively. In lake trout, the mean and median concentrations in 33 liver samples were 1.15 and 0.87 ng/g dry weight, respectively, and in 34 muscle samples were 0.46 and 0.26 ng/g dry weight, respectively (Allen-Gil et al. 1997a). Hexachlorobenzene concentrations in sea organisms from the Barents Sea were as follows (units=ng/g lipid weight): copepods (13.5), euphausiids (16.5), amphipods (19.5), polar cod ( $39 \pm 1.7$ ), and cod ( $65 \pm 7.7$ ) (Borgå et al. 2001). In 1991, the concentrations of hexachlorobenzene in amphipods, isopods, and sculpins from the Bothnian Bay (Baltic Sea) were 340 (n=3), 370 (n=5), and 37 (n=3) ng/g dry weight, respectively (Strandberg et al. 2000).

The bioaccumulative tendencies of hexachlorobenzene have made it a candidate for monitoring in the U.S. Fish and Wildlife Service National Pesticide Monitoring Program (Schmitt et al. 1990) and the National Study of Chemical Residues in Fish which was started in 1986 (NSCRF) (EPA 1992b). Maximum hexachlorobenzene tissue concentrations (wet weight) detected in whole fish were 700, 130, 120, and 410 ppb in the 1976–1977, 1978–1979, 1980–1981, and 1984 sampling years, respectively. The geometric mean tissue concentration was 10 ppb for 1976–1977 and <10 ppb for all other sampling years (Schmitt et al. 1990). The highest hexachlorobenzene concentrations in the 1984 sampling period (410 ppb) were detected in whole fish from the Tombigbee River, Alabama in the vicinity of a pesticide production facility where concentrations during all sampling years had been the highest nationally. The most recent national results from the ongoing study conducted by NSCRF show that hexachlorobenzene was detected at 46% of the 362 sites surveyed for fish tissue analysis. The mean hexachlorobenzene concentration for fish tissue samples analyzed in this program was 5.8 ppb. The five sites with the

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highest concentrations are listed in Table 6-3 (EPA 1992b). The Freeport, Texas site is near a pesticide plant and the other four sites are close to a variety of chemical manufacturing plants. The Calcasieu River, Louisiana site is close to a Superfund site involving a variety of organic solvents (EPA 1992b).

Hazardous waste dumping during the early 1940s and 1950s contaminated the Devil's Swamp, Louisiana with chlorinated hydrocarbons, which has greatly affected fish species. As fish is an important food

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**Table 6-3. Sites with the Five Highest Concentrations of Hexachlorobenzene in Fish<sup>a</sup>**

Whole body hexachlorobenzene concentration (ppb; wet weight)	Type of sample (fish)	Location
913	Sea catfish	Brazos River, Freeport, Texas
202	Catfish	Bayou D'Inde, Sulfur, Louisiana
93.7	Carp	Mississippi River, St. Francisville, Louisiana
85.5	White sucker	Quinipiac River, North Haven, Connecticut
75	Sea catfish	Calcasieu River, Moss Lake, Louisiana

<sup>a</sup>From the EPA 1992b National Study of Chemical Residues in Fish

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source for the community surrounding this area, concentrations of contaminants are of great concern. Levels of hexachlorobenzene in various fish species collected from Devil's Swamp, Louisiana, was compared to those from a control site, Tunica's Swamp, Louisiana. Mean hexachlorobenzene concentrations calculated from concentrations of 13 different edible fish species tissues were 23.65 ng/g compared to 2.0 ng/g calculated from 10 different edible fish species from Tunica's Swamp (Tchounwou et al. 1998).

Hexachlorobenzene has been detected in tissues of various wildlife species throughout North America, but especially in wildlife indigenous to the Great Lakes region. Swift et al. (1993) reported mean concentrations of hexachlorobenzene of 0.02 ppm (20 ppb) wet weight (0.04 ppm [40 ppb] lipid weight basis) and 0 ppm wet weight (0.07 ppm [70 ppb] lipid weight basis) in mesenteric and subcutaneous fat and breast tissue, respectively, of common goldeneye waterfowl wintering in New York state. The detection limit in this study was 0.002 ppm. Gebauer and Weseloh (1993) reported that the geometric mean hexachlorobenzene concentrations of 0.4 and 0.9  $\mu\text{g}/\text{kg}$  (ppb) in muscle tissue in mallard ducks using a contaminated sediment site, and sewage lagoon site, respectively, as a resting and feeding area were significantly greater than levels found in ducks using a natural marsh area. Foley (1992) reported hexachlorobenzene residues in muscle tissues of several species of ducks and geese collected in New York State in 1983–1984. Statewide residues were 64 ppb (wet weight) for buffleheads, 49 ppb for scaups, 26 ppb for mallards, 20 ppb for black ducks, 6 ppb for wood ducks, and 11 ppb for Canada geese. Adult sea otters that had died along the coast of California were collected by the U.S. Fish and Wildlife Service and the California Department of Fish and Game. Hexachlorobenzene concentrations in liver, kidney, and brain tissues were 0.74–8, 0.28–2.6, and 0.28–0.74 ng/g wet weight, respectively (Nakata et al. 1998). The mean hexachlorobenzene concentration for 207 wild mink liver tissue samples, collected from 1991 to 1995 in the Northwest Territories, Canada from seven mink communities, ranged from 0.21 to 0.67 ng/g wet weight (Poole et al. 1998). Snail composite samples, without shells, were collected from two lakes (Feniak and Elusive) from the foothills of the Brooks Range, Alaska. All lakes were oligotrophic, and the pH was neutral to slightly alkaline. The mean concentration among these six samples was 0.15 ng/g dry weight with a median of 0.10 ng/g dry weight (Allen-Gil et al. 1997a).

Hexachlorobenzene has also been detected in the eggs of various wildlife species in the Great Lakes region and Canada. Yamashita et al. (1992) reported hexachlorobenzene residues ranges of 8–36 ng/g (ppb) and 18–26 ng/g (ppb) on a wet weight basis in the eggs of the double-crested cormorant and the Caspian tern, respectively, collected during 1988 from the Great Lakes region. Somers et al. (1993) reported geometric mean concentrations of 0.013  $\mu\text{g}/\text{g}$  (13 ppb) (wet weight) of hexachlorobenzene in

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double-crested cormorant eggs collected in southern Alberta, Canada. Elliott and Martin (1994) reported mean hexachlorobenzene concentrations in sharp-shinned hawk eggs in south central Ontario ranging from 0.010 to 0.051 mg/kg (10–51 ppb) from 1986 to 1989. Hexachlorobenzene concentrations in Cooper's hawk eggs ranged from 0.005 to 0.012 mg/kg (5–12 ppb) during the same period. Cobb et al. (1994) reported mean residues of 18.0 ng/g (18 ppb) in the chorio-allantoic membranes removed from great blue heron eggs collected from Puget Sound, Washington. Jarman et al. (1996) conducted an experiment with prairie falcon eggs that were collected from eyries in northern and central California between 1989 and 1991. Addled and unhatched eggs were frozen until chemical analysis. The following are the geometric mean concentrations (in mg/kg wet weight) of hexachlorobenzene at their respective sampling sites: Frog/Hand Nest 800; Pig Cyn 17; Crowley Tower 11; Willow Sp. 8.0; Goat Rock 10; Mt. Dome 20; and Mt. Diablo 81. Mean hexachlorobenzene residues in peregrine falcon eggs from Rankin Inlet (Hudson Bay, Canada) were 0.03 µg/g wet weight (n=2; range 0–0.15 µg/g wet weight) between 1982 and 1986, and 0.030 µg/g wet weight (n=20; range 0–0.165 µg/g wet weight) between 1991 and 1994 (Braune et al. 1999).

Hexachlorobenzene residues were also detected in snapping turtle eggs collected from a wetland area on Lake Ontario. Residues ranged from 43.9, 16.6, and 20.9 ng/g (ppb) (wet weight) to 494.7, 282.1, and 262.2 ng/g (ppb) (lipid weight) for the first five eggs, a composite of five eggs, and the last five eggs, respectively (Bishop et al. 1995). Bishop et al. (1996) conducted another study with snapping turtle eggs that were collected from nests at five locations from the Great Lakes Basin in 1990–1991. These eggs were analyzed for hexachlorobenzene and the results were compared to data collected from the same sites in the years 1981, 1984, 1988, and 1989. Residue concentrations for all locations and their respective years are listed in Table 6-4. Based on the results, the hexachlorobenzene concentration was the highest in eggs from Cootes Paradise and lowest in eggs from Algonquin Park. Although the concentration of hexachlorobenzene at Cootes Paradise has been continuously declining since 1984, residues in eggs from this site are consistently higher than those from the other sites, and are at least 3 times higher than eggs from the next most contaminated site, Lynde Creek. On the whole, the hexachlorobenzene mean concentration from the five sites in the Great Lakes Basin showed a decrease from the year 1984 to 1990 (Bishop et al. 1996).

Langlois and Langis (1995) reported that the concentration of hexachlorobenzene in the blubber of beluga whales from the St. Lawrence Estuary to Northern Quebec Province ranged from 0.22 to

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**Table 6-4. Residue Concentrations (ng/g) in Snapping Turtle Eggs from Five Locations Collected in 1981–1991**

Sites	Year				
	1981	1984	1988	1989	1990/1991
Algonquin Park	20	NA	10	3	NA
Cranberry Park	NA	NA	40	30	NA
Lynde Creek	NA	70	80	60	80
Cootes Paradise	NA	350	300	170	170
Big Creek Marsh	50	NA	NA	40	NA
Rondeau Park	NA	60	NA	20	NA

NA = Snapping turtle eggs were not available or were not collected during those years.

Source: Bishop et al. 1996

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0.93 mg/kg (220–930 ppb) wet weight. Consumption of blubber and organ meats from these whales by native peoples may constitute a potential health risk if these tissues are a significant part of the diet (Langlois and Langis 1995). In 1997, Gauthier et al. (1997) analyzed blubber biopsies from Northwestern Atlantic Balaenopterid whales summering in the Gulf of St. Lawrence. Samples were collected in the summer and fall of 1991 and 1992 from 21 minke, 15 fin, 6 blue, and 8 humpback whales. Hexachlorobenzene concentrations in the blubber of these whales were 101, 96, 110, and 177 ng/g lipid, respectively, and in all species, the concentrations were higher in males (140 ng/g lipid) than in females (103 ng/g lipid).

Becker et al. (1997) analyzed the blubber of 7 pilot whales, 5 harbor porpoises, 12 beluga whales, 2 northern fur seals, and 2 ringed seals that were obtained from the U.S. National Biomonitoring Specimen Bank. Hexachlorobenzene concentration ranges were 43–465 ng/g wet weight for pilot whales, 223–1,070 ng/g wet weight for harbor porpoises, 81.9–952 ng/g wet weight for beluga whales, 138–741 ng/g wet weight for northern fur seals, and 125–156 ng/g wet weight for ringed seals (Becker et al. 1997). Elkin and Bethke (1995) reported that hexachlorobenzene was the most predominant organochlorine residue present in tissues of the caribou collected in the Northwest Territory of Canada. Residues ranged from a lipid corrected mean of 32.83 ng/g (ppb) in fat from Bathurst caribou to 129.41 ng/g (ppb) in Lake Harbor animals (Baffin Island). Consumption of meat and organs from these range animals by native peoples, including native American populations of Inuits in Alaska, may constitute a potential human health risk if these tissues are a significant part of the diet.

The Florida Department of Environmental Protection and the Florida Marine Research Facility in St. Petersburg, Florida maintain archives of tissues obtained from dead Florida Manatees (*Trichechus manatus latirostris*). In 1996, Ames and Van Vleet (1996) obtained and analyzed 19 manatee samples from the Florida EPA. Of these samples, hexachlorobenzene was found at concentrations of 0.038 and 0.085 µg/g in one blubber and one liver sample, respectively. The authors did not find a correlation between the contamination in manatees by hexachlorobenzene and other pesticides and the location in which the manatees were found dead; thus, the authors concluded that these manatees must have been contaminated elsewhere, especially since manatees are known to travel long distances.

Corsolini et al. (1999) analyzed chlorinated hydrocarbon concentrations in muscle and fat samples of the red fox collected from Sienna, Italy in 1992. Hexachlorobenzene mean concentrations in muscle and fat were 0.47 and 0.23 µg/g lipid basis, respectively, and were the lowest of all of the chlorinated hydrocarbons that were tested (Corsolini et al. 1999).

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Sitarska et al. (1995) collected tissue samples from 18 cows just after slaughtering, always from the same parts of the studied organs. Hexachlorobenzene mean concentrations were 1.394  $\mu\text{g}/\text{kg}$  wet mass in the ovaries, 1.061  $\mu\text{g}/\text{kg}$  wet mass in the mammary glands, and 0.550  $\mu\text{g}/\text{kg}$  wet mass in the liver.

Beyer (1996) subjected earthworms (*Lubricous terrestris*) to hexachlorobenzene in artificial soil. Over the course of 28 weeks, hexachlorobenzene concentrations in these earthworms ranged from 1.8 to 3 ppm. Beyer (1996) also conducted three 8-week experiments in which earthworm survival rates were 97, 99, and 100%, respectively.

Hexachlorobenzene was detected in composited milk samples collected through the U.S. Pasteurized Milk Network during 1990–1991 (Trotter and Dickerson 1993). The milk samples were collected at approximately 63 sites located in the United States, Puerto Rico, and the Panama Canal Zone. Hexachlorobenzene was detected in trace amounts in one sample collected in each of seven metropolitan areas (Cristobal, Panama Canal Zone; Kansas City, Missouri; Los Angeles, California; Memphis, Tennessee; Portland, Oregon; Spokane, Washington; Wichita, Kansas) and was detected at 0.001 ppm (1 ppb) in one sample from Rapid City, South Dakota.

Pesticide residue data from the FDA Adult Total Diet Study conducted from 1980 to 1982 were evaluated by Gartrell et al. (1986). These authors reported that hexachlorobenzene was detected in a wide variety of domestic foods: dairy products, meat, fish and poultry, oils and fats, and sugar and adjuncts. The highest mean concentrations of hexachlorobenzene were detected in oils and fats (0.9 ppb) and in meat, poultry, and fish (0.2 ppb). Concentrations of hexachlorobenzene in ready-to-eat foods were monitored for 10 years from 1982–1991 through the FDA's Revised Market Basket Survey. Hexachlorobenzene was detected in 618 samples of 81 different foods at a mean concentration of 0.0006  $\mu\text{g}/\text{g}$  (0.6 ppb) (KAN-DO Office and Pesticide Teams 1995). In food composites from six Canadian cities, the mean concentration of hexachlorobenzene in positive samples (4.8% of 913 total analysis) was 0.5 ng/g (Newsome et al. 2000). The U.S. Food and Drug Administration monitored domestic and imported apples and rice by collecting random samples for a period of 12 months beginning in October, 1993. Hexachlorobenzene was not determined to be in violation according to the concentration limits set for this compound in any of the domestic and imported apple and rice samples; however, it was found in 1 out of 612 imported rice samples (0.02 ppm), but this concentration does not violate any limit set by the EPA (Roy et al. 1997). The concentrations and occurrences of hexachlorobenzene residues in butter from Spain ( $n=36$ , 89% positive) and the rest of Europe ( $n=20$ , 70% positive) were  $5.864\pm 3.171$  ng/g wet weight and  $3.022\pm 3.964$  ng/g wet weight, respectively (Badia-Vila et al. 2000).

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The frequency of detection of hexachlorobenzene in the FDA Total Diet Study conducted in 1982–1984 was 9% (Gunderson 1988). Hexachlorobenzene intakes, in  $\mu\text{g}/\text{kg}$  body weight/day, estimated for these total diet analyses were 0.0020 and 0.0011 for 14–16-year-old males and 60–65-year-old females, respectively. In more recent FDA Total Diet Studies, the frequency of detection of hexachlorobenzene residues declined to 7% in 1988 (FDA 1989), 5% in 1989 (FDA 1990), 4% in 1990 (FDA 1991), 2% in 1991 (FDA 1992), <2% on 1991–1993 (FDA 1994), and <2% in 1994 (FDA 1995). Hexachlorobenzene intakes ( $\mu\text{g}/\text{kg}$  body weight/day) estimated for the Total Diet Analyses also declined from intakes estimated in the 1982–1984 analysis and were 0.0011 and 0.0006 in 1988 (FDA 1989); 0.0009 and 0.0005 in 1989 (FDA 1990); 0.0005 and 0.0002 in 1990 (FDA 1991); and 0.0004 and 0.0002 in 1991 (FDA 1992) for 14–16-year-old males and 60–65-year-old women, respectively.

Domestic samples of mixed feed rations were collected and analyzed by the FDA for pesticide surveillance during fiscal years 1989–1994. Hexachlorobenzene residue was detected in 1 of 457 samples in trace amounts (Lovell et al. 1996).

Burton and Bennett (1987) estimated a human body burden for hexachlorobenzene of 0.7 mg derived primarily from dietary intake of fatty foods (0.2  $\mu\text{g}/\text{day}$ ). Inhalation was estimated to contribute 100 times less than dietary intake (0.002  $\mu\text{g}/\text{day}$ ) and consumption of drinking water was also considered to contribute only negligible amounts of hexachlorobenzene (0.06  $\mu\text{g}/\text{year}$ ).

An exploratory study of chemical exposure was conducted among Vietnamese, Bangladeshi, and local resident sportfish consumers in the Montreal region of the St. Lawrence River. The concentration ranges for the respective groups are as follows: 0.01–0.04; 0.01–0.02; and 0.01–0.07  $\mu\text{g}/\text{L}$ , indicating a positive correlation between local residents consuming sportfish from the St. Lawrence River and hexachlorobenzene concentrations (Kosatsky et al. 1999). Anderson et al. (1998) conducted a study to assess hexachlorobenzene contamination in human serum and urine samples from frequent consumers of sport fish from Lakes Michigan, Erie, and Huron. A telephone survey was conducted requesting fish eating habits with special attention to lake trout, brown trout, rainbow trout, or chinook or coho salmon, carp or catfish, and walleye or perch or smelt. After the survey, each angler was invited to give a serum sample. The minimum and maximum hexachlorobenzene concentrations of all 30 participating subjects were 0.02 and 0.2 ppb, respectively, with a median concentration of 0.1 ppb. Eight participants from Lake Michigan had minimum and maximum concentrations of 0.09 and 0.2 ppb, respectively, with a median concentrations of 0.1 ppb, and 11 participants from Lake Huron and Lake Erie had respective minimum and maximum concentrations of 0.04 and 0.2 ppb and 0.02 and 0.2 ppb with median concentrations of

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0.1 and 0.09 ppb. A comparison group from Arkansas (180 serum samples) had hexachlorobenzene concentrations ranging from not detected to 0.3 ppb with a median of 0.1 ppb (Anderson et al. 1998). This study illustrates that since the comparison group had the highest range in concentration, there is a wide spread of hexachlorobenzene contamination and any population may possibly be affected.

Sinkkonen et al. (1995b) discovered concentrations of hexachlorobenzene in pine needles in the vicinity of a metal reclamation plant. Five sites sampled and analyzed for hexachlorobenzene in the wax of the needles and the rest of the needles in 1991 (0.257–0.731 ng/g; 0.758–3.170 ng/g), 1992 (0.142–0.692 ng/g; 0.255–1.785 ng/g), and 1993 (0 concentration found in the wax of the needles; 0.217–0.885 ng/g) show decreasing concentrations (Sinkkonen et al. 1995b). In 1996, Sinkkonen et al. (1996) analyzed pine needles in and around the metal reclamation plant again. Composite samples from the years 1993, 1994, and 1995 had hexachlorobenzene concentrations of 6.9–8.3 ng/g in the wax of the needles and 0.2–2.2 ng/g in the rest of the needles, contrary to the decreasing trends found from the analysis conducted during 1991–1993.

### 6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Hexachlorobenzene is no longer produced (as an end-product) or used as a pesticide in the United States. Consequently, the current potential for exposure of the general population appears to be very limited. Members of the general population may be exposed to very low concentrations of hexachlorobenzene through ingestion of contaminated foodstuffs, particularly those with high lipid content such as meat, poultry, and fish. General population exposure to hexachlorobenzene via inhalation or dermal contact would be much less. Occupational exposure is possible for workers involved in the production of chlorinated hydrocarbons, which releases hexachlorobenzene as a by-product. One recent study has also shown farmers to be susceptible to hexachlorobenzene.

Brock et al. (1998) investigated four families in Iowa and two families in North Carolina for exposure to several organochlorine pesticides by analyzing the pesticide levels in their serum. Among the farmers from Iowa, mean hexachlorobenzene concentrations in serum ranged from 0.12 to 0.26 ng/mL, and their spouses had mean levels ranging from 0.05 to 0.24 ng/mL. The two farmers from North Carolina had mean levels of 0.15 and <0.05 ng/mL, and their respective spouses had levels of 0.16 and 0.17 ng/mL. It was shown that in one family, the pesticide serum level in the spouse (0.17 ng/mL) was higher than that in the farmer (<0.05). Glynn et al. (2000) studied the serum concentration of hexachlorobenzene in a group of 790 men ages 40–75 who were randomly selected from both rural and urban areas of Uppsala,

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Sweden. The mean concentration of hexachlorobenzene was  $83.1 \pm 133.6$  ng/g lipid for this group. This study group had lower serum concentrations than males who had recent occupational exposure or high environmental exposure. Hagmar et al. (2001) examined blood samples from 110 men who consumed varying amounts of fish from the Baltic sea. The median plasma levels of hexachlorobenzene in the 43 Swedish and 67 Latvian adult males in this study group was 84 ng/g lipid. Recently, the serum concentrations of pregnant women from the Disko Bay area, Greenland were studied by Bjerregaard and Hansen (2000). The women in this study consume a high level of meat and blubber from marine animals. The concentration of hexachlorobenzene in plasma taken from these women between the years 1994 and 1996 was 1.2 ng/mL wet weight (range, 0.1–7.0 ng/mL wet weight). Hexachlorobenzene concentrations in serum in study groups of active smoking mothers, passive smoking mothers, and nonsmoking mothers from Germany were 0.87 ng/mL (range, 0.23–4.38 ng/mL), 0.55 ng/mL (range, <0.10–3.27 ng/mL), and 0.46 ng/mL (range, <0.10–2.73 ng/mL) (Lackman et al. 2000). The mean concentration of hexachlorobenzene in whole blood from infant children ranged from 0.13 to 0.23 ng/mL (Karmaus et al. 2001). The highest concentration was observed in children who were breastfed for over 12 weeks after birth.

Nonoccupational exposure to hexachlorobenzene for residents of two U.S. cities (Jacksonville, Florida and Springfield, Massachusetts) were studied over three seasons; summer 1986, spring 1987, and winter 1988 (Whitmore et al. 1994). The study focused primarily on inhalation exposures with primary environmental monitoring consisting of 24-hour indoor, personal, and outdoor air. For the Jacksonville, Florida population, the estimated mean hexachlorobenzene concentration ranged from 0.3 to 1.3 ng/m<sup>3</sup> for indoor air, from not detected to 0.2 ng/m<sup>3</sup> for outdoor air, and from 0.4 to 0.9 ng/m<sup>3</sup> for personal air. For the Springfield, Massachusetts population, mean exposures were much less. The estimated hexachlorobenzene concentrations ranged from not detected to 0.1 ng/m<sup>3</sup> for indoor air, were not detected in outdoor air, and ranged from not detected to <0.05 ng/m<sup>3</sup> for personal air. The mean air exposure estimated for hexachlorobenzene in Jacksonville, Florida, was 10 ng/day, while dietary exposure ranged from 70 to 120 ng/day. The mean air exposure for Springfield, Massachusetts, was not detected in the personal air samplers, while the dietary exposure was 105 ng/day. In both the Jacksonville, Florida population, characterized as a high pesticide use area, and in the Springfield, Massachusetts population, characterized as a low pesticide use area, the dietary exposure to hexachlorobenzene was the predominant exposure pathway.

In the most recent National Human Adipose Tissue Survey, hexachlorobenzene was found in 35 of 46 human adipose tissue samples from all regions of the United States at levels ranging from 12 to 1,300 ppb (EPA 1986f). In other studies of the general population, hexachlorobenzene has been found in

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human fat samples from residents of the Texas Gulf Coast at concentrations ranging from 18 to 35 ppb (Ansari et al. 1986). Kutz et al. (1991) summarized data on hexachlorobenzene residues in human adipose tissue collected in the United States from 1973 through 1983. The geometric mean concentrations increased slightly from 0.02 ppm (20 ppb) in 1973 to 0.05 ppm (50 ppb) in 1976, and then declined to 0.031 ppm (31 ppb) in 1983.

Human breast adipose tissue samples from 36 females of 50–80 years in age were collected from the Yale-New Haven hospital in Connecticut. A correlation was made between breast adipose tissue and serum residues using Pearson's correlation coefficient. On a lipid adjusted basis, all 36 human adipose tissue samples were found to contain residues of hexachlorobenzene. The range of concentration was 2.5–33.3 ng/g with a median of 17.7 ng/g (Archibeque-Engle et al. 1997). A study conducted in British Columbia, Canada, Mes (1992) reported median and maximum hexachlorobenzene residues in biopsied fatty tissue of 18.8 and 87 ng/g (ppb), respectively. In a more recent study, small amounts of breast tissue were collected from 60 women undergoing breast surgery at Stanford University, California. The mean hexachlorobenzene concentration was 46 ng/g fat with a minimum and maximum of 14 and 170 ng/g fat, respectively (Petreas et al. 1998). Weistrand and Noren (1998) collected adipose tissue and liver samples from five Swedish men and two Swedish women. Hexachlorobenzene concentrations ranged from 12 to 129 ng/g lipids with a mean of 56 ng/g lipids in adipose tissue and 17 to 156 ng/g lipids with a mean of 58 ng/g lipids in the liver. Hexachlorobenzene levels in human adipose tissue from 64 mothers living in Veracruz, Mexico averaged 0.065 mg/kg (range, 0.010–0.401 mg/kg) on a lipid adjusted basis (Waliszewski et al. 2000a). The mean concentrations of hexachlorobenzene in autopsy tissue samples from Greenlanders were 594 µg/kg lipid (range, 476–742 µg/kg lipid), 588 µg/kg lipid (range, 156–1,890 µg/kg lipid), 260 µg/kg lipid (range, 175–387 µg/kg lipid), and 754 µg/kg lipid (range, 603–943 µg/kg lipid) for subcutaneous fat, omental fat, brain, and liver tissues, respectively (Dewailly et al. 1999).

In the National Health and Nutrition Examination Survey (NHANES II) conducted by the EPA, hexachlorobenzene levels in blood from the general population collected from 1976 to 1980 revealed a median concentration of 1.7 ppb, which did not vary among the three age groups studied (Murphy and Harvey 1993). Hexachlorobenzene levels in normal human blood serum samples were reported to be 2.2 ppb and were higher (4.6 ppb) in uremic serum samples (Rutten et al. 1988). In a recent study conducted in British Columbia, Canada, Mes (1992), reported median and maximum whole blood levels of 0.11 and 0.34 ng/g (ppb) in individuals from the general population.

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Although all uses of hexachlorobenzene as a pesticide in the United States were voluntarily canceled in 1984, occupational exposures may still occur among workers in the chlorinated solvent manufacturing industry, and workers currently involved in the manufacture and application of pesticides contaminated with hexachlorobenzene. Military or firefighting personnel who use pyrotechnic mixtures that release hexachlorobenzene and workers involved in the disposal of hexachlorobenzene contaminated materials, via combustion processes associated with municipal incinerators or those involved in the handling and treatment of wastes at hazardous waste sites, may be exposed to higher than background concentrations.

No information was located on concentrations of hexachlorobenzene in occupationally exposed populations in the United States. However, in a 10-year study (1976–1985), human adipose tissue samples and human milk from patients exposed to PCBs or pesticides in Ontario, Canada were analyzed for a variety of pesticides and industrial chemicals (Frank et al. 1988). Residues of hexachlorobenzene in adipose tissues averaged at or below 0.2 ppb in the extractable fat. Concentrations of hexachlorobenzene in milk ranged from a mean of 0.52 ppb (in whole milk) in 1983–1984 to a mean of 0.26 ppb (in whole milk) in 1985. The highest mean concentration (1.33 ppb) was observed in central Ontario residents. Urban residents had a higher mean concentration (0.57 ppb) as compared to rural residents with a mean of 0.27 ppb.

Plasma hexachlorobenzene concentrations in a Louisiana population living in a hexachlorobenzene-contaminated area averaged  $3.6 \pm 4.3$  ppb. The highest plasma level (345 ppb) was detected in a waste disposal facility worker, while the highest plasma level in the general population was 23 ppb (Burns and Miller 1975). Workers at a carbon tetrachloride and perchloroethylene production facility had plasma hexachlorobenzene levels of up to 223 ppb. Hexachlorobenzene blood levels were determined over a 4-year period in men employed in the manufacture of chlorinated solvents (Currier et al. 1980). Blood levels ranged from 5 to 1,121 ppb (310.7 ppb mean) in 1974, 30–990 ppb (311.5 mean) in 1975, 3–600 ppb (159.9 mean) in 1976, and 22–467 ppb (170.3 mean) in 1977. The hexachlorobenzene blood levels were strongly associated with the number of years worked in the chlorinated solvents plant, but they were poorly correlated with airborne hexachlorobenzene concentrations ranging from <1 to 13 ppb or wipe samples from work areas ranging from 0.03 to 124  $\mu\text{g}/100 \text{ m}^2$ .

Vegetable sprayers applying hexachlorobenzene-contaminated dimethyltetrachloroterephthalate (DCPA) had plasma levels of hexachlorobenzene ranging from 0 to 310 ppb (mean  $40 \pm 63$  ppb), accompanied by elevated levels of delta-aminolevulinic acid, but no health related adverse effects (Burns et al. 1974).

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Elevated urinary uroporphyrin and coproporphyrin were found in 1 of 54 men occupationally exposed to hexachlorobenzene (Morley et al. 1973).

Workers at a new hazardous waste incinerator in Constanti, Spain had mean plasma levels of hexachlorobenzene at 152 µg/kg lipid (range, 19.4–854.0 µg/kg lipid) (Domingo et al. 2001). Residents (n=608) living near an electrochemical factory in Catalonia, Spain had mean serum concentrations of hexachlorobenzene as follows (units ng/mL): general population, male (50.2), female (48.0), all (48.9); nonfactory workers, male (39.8), female (47.9), all (46.3); and living with a worker of the factory, yes (46.8), no (46.8) (Ballester et al. 2000).

Individuals employed in industries that manufacture or process hexachlorobenzene or products containing hexachlorobenzene may be exposed to the highest concentrations. The National Occupational Exposure Survey (NOES), conducted by NIOSH from 1981 to 1983, estimated that 1,038 workers employed at 10 facilities were potentially exposed to hexachlorobenzene in the United States (NOES 1990). The NOES database does not contain information on the frequency, concentration, or duration of exposure; the survey provides only estimates of workers potentially exposed to chemicals in the workplace.

## 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 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).

Children are particularly susceptible to hexachlorobenzene by ingestion of breast milk. Table 6-5 summarizes the concentrations of hexachlorobenzene in human breast milk taken from women living in different regions of the world. Hexachlorobenzene was detected in human milk samples collected from

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54 residents of Hawaii during 1979–1980 (Takei et al. 1983). The incidence of detection of hexachlorobenzene in the sampled population was 100% and the mean concentration of positive detections was  $46 \pm 49$  ppb (ng/g lipid basis) with residues ranging from 18 to 38 ppb (ng/g lipid basis). The authors state that the levels of hexachlorobenzene in human milk from residents of Hawaii are consistent with levels detected in an earlier human milk study conducted on women on the mainland United States. Schechter et al. (1998) found that hexachlorobenzene residues in the breast milk of a mother with nursing twins decreased from 10.7 ng/g lipid to not detectable in 30 months. Thus, nursing infants are particularly susceptible to hexachlorobenzene poisoning due to the mother's decrease in body burden and the infant's intake (Schechter et al. 1998). A recent study of organochlorine pesticide concentrations in human milk sampled throughout Canada during 1992 found that hexachlorobenzene was present in all 497 milk samples at a mean concentrations of 0.44 ng/g (ppb) in whole milk and 14.5 ng/g (ppb) in milk fat (Newsome et al. 1995). A comparison by Canada Health of human milk contamination in whole milk from 1967 to 1992 was conducted in Canada, Quebec and Ontario. This study showed a decrease in hexachlorobenzene concentration in Canada (mean concentration; 2–0.44 ng/g), Quebec (median concentration; 2–0.40 ng/g), and Ontario (median concentration; 2–0.48 ng/g) (Craan and Haines 1998). Newsome et al. (1995) reported that concentrations of hexachlorobenzene were higher in women from

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**Table 6-5. Mean Levels of Hexachlorobenzene in Breast Milk**

Location of study	N/n	Concentration <sup>a</sup>	Reference
New Zealand			Bates et al. (1994)
Auckland, urban	11/n/a	0.020	
Northland, rural	10/n/a	0.021	
Christchurch, urban	9/n/a	0.030	
Canterbury, rural	8/n/a	0.063	
Porto Alegre, Brazil	30/19	0.02	Beretta and Dick (1994)
France (multiple locations)	20/19	0.147	Bordet et al. (1993)
Madrid, Spain	63/52	1.0	Conde et al. (1993)
Industrialized area		1.74	
Canada (1967–1992)	no data	0.002–0.00044 <sup>b</sup>	Craan and Haines (1998)
Quebec		0.002–0.00040 <sup>b</sup>	
Ontario		0.002–0.00048 <sup>b</sup>	
Arctic Quebec			Dewailly et al. (1993)
Inuit women	107/107	0.136	
Caucasian women	50/48	0.028	
Italy	27/no data		Larsen et al. (1994)
Rome		0.25	
Pavia		0.12	
Milan		0.20	
Florence		0.14	
Arkansas, USA	942/57	0.03	Mattison et al. (1992)
Canada	412/no data	0.026	Mes et al. (1993)
Victoria, Australia (1985/1986)	158/153	0.005 <sup>b</sup>	Monheit and Luke (1990)
Canada (multiple locations, in 1992)	497/497	0.0044 <sup>b</sup> 0.015 <sup>c</sup>	Newsome et al (1995)
Sweden (1972–80)	227–1,500/ no data	0.110–220	Norén and Meironyté (2000)
Akumadan, Ghana	20/19	0.04	Ntow (2001)
Bratislava, Slovak Republic	26/26	0.339	Prachar et al (1993)
Victoria, Australia	60/59	0.41	Quinsey et al (1995)
Czech Republic			Schoula et al (1996)
Prague	17	0.639	
Kladno	12	0.570	
Uherske Hradiste	7	0.482	
Northern Thailand	25/9	0.0051 <sup>b</sup>	Stuetz et al (2001)
Hawaii, USA (1979–1980)	54/54	0.046±0.049	Takei et al. (1983)
Veracruz, Mexico	43/43	0.047	Waliszewski et al (1996)

Source: Pohl and Tylenda (2000)

<sup>a</sup>µg/g on lipid basis<sup>b</sup>whole milk sample<sup>c</sup>milk fat sample

N = number of samples; n = number of samples with measurable levels

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the Great Lakes Basin area as compared to the rest of Canada. Concentrations of hexachlorobenzene were higher in the breast milk of women who consumed more than 100 g of fish weekly.

Children may also be exposed to chemicals via ingestion of contaminated foods. Hexachlorobenzene residues have been detected in 76% of samples analyzed as part of the National Human Adipose Tissue Survey (FY82) (EPA 1986f). These hexachlorobenzene residues are most likely the result of consumption of low levels of hexachlorobenzene in food, with calculated yearly intakes of 68, 22, and 5  $\mu\text{g}$  for adults, toddlers, and infants, respectively (EPA 1986e). More recently, Yess et al. (1993) evaluated hexachlorobenzene residues from 1985 to 1991 detected in the Total Diet Studies of infant and adult foods that are consumed by infants and young children. These authors reported maximum hexachlorobenzene residues detected in various food groups as follows: combination meat dinners—pork (0.4 ppb), beef (0.3 ppb), chicken/turkey (0.3 ppb), chicken/turkey/vegetable (0.3 ppb), beef and vegetable (0.1 ppb); vegetables and fruits—pears (1.0 ppb), apples (0.4 ppb), and carrots (0.2 ppb); milk products—canned evaporated milk (0.5 ppb), whole milk (0.2 ppb), and low-fat (2%) milk (0.1 ppb); and peanut butter (5.0 ppb).

Hexachlorobenzene intakes, in  $\mu\text{g}/\text{kg}$  body weight/day, estimated for these total diet analyses (1982–1984) were 0.0015 for 6–11-month-old infants. A follow-up study found a decrease in intakes that were estimated in 1982–1984. Hexachlorobenzene intakes ( $\mu\text{g}/\text{kg}$  body weight/day) were estimated to be 0.0016 in 1988 (FDA 1989); 0.0007 in 1989 (FDA 1990); 0.0004 in 1990 (FDA 1991); and 0.0003 in 1991 (FDA 1992) for 6–11-month-old infants.

Although inhalation exposures of hexachlorobenzene in children have not been studied, it is anticipated that exposure by this route will not be significant in outdoor environments. The Henry's law constant of hexachlorobenzene is  $5.8 \times 10^{-4}$  atm-m<sup>3</sup>/mol (Ten Hulscher et al. 1992), indicating that this compound will volatilize rapidly, especially in moist soils with low organic content. Hexachlorobenzene's high log  $K_{oc}$  of 6.08 (EPA 1981a), however, indicates that volatilization from soil surfaces will be greatly attenuated. Considering that hexachlorobenzene concentrations in the environment are extremely low, exposure of children by inhalation is expected to be insignificant. After a hexachlorobenzene spill, inhalation exposure may be important before environmental equilibrium is attained. Under these conditions, high concentrations of hexachlorobenzene would be found in the atmosphere, due to hexachlorobenzene's calculated vapor density of 10. This situation, however, is not expected to occur since hexachlorobenzene is no longer produced or used commercially and is only found as an impurity in pesticides and as a by-product of chlorinated hydrocarbons.

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The EPA issued a warning regarding pesticides and advised that potential exposure of pesticides to young children via dermal absorption and ingestion was more important than inhalation routes (Jantunen et al. 1997).

**6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES**

In addition to those individuals occupationally exposed to hexachlorobenzene identified in Section 6.5, several groups within the general population may receive potentially higher exposures to hexachlorobenzene. These groups within the general population include individuals living near facilities where hexachlorobenzene is produced as a byproduct, individuals living near the 101 current or former NPL hazardous waste sites where this compound is present, recreational and subsistence fishermen who consume higher amounts of fish than the general population, and native populations (including Native American populations such as the Inuits of Alaska) who may be exposed to higher levels of hexachlorobenzene associated with dietary intakes of caribou and other game species.

Consumption of contaminated groundwater by individuals living in the vicinity of production facilities or hazardous waste sites may be an important source of exposure for both adults and children. Hexachlorobenzene has been detected in 42 groundwater samples from 107 NPL hazardous waste sites (HazDat 2002). Skin contact with or ingestion of hexachlorobenzene contaminated soil on their hands may be an additional source of exposure for children living near hazardous waste facilities. Hexachlorobenzene has been detected in 76 soil samples from 107 NPL hazardous waste sites (HazDat 2002).

Recreational and subsistence fishermen who consume appreciably higher amounts of locally caught fish from contaminated water bodies may be exposed to higher levels of hexachlorobenzene associated with dietary intake than members of the general population (EPA 1995b). Hexachlorobenzene contamination in fish and shellfish has triggered the issuance of several human health advisories. As of September 1994, hexachlorobenzene was identified as the causative pollutant in fish consumption advisories in Louisiana and Ohio. This information is summarized in Table 6-6. EPA has identified hexachlorobenzene as a target analyte and recommended that this chemical be monitored in fish and shellfish tissue samples collected as part of state toxics monitoring programs. EPA recommends that

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**Table 6-6. Fish Consumption Advisories<sup>a</sup>**

State	Waterbody	Extent	Species
Louisiana	Devil's Swamp Lake and Bayou Baton Rouge	7 miles	All fish
	Calcasieu and Cameron parishes	6 miles	All fish and shellfish
Ohio	Tuscarawas River	Turkey Foot Rd. (SR 619), Barberton, to South Broadway St (SR 416), New Philadelphia (Tuscarawas County)	Carp-common, bass- smallmouth, bullhead- yellow, bass-rock, catfish-channel, bass- largemouth

<sup>a</sup>From EPA 1997b National Listing of Fish Consumption Advisories

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residue data obtained from these monitoring programs should then be used by the states to conduct risk assessments to determine the need for issuing fish and shellfish consumption advisories for the protection of the general public as well as recreational and subsistence fishermen (EPA 1997b).

Native American populations such as the Inuits of Alaska or other subsistence hunters living in high latitude areas of the United States and Canada may be exposed to hexachlorobenzene residues in caribou, beluga whales, polar bears, seals, and other game species. Significantly higher concentrations of hexachlorobenzene (mean 136 ng/g [ppb]) were reported in breast milk of Inuit mothers from eastern Canada (Quebec Province) as compared with residues of 28 ng/g (ppb) in Caucasian mothers (Dewailly et al. 1993). By analogy, it is possible that Inuit populations in western North America (Alaska) may receive potentially higher hexachlorobenzene exposures from their dietary habits. In a follow-up study by Dewailly et al. (1999) 26 subcutaneous fat samples, 41 omental fat samples, 17 brain samples, and 26 liver samples were collected in November 1992 to Mid-October 1994 from Inuit Greenlanders. Mean hexachlorobenzene concentrations were 594, 588, 260, and 754  $\mu\text{g}/\text{kg}$  lipid basis, respectively. A comparison of these data clearly suggest an increase in Inuit population's hexachlorobenzene levels from dietary habits. Maternal body burden and lactational transfer of hexachlorobenzene can increase tissue levels in the neonate (Ando et al. 1985; Frank et al. 1988).

## 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 hexachlorobenzene 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 hexachlorobenzene.

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.

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**6.8.1 Identification of Data Needs**

**Physical and Chemical Properties.** The physical and chemical properties of hexachlorobenzene are sufficiently well documented to permit estimation of the compound's environmental fate (Budavari 1996; EPA 1981a; Hansch et al. 1995; Lide 1998; Ten Hulscher et al. 1992; Verschueren 1996). No further information is needed.

**Production, Import/Export, Use, Release, and Disposal.** Hexachlorobenzene is not currently manufactured as a commercial end-product in the United States and has not been commercially produced since the late 1970s (EPA 1986e). However, hexachlorobenzene currently is produced as a by-product or impurity in the manufacture of chlorinated solvents, other chlorinated compounds, and several currently registered pesticides (Bailey 2001; EPA 1986e, 1994c; IARC 1979).

The total amount of hexachlorobenzene released as a by-product in the production of all chlorinated solvents was estimated as 0.3 kg/year in the mid 1990s (Bailey 2001), while hexachlorobenzene released through use of eight major pesticides containing hexachlorobenzene accounted for 1,270 kg/year (Bailey 2001). Current production estimates for hexachlorobenzene as a by-product or impurity are not available. Current, quantitative estimates of production of hexachlorobenzene from all sources are needed to evaluate potential exposures and risks to human health.

There are no current commercial uses of hexachlorobenzene in the United States, although the compound was used as a fungicide until 1984 when the last registered use as a pesticide was voluntarily cancelled (Beyer 1996). Prior to the registration cancellations, hexachlorobenzene was registered as a seed protecting for use on several grains (principally wheat) and field crops (EPA 1986e). Hexachlorobenzene was also used in pyrotechnic and ordinance materials and in synthetic rubber production (EPA 1986e). Impurities of hexachlorobenzene in currently registered pesticides (picloram, PNCB, chlorothalonil, Dacthal<sup>®</sup>, atrazine, simazine, lindane, and PCP) (Bailey 2001; EPA 1986e, 1993a; Farm Chemicals Handbook 1993) appear to be a continuing source of hexachlorobenzene exposure for the general population. Five of the pesticides containing impurities of hexachlorobenzene (PCNB, chlorothalonil, Dacthal<sup>®</sup>, lindane, and PCP) are used in home gardens, lawn care, and other applications around residences and in urban areas (Farm Chemicals Handbook 1993). Currently, data regarding the release of hexachlorobenzene into the environment as an impurity via the use of other pesticides is not available.

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No current information was located on import/export volumes for hexachlorobenzene, although import/export volumes for hexachlorobenzene/DDT combined are available (NTDB 1995).

Hexachlorobenzene is listed as a hazardous waste. It is regulated under the Clean Water Effluent Guidelines as stated in Title 40, Section 400–475, of the Code of Federal Regulations and the Resource Conservation and Recovery Act (RCRA) (see Chapter 8). Past disposal methods have included incineration, landfills, discharges to municipal sewage treatment plants, and emissions to the atmosphere. The recommended method of disposal for hexachlorobenzene is incineration (Clayton and Clayton 1981; EPA 1988a, 1989a; IRPTC 1985; Lamb et al. 1994). No further information on disposal practices is needed; however, estimates on the volume of hexachlorobenzene disposed of annually and the disposal method used are needed to assess exposure pathways.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The TRI, which contains this information for 1999, became available in 2001. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

**Environmental Fate.** Hexachlorobenzene released to the environment partitions to several environmental compartments (air, water, soil and sediment, and biological organisms). Hexachlorobenzene partitions to the atmosphere from soil surfaces through volatilization (Nash and Gish 1989). The remainder is adsorbed strongly to soil where it persists for extended periods (half-life of months to years) due to its resistance to biodegradation (Beall 1976; Beck and Hansen 1974; Isensee et al. 1976). Leaching of hexachlorobenzene into groundwater is not expected to occur very rapidly under most circumstances due to the compound's high sorption characteristics (Swann et al. 1983). Yuan et al. (1999) have recently reported that hexachlorobenzene can be dechlorinated to dichlorobenzenes under anaerobic conditions in the laboratory using sewage sludge as inoculum.

Once in the atmosphere, hexachlorobenzene exists in both the vapor and particulate phase; however, the vapor phase predominates (Ballschmiter and Wittlinger 1991; Bidleman et al. 1989; Lane et al. 1992). Degradation of hexachlorobenzene in the atmosphere is quite slow (1.69 years) (Brubaker and Hites 1998). Since hexachlorobenzene is hydrophobic, wet deposition will not be an important loss process. In cold high latitude zones, dry deposition of hexachlorobenzene aerosols is encouraged (Ballschmiter and Wittlinger 1991; Lane et al. 1992; Wania and Mackay 1993). Atmospheric transport of hexachlorobenzene is a major mechanism for global translocation of this compound (Eisenreich et al. 1981; Kelly et

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al. 1991). Long-range global transport of hexachlorobenzene released anywhere in the world can occur via atmospheric or oceanic systems (Ballschmiter and Wittlinger 1991; Wania and MacKay 1993).

Hexachlorobenzene released to water will volatilize, adsorb to sediments, or bioaccumulate in fish and other aquatic organisms (Bishop et al. 1995; EPA 1992b; Kelly et al. 1991; Langlois and Langis 1995; Oliver and Nichol 1982a; Quemerais et al. 1994; Rostad et al. 1993; Schmitt et al. 1990; Zabik et al. 1995). Hydrolysis and biodegradation are not significant processes in water. Information on biodegradation of hexachlorobenzene under anaerobic conditions in a laboratory study exists (Yuan et al. 1999), but degradation under field conditions were not found. Further information on these processes, including degradation products, are needed to determine potential mechanisms and sources of hexachlorobenzene releases from soils and the potential for the compound and its degradation products to contaminate groundwater.

Both bioaccumulation and biomagnification of hexachlorobenzene were reported to occur in an aquatic laboratory microcosm system (Burkhard et al. 1997; Isensee et al. 1976); however, data by Russell et al. (1995) suggests that hexachlorobenzene bioaccumulates, but is not biomagnified in certain fish populations in Lake Erie. In terrestrial ecosystems, hexachlorobenzene can also be accumulated in several agricultural plant species in the roots and parts of the plants closest to the soil (Kraaij and Connell 1997; Scheunert et al. 1983; Schroll et al. 1994; Smelt and Leistra 1974). In lichens, a high latitude forage food for caribou, hexachlorobenzene was found to be bioconcentrated 8,800,000–17,000,000 times the concentration in the atmosphere (Muir et al. 1993). Although the issue of biomagnification in some ecosystems needs to be clarified, there are adequate data on the bioconcentration of hexachlorobenzene in both aquatic and terrestrial ecosystems.

**Bioavailability from Environmental Media.** Hexachlorobenzene can be absorbed following inhalation of contaminated workplace air (Burns et al. 1974; Currier et al. 1980; Richter et al. 1994). Since hexachlorobenzene is only moderately volatile, inhalation may not be a major concern except at hazardous waste sites or in industrial settings. Hexachlorobenzene can be absorbed following ingestion of contaminated food or water. Exposure to hexachlorobenzene through ingestion of food contaminated with low levels of the compound is probably the greatest source of exposure for the general population. Exposure to hexachlorobenzene through ingestion of contaminated drinking water is not expected to be an important source of concern since the compound is not very soluble in water. Although there are no quantitative data on the human absorption of orally administered hexachlorobenzene, gastrointestinal absorption has been demonstrated for rats (Albro and Thomas 1974; Ingebrigtsen and Nafstad 1983;

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Ingebrigtsen et al. 1981). The lymphatic system has also been shown to play an important part in the absorption of hexachlorobenzene in the intestines. Hexachlorobenzene is absorbed by the lymphatic system in the region of the duodenum and jejunum-ileum and is deposited in the adipose tissue, bypassing the portal circulation (Iatropoulos et al. 1975). Since hexachlorobenzene is tightly bound to soil particles, ingestion of hexachlorobenzene-contaminated soil, particularly by children, may also be an important route of exposure near production and processing facilities or near hazardous waste disposal sites. No information was available regarding absorption of hexachlorobenzene following dermal contact. Information regarding the bioavailability of hexachlorobenzene from both ingestion of soil-bound hexachlorobenzene particularly in children and from dermal contact with contaminated soils are needed, particularly in assessing health risks to populations living near hazardous waste sites.

**Food Chain Bioaccumulation.** Like many of the other organochlorine pesticides, hexachlorobenzene is lipophilic and has a high bioaccumulation potential. Hexachlorobenzene is bioaccumulated in fish and other aquatic organisms (Bishop et al. 1995; EPA 1992b; Langlois and Langis 1995; Murray et al. 1980, 1981; Oliver and Nichol 1982a; Schmitt et al. 1990; Zabik et al. 1995) as well as waterfowl (Cobb et al. 1994; Foley 1992; Gebauer and Weseloh 1993; Somers et al. 1993; Swift et al. 1993; Yamashita et al. 1992). Hexachlorobenzene is bioaccumulated in aquatic food chains with virtually no degradation of the compound by the exposed organisms (Isensee et al. 1976). The results of a laboratory aquatic ecosystem study suggest that bioaccumulation as well as biomagnification of hexachlorobenzene occurs (Isensee et al. 1976); however, authors of a more recent study conducted in natural fish populations suggest that hexachlorobenzene is not biomagnified (Russell et al. 1995). In terrestrial ecosystems, several agricultural crops have been found to accumulate hexachlorobenzene in their roots and in portions growing closest to soil level (Ecker and Horak 1994; Scheunert et al. 1983; Schroll et al. 1994; Smelt and Leistra 1974). The edible root portion of carrots accumulated the highest hexachlorobenzene concentration with a BCF of 19 (Smelt and Leistra 1974). Lichens, a primary forage for caribou, were also shown to bioaccumulate hexachlorobenzene (Muir et al. 1993). A field study on a terrestrial ecosystem suggested that hexachlorobenzene was biomagnified through various trophic levels of the food web (Hebert et al. 1994). Further studies are needed to resolve whether hexachlorobenzene is biomagnified in both aquatic and terrestrial ecosystems.

**Exposure Levels in Environmental Media.** Environmental monitoring data are available for hexachlorobenzene in air (Currier et al. 1980; Davis and Morgan 1986; Eisenreich et al. 1981; EPA 1975b, 1985g; Hoff et al. 1996; Lee et al. 2000; Mann et al. 1974; Poissant et al. 1997; Tiernan et al. 1985), water (Chan et al. 1994; Davis and Morgan 1986; EPA 1976a; Hoff et al. 1996; Laska et al. 1976;

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Oliver and Nichol 1982a; Quemerais et al. 1994), soil (Elder et al. 1981; EPA 1985g; Laseter et al. 1976; Laska et al. 1976), and sediment (Davis and Morgan 1986; Elder et al. 1981; Murray et al. 1981; Oliver and Nichol 1982a; Ray et al. 1983; Rostad et al. 1999). Groundwater monitoring data are lacking; however, hexachlorobenzene has been detected in 42 groundwater samples from 107 NPL hazardous waste sites. Current information on hexachlorobenzene concentrations in groundwater is needed.

Human intake estimates for exposure from environmental media are available (Whitmore et al. 1994), but are limited. In general, while monitoring data are available for most environmental media, much of the information on environmental levels was collected during the 1970s through the mid 1980s. More recent monitoring data from all environmental media would provide more accurate information for estimating human and animal intakes.

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

**Exposure Levels in Humans.** Hexachlorobenzene has been detected in human adipose tissue (Ansari et al. 1986; EPA 1986f; Frank et al. 1988; Kutz et al. 1991; Mes 1992;), blood (Burns and Miller 1975; Burns et al. 1974; Currier et al. 1980; Murphy and Harvey 1993; Rutten et al. 1988), and milk (Craan and Haines 1998; Frank et al. 1988; Newsome et al. 1995; Schechter et al. 1998; Takei et al. 1983). Studies exist that relate occupational exposure to blood levels of hexachlorobenzene (Burns et al. 1974; Currier et al. 1980). Studies to compare the steady-state intake of hexachlorobenzene as measured by urinary and fecal excretion as it relates to blood levels in occupationally exposed workers would be particularly useful. Since hexachlorobenzene has been detected in both urine and feces, a study of this nature could be conducted. These studies might also address possible individual differences in the metabolism of this compound. This information is necessary for assessing the need to conduct health studies on these populations.

**Exposures of Children.** Exposure pathways for children have been well documented in breast milk (Newsome et al. 1995; Schechter et al. 1998) and diet (FDA 1992; Yess et al. 1993). Data documenting body burdens for children are needed. Data addressing exposure to children who live, play, or attend school near NPL sites, industrial sites, such as chlorinated hydrocarbon production factories, or on farmlands where hexachlorobenzene is being released as an impurity of another pesticide would allow for a better assessment of hexachlorobenzene exposure. As hexachlorobenzene is released due to the use of

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other pesticides on foods, an evaluation of possible hexachlorobenzene residues in children's food substances would further enhance the ability to construct a complete picture of exposure. Studies revealing contamination of drinking water or groundwater would also prove essential in this assessment. Attention should also focus on the use of tap water as a contaminant source when used to prepare infant formulas from condensed or powdered forms. As children are often bound to pick up soil off the ground and maybe even put this soil in their mouths, studies regarding exposure to children through soil would be helpful. Information concerning childhood-specific means to decrease exposure would be useful.

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

**Exposure Registries.** No exposure registries for hexachlorobenzene were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for subregistries 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. Currently, Inuit communities appear to have potentially higher exposures to hexachlorobenzene and should be further monitored (Dewailly et al. 1993, 1999).

### 6.8.2 Ongoing Studies

As part of the Third National Health and Nutrition Evaluation Survey, the Environmental Health Laboratory Sciences Division of the National Center for Environmental Health and Injury Control, Centers for Disease Control and Prevention, will be analyzing human blood samples for hexachlorobenzene and other volatile organic compounds. These data will give a more current indication of the frequency of occurrence and background levels of these compounds in the general population.

According to FEDRIP (2001), there is one ongoing study on hexachlorobenzene being conducted at the Virginia Polytechnic Institute. This study involves an effort to reveal the aryl dehalogenation mechanism and to evaluate the ability of carbon monoxide reduced carbon monoxide dehydrogenase to reductively dehalogenate hexachlorobenzene.



## 7. ANALYTICAL METHODS

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

Methods for the determination of organochlorine compounds such as hexachlorobenzene generally consist of the following steps: extraction of the analyte from the sample matrix; clean-up to remove interfering compounds; and analysis (separation and quantitation). The primary method of analysis is gas chromatography (GC) coupled with electron capture detection (ECD) or mass spectrometry (MS). Analytical methods have been developed for the determination of hexachlorobenzene in blood or serum, urine, feces, adipose tissue, and breast milk. A summary of methods is shown in Table 7-1.

Several cautions should be noted. Interferences may result from organics of biological origin that are extracted from the sample, and from contaminated glassware, solvent, etc. Sample interferences are usually removed using fractionation and clean-up procedures. Rigorous sample collection and preparation methods must be followed to prevent contamination of the sample. Good quality control procedures must be used to identify and remove interferences caused by sample contamination.

Blood (or serum) is a body fluid often utilized to assess human exposure to chlorinated organics, including hexachlorobenzene. Blood is usually extracted with solvent (Bristol et al. 1982; Burse et al. 1990; EPA 1980c; Langhorst and Nestruck 1979; Mes et al. 1982), and the extract is cleaned up (and sometimes fractionated) by column chromatography utilizing silica gel (Langhorst and Nestruck 1979),

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Adipose tissue	Extraction, GPC clean-up, Florisil fractionation, optional additional clean-up	cap. GC/MS	12 ng/g	No data	EPA 1986f
Adipose tissue	Maceration with sodium sulfate, extraction and back extraction, Florisil fractionation	GC/ECD	No data	No data	EPA 1980c
Adipose tissue	Soxhlet extraction, clean-up on Florisil	cap. GC/ECD; confirmation on second column	0.001 µg/g	82	Alawi et al. 1992
Adipose tissue	Solvent extraction, filtration, Florisil fractionation	cap. GC/ECD; confirmation by GC/MS	0.12 ng/g	86	Mes et al. 1982
Adipose tissue	SFE with alumina (to remove lipids, purification by column chromatography)	cap. GC/ECD	10 µg/kg (fatty tissue)	115	Djordjevic et al. 1994
Breast milk	Separation of fat; column clean-up	cap GC/ECD	0.4 ng/g fat	No data	Abraham et al. 1994
Breast milk	Acid treatment, elute from silica gel, concentrate	GC/ECD	0.009 mg/kg	91	Stachel et al. 1989
Blood	Solvent (hexane) extraction, concentration	GC/ECD	No data	No data	EPA 1980c
Blood	Solvent extraction, clean up on silica gel, concentration	GC/PID	16 ng/g	79	Langhorst and Nestrick 1979
Blood	Homogenization with benzene, filtration, Florisil fractionation	cap. GC/ECD; confirmation by GC/MS	0.2 ng/g	80	Mes et al. 1982

**Table 7-1. Analytical Methods for Determining Hexachlorobenzene in Biological Samples (continued)**

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood	Hexane extraction, concentration	GC/ECD; confirmation by GC/MS	0.16 ng/g	72	Bristol et al. 1982
Serum	Solvent extraction of denatured serum, fractionation on micro-Florisil column, acid treatment/silica gel clean-up	GC/ECD	1 ppb	58–76	Burse et al. 1990
Urine	Solvent extraction, clean-up on silica gel, concentration	GC/PID	4.1 ng/g	84	Langhorst and Nestrick 1979
Semen	Solvent extraction, clean-up on Florisil, concentration	cap. GC/ECD; confirmation by NICI	0.3 ng/mL	80	Stachel et al. 1989
Feces	Boiling with solvent, clean-up on alumina	cap. GC/ECD	No data	No data	Abraham et al. 1994

cap. = capillary; ECD = electron capture detector; GC = gas chromatography; GPC = gel permeation chromatography; MS = mass spectrometry; NICI = negative ionization chemical ionization; PID = photoionization detector; SFE = supercritical fluid extraction

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Florisil (Mes et al. 1982), or a combination of columns (Burse et al. 1990). Analysis is usually by GC/ECD (Bristol et al. 1982; Burse et al. 1990; EPA 1980c; Mes et al. 1982), although GC coupled with photoionization detection (PID) may be used as well (Langhorst and Nestruck 1979). Confirmation by GC/MS is recommended (Bristol et al. 1982; Mes et al. 1982). Recovery for all methods is acceptable (. 70–80%) (Bristol et al. 1982; Burse et al. 1990; Langhorst and Nestruck 1979; Mes et al. 1982); precision is also acceptable (#20% relative standard deviation [RSD]) (Bristol et al. 1982; Burse et al. 1990; Langhorst and Nestruck 1979; Mes et al. 1982). Detection limits are in the low-ppb (ng/g) range (Bristol et al. 1982; Burse et al. 1990; Langhorst and Nestruck 1979; Mes et al. 1982).

Adipose tissue is usually solvent extracted (EPA 1980c; Mes et al. 1982), and the hexachlorobenzene is separated from the extracted fat by Florisil column fractionation (Mes et al. 1982). Analysis is by GC/ECD (EPA 1980c; Mes et al. 1982). Confirmation by GC/MS (Mes et al. 1982) or a second GC column is recommended. Recovery is good (82–86%) (Mes et al. 1982); precision is very good (<10% RSD) (Mes et al. 1982). Solvent extraction followed by gel permeation chromatography (GPC) clean-up and Florisil column fractionation was utilized for a large adipose tissue monitoring study (EPA 1986f). Additional clean-up measures may be required if fractions are not clean enough for capillary GC/MS analysis (EPA 1986f). Supercritical fluid extraction (SFE) and treatment with alumina for lipid removal have been combined; additional purification was carried out by column chromatography (Djordjevic et al. 1994). Recovery was 115%, precision 10.5% RSD. Detection limits for all methods are in the low-ppb (ng/g) range (Alawi and Ababneh 1991; Djordjevic et al. 1994; EPA 1986f; Mes et al. 1982).

Few methods are available for monitoring other tissues and fluids. Breast milk has been analyzed with a combination of fat separation, column clean-up, and capillary GC/ECD (Abraham et al. 1994). Detection limits were 0.4 ng/g fat; other performance data were not reported. Methods for urine (Langhorst and Nestruck 1979) and semen (Stachel et al. 1989) have been reported. Both provide good recovery (80–84%). A method for feces has been reported, and involves boiling with solvent and clean-up on alumina followed by capillary GC/ECD analysis (Abraham et al. 1994). Performance data were not reported.

It is well known that ingestion of hexachlorobenzene can produce porphyria (see Section 3.2.2.2). Urinary porphyrins from humans with porphyria cutanea tarda (PCT) can be analyzed using thin layer chromatography (TLC). Separation and estimation of porphyrins are carried out on a TLC plate by extraction and esterification of porphyrins, 2-dimensional development, and fluorescent scanning (Miura and Torinuki 1977). Other analysis methods for porphyrins include spectrophotometry. Analysis by this

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method is carried out by extraction of porphyrins using an anion exchange column, esterification of porphyrins, separation by chromatography, and quantification spectrophotometrically (Grinstein 1977).

## 7.2 ENVIRONMENTAL SAMPLES

Most environmental analyses have been performed using multiresidue methods involving solvent extract of the analytes from the sample matrix, clean-up to remove interfering compounds, determination by GC with ECD, and confirmation using an ancillary method such as MS. New methods and technologies are evolving, and this has resulted in lower detection limits. For example, detection limits are in the low ppb to ppt range for water matrices and the low ppm to ppb range for food. Analytical methods for the determination of hexachlorobenzene in environmental samples is given in Table 7-2.

Atmospheric hexachlorobenzene is usually sampled by pulling a volume of air through an adsorbent trap (EPA 1988d, 1988h; Hippelein et al. 1993; Langhorst and Nestruck 1979). A filter may be included in the sampling system in order to determine the amount of hexachlorobenzene in particulate (Atlas and Giam 1981; Brorström-Lundén et al. 1994; Hippelein et al. 1993). Filters and polyurethane foam (PUF) adsorbent are Soxhlet extracted (EPA 1988c, 1988h; Hippelein et al. 1993); XAD-2 adsorbent is extracted in a Soxhlet apparatus (Hippelein et al. 1993) or by solvent desorption (Langhorst and Nestruck 1979). Clean-up on adsorbent columns may be utilized (EPA 1988d; Hippelein et al. 1993). A variety of analytical methods are used: GC/ECD (Atlas and Giam 1981; EPA 1988c), capillary GC/ECD (Brorström-Lundén et al. 1994; EPA 1988h), GC/PID (Langhorst and Nestruck 1979), and capillary GC/MS (Hippelein et al. 1993). Confirmation on a second GC column or by GC/MS is recommended (Atlas and Giam 1981; EPA 1988h). Reported recovery is good (82–103%) (EPA 1988h; Langhorst and Nestruck 1979); precision is also good (<10%) (Hippelein et al. 1993). Detection limits depend upon the amount of air sampled, but may be in the ppb to sub-ppt range (EPA 1988h; Hippelein et al. 1993; Langhorst and Nestruck 1979).

Hexachlorobenzene is usually extracted from water with organic solvents for analysis (EPA 1988e, 1988f; Munch et al. 1990). Hexachlorobenzene may also be extracted and concentrated by adsorption on adsorbent cartridges or disks, with subsequent solvent desorption (EPA 1988a). Clean-up of the extracts is usually not necessary; however, methods are available for samples that contain interfering compounds (Chan et al. 1994; Driscoll et al. 1991; Garrison and Pellizzari 1987). Analysis is usually by capillary

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Collection on PUF; Soxhlet extraction; cleanup on alumina	(EPA Method TO-10) GC/ECD	No data	No data	EPA 1988d
Ambient air	. 2,200 m <sup>3</sup> collected on GFF and XAD-2; Soxhlet extraction; cleanup on layered silica gel; alumina partition	cap. GC/MS	0.18 pg/m <sup>3</sup> (calculated)	No data	Hippelein et al. 1993
Ambient air	Collection on XAD-2; solvent desorption	GC/PID	70 ppb	95	Langhorst and Nestrack 1979
Ambient air	Collection on PUF; Soxhlet extraction; concentration	dual column megabore GC/ECD or GC/ECD and GC/MS	5 ng/m <sup>3</sup>	82–103	EPA 1988h
Rain, snow	Modified collector; solvent extraction; solvent exchange; cleanup on silica gel	cap. GC/ECD	0.4 ng/L	No data	Chan et al. 1994
Drinking water	Solid-phase extraction (disk or cartridge)	(EPA Method 525.1) cap. GC/MS	0.1–0.2 µg/L	98–109	EPA 1988c
Drinking water	Solvent extraction; solvent exchange	(EPA Method 508) cap. GC/ECD; confirmation using second column	0.077 µg/L (estimated)	68–82	EPA 1988f

**Table 7-2. Analytical Methods for Determining Hexachlorobenzene in Environmental Samples (continued)**

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Drinking water	Solvent extraction	(EPA Method 505) GC/ECD, confirmation using second column	0.003 µg/L	91–100	EPA 1988e
Drinking water	pH adjustment; concentration on XAD-4; cleanup on silica gel	(Master Scheme) cap. GC/MS	0.1 µg/L (target)	73	Garrison and Pellizzari 1987
Groundwater	Solvent extraction; solvent exchange	(National Pesticide Survey Method 2) cap. GC/ECD, confirmation using second column	0.12 µg/L	96	Munch et al. 1990
River water	Centrifugation; chromic acid digestion; extraction	cap. GC/ECD	No data	97.5	Driscoll et al. 1991
Municipal and industrial waste	Solvent extraction; solvent exchange; optional cleanup on Florisil	(EPA Method 612) GC/ECD	0.05 µg/L	95	EPA 1984e
Municipal and industrial waste	pH adjustment; solvent extraction; concentration	(EPA Method 625) GC/MS	1.9 µg/L	79	EPA 1984f
Waste water, soil, sediments, solid wastes	Solvent extraction	(EPA Method 8410) cap. GC/FTIR	20 µg/L	Not applicable	EPA 1986c

**Table 7-2. Analytical Methods for Determining Hexachlorobenzene in Environmental Samples (continued)**

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Groundwater, soils, solid wastes	Various extraction; cleanup methods	(EPA Method 8270B) cap. GC/MS	660 µg/kg (soil, sediment); 10 µg/L (ground water)	72.6 (automated Soxhlet extraction)	EPA 1994a
Soil	Solvent extraction; liquid-liquid partition; cleanup by sulfuric acid treatment	GC/ECD	No data	98	Waliszewski and Szymczyński 1985
Soil	Soxhlet and sonication extraction; acetylation; solvent extraction; fractionation on silica gel	dual column cap. GC/ECD	No data	83–106	Ojala 1993
Sediments	Microwave extraction centrifugation; filtration	cap. GC/ECD	No data	91.7	Onuska and Terry 1993
Fish tissue	Grind with sodium sulfate; extract with hexane/acetone	GC/ECD	No data	No data	Oliver and Nicol 1982b
Fish	Homogenization; Soxhlet extraction; GPC fractionation; silica gel fractionation	cap. GC/MS	12.5 ng/g	96	Tiernan et al. 1990
Fish	Maceration; Soxhlet extraction; cleanup with sulfuric acid/silica gel	dual cap. GC/ECD	5 ng/g (lipid basis)	95	Rahman et al. 1993

**Table 7-2. Analytical Methods for Determining Hexachlorobenzene in Environmental Samples (continued)**

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Fish, aquatic biota	Homogenization with solvent; solvent exchange; cleanup on Florisil	cap. GC/ECD, confirmation on second column	0.01 mg/kg	~94	Miskiewicz and Gibbs 1994
Aquatic organisms	Homogenization; Soxhlet extraction; GPC fractionation; SPE fractionation; solvent exchange	(USGS method) cap. GC/ECD	No data	50–75	Shan et al. 1994
Butterfat, fish	Isolation on Florisil column; solvent partition; partition on Florisil	GC/ECD	No data	95–98 (fish), 99–104 (butterfat)	Bong 1975
Fatty foods	SFE/SFC (on-line cleanup)	cap. GC/ECD	4 ppb	85	Nam and King 1994
Fatty foods	Extraction and pretreatment; Florisil cleanup	(DFG Method S9) GC/ECD; confirmation by TLC	0.01 mg/kg	90	Thier and Zeumer 1987b
Milk	Solid phase extraction	GC/ECD	No data	88–94	Manes et al. 1993
Milk	Solvent extraction; solvent partition; solvent exchange; GPC cleanup; optional alumina cleanup	GC/ECD, confirmation on second column	<0.5 ppb	88–91	Trotter and Dickerson 1993

**Table 7-2. Analytical Methods for Determining Hexachlorobenzene in Environmental Samples (continued)**

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Vegetable oils, oil seeds	Sandwich-type extraction fractionation	GC/ECD	1–2 ppb	80–100	Seidel and Linder 1993
Fruits, vegetables	Chop and blend; blend with solvent; partition with water; dry	GC/ECD, confirmation by GC/MS	0.002 ppm	93	Pylypiw 1993
Crops and foods	Solvent extraction; GPC cleanup; optional silica gel cleanup	(DFG Method S19) dual GC/ECD	No data	>70	Thier and Zeumer 1987a
Pine needles	Dry and mince; homogenization; Soxhlet extraction; sulfuric acid cleanup; fractionation on Florisil	cap. GC/ECD	0.1 ng/g (dry weight)	80–100	Calamari et al. 1994

cap. = capillary; ECD = electron capture detector; FTIR = Fourier transform infrared spectrometry; GC = gas chromatography; GFF = glass fiber filter; GPC = gel permeation chromatography; MS = mass spectrometry; PID = photoionization detector; PUF = polyurethane foam; SFC = supercritical fluid chromatography; SFE = supercritical fluid extraction; SPE = solid phase extraction; TLC = thin-layer chromatography; USGS = U.S. Geological Survey

## 7. ANALYTICAL METHODS

GC/ECD (Chan et al. 1994; Driscoll et al. 1991; EPA 1988f; Munch et al. 1990). Confirmation using a second method is recommended (EPA 1988e, 1988f; Munch et al. 1990). Capillary GC/MS is also utilized for analysis (EPA 1988c; Garrison and Pellizzari 1987). Accuracy ranges from acceptable (. 60–80%) (EPA 1988a; Garrison and Pellizzari 1987) to excellent (>90%) (Driscoll et al. 1991; EPA 1988c, 1988e; Munch et al. 1990). Precision is rarely reported; 16% RSD was reported for the Master Scheme (Garrison and Pellizzari 1987). Detection limits are in the low- to sub-ppb range (EPA 1988c; Garrison and Pellizzari 1987; Munch et al. 1990). Detection limits in the ppt range have been achieved by methods utilizing solvent extraction with capillary GC/ECD analysis (Chan et al. 1994; EPA 1988e). Waste water is solvent extracted with analysis by GC/ECD (EPA 1984e) or GC/MS (EPA 1988e). Reported recovery is good (79–95%) (EPA 1984e, 1984f). Detection limits are in the low-ppb range, with lower detection limits reported for the GC/ECD analysis (EPA 1984e).

Soxhlet or sonication extraction is most commonly used to extract hexachlorobenzene from solid matrices such as soils and sediments, and wastes (EPA 1984e; Ojala 1993). Solvent extraction (Waliszewski and Szymczynski 1985) and microwave extraction techniques (Onuska and Terry 1993) may be used as well. Clean-up is usually required for the extracts (EPA 1994a; Ojala 1993; Waliszewski and Szymczynski 1985), with subsequent analysis by GC/ECD (Waliszewski and Szymczynski 1985), capillary GC/ECD (Ojala 1993; Onuska and Terry 1993), or capillary GC/MS (EPA 1994a). Reported recovery is good (73–106%) (EPA 1994a; Ojala 1993; Onuska and Terry 1993; Waliszewski and Szymczynski 1985). Precision, where reported, is acceptable (#20% RSD) (EPA 1984e, 1984f; Ojala 1993). Little information is available on detection limits. Detection limits of 660 µg/kg (ppb) have been reported for automated Soxhlet extraction with capillary GC/MS analysis (EPA 1994a).

Fish and aquatic organisms are homogenized, then extracted with solvent (Miskiewicz and Gibbs 1994; Oliver and Nichol 1982b), isolated on Florisil columns (Bong 1975), or Soxhlet extracted (Rahman et al. 1993; Shan et al. 1994; Tiernan et al. 1990). Clean-up is usually necessary to remove lipids and interfering substances (Bong 1975; Miskiewicz and Gibbs 1994; Rahman et al. 1993; Shan et al. 1994; Tiernan et al. 1990). Capillary GC/ECD analysis is used most often (Miskiewicz and Gibbs 1994; Rahman et al. 1993; Shan et al. 1994). Capillary GC/MS (Tiernan et al. 1990) and GC/ECD (Bong 1975; Oliver and Nichol 1982b) are also utilized. Reported recovery ranges from moderate (50–75%) (Shan et al. 1994) to excellent (>90%) (Bong 1975; Miskiewicz and Gibbs 1994; Rahman et al. 1993; Tiernan et al. 1990). Precision is usually not reported; however, 4–6% RSD has been achieved (Shan et al. 1994). Detection limits, where reported, are in the low-ppb range (ng/g) (Miskiewicz and Gibbs 1994; Rahman et al. 1993; Tiernan et al. 1990).

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Fatty foods, including milk, have been extracted with solvent to remove the fat, then cleaned up to separate the hexachlorobenzene from the fat (AOAC 1990; Bong 1975; Thier and Zeumer 1987b; Trotter and Dickerson 1993). Newer methods for combined separation and clean-up are supercritical fluid techniques (Nam and King 1994), solid-phase extraction (SPE) (Manes et al. 1993), and a sandwich system (Seidel and Linder 1994). Analysis is by GC/ECD (AOAC 1990; Bong 1975; Manes et al. 1993; Seidel and Linder 1993; Thier and Zeumer 1987b; Trotter and Dickerson 1993). Confirmation on a second GC column (Trotter and Dickerson 1993) or by thin-layer chromatography (TLC) (Thier and Zeumer 1987b) is recommended. Capillary GC/ECD has also been utilized (Nam and King 1994). Reported recoveries are good (>80%) (Bong 1975; Manes et al. 1993; Nam and King 1994; Seidel and Linder 1993; Trotter and Dickerson 1993). Precision, where reported, is very good (<15% RSD) (Bong 1975; Nam and King 1994; Thier and Zeumer 1987b; Trotter and Dickerson 1993). Limit of detection, where reported, is in the low-ppb (ng/g) range (Nam and King 1994; Seidel and Linder 1993; Thier and Zeumer 1987b; Trotter and Dickerson 1993).

Fruits, vegetables, and crops are blended, solvent extracted, and then cleaned up and fractionated (Pylypiw 1993; Thier and Zeumer 1987a). Capillary GC/ECD is the analytical method. Recovery is acceptable (>70%) (Pylypiw 1993; Thier and Zeumer 1987a). Precision was not reported. The reported detection limit is 2 ppb (Pylypiw 1993).

### 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 hexachlorobenzene 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 hexachlorobenzene.

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. ANALYTICAL METHODS

**7.3.1 Identification of Data Needs**

**Methods for Determining Biomarkers of Exposure and Effect.** Methods exist for measuring hexachlorobenzene in blood (Bristol et al. 1982; Burse et al. 1990; Langhorst and Nestruck 1979; Mes et al. 1982) and adipose tissue (Alawi and Ababneh 1991; Djordjevic et al. 1994; EPA 1980c, 1986f; Mes et al. 1982). The methods for blood and adipose are sensitive (low-ppb range), but improved accuracy is needed for blood analysis. The data on determination of hexachlorobenzene in urine, breast milk, and tissues are limited, and the methods may not be sufficiently sensitive. Methods that could be used to measure low levels in human tissues would be useful for determining the relationship between chronic low-level exposure and the effects observed in specific tissues. Improved methods to detect phenolic metabolites are not needed since these metabolites are not unique to hexachlorobenzene. Representative methods for determining pentachlorophenol and other phenolic metabolites using GC/ECD and GC/MS are shown in Table 7-3.

Biomarkers for effects of hexachlorobenzene are porphyric symptoms and increased gamma-glutamic transferase activity. Since these effects are also indicative of exposure to other toxicants, additional studies are needed for more specific biomarkers for effects of hexachlorobenzene exposure.

**Methods for Determining Parent Compounds and Degradation Products in Environmental Media.** Methods for determining hexachlorobenzene in air (EPA 1988d, 1988h; Hippelein et al. 1993; Langhorst and Nestruck 1979) and water (Chan et al. 1994; EPA 1988c, 1988e, 1988f; Garrison and Pellizzari 1987), the media of most concern for human exposure, are reliable, but may not be sensitive enough to measure background levels in the environment. Limited performance data are available for methods for soil and other solid media. In addition, there is insufficient performance information for methods for determining hexachlorobenzene in media such as shellfish, fish, and plants. Some exposure to hexachlorobenzene may occur via ingestion of food and standardized methods for foods are needed. Methods with sufficient sensitivity for measuring background levels in foods would be helpful as well.

## 7. ANALYTICAL METHODS

**Table 7-3. Analytical Methods for Determining Biomarkers of Hexachlorobenzene**

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood (pentachlorophenol)	pH adjustment, solvent extraction, derivatization	GC/ECD	10 ppb	92	EPA 1980c
Urine (chlorinated phenol metabolites)	Hydrolysis; solvent extraction, derivatization	GC/ECD, confirmation by GC/MS	No data	>90 (PCP); most other metabolites >80	EPA 1980c

ECD = electron capture detector; GC = gas chromatography; MS = mass spectrometry; PCP = pentachlorophenol

## 7. ANALYTICAL METHODS

**7.3.2 Ongoing Studies**

The Environmental Health Laboratory Sciences Division of the National Center for Environmental Health and Injury Control, Centers for Disease Control and Prevention, is developing methods for the analysis of pentachlorophenol and other phenolic compounds in urine. These methods use high resolution GC and magnetic sector MS, which gives detection limits in the low ppt range.



## 8. REGULATIONS AND ADVISORIES

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

ATSDR has derived an acute oral MRL of  $8 \times 10^{-3}$  mg/kg/day on the basis of developmental neurotoxic effects in rats. This MRL is based on a LOAEL of 2.5 mg/kg/day for hyperactivity in rat offspring whose mothers were exposed to hexachlorobenzene for 4 days prior to mating (Goldey and Taylor 1992).

An intermediate oral MRL of  $1 \times 10^{-4}$  mg/kg/day, based on reproductive effects in monkeys (Babineau et al. 1991; Bourque et al. 1995; Jarrell et al. 1993) has also been derived for hexachlorobenzene by ATSDR. This MRL is based on degenerative changes in the ovaries of female monkeys exposed to hexachlorobenzene doses of  $0.01$  mg/kg/day for 90 days.

ATSDR has also derived a chronic oral MRL of  $5 \times 10^{-5}$  mg/kg/day, based on a LOAEL of 0.016 mg/kg/day for peribiliary lymphocytosis and fibrosis of the liver in adult  $F_1$  generation male rats fed hexachlorobenzene for 130 weeks in a 2-generation study by Arnold et al. (1985).

The EPA oral reference dose for hexachlorobenzene (IRIS 2002) is  $8 \times 10^{-4}$  mg/kg/day based on liver effects in the Arnold et al. (1985) rat study. No reference concentration exists for the compound. These EPA assessments are currently undergoing re-evaluation.

EPA has classified hexachlorobenzene in weight-of-evidence Group B2 as a probable human carcinogen (IRIS 2001). EPA derived an oral slope factor of 1.6 per (mg/kg)/day and an inhalation unit risk of  $4.6 \times 10^{-4}$  per ( $\mu\text{g}/\text{m}^3$ ) based on hepatocellular carcinoma in rats exposed orally. This EPA assessment is currently being re-evaluated. IARC classifies the chemical as 2B, possibly carcinogenic to humans (IARC 2001). The National Toxicology Program (2001) concluded that hexachlorobenzene is reasonably anticipated to be a human carcinogen.

Hexachlorobenzene is on the list of chemicals appearing in "The Emergency Planning and Community Right-to-Know Act of 1986" (EPCRA) (EPA 2001a). Section 313 of Title III of EPCRA requires owners and operators of certain facilities that manufacture, import, process, or otherwise use the chemicals on this list to report annually their release of those chemicals to any environmental media.

## 8. REGULATIONS AND ADVISORIES

Although no Occupational Safety and Health Administration standards exist for hexachlorobenzene, the American Conference of Governmental Industrial Hygienists has set a threshold limit value (8-hour time weighted average) of 0.002 mg/m<sup>3</sup> (ACGIH 2001), based on a route-to-route extrapolation from an oral study in Rhesus monkeys (Rozman et al. 1978).

Hexachlorobenzene is regulated by the Clean Water Effluent Guidelines as stated in Title 40, Section 400–475, of the Code of Federal Regulations. For each point source category, hexachlorobenzene may be regulated as one of a group of chemicals that are controlled as Total Toxic Organics, or may have a specific Regulatory Limitation, or may have a Zero Discharge Limitation. The point source categories for which hexachlorobenzene is controlled as a Total Toxic Organic are electroplating (EPA 2001b), metal finishing (EPA 2001c), and coil coating. The point source categories for which hexachlorobenzene has a specific Regulatory Limitation include primary rare earth metals (EPA 2001d) and organic chemicals, plastics, and synthetic fibers (EPA 2001e).

The Resource Conservation and Recovery Act (RCRA) identifies hexachlorobenzene as a hazardous waste in two ways: (1) when it exceeds a toxicity characteristic leaching procedure test concentration of 0.13 mg/L (EPA 2000p), and (2) when discarded as a commercial product, off-spec species, container residue, or spill residue (EPA 2001i).

## 8. REGULATIONS AND ADVISORIES

**Table 8-1. Regulations and Guidelines Applicable to Hexachlorobenzene**

Agency	Description	Information	Reference
<u>INTERNATIONAL</u>			
Guidelines:			
IARC	Carcinogenicity classification	Group 2B <sup>a</sup>	IARC 2001
WHO	Drinking water guideline	1 µg/L	WHO 1996
	Total daily intake in humans		WHO 1997
	Non-cancer effects	0.17 µg/kg b.w./day	
	Neoplastic effects	0.16 µg/kg b.w./day	
<u>NATIONAL</u>			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)	0.002 mg/m <sup>3</sup>	ACGIH 2001
NIOSH	REL	No data	
OSHA	PEL	No data	
USC	Listed as a hazardous air pollutant		USC 2001 42 USC 7412
b. Water			
EPA	Drinking water standard	0.001 ppm	EPA 2001m 40CFR141.32(e)(68)
	MCL	0.001 mg/L	EPA 2001k 40CFR141.61(c)
	MCLG	Zero	EPA 2001l 40CFR141.50(a)(22)
	Effluent guidelines and standards—electroplating point source category	Total toxic organics	EPA 2001b 40CFR413.02
	Effluent guidelines and standards—metal finishing point source category	Total toxic organics	EPA 2001c 40CFR433.11
	Effluent guidelines and standards—nonferrous metals manufacturing point source category	New source performance standards for the primary rare earth metals subcategory	EPA 2001d 40CFR421.274
	Effluent guidelines and standards—organic chemicals, plastics, and synthetic fibers		EPA 2001e 40CFR414

## 8. REGULATIONS AND ADVISORIES

**Table 8-1. Regulations and Guidelines Applicable to Hexachlorobenzene  
(continued)**

Agency	Description	Information	Reference
<u>NATIONAL</u> (cont.)			
EPA	Groundwater monitoring Suggested methods 8120 8270	<u>PQL</u> 0.5 µg/L 10 µg/L	EPA 2001f 40CFR264, Appendix IX
	Land disposal restrictions; universal treatment standards Waste water Non-waste water	0.055 mg/L <sup>2</sup> 10 mg/kg <sup>3</sup>	EPA 2001j 40CFR268.48(a)
c. Food			
USDA	Labeling of treated seed with commonly accepted chemical (generic) name of substance		USDA 2001 7CFR201.31a(b)
d. Other			
ACGIH	Carcinogenicity classification	A3 <sup>b</sup>	ACGIH 2001
EPA	Carcinogenicity classification	B2 <sup>c</sup>	IRIS 2001
	Oral slope factor	1.6 per (mg/kg)/day	
	Inhalation unit risk	4.6x10 <sup>-4</sup> per (µg/m <sup>3</sup> )	
	RfD RfC	8x10 <sup>-4</sup> mg/kg/day No data	
	Health-based limits for exclusion of waste-derived residues— concentration limits for residues	2x10 <sup>-4</sup> mg/kg	EPA 2001h 40CFR266, Appendix VII
	Identification and listing of hexachlorobenzene as a hazardous waste—hazardous waste number	U127	EPA 2001i 40CFR261.33(f)
	Maximum concentration of contaminants for the toxicity characteristic—regulatory level	0.13 mg/L	EPA 2001p 40CFR261.24

## 8. REGULATIONS AND ADVISORIES

**Table 8-1. Regulations and Guidelines Applicable to Hexachlorobenzene  
(continued)**

Agency	Description	Information	Reference
<u>NATIONAL</u> (cont.)			
EPA	Reportable quantity regarded as a CERCLA hazardous substance under Section 307(a) of the Clean Water Act, Section 112 of the Clean Air Act, and Section 3001 of RCRA	10 pounds	EPA 2001a 40CFR302.4
	Hazardous waste management		EPA 2001g 40CFR266, Appendix V
	Unit risk	$4.9 \times 10^{-4} \mu\text{g}/\text{m}^3$	
	Risk specific dose	$2.0 \times 10^{-2} \mu\text{g}/\text{m}^3$	
	Toxic chemical release reporting; community right-to-know—alternate reporting threshold for PBT compounds	10 pounds	EPA 2001o 40CFR372.27
	Toxic chemical release reporting; community right-to-know—effective date of reporting	01/01/87	EPA 2001n 40CFR372.65
NTP	Carcinogenicity classification	Reasonably anticipated to be a human carcinogen	NTP 2001
<u>STATE</u>			
a. Air			
Idaho	Acceptable ambient concentration for a carcinogen Emissions level	$2 \times 10^{-3} \mu\text{g}/\text{m}^3$ $1.3 \times 10^{-5}$ pounds/hour	ID Dept. of Health and Welfare 1999
Washington	Acceptable source impact levels (at $10^{-6}$ risk), annual average	$0.0022 \mu\text{g}/\text{m}^3$	WA Dept. of Ecology 1998
Wisconsin	Hazardous air contaminants without acceptable ambient concentrations requiring application of best available control technology	25 pounds/year <sup>2</sup>	WI Dept. of Natural Resources 1997
b. Water			
Alaska	MCL	0.001 mg/L	AK Dept. of Environ. Conservation 1999
Arizona	Drinking water guideline	0.02 ug/L	HSDB 2001

8. REGULATIONS AND ADVISORIES

**Table 8-1. Regulations and Guidelines Applicable to Hexachlorobenzene  
(continued)**

Agency	Description	Information	Reference
<i>STATE (cont.)</i>			
California	MCL	0.001 mg/L	CA Dept. of Health Services 2000
Colorado	Groundwater standard	1 µg/L	CO Dept. of Public Health and Environ. 1999
Hawaii	MCL applying to community and non-transient, non-community water systems	0.001 mg/L	HI Dept. of Health 1999a
Hawaii	Toxic pollutant standards <sup>e</sup>		HI Dept. of Health 1999b
	Freshwater		
	Acute	No standard	
	Chronic	No standard	
	Saltwater		
	Acute	No standard	
	Chronic	No standard	
	Fish consumption	2.4x10 <sup>-4</sup> µg/L	
Kansas	Water quality standards		KS Dept. of Health and Environ. 1999
	Aquatic life		
	Acute	6.0 mg/L	
	Chronic	3.7 mg/L	
	Public health		
	Food procurement	7.4x10 <sup>-4</sup> mg/L	
	Domestic water supply	1 mg/L	
Maine	Drinking water guideline	0.2 µg/L	HSDB 2001
Minnesota	Drinking water guideline	0.2 µg/L	HSDB 2001
New Jersey	Groundwater quality criteria	0.02 µg/L	NJ Dept. of Environ. Protection 1993
	PQL	10 µg/L	
South Dakota	MCL for drinking water	0.001 mg/L	SD Dept. of Environ. Natural Resources 1998
c. Food	No data		
d. Other			
California	Proposition 65 chemical; known to the state to cause cancer and developmental toxicity	Any manufacturer, packager, or producer required to add specific warnings to products and shipments	BLR 2002

8. REGULATIONS AND ADVISORIES

**Table 8-1. Regulations and Guidelines Applicable to Hexachlorobenzene  
(continued)**

Agency	Description	Information	Reference
<i>STATE (cont.)</i>			
Florida	Toxic substance	A toxic substance is present in any mixture if it is 1% or more of the mixture	BLR 2002
Massachusetts	Hazardous substance	Carcinogen, teratogen, and extraordinary hazardous	BLR 2002
Minnesota	Hazardous substance	Potential hazard from absorption through skin contact	BLR 2002
New Jersey	Right to know hazardous substance; required to submit surveys listing the hazardous substances present at their facilities in quantities >500 pounds; and report their inventories of any chemical that requires a MSDS and is present on site in quantities >10,000 pounds		BLR 2002
New York	Hazardous substance—reportable quantities		BLR 2002
	Air	10 pounds	
	Land	1 pound	

<sup>a</sup>Group 2B: possibly carcinogenic to humans

<sup>b</sup>A3: confirmed animal carcinogen with unknown relevance to humans

<sup>c</sup>B2: probable human carcinogen

<sup>d</sup>Indicates value derived using an oral cancer potency factor as a surrogate.

ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; BLR = Business & Legal Reports, Inc.; b.w. = body weight; CERCLA = Comprehensive Environmental Response Compensation and Liability Act; CFR = Code of Federal Regulations; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; MRLs = Minimal Risk Levels; MSDS = Material Safety Data Sheets; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; PQL = practical quantitation limit; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit value; TWA = time-weighted average; USC = United States Code; USDA = United States Department of Agriculture; WHO = World Health Organization



## 9. REFERENCES

- \*Abd-Allah AMA. 1999. Organochlorine contaminants in microlayer and subsurface water of Alexandria Coast, Egypt. *J AOAC Int* 82(2):391-398.
- \*Abraham K, Hille A, Ende M, et al. 1994. Intake and fecal excretion of PCDDs, PCDFs, HCB and PCBs, (138,153,180) in a breast-fed and a formula-fed infant. *Chemosphere* 29(9-11):2279-2286.
- \*Abraham K, Papke O, Wahn U, et al. 2000. Pop accumulation in infants during breast feeding. *Organohalogen Compounds* 48:25-26.
- \*ACGIH. 1999. Threshold limit values for chemical substances and physical agents: Biological exposure indices. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.
- \*ACGIH. 2001. Threshold limit values for chemical substances and physical agents and biological exposure indices. American Conference of Governmental Industrial Hygienists. Cincinnati, OH.
- Adami H, Lipworth L, Titus-Ernstoff L, et al. 1995. Organochlorine compounds and estrogen-related cancers in women. *Cancer Causes Control* 6:551-566.
- \*Adinolfi M. 1985. The development of the human blood-CSF-brain barrier. *Dev Med Child Neurol* 27:532-537.
- \*Adjarov DG. 1990. Decreased activity of liver coproporphyrinogen oxidase in hexachlorobenzene-induced porphyria. *Exp Pathol* 40:117-122.
- Adjarov DJ, Elder GH. 1986. Accumulation of uroporphyrin does not provoke further inhibition of liver uroporphyrinogen decarboxylase activity in hexachlorobenzene-induced porphyria. In: *Hexachlorobenzene: Proceedings of an international symposium*. IARC Sci Publ 77:467-469.
- \*Adjarov D, Ivanov E, Keremidchiev D. 1982. Gamma-glutamyl transferase: A sensitive marker in experimental hexachlorobenzene intoxication. *Toxicology* 23:73-77.
- \*Adlercreutz H. 1995. Phytoestrogens: Epidemiology and a possible role in cancer protection. *Environ Health Perspect Suppl* 103(7):103-112.
- AFOSR. 1998. Interdisciplinary and alternative approach to assess carcinogenicity of chlorobenzenes. Washington, DC: Air Force Office of Scientific Research.
- Ahlborg UG, Larsson K, Thunberg T. 1978. Metabolism of pentachlorophenol *in vivo* and *in vitro*. *Arch Toxicol* 40:45-53.
- \*AK Dept of Environ Conservation. 1999. Drinking water regulations. Alaska Department of Environmental Conservation. <http://www.state.ak.us/local/akpages/ENV.CONSERV/home.htm>.

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\*Cited in text

## 9. REFERENCES

- Akhtar RA, Smith AG. 1998. Chromosomal linkage analysis of porphyria in mice induced by hexachlorobenzene-iron synergism: A model of sporadic porphyria cutanea tarda. *Pharmacogenetics* 8:485-494.
- \*Alawi MA, Ababneh M. 1991. Residue analysis of chlorinated pesticides in Jordanian human adipose tissue. *Anal Lett* 25(10):1897-1911.
- \*Alawi MA, Ammari N, Al-Shuraiki Y. 1992. Organochlorine pesticide contaminations in human milk samples from women living in Amman, Jordan. *Arch Environ Contam Toxicol* 23:235-239.
- Albers JMC, Kreis IA, Liem AKD, et al. 1996. Factors that influence the level of contamination of human milk with poly-chlorinated organic compounds. *Arch Environ Contam Toxicol* 30:285-291.
- \*Albro PW, Thomas R. 1974. Intestinal absorption of hexachlorobenzene and hexachlorocyclohexane isomers in rats. *Bull Environ Contam Toxicol* 12:289-294.
- Alleman MA, Koster JF, Wilson JHP, et al. 1985. The involvement of iron and lipid peroxidation in the pathogenesis of HCB induced porphyria. *Biochem Pharmacol* 34(2):161-166.
- \*Allen-Gil SM, Gubala CP, Wilson R, et al. 1997a. Organochlorine pesticides and polychlorinated biphenyls (PCBs) in sediments and biota from four US arctic lakes. *Arch Environ Contam Toxicol* 33:378-387.
- Allen-Gil SM, Landers DH, Wade TL, et al. 1997b. Heavy metal, organochlorine pesticide and polychlorinated biphenyl contamination in arctic ground squirrels (*Spermophilus parryi*) in northern Alaska. *Arctic* 50(4):323-333.
- Almeida MG, Fanini F, Davino SC, et al. 1997. Pro- and anti-oxidant parameters in rat liver after short term exposure to hexachlorobenzene. *Human Exp Toxicol* 16:257-261.
- \*Altman PL, Dittmer DS. Eds. 1974. In: *Biological handbooks: Biology data book*. Vol. III. 2<sup>nd</sup> ed. Bethesda, MD: Federation of American Societies for Experimental Biology, 1987-2008, 2041.
- Altshul L, Korrick S, Tolbert P, et al. 1999. Cord blood levels of PCBs, *p,p'*-DDE and HCB in infants born in communities adjacent to a PCB-contaminated hazardous waste site. In: *Organohalogen Compounds* 44:67-70.
- Alvarez L, Randi A, Alvarez P, et al. 1999. Effect of hexachlorobenzene on NADPH-generating lipogenic enzymes and L-glycerol-3-phosphate dehydrogenase in brown adipose tissue. *J Endocrinol Invest* 22:436-445.
- \*Alvarez L, Randi A, Alvarez P, et al. 2000. Reproductive effects of hexachlorobenzene in female rats. *J Appl Toxicol* 20:81-87.
- Amdur MO, Doull J, Klaasen CD. 1991. *Casarett and Doull's toxicology: The basic science of poisons*. New York, NY: Pergamon Press, 478-479.
- \*Ames A, Van Vleet E. 1996. Organochlorine residues in the Florida Manatee, *Trichechus manatus latirostris*. *Mar Pollut Bull* 32:374-377.

## 9. REFERENCES

- \*Andersen ME, Krishnan K. 1994. Relating *in vitro* to *in vivo* exposures with physiologically based tissue dosimetry and tissue response models. In: Salem H, ed. Animal test alternatives: Refinement, reduction, replacement. New York: Marcel Dekker, Inc., 9-25.
- \*Andersen ME, Clewell HJ III, Gargas ML, et al. 1987. Physiologically based pharmacokinetics and the risk assessment process for methylene chloride. *Toxicol Appl Pharmacol* 87:185-205.
- \*Anderson HA, Falk C, Hanrahan L, et al. 1998. Profiles of Great Lakes critical pollutants: A sentinel analysis of human blood and urine. *Env Health Persp* 106(5):279-289.
- \*Ando M, Hirano S, Itoh Y. 1985. Transfer of hexachlorobenzene (HCB) from mother to new-born baby through placenta and milk. *Arch Toxicol* 56:195-200.
- Andrews JE, Courtney KD. 1986. Hexachlorobenzene- induced renal maldevelopment in CD-1 mice and CD rats. In: Hexachlorobenzene: Proceedings of an international symposium. IARC Sci Publ 77:381-391.
- \*Andrews JE, Courtney KD, Donaldson WE. 1988. Impairment of calcium homeostasis by hexachlorobenzene (HCB) exposure in Fischer 344 rats. *J Toxicol Environ Health* 23:311-320.
- \*Andrews JE, Courtney KD, Stead AG, et al. 1989. Hexachlorobenzene- induced hyperparathyroidism and osteosclerosis in rats. *Fundam Appl Toxicol* 12:242-251.
- \*Andrews JE, Jackson LD, Stead AG, et al. 1990. Morphometric analysis of osteosclerotic bone resulting from hexachlorobenzene exposure. *J Toxicol Environ Health* 31:193-201.
- Anger WK. 1990. Worksite behavioral methods, test research: Results, batteries and the sensitive laboratory transition from data to human health. *Neurotoxicology* 11:629-670.
- Ansari GAS, Hendrix PY. 1985. Rapid and convenient separation of pentachlorophenol from human fat using silica Sep-pak cartridges. *J Chromatog* 346:435-439.
- \*Ansari GAS, James GP, Hu AL, et al. 1986. Organochlorine residues in adipose tissue of residents of the Texas gulf coast. *Bull Environ Contam Toxicol* 36:311-316.
- Anwar WA. 1997. Biomarkers of human exposure to pesticides. *Environ Health Perspect Suppl* 105(Suppl. 4):801-806.
- \*AOAC. 1990. Official methods of analysis of the association of official analytical chemists. Association of Official Analytical Chemist, Inc. 15 Edition, Arlington, Virginia.
- \*Archibeque-Engle S, Tessari J, Winn D, et al. 1997. Comparison of organochlorine pesticide and polychlorinated biphenyl residues in human breast adipose tissue and serum. *J Toxicol Environ Health* 52:285-293.
- Arnold DL, Krevski D. 1988. Long-term toxicity of hexachlorobenzene. *Food Chem Toxicol* 26:169-174.
- \*Arnold DL, Bryce FR, Clegg DJ, et al. 2000. Dosing via gavage or diet for reproduction studies: a pilot study using two fat-soluble compounds-hexachlorobenzene and Aroclor 1254. *Food Chem Toxicol* 38:697-706.

## 9. REFERENCES

- \*Arnold DL, Moodie CA, Charbonneau SM, et al. 1985. Long-term toxicity of hexachlorobenzene in the rat and the effect of dietary vitamin A. *Food Chem Toxicol* 23:779-793.
- Arnold DL, Moodie CA, Collins BT, et al. 1986. Two-generation chronic toxicity study with hexachlorobenzene in the rat. *IARC Sci Publ* 77:405-410.
- Artigas F, Martinez E, Gelpi E. 1988. Organochlorine pesticides by negative ion chemical ionization. Brain metabolites of lindane. *Biomedical Environ Mass Spectrom* 16:279-284.
- ASTM. 1988. Standard test method for organochlorine pesticides in water- method D3086-85. In: 1988 annual book of ASTM standards. Vol. 11.02: Water and environmental technology. Philadelphia, PA: American Society for Testing and Materials, 163-178.
- \*Ataniyazova OA, Baumann RA, Liem AKD, et al. 2001. Levels of certain metals, organochlorine pesticides and dioxins in cord blood, maternal blood, human milk and some commonly used nutrients in the surroundings of the Aral Sea (Karakalpakstan, Republic of Uzbekistan). *Acta Paediatr* 90:801-808.
- Atkinson R, Guicherit R, Hites RA, et al. 1999. Transformations of pesticides in the atmosphere: a state of the art. *Water Air Soil Pollut* 115(1-4):219-243.
- \*Atlas E, Giam CS. 1981. Global transport of organic pollutants: ambient concentrations in the remote marine atmosphere. *Science* 211:163-165.
- \*Atlas E, Foster R, Giam CS. 1982. Air-sea exchange of high molecular weight organic pollutants: laboratory studies. *Environ Sci Technol* 16:283-286.
- \*ATSDR. 1989. Decision guide for identifying substance-specific data needs related to toxicological profiles; Notice. Atlanta, GA: Agency for Toxic Substances and Disease Registry. *Federal Register* 54(174):37618-37634.
- \*ATSDR/CDC. 1990. Subcommittee report on biomarkers of organ damage and dysfunction. Atlanta, GA: Agency for Toxic Substances and Disease Registry/Centers for Disease Control.
- Ausmus BS, Kimbrough S, Jackson DR, et al. 1979. The behavior of hexachlorobenzene in pine forest microcosms: Transport and effects on soil processes. *Environ Pollut* 20:103-111.
- \*Avrahami M. 1975. Hexachlorobenzene: IV. Accumulation and elimination of HCB in pigs after oral dosing. *New Zealand J Expt Agri* 3:285-287.
- Avrahami M, Steele RT. 1972a. Hexachlorobenzene: I. Accumulation and elimination of HCB in sheep after oral dosing. *New Zealand J Agr Res* 15:476-481.
- Avrahami M, Steele RT. 1972b. Hexachlorobenzene: II. Residues in laying pullets fed hexachlorobenzene in their diet and the effects on egg production, egg hatchability, and on chickens. *New Zealand J Agr Res* 15:482-488.
- Avrahami M, Steele RT. 1972c. Hexachlorobenzene: III. The effects of feeding Hexachlorobenzene to growing chickens. *New Zealand J Agri Res* 15:489-494.
- \*Axelson O. 1986. A review of porphyria and cancer and the missing link with human exposure to hexachlorobenzene. *IARC Sci Publ* 77:585-589.

## 9. REFERENCES

- \*Babineau KA, Singh A, Jarrell, JF, et al. 1991. Surface epithelium of the ovary following oral administration of hexachlorobenzene to the monkey. *J Submicrosc Cytol Pathol* 23:457-464.
- \*Badia-Vila M, Ociepa M, Mateo R, et al. 2000. Comparison of residue levels of persistent organochlorine compounds in butter from Spain and from other European countries. *J Environ Sci Health B35(2)*:201-210.
- \*Bailey J, Knauf V, Mueller W, et al. 1980. Transfer of hexachlorobenzene and polychlorinated biphenyls to nursing infant rhesus monkeys: Enhanced toxicity. *Environ Res* 21:190-196.
- \*Bailey RE. 2001. Global hexachlorobenzene emissions. *Chemosphere* 43:167-182.
- \*Ballester F, Sala M, Sunyer J, et al. 2000. Serum concentrations of hexachlorobenzene in family members of workers in an electrochemical factory. *Scand J Work Environ Health* 26(1):67-70.
- \*Ballschmiter K, Wittlinger R. 1991. Interhemisphere exchange of hexachlorocyclohexanes, hexachlorobenzene, polychlorobiphenyls, and 1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane in the lower troposphere. *Environ Sci Technol* 25(6):1103-1111.
- Banerjee BD, Koner BC, Ray A. 1996. Immunotoxicity of pesticides: Perspectives and trends. *Indian J Exp Biol* 34:723-733.
- \*Barnes DG, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessments. *Reg Toxicol Pharmacol* 8:471-486.
- \*Barnett JB, Barfield L, Walls R, et al. 1987. The effect of *in utero* exposure to hexachlorobenzene on the developing immune response of Balb/c mice. *Toxicol Lett* 39:263-274.
- \*Bates MN, Hannah DJ, Buckland SJ, et al. 1994. Chlorinated organic contaminants in breast milk of New Zealand women. *Environ Health Perspect* 102(Suppl 1):211-217.
- \*Beall ML Jr. 1976. Persistence of aerially applied hexachlorobenzene on grass and soil. *J Environ Qual* 5:367-369.
- Beck AJ, Alcock RE, Wilson SC, et al. 1995. Long-term persistence of organic chemicals in sewage sludge-amended agricultural land: A soil quality perspective. In: Sparks DL, ed. *Advances in agronomy*. New York, NY: Academic Press, 345-391.
- \*Beck J, Hansen KE. 1974. The degradation of quinterozone, pentachlorobenzene, hexachlorobenzene and pentachloraniline in soil. *Pestic Sci* 5:41-48.
- \*Becker PR, Mackey EA, Demiralp R, et al. 1997. Concentrations of chlorinated hydrocarbons and trace elements in marine mammal tissues archived in the U.S. National Biomonitoring Specimen Bank. *Chemosphere* 34:2067-2098.
- \*Belfroid A. 1995. Uptake, bioavailability and elimination of hydrophobic compounds in earthworms (*Eisenia andrei*) in field-contaminated soil. *Environ Toxicol Chem* 14(4):605-612.
- Belfroid A, Meling J, Sijm D, et al. 1994. Uptake of hydrophobic halogenated aromatic hydrocarbons from food by earthworms (*Eisenia andrei*). *Arch Environ Contam Toxicol* 27(2):260-265.

## 9. REFERENCES

- \*Belles-Isles M, Bilrha H, Moreau B, et al. 2000. Immunological effects in newborns from Saint-Lawrence River Coastal populations exposed to POPs and heavy metals. *Organohalogen Compounds* 48:227-230.
- \*Beretta M, Dick T. 1994. Organochlorine compounds in human milk, porto alegre, Brazil. *Environ Contam Toxicol* 53(3):357-360.
- \*Berger GS. 1994. Epidemiology of endometriosis. In: Berger GS, ed. *Endometriosis: Advanced management and surgical techniques*. New York, NY: Springer-Verlag, 3-7.
- \*Bernhoft A, Skaare JU, Wiig O, et al. 2000. Possible immunotoxic effects of organochlorines in polar bears (*Ursus maritimus*) at Svalbard. *J Toxicol Environ Health* 59(Part A):561-574.
- Bertram HP, Kemper FH, Muller C. 1986. Hexachlorobenzene content in human whole blood and adipose tissue: Experiences in environmental specimen banking. *IARC Sci Publ* 77:173-183.
- Bestervelt LL, Pitt JA, Piper WN. 1998. Evidence for Ah receptor mediation of increased ACTH concentrations in primary cultures of rat anterior pituitary cells exposed to TCDD. *Toxicol Sci* 46:294-299.
- Beyer A, Mackay D, Matthies M, et al. 2000. Assessing long-range transport potential of persistent organic pollutants. *Environ Sci Technol* 34:699-703.
- \*Beyer WN. 1996. Accumulation of chlorinated benzenes in earthworms. *Bull Environ Contam Toxicol* 57:729-736.
- \*Bidleman TF, Patton GW, Walla MD, et al. 1989. Toxaphene and other organochlorines in Arctic Ocean fauna: Evidence for atmospheric delivery. *Arctic* 42(4):307-313.
- Billi SC, Koss G, San Martin de Viale LC. 1986a. Ability of several hexachlorobenzene metabolites to decrease rat-liver porphyrinogen carboxy-lyase and to produce porphyrin accumulation in chick-embryo liver. *IARC Sci Publ* 77:471-476.
- Billi SC, Wainstok de Calmanovici RW, San Martin de Viale LC. 1986b. Rat-liver porphyrinogen carboxy-lyase inhibition as a function of the degree of hexachlorobenzene-induced porphyria. *IARC Sci Publ* 77:487-491.
- \*Billi de Catabbi S, Aldonatti C, San Martin de Viale LC. 2000a. Heme metabolism after discontinued hexachlorobenzene administration in rats: possible irreversible changes and biomarker for hexachlorobenzene persistence. *Comp Biochem Physiol C* 127:165-175.
- Billi de Catabbi S, Koss G, San martin de Viale LC. 1994. Studies on the active centres of rat liver porphyrinogen carboxylyase. *In vivo* effects of hexachlorobenzene on decarboxylation sites of porphyrinogens. *Int J Biochem* 26(4):595-600.
- \*Billi de Catabbi S, Rios de Molina MC, San Martin de Viale LC. 1991. Studies on the active center of rat liver porphyrinogen carboxylase *in vivo* effect of hexachlorobenzene. *Int J Biochem* 23:675-679.
- \*Billi de Catabbi S, Setton-Advruj CP, Sterin-Speziale N, et al. 2000b. Hexachlorobenzene-induced alterations on neutral and acidic sphingomyelinases and serine palmitoyltransferase activities. A time course study in two strains of rats. *Toxicology* 149:89-100.

## 9. REFERENCES

- Billi de Catabbi S, Sterin-Speziale N, Fernandez MC, et al. 1997. Time course of hexachlorobenzene-induced alterations of lipid metabolism and their relation to porphyria. *Int J Biochem Cell Biol* 29(2):335-344.
- Bishop CA, Gendron AD. 1998. Reptiles and amphibians: Shy and sensitive vertebrates of the Great Lakes Basin and St. Lawrence River. *Environ Monit Assess* 53:225-244.
- \*Bishop CA, Lean DRS, Brooks RJ, et al. 1995. Chlorinated hydrocarbons in early life stages of the common snapping turtle (*Chelydra serpentina serpentina*) from a coastal wetland on Lake Ontario, Canada. *Environ Toxicol Chem* 14(3):421-426.
- Bishop CA, Mahony NA, Trudeau S, et al. 1999. Reproductive success and biochemical effects in tree swallows (*Tachycineta bicolor*) exposed to chlorinated hydrocarbon contaminants in wetlands of the Great Lakes and St. Lawrence River Basin, USA and Canada. *Environ Toxicol Chem* 18(2):263-271.
- \*Bishop CA, Ng P, Norstrom RJ, et al. 1996. Temporal and geographic variation of organochlorine residues in eggs of the common snapping turtle (*Chelydra serpentina serpentina*) (1981-1991) and comparisons to trends in the herring gull (*Larus argentatus*) in the Great Lakes Basin in Ontario, Canada. *Arch Environ Contam Toxicol* 31:512-524.
- \*Bjerregaard P, Hansen JC. 2000. Organochlorines and heavy metals in pregnant women from the Disko Bay area in Greenland. *Sci Total Environ* 245:195-202.
- Bleavins MR, Aulerich RJ, Ringer RK. 1984. Effects of chronic dietary hexachlorobenzene exposure on the reproductive performance and survivability of mink and European ferrets. *Arch Environ Contam Toxicol* 13:357-365.
- Bleavins MR, Breslin WJ, Aulerich RJ, et al. 1982. Excretion and placental and mammary transfer of hexachlorobenzene in the European ferret (*Mustela putorius furo*). *J Toxicol Environ Health* 10:929-940.
- Bleavins MR, Bursian SJ, Brewster JS, et al. 1984. Effects of dietary hexachlorobenzene exposure on regional brain biogenic amine concentrations in mink and European ferrets. *J Toxicol Environ Health* 14:363-377.
- \*Bleckenhorst GH, Pimstone NR, Weber BL, et al. 1976. Hepatic haem metabolism in porphyria cutanea tarda (PCT): Enzymatic studies and their relation to liver ultrastructure. *Ann Clin Res* 8(Supp 17):108-121.
- \*BLR. 2002. Book of chemical lists. State lists. Business & Legal Reports, Inc. Old Saybrook, CT.
- Bohme F, Welsch-Pausch K, Mclachlan MS. 1999. Uptake of airborne semivolatile organic compounds in agricultural plants: Field measurements of interspecies variability. *Environ Sci Technol* 33:1805-1813.
- \*Bong RL. 1975. Determination of hexachlorobenzene and mirex in fatty products. *J AOAC* 58(3):557-561.
- Booij K, van Drooge BL. 2001. Polychlorinated biphenyls and hexachlorobenzene in atmosphere, sea-surface microlayer, and water measured with semi-permeable membrane devices (SPMDs). *Chemosphere* 44:91-98.

## 9. REFERENCES

- \*Booth NH, McDowell JR. 1975. Toxicity of hexachlorobenzene and associated residues in edible animal tissues. *JAVMA* 166(6):591-595.
- \*Bordet F, Mallet J, Maurice L et al. 1993. Organochlorine pesticide and PCB congener content of French human milk. *Bull Environ Contam Toxicol* 50:425-432.
- \*Borga K, Gabrielsen GW, Skaare JU. 2001. Biomagnification of organochlorines along a Barents Sea food chain. *Environ Pollut* 113:187-198.
- Borglin S, Wilke A, Jepsen R, et al. 1996. Parameters affecting the desorption of hydrophobic organic chemicals from suspended sediments. *Environ Toxicol Chem* 15(10):2254-2262.
- \*Bourque AC, Singh A, Lakhanpal N, et al. 1995. Ultrastructural changes in ovarian follicles of monkeys administered hexachlorobenzene. *Am J Vet Res* 56(12):1673-1677.
- \*Bouthillier L, Greselin E, Brodeur J, et al. 1991. Male rat specific nephrotoxicity resulting from subchronic administration of hexachlorobenzene. *Toxicol Appl Pharmacol* 110:315-326.
- \*Brady MN, Siyali DS. 1972. Hexachlorobenzene in human body fat. *Med J Aust* 1:158-161.
- \*Braune B, Muir D, DeMarch B, et al. 1999. Spatial and temporal trends of contaminants in Canadian Arctic freshwater and terrestrial ecosystems: a review. *Sci Total Environ* 230:145-207.
- \*Bristol DW, Crist HL, Lewis RG, et al. 1982. Chemical analysis of human blood for assessment of environmental exposure to semivolatile organochlorine chemical contaminants. *J Anal Toxicol* 6:1-7.
- \*Brock J, Melnyk L, Caudill S, et al. 1998. Serum levels of several organochlorine pesticides in farmers correspond with dietary exposure and local use history. *Toxicol Ind Health* 14(1-2):275-289.
- \*Brorstrom-Lunden E, Lindskog A, Mowrer J. 1994. Concentrations and fluxes of organic compounds in the atmosphere of the Swedish west coast. *Atmos Environ* 28(22):3605-3615.
- Brouwer A. 1998. Structure-dependent multiple interactions of polyhalogenated aromatic hydrocarbons with the thyroid hormone system. *Organohalogen Compounds* 37:225-232.
- Brouwer A, Morse DC, Lans MC, et al. 1998. Interactions of persistent environmental organohalogenes with the thyroid hormone system: Mechanisms and possible consequences for animal and human health. *Toxicol Ind Health* 14:59-84.
- \*Brubaker WW, Hites RA. 1998. OH reaction kinetics of gas-phase  $\alpha$ - and  $\gamma$ -hexachlorocyclohexane and hexachlorobenzene. *Env Sci Technol* 32:766-769.
- Brusick DJ. 1986. Genotoxicity of hexachlorobenzene and other chlorinated benzenes. *IARC Sci Publ* 77:393-397.
- \*Bryson PD. 1989. Chlorinated hydrocarbons (organochlorines). In: *Comprehensive review in toxicology*. Rockville, MD: Aspen Publication, 527-529.
- \*Bucholski KA, Begerow J, Winneke G, et al. 1996. Determination of polychlorinated biphenyls and chlorinated pesticides in human body fluids and tissues. *J Chromatogr* 754:479-485.

## 9. REFERENCES

Buckley R, Liddle J, Ashley D, et al. 1997. Environmental and biomarker measurements in nine homes in the lower Rio Grande Valley: Multimedia results for pesticides, metals, PAHs, and VOCs. *Environ Int* 23:705-732.

\*Budavari S. 1996. 4714-Hexachlorobenzene- The merck index: An encyclopedia of chemicals, drugs, and biologicals. 12<sup>th</sup> ed. Whitehouse Station, NJ: Merck and Co. Inc., 800.

\*Burkhard LP, Sheedy BR, McCauley DJ, et al. 1997. Bioaccumulation factors for chlorinated benzenes, chlorinated butadienes and hexachloroethane. *Environ Toxicol Chem* 16(8):1677-1686.

\*Burns JE, Miller FM. 1975. Hexachlorobenzene contamination: Its effects in a Louisiana population. *Arch Environ Health* 30:44-48.

\*Burns JE, Miller FM, Gomes ED, et al. 1974. Hexachlorobenzene exposure from contaminated DCPA in vegetable spraysmen. *Arch Environ Health* 29:192-194.

\*Burse VW, Head SL, Korver MP, et al. 1990. Determination of selected organochlorine pesticides and polychlorinated biphenyls in human serum. *J Anal Toxicol* 14:137-146.

\*Burse VW, Najam AR, Williams CC, et al. 2000. Utilization of umbilical cords to assess in utero exposure to persistent pesticides and polychlorinated biphenyls. *J Expo Anal Environ Epidemiol* 10:776-788.

\*Burton MA, Bennett BG. 1987. Exposure of man to environmental hexachlorobenzene (HCB)--an exposure commitment assessment. *Sci Total Environ* 66:137-146.

\*CA Dept of Health Services. 2000. Draft, proposed and recently adopted regulations- drinking water. California Department of Health Services, Division of Drinking Water and Environmental Management. <http://www.dhs.cahwnet.gov/ps/ddwem/>.

Cabral JR, Shubik P. 1986. Carcinogenic activity of hexachlorobenzene in mice and hamsters. In: *Hexachlorobenzene: Proceedings of an international symposium*. IARC Sci Publ 77:411-416.

\*Cabral JRP, Mollner T, Raitano F, et al. 1979. Carcinogenesis of hexachlorobenzene in mice. *Int J Cancer* 23:47-51.

\*Cabral JR, Shubik P, Mollner T, et al. 1977. Carcinogenic activity of hexachlorobenzene in hamsters. *Nature* 269:510-511.

Cabral R, Hoshiya T, Hakoi K, et al. 1996. Medium-term bioassay for the hepatocarcinogenicity of hexachlorobenzene. *Cancer Lett* 100:223-226.

\*Calamari D, Tremolada P, Guardo AD, et al. 1994. Chlorinated hydrocarbons in pine needles in Europe: Fingerprint for the past and recent use. *Environ Sci Technol* 28:429-434.

\*Calaminus B, Trouve G, Delforsse L. 1993. Experimental study of the quantitative conversion of hexachlorobenzene during high temperature pyrolysis. *J Analyt Appl Pyrolysis* 27(2):281-292.

Callen JP. 1980. Internal disorders associated with bullous disease of the skin. *J Am Acad Dermatol* 3(2):107-119.

## 9. REFERENCES

- \*Cam C, Nigogosyan G. 1963. Acquired toxic porphyria cutanea tarda due to hexachlorobenzene: Report of 348 cases caused by this fungicide. *JAMA* 183:88-91.
- \*Canonero R, Campart GB, Mattioli F, et al. 1997. Testing of *p*-dichlorobenzene and hexachlorobenzene for their ability to induce DNA damage and micronucleus formation in primary cultures of rat and human hepatocytes. *Mutagenesis* 12(1):35-39.
- \*Cantoni L, Budillon G, Cuomo R, et al. 1990. Protective effect of S-adenosyl-L-methionine in hepatic uroporphyrin. Evaluation in an experimental model. *Scand J Gastro* 25:1034-1040.
- Cantoni L, Graziani A, Rizzardini M, et al. 1986. Porphyrinogenic effect of hexachlorobenzene and 2,3,7,8-tetrachlorodibenzo-para-dioxin: Is an inhibitor involved in uroporphyrinogen decarboxylase inactivation? *IARC Sci Publ* 77:449-456.
- Cantoni L, Rizzardini M, Graziani A, et al. 1987. Effects of chlorinated organics on intermediates in the heme pathway and on uroporphyrinogen decarboxylase. *Ann N Y Acad Sci* 514:128-140.
- Capuano G, Gentile S, Cuomo R, et al. 1994. Evaluation of bromosulphthalein clearance in experimental porphyria by isolated and perfused rat liver technique. *Bull Mol Biol Med* 19:77-85.
- Carey AE, Dixon TE, Yang HSC. 1986. Environmental exposure to hexachlorobenzene in the USA. In: Morris CR, Cabral JRP, ed. *Hexachlorobenzene: Proceedings of an International Symposium*. Lyon, France: IARC Scientific Publications, 115-120.
- Carey AE, Gowen JA, Tai H, et al. 1979. Pesticide residue levels in soils and crops from 37 states, 1972 - National soils monitoring program (IV). *Pestic Monit J* 12:209-229.
- Carpenter HM, Williams DE, Henderson MC, et al. 1984. Hexachlorobenzene-induced porphyria in Japanese quail: Effect of pretreatment with phenobarbital or beta-naphthoflavone. *Biochem Pharmacol* 33:3875-3881.
- \*Carthew P, Smith AG. 1994. Pathological mechanisms of hepatic tumor formation in rats exposed chronically to dietary hexachlorobenzene. *J Appl Toxicol* 447-452.
- \*Carthew P, Edwards RE, Smith AG. 1990. Immunotoxic effects of hexachlorobenzene on the pathogenesis of systemic, pneumonic and hepatic virus infections in the mouse. *Human Exp Toxicol* 9:403-411.
- Catallo WJ, Junk T. 1995. Sonochemical dechlorination of hazardous waste in aqueous systems. *Waste Manage* 15(4):303-309.
- CELDs. 1993. Computer-aided Environmental Legislative Database. University of Illinois at Urbana.
- \*Chaisuksant Y, Yu Q, Connell DW. 1997. Bioconcentration of bromo- and chlorobenzenes by fish (*Gambusia affinis*). *Water Res* 31(1):61-68.
- \*Chan CH, Bruce G, Harrison B. 1994. Wet deposition of organochlorine pesticides and polychlorinated biphenyls to the great lakes. *J Great Lakes Res* 20(3):546-560.
- Chaufan G, de Molina MdCR, de Viale LCSM. 2001. How does hexachlorobenzene treatment affect liver uroporphyrinogen decarboxylase? *Int J Biochem Cell Biol* 33:621-630.

## 9. REFERENCES

Chemical Marketing Reporter. 1993. Schnell Publishing Co. December 6, 1993.

Chen W, Kan AT, Fu G, et al. 1999. Adsorption-desorption behaviors of hydrophobic organic compounds in sediments of Lake Charles, Louisiana, USA. *Environ Toxicol Chem* 18(8):1610-1616.

\*Chevreuil M, Garmouma M, Teil MJ, et al. 1996. Occurrence of organochlorines (PCBs, pesticides) and herbicides (*Triazines, phenylureas*) in the atmosphere and in the fallout from urban and rural stations of the Paris area. *Sci Total Environ* 182:25-37.

Choudhry GG, Webster GRB, Hutzinger O. 1986. Environmentally significant photochemistry of chlorinated benzenes and their derivatives in aquatic systems. *Toxicol Environ Chem* 13:27-84.

Chuang T-Y, Mirowski GW, Reizner GT. 1998. Dermatoepidemiology. III. ABC principles for a critical review of the literature. *Int J Dermatol* 37(1):1-6.

Clansky KB, ed. 1986. Chemical guide to the OSHA hazard communication standard. Burlingame, CA: Roytech Publications Inc., 72, 653-655.

Clark DE, Ivie GW, Camp BJ. 1981. Effects of dietary hexachlorobenzene on *in vivo* biotransformation, residue deposition, and elimination of certain xenobiotics by rats. *J Agric Food Chem* 29:600-608.

\*Clayton GD, Clayton FE, eds. 1981. Patty's industrial hygiene and toxicology: 3rd revised ed. Volume 2B: Toxicology. New York, NY: Wiley-Interscience Publication, 3626-3684.

\*Clewell HJ III, Andersen ME. 1985. Risk assessment extrapolations and physiological modeling. *Toxicol Ind Health* 1(4):111-131.

\*CO Dept of Public Health and Environ. 1999. Hexachlorobenzene: Ground water organic chemical standards. <http://www.cdphe.state.co.us/cdphehom.asp>.

\*Cobb GP, Norman DM, Kendall RJ. 1994. Organochlorine contaminant assessment in great blue herons using traditional nonlethal monitoring techniques. *Environ Pollut* 83(3):299-309.

Cochon AC, San Martin de Viale LC, Billi de Catabbi S. 1999. Effects of hexachlorobenzene on phospholipid and porphyrin metabolism in Harderian glands: a time-course study in two strains of rats. *Toxicol Lett* 106:129-136.

\*Cochon AC, San Martin de Viale LC, Billi de Catabbi S. 2001. Phospholipid alterations elicited by hexachlorobenzene in rat brain are strain-dependent and porphyria-independent. *Comp Biochem Physiol C* 130:199-207.

\*Cohn WJ, Boylan JJ, Blanke RV, et al. 1978. Treatment of chlordecone kepone toxicity with cholestyramine: Results of a controlled clinical trial. *NE J Med* 298:243-248.

\*Colborn T, Clement C, eds. 1992. Chemically-induced alterations in sexual and functional development: The wildlife-human connection. In: *Advances in modern environmental toxicology*, Vol. XXI, Princeton, NJ: Princeton Scientific Publishing.

\*Conde C, Maluenda C, Arrabal C. 1993. Organochlorine residues in human milk in Spain. Polychlorinated biphenyls (PCBs) from 1988 to 1991. *Bull Environ Contam Toxicol* 51:832-837.

## 9. REFERENCES

- \*Connell DW, Bowman M, Hawker DW. 1988. Bioconcentration of chlorinated hydrocarbons from sediment by oligochaetes. *Ecotoxicol Environ Saf* 16:293-302.
- Cook J, Engel M. 1999. Multiresidue screening of pesticides in foods using retention time locking, GC-AED, database search, and GC/MS identification. *J AOAC Int* 82(2):313-326.
- Cornelissen G, Van der Pal M, van Noort PCM, et al. 1999. Competitive effects on the slow desorption of organic compounds from sediments. *Chemosphere* 39(11):1971-1981.
- \*Corsolini S, Focardi S, Leonzio C, et al. 1999. Heavy metals and chlorinated hydrocarbon concentrations in the red fox in relation to some biological parameters. *Environ Monitor Assess* 54:87-100.
- Cortes DR, Hites RA. 2000. Detection of statistically significant trends in atmospheric concentrations of semivolatile compounds. *Environ Sci Technol* 34:2826-2829.
- \*Courtney KD, Andrews JE. 1985. Neonatal and maternal body burdens of hexachlorobenzene (HCB) in mice: Gestational exposure and lactational transfer. *Fund Appl Toxicol* 5:265-277.
- Courtney KD, Andrews JE, Grady MA, et al. 1984. Postnatal effects of hexachlorobenzene on cardiac lactic dehydrogenase (LDH) and creatine kinase (CK) isozymes in CD-1 mice. *Toxicol Lett* 22:223-228.
- Courtney KD, Andrews JE, Grady MA. 1985. Placental transfer and fetal deposition of hexachlorobenzene in the hamster and guinea pig. *Environ Res* 37:239-249.
- \*Courtney KD, Andrews, JE, Svendsgaard DJ. 1979. Hexachlorobenzene (HCB) deposition in maternal and fetal tissues of rat and mouse: 1. Chemical quantification of HCB in tissues. *Environ Res* 19:1-13.
- \*Courtney KD, Copeland MF, Robbins A. 1976. The effects of pentachloronitrobenzene, hexachlorobenzene, and related compounds on fetal development. *Toxicol Appl Pharmacol* 35:239-256.
- Cousins IT, Beck AJ, Jones KC. 1999. A review of the processes involved in the exchange of semi-volatile organic compounds (SVOC) across the air-soil interface. *Sci Total Environ* 228:5-24.
- \*Craan A, Haines D. 1998. Twenty-five years of surveillance for contaminants in human breast milk. *Arch Environ Contam Toxicol* 35:702-710.
- Crane JL. 1996. Carcinogenic human health risks associated with consuming contaminated fish from five Great Lakes Areas of Concern. *J Great Lakes Res* 22(3):653-668.
- Cripps DJ. 1986. Porphyria: Genetic and acquired. *IARC Sci Publ* 77:549-566.
- Cripps DJ. 1987. Diet and alcohol effects on the manifestation of hepatic porphyrias. *Fed Proc* 46:1894-1900.
- \*Cripps DJ. 1990. Transplacental and mammary absorption of hexachlorobenzene: Experimental pembe yara porphyria in neonates. *Mol Aspects Med* 11(1-2):81-82.
- Cripps DJ, Peters HA, Gocmen A. 1981. Porphyria turcica (hexachlorobenzene intoxication) twenty years later. *Br J Dermatol* 105:15.

## 9. REFERENCES

- \*Cripps DJ, Peters HA, Gocmen A, et al. 1984. Porphyria turcica due to hexachlorobenzene: A 20 to 30 year follow-up study on 204 patients. *Br J Dermatol* 111:413-422.
- Crisp T, Clegg E, Cooper R, et al. 1998. Environmental endocrine disruption: an effects assessment and analysis. *Environ Health Perspect* 106(Suppl. 1):11-56.
- \*Cuomo R, Rodino S, Rizzoli R, et al. 1991. Bile and biliary lipid secretion in rats with hexachlorobenzene-induced porphyria. Effect of S-adenosyl-L-methionine administration. *J Hepatol* 12:87-93.
- \*Currier MF, McClimans CD, Barna-Lloyd G. 1980. Hexachlorobenzene blood levels and the health status of men employed in the manufacture of chlorinated solvents. *J Toxicol Environ Health* 6:367-377.
- Custer TW, Custer CM. 1995. Transfer and accumulation of organochlorines from black-crowned night-heron eggs to chicks. *Environ Toxicol Chem* 14(3):533-536.
- Custer TW, Custer CM, Hines RK, et al. 1999. Organochlorine contaminants and reproductive success of double-crested cormorants from Green Bay, Wisconsin, USA. *Environ Toxicol Chem* 18(6):1209-1217.
- Custer TW, Custer CM, Stromborg KL. 1997a. Distribution of organochlorine contaminants in double-crested cormorant eggs and sibling embryos. *Environ Toxicol Chem* 16(8):1646-1649.
- Custer TW, Hines RK, Melancon MJ, et al. 1997b. Contaminant concentrations and biomarker response in great blue heron eggs from 10 colonies on the upper Mississippi River, USA. *Environ Toxicol Chem* 16(2):260-271.
- Custer TW, Sparks DW, Sobiech SA, et al. 1996. Organochlorine accumulation by sentinel mallards at the Winston-Thomas Sewage Treatment Plant, Bloomington, Indiana. *Arch Environ Contam Toxicol* 30:163-169.
- \*Czaja K, Ludwicki JK, Goralczyk K, et al. 1997. Organochlorine pesticides, HCB, and PCBs in human milk in Poland. *Bull Environ Contam Toxicol* 58(5):769-775.
- Czaja K, Ludwicki JK, Goralczyk K, et al. 1998. Exposure of infants to polychlorinated biphenyls and organochlorine pesticides from mother's milk. *Organohalogen Compounds* 38:109-112.
- Czaja K, Ludwicki JK, Goralczyk K, et al. 1999. Effect of changes in excretion of persistent organochlorine compounds with human breast milk on related exposure of breast-fed infants. *Arch Environ Contam Toxicol* 36(4):498-503.
- \*D'Amour M, Charbonneau M. 1992. Sex-related difference in hepatic glutathione conjugation of hexachlorobenzene in the rat. *Toxicol Appl Pharmacol* 112:229-234.
- \*Daniel V, Huber W, Bauer K, et al. 2001. Associations of blood levels of PCB, HCHs, and HCB with numbers of lymphocyte subpopulations, in vitro lymphocyte response, plasma cytokine levels, and immunoglobulin autoantibodies. *Environ Health Perspect* 109(2):173-178.
- Daniell WE, Stockbridge HL, Labbe RF, et al. 1997. Environmental chemical exposures and disturbances of heme synthesis. *Environ Health Perspect Suppl* 105(1):37-53.

## 9. REFERENCES

- \*Darvill T, Lonky E, Reihman J, et al. 2000. Prenatal exposure to PCBs and infant performance on the fagan test of infant intelligence. *Neurotoxicology* 21(6):1029-1038.
- \*da Silva Augusto LG, Lieber SR, Ruiz MA, et al. 1997. Micronucleus monitoring to assess human occupational exposure to organochlorides. *Environ Mol Mutagen* 29:46-52.
- \*Davis BD, Morgan RC. 1986. Hexachlorobenzene in hazardous waste sites. *IARC Sci Publ* 77:23-30.
- Debets FM, Hamers WJ, Strik JJ. 1980b. Metabolism as a prerequisite for the porphyrinogenic action of polyhalogenated aromatics, with special reference to hexachlorobenzene and polybrominated biphenyls (firemaster BP-6). *Int J Biochem* 12:1019-1025.
- Debets F, Reinders J-H, Koss G, et al. 1981. Effects of dietary antioxidants on the biotransformation and porphyrinogenic action of hexachlorobenzene in two strains of rats. *Chem Biol Interact* 37:77-94.
- \*Debets FM, Strik JJ, Olie K. 1980a. Effects of pentachlorophenol on rat liver changes induced by hexachlorobenzene, with special reference to porphyria, and alterations in mixed function oxygenases. *Toxicology* 15:181-195.
- \*Dellinger B, Taylor PH, Tirey DA. 1989. Pathways of formation of chlorinated PICs from the thermal degradation of simple chlorinated hydrocarbons. *J Hazardous Materials* 22:175-186.
- De Matteis F. 1986. Experimental hepatic porphyria caused by hexachlorobenzene: Mechanism of the metabolic block. *IARC Sci Publ* 77:427-431.
- \*De Matteis F, Prior BE, Rimington C. 1961. Nervous and biochemical disturbances following hexachlorobenzene intoxication. *Nature* 191:363-366.
- \*Den Besten C, Bennik MHJ, Bruggeman I, et al. 1993. The role of oxidative metabolism in hexachlorobenzene-induced porphyria and thyroid hormone homeostasis: A comparison with pentachlorobenzene in a 13-week feeding study. *Toxicol Appl Pharmacol* 119:181-194.
- \*Den Besten C, Bennik MHJ, van Iersel M, et al. 1994. Comparison of the urinary metabolite profiles of hexachlorobenzene and pentachlorobenzene in the rat. *Chem Biol Interact* 90:121-137.
- \*Den Tonkelaar EM, Verschuuren HG, Bankovska J, et al. 1978. Hexachlorobenzene toxicity in pigs. *Toxicol Appl Pharmacol* 43:137-145.
- \*DeVault DS. 1985. Contaminants in fish from Great Lakes Harbors and tributary mouths. *Arch Environ Contam Toxicol* 14:587-594.
- \*Dewailly E, Ayotte P, Bruneau S, et al. 1993. Inuit exposure to organochlorines through the aquatic food chain in arctic Quebec. *Environ Health Persp* 101(7):618-620.
- \*Dewailly E, Ayotte P, Bruneau S, et al. 2000. Susceptibility to infections and immune status in inuit infants exposed to organochlorines. *Environ Health Perspect* 108(3):205-211.
- \*Dewailly E, Dodin S, Verreault R, et al. 1994. High organochlorine body burden in women with estrogen receptor-positive breast cancer. *J Natl Cancer Inst* 86(3):232-234.

## 9. REFERENCES

- \*Dewailly E, Mulvad G, Pedersen HS, et al. 1999. Concentration of organochlorines in human brain, liver, and adipose tissue autopsy samples from Greenland. *Environ Health Perspect* 107(10):823-828.
- \*Djordjevic MV, Hoffmann D, Fan J, et al. 1994. Assessment of chlorinated pesticides and polychlorinated biphenyls in adipose breast tissue using a supercritical fluid extraction method. *Carcinogenesis* 15(11):2581-2585.
- Dobson S, Howe P. 1986. Evaluation of environmental impact of hexachlorobenzene. *IARC Sci Publ* 77:203-209.
- \*Dogramaci I. 1964. Porphyrins and porphyrin metabolism with special reference to porphyria in childhood. *Adv Pediatr* 13:11-63.
- \*Domingo JL, Schuhmacher M, Agramunt MC, et al. 2001. Levels of metals and organic substances in blood and urine of workers at a new hazardous waste incinerator. *Int Arch Occup Environ Health* 74:263-269.
- Donald DB, Syrgiannis J, Crosley RW, et al. 1999. Delayed deposition of organochlorine pesticides at a temperate glacier. *Environ Sci Technol* 33:1794-1798.
- Donaldson GM, Shutt JL, Hunter P. 1999. Organochlorine contamination in bald eagle eggs and nestlings from the Canadian Great Lakes. *Arch Environ Contam Toxicol* 36:70-80.
- \*Dorgan JF, Brock JW, Rothman N, et al. 1999. Serum organochlorine pesticides and PCBs and breast cancer risk: results from a prospective analysis (USA). *Cancer Causes Control* 10:1-11.
- \*Dowdele E, Mustard P, Eagles L. 1967. Delta aminolevulinic acid synthetase activity in normal and porphyric human livers. *S Afr Med J* 41:1093-1096.
- \*Dreisbach RH. 1983. *Handbook of poisoning*. Norwalk, Connecticut: Appleton & Lange, Lange Medical Publications, 88-89.
- \*Driscoll MS, Hassett JP, Fish CL, et al. 1991. Extraction efficiencies of organochlorine compounds from Niagara River (New York, USA) water. *Environ Sci Technol* 25(8):1432-1439.
- \*Drobacheff C, Derancourt C, Van Landuyt, et al. 1998. Porphyria cutanea tarda associated with human immunodeficiency virus infection. *Eur J Dermatol* 8(7):492-496.
- \*Dubois M, Grosse Y, Thome JP, et al. 1997. Metabolic activation and DNA-adducts detection as biomarkers of chlorinated pesticide exposures. *Biomarkers* 2:17-24.
- Dubus IG, Hollis JM, Brown CD. 2000. Pesticides in rainfall in Europe. *Environ Pollut* 110(10):331-344.
- Dunstan RH, Donohoe M, Taylor W, et al. 1995. A preliminary investigation of chlorinated hydrocarbons and chronic fatigue syndrome. *Med J Aust* 163:294-297.
- Dunstan R, Roberts T, Donohoe M, et al. 1996. Bioaccumulated chlorinated hydrocarbons and red/white blood cell parameters. *Biochem Mol Med* 58:77-84.

## 9. REFERENCES

- \*Ecker S, Horak O. 1994. Pathways of HCB contamination to oil pumpkin seeds. *Chemosphere* 29(9-11):2135-2145.
- \*Egger NG, Goeger DE, Payne DA, et al. 2002. Porphyria cutanea tarda: Multiplicity of risk factors including HFE mutations, hepatitis C, and inherited uroporphyrinogen decarboxylase deficiency. *Dig Dis Sci* 47(2):419-426.
- \*Eicman GA, Clement RE, Karasek FW. 1981. Variations in concentrations of organic compounds including polychlorinated dibenzo-*p*-dioxins and polynuclear aromatic hydrocarbons in fly ash from a municipal incinerator. *Anal Chem* 53:955-959.
- \*Eisenreich SJ, Looney BB, Thornton JD. 1981. Airborne organic contaminants in the Great Lakes ecosystem. *Environ Sci Tech* 15(1):30-38.
- Ejobi F, Kanja LW, Kyule MN, et al. 1996. Organochlorine pesticide residues in mothers' milk in Uganda. *Bull Environ Contam Toxicol* 56(6):873-880.
- Elder GH. 1986. Introduction to the porphyrias. *IARC Sci Publ* 77:545-547
- Elder GH, Deam S. 1990. Iron and porphyria cutanea tarda. *Mol Aspects Med* 11:82.
- \*Elder GH, Urquhart AJ. 1986. Immunochemical studies of the uroporphyrinogen decarboxylase defect caused by hexachlorobenzene. In: Morris CR, Cabral JRP, eds. *As: Hexachlorobenzene: Proceedings of an International Symposium*. IARC Sci Publ 77:441-448.
- \*Elder GH, Evans JO, Maltin S. 1976. The effect of the porphyrinogenic compound, hexachlorobenzene on the activity of hepatic uroporphyrinogen decarboxylase in rat liver. *Clin Sci Mol Med* 51:71.
- \*Elder VA, Proctor BL, Hites RA. 1981. Organic compounds found near dump sites in Niagara Falls, New York. *Environ Sci Technol* 15:1237-1243.
- \*Elkin BT, Bethke RW. 1995. Environmental contaminants in caribou in the Northwest Territories, Canada. *Sci Total Environ* 160-161:307-321.
- \*Ellenhorn MJ, Barceloux DG. 1988. *Medical toxicology: Diagnosis and treatment of human poisoning*. New York, NY: Elsevier Press, 1078-1080.
- \*Elliott JE, Martin PA. 1994. Chlorinated hydrocarbons and shell thinning in eggs of (*Accipiter*) hawks in Ontario, 1986-1989. *Environ Pollut* 86(2):189-200.
- \*Engst R, Macholz RM, Kujawa M. 1976a. The metabolism of hexachlorobenzene (HCB) in rats. *Bull Environ Contam Toxicol* 16:248-252.
- Engst R, Macholz RM, Kujawa M. 1976b. [Hexachlorocyclohexane metabolites in human urine]. *Z Gesamte Hyg Ihre Grenzgeb* 22:205-208. (German)
- Enriquez De Salamanca RE, Lopez-Miras A, Munoz JJ, et al. 1990. Is hexachlorobenzene human overload related to porphyria cutanea tarda? A speculative hypothesis. *Med. Hypotheses* 33(1):69-71.
- EPA. 1971a. Toxicologic study of female rats administered hexachlorobutadiene or hexachlorobenzene for thirty days. Washington, DC: U.S. Environmental Protection Agency. OTS0205867.

## 9. REFERENCES

- EPA. 1971b. Toxicologic study of female rats administered hexachlorobutadiene or hexachlorobenzene for thirty days (final report). Washington, DC: U.S. Environmental Protection Agency. OTS0537066.
- EPA. 1973. Guidelines establishing test procedures for the analysis of pollutants. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 136.
- EPA. 1975a. National primary drinking water regulations. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.
- \*EPA. 1975b. Survey of industrial process data. Task 1. Hexachlorobenzene and hexachlorobutadiene pollution from chlorocarbon processing. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances. PB 243-641.
- \*EPA. 1976a. An ecological study of hexachlorobenzene (HCB) [Abstract]. Washington, DC: U.S. Environmental Protection Agency. EPA/560/6-76/009.
- \*EPA. 1976b. Sampling and analysis of selected toxic substances. Task 1A- Hexachlorobenzene. OTS, Washington, DC: U.S. Environmental Protection Agency. EPA-560/676/001.
- EPA. 1978. Quantification of chlorinated hydrocarbons in previously collected air samples. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards. EPA-450/3-78-112.
- EPA. 1979a. Design and evaluation of a terrestrial model ecosystem for evaluation of substitute pesticide chemicals. Corvallis, OR: U.S. Environmental Protection Agency, Office of Research and Development. (authors: Metcalf RL, et al). EPA-600/3-79-004.
- EPA. 1979b. Status assessment of toxic chemicals: Hexachlorobenzene. Cincinnati, OH: U.S. Environmental Protection Agency, Office of Research and Development. EPA-600/2-79-210g.
- EPA. 1979c. National primary drinking water regulations. Effective dates. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.6.
- \*EPA. 1980a. Hazardous Waste Management System: Identification and listing of hazardous waste. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261.
- \*EPA. 1980b. Ambient water quality criteria for chlorinated benzenes. Washington, DC: U.S. Environmental Protection Agency, Office of Water, Regulations and Standards. EPA-440/5-80-028.
- \*EPA. 1980c. Analysis of pesticide residues in human and environmental samples: A compilation of methods selected for use in pesticide monitoring programs. Research Triangle Park, NC: U.S. Environmental Protection Agency, Health Effects Research Laboratory, Environmental Toxicology Division. EPA-600/8-80-038.
- EPA. 1980d. Pentachlorophenol (PCP) and chlorinated phenol metabolites of PCP and HCB. Manual of analytical methods for the analysis of pesticides in humans and environmental samples. Washington, DC: U.S. Environmental Protection Agency. EPA 600/8-80-38.
- EPA. 1980e. Determination of pentachlorophenol (rapid method) in blood. Manual of analytical methods for the analysis of pesticides in humans and environmental samples. Washington, DC: U.S. Environmental Protection Agency. EPA 600/8-80-38.

## 9. REFERENCES

- EPA. 1980f. U.S. Environmental Protection Agency. Federal Register. 49 FR 79318.
- EPA. 1980g. A study of the mortality of those who have worked at Hooker Chemical's plant at Montague, Michigan. Washington, DC: U.S. Environmental Protection Agency. OTS0512825.
- \*EPA. 1981a. Aquatic fate process data for organic priority pollutants. Washington, DC: U.S. Environmental Protection Agency, Office of Water Regulations and Standards. EPA-440/4-81-014.
- \*EPA. 1981b. Electroplating point source category. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 413.
- EPA. 1982a. Test method: Chlorinated hydrocarbons - method 612. In: Longbottom JE, Lichtenberg JJ, eds. Methods for organic chemical analysis of municipal and industrial wastewater. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Monitoring and Support Laboratory. EPA-600/4-82-057.
- EPA. 1982b. Test method: Base/neutrals and acids - method 625. In: Longbottom JE, Lichtenberg JJ, eds. Methods for organic chemical analysis of municipal and industrial wastewater. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Monitoring and Support Laboratory. EPA-600/4-82-057.
- EPA. 1982c. Steam electric power generating point source category. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 423.
- EPA. 1982d. Effects of selected organic drinking water contaminants on male reproduction. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development. EPA-600/1-82-009.
- EPA. 1982e. Treatability manual: Volume I. Treatability Data. Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development. EPA-600/2-82-001a.
- EPA. 1982f. Preliminary quantitative usage analysis of picloram. Washington, DC: U.S. Environmental Protection Agency, Office of Pesticide Programs.
- \*EPA. 1983a. EPA administered permit programs: The national pollutant discharge elimination system. Code of Federal Regulations. 40 CFR 122.
- EPA. 1983b. Metal finishing point source category. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 433.11.
- EPA. 1983c. Reportable quantity document for benzene, hexachloro-. External review draft. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office ECAO-CIN-RO32.
- EPA. 1983d. List of chemicals produced by affected facilities. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 60.489.
- \*EPA. 1984a. Primary rare earth metals. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 421.

## 9. REFERENCES

- \*EPA. 1984b. Health effects assessment for hexachlorobenzene. Cincinnati, OH: U.S. Environmental Protection Agency, Office of Research and Development. EPA/540/1-86/017.
- EPA. 1984c. Nonindustrial sources of potentially toxic substances and their applicability to source apportionment. Research Triangle Park, NC: U.S. Environmental Protection Agency. EPA-450/4-84-003.
- EPA. 1984d. Guidelines establishing test procedures for the analysis of pollutants. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 136.
- \*EPA. 1984e. Methods for organic chemical analysis of municipal and industrial wastewater. Washington, DC: U.S. Environmental Protection Agency. PB83-201 798 Chlorinated Hydrocarbons- (Method 612)
- \*EPA. 1984f. Methods for organic chemical analysis of municipal and industrial wastewater. Washington, DC: U.S. Environmental Protection Agency. PB83-201 798 Base/Neutral and Acids- (Method 625)
- EPA. 1985a. Health assessment document for chlorinated benzenes: Final Report. Cincinnati, OH: U.S. Environmental Protection Agency, Office of Research and Development. EPA/600/8-84/015F.
- EPA. 1985b. Drinking water criteria document for hexachlorobenzene. Washington, DC: U.S. Environmental Protection Agency, Office of Drinking Water. EPA/600/x-84/1790-1. NTIS No. PB86-117777.
- \*EPA. 1985c. Standards for the management of specific hazardous wastes and specific types of hazardous waste management facilities. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 266.
- EPA. 1985d. Designation of reportable quantities, and notification. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 302.
- EPA. 1985e. Standards for the management of specific hazardous wastes and specific types of hazardous waste management facilities. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 266.
- EPA. 1985f. National primary drinking water regulations. Maximum contaminant level goals. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.50.
- \*EPA. 1985g. Environmental exposure to hexachlorobenzene in the United States. Washington, DC: U.S. Environmental Protection Agency, Office of Pesticides and Toxic Substances. TS-769-c.
- EPA. 1985. Preliminary quantitative usage analysis of PCNB (056502). Washington, DC: U.S. Environmental Protection Agency, Office of Pesticide Programs.
- \*EPA. 1986a. Method 8250: Gas chromatography/mass spectrometry for semivolatile organics: Packed column technique. In: Test methods for evaluating solid waste. 3rd ed. SW-846. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response.
- EPA. 1986b. Method 8270: Gas chromatography/mass spectrometry for semivolatile organics: Capillary column technique. In: Test methods for evaluating solid waste. 3rd ed. SW-846.

## 9. REFERENCES

Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response.

\*EPA. 1986c. Method 8410: Capillary column analysis of semivolatile organic compounds by gas chromatography/Fourier transform infrared (GC/FT-IR) spectrometry. In: Test methods for evaluating solid waste. 3rd ed. SW-846. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response.

EPA. 1986d. Land disposal restrictions. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 268.

\*EPA. 1986e. Exposure assessment for hexachlorobenzene. Washington, DC: U.S. Environmental Protection Agency, Office of Pesticides and Toxic Substances. EPA-560/5-86-019.

\*EPA. 1986f. Broad scan analysis of the FY82 national human adipose tissue survey specimens: Volume I - Executive summary. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances. EPA-560/5-86-035.

EPA. 1986g. Report on the interim data base for state and local air toxic volatile organic chemical measurements. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards. EPA-450/4-86-012.

\*EPA. 1987a. Organic chemicals, plastics, and synthetic fibers. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 414.

EPA. 1987b. Hexachlorobenzene health advisory. Washington, DC: U.S. Environmental Protection Agency, Office of Drinking Water.

EPA. 1987c. U.S. Environmental Protection Agency. Federal Register. 52:25942-25953.

EPA. 1987d. National primary drinking water regulations. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.

EPA. 1987e. Land Disposal Restrictions. Treatment standards applicability. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 268.40.

EPA. 1987f. Reference dose (RfD): Description and use in health risk assessments. Vol. I, Appendix A: Integrated risk information system supportive documentation. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. EPA/600/8-86/032a.

\*EPA. 1987g. Measurement of hydrolysis rate constants for evaluation of hazardous waste land disposal. Vol 2. Washington, DC: U.S. Environmental Protection Agency. EPA-600/53-87-/019.

\*EPA. 1988a. Drinking water criteria document for hexachlorobenzene. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment. ECAO-CIN 424.

EPA. 1988b. Toxic chemical release reporting: Community right-to-know. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 372.

## 9. REFERENCES

\*EPA. 1988c. Methods for the determination of organic compounds in drinking water. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Monitoring Systems Laboratory, Office of Research and Development. EPA-600/4-88-039.

\*EPA. 1988d. Compendium of methods for the determination of toxic organic compounds in ambient air. Research Triangle Park, NC: U.S. Environmental Protection Agency, Quality Assurance Division, Environmental Monitoring Systems Laboratory. EPA-600/4-89-017.

\*EPA. 1988e. Method 505: Method for the determination of organic compounds in drinking water. Washington, DC: U.S. Environmental Protection Agency. EPA 600/4-88/039.

\*EPA. 1988f. Method 508: Method for the determination of organic compounds in drinking water. Washington, DC: U.S. Environmental Protection Agency. EPA 600/4-88/039.

EPA. 1988g. The emergency planning and community right-to-know act of 1986. Washington, DC: U.S. Environmental Protection Agency.

\*EPA. 1988h. Analytical and sampling methods of the Nonoccupational Pesticide Exposure Study (NOPEs). Washington, DC: U.S. Environmental Protection Agency. EPA 600/9-88-015.

\*EPA. 1989a. U.S. Environmental Protection Agency: Part II. Federal Register. 54:1056-1120.

EPA. 1989b. U.S. Environmental Protection Agency. Federal Register 54 FR 33418.

EPA. 1989c. Mortality among Dow Chemical employees of a Texas operations per-tete manufacturing plant. Washington, DC: U.S. Environmental Protection Agency. OTS0516752.

\*EPA. 1990. Interim methods for development of inhalation reference concentrations. Washington DC: U.S. Environmental Protection Agency. EPA/600/8-90/066A.

EPA. 1991. Criteria for municipal solid waste landfills (Eff. 10-9-93). Washington, DC: U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 258.

EPA. 1992a. Drinking water regulations and health advisories. Washington, DC: U.S. Environmental Protection Agency, Office of Water.

\*EPA. 1992b. "National study of chemical residues in fish." and "Guidance for assessing chemical contaminants data for use in fish advisories." 2 Volumes. Washington, DC: U.S. Environmental Protection Agency, Office of Water, Office of Science and Technology. EPA-823-R-92-008a and -008b.

EPA. 1992c. General pretreatment regulations for existing and new sources of pollution. U.S. Environmental Protection Agency. 40 CFR 403.

EPA. 1992d. Initial submission: Letter submitting studies on dibromohexachlorooctahydro-dimethylnaphthalene, decachlorooctahydrodimethanonaphthalene, and Hexabromodiphenylamine (final report). Washington, DC: U.S. Environmental Protection Agency. OTS0537064.

EPA. 1992e. Initial submission: 28-day dietary feeding study in rats on 7 chemicals: Hexachlorobenzene; technical DAC 839, dacthal; pure dacthal; DAC 1209; DAC 976 W-letter 022192. Washington, DC: U.S. Environmental Protection Agency. OTS0537065.

## 9. REFERENCES

- \*EPA. 1993a. Guidance for assessing chemical contaminant data for use in fish advisories. Vol. 1. Fish sampling and analysis. Washington DC: U.S. Environmental Protection Agency, Office of Water. EPA-823-R-93-002.
- EPA. 1993b. Status of pesticides in reregistration and special review. Washington, DC: U.S. Environmental Protection Agency. Office of Pesticide Programs, Special Review and Reregistration Division. EPA-738-R-93-009.
- \*EPA. 1994a. Test methods for evaluating solid waste. Volume IB: Laboratory Manual Physical/Chemical Methods. U.S. Environmental Protection Agency. Method 8270B.
- \*EPA. 1994b. Hexachlorobenzene carcinogenicity summary table. Office of health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. Washington DC: Office of air quality planning and standards. EPA 600/8-84-015F.
- \*EPA. 1994c. Personal communication to Dr. Patricia Cunningham, Research Triangle Institute, regarding percent contamination of hexachlorobenzene in pentachlorophenol. U.S. Environmental Protection Agency, Office of Pesticide Programs, Washington DC (April 13, 1994).
- EPA. 1995a. The National listing of fish consumption advisories. Office of Science and Technology, Washington, DC: U.S. Environmental Protection Agency. EPA-823-C-95-001.
- \*EPA. 1995b. Guidance for assessing chemical contaminant data for use in fish advisories. Vol 1: Fish sampling and analysis. Second Edition. Washington, DC: U.S. Environmental Protection Agency, Office of Science and Technology. EPA 823-R-95-007.
- \*EPA. 1995c. Toxic chemical release inventory. Reporting form R and instructions. Washington DC: U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics. EPA 745-K-95-051.
- EPA. 1995d. Universal Treatment Standards. U.S. Environment Protection Agency. 60 FR 242.
- EPA. 1995e. Drinking water regulations and health advisories. Washington, DC: U.S. Environmental Protection Agency, Office of Water.
- EPA. 1996. National listing of fish consumption advisories summary report. Washington, DC: U.S. Environmental Protection Agency.
- \*EPA. 1997a. Automated Form R for Windows: User's guide (RY97). Washington, DC: U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics.
- \*EPA. 1997b. Listing of fish and wildlife consumption advisories. Washington, DC: U.S. Environmental Protection Agency. <http://fish.rti.org/>.
- \*EPA. 1997c. Special report on environmental endocrine disruption: An effects assessment and analysis. Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. EPA/630/R-96/012.
- \*EPA. 1999a. Chemicals and chemical categories to which this part applies. Washington, DC: U.S. Environmental Protection Agency. 40CFR 372.65 Subpart D.
- \*EPA. 1999b. Consumer confidence reports. Washington, DC: U.S. Environmental Protection Agency. 40 CFR 141 Subpart O.

## 9. REFERENCES

- EPA. 1999c. Demonstration of early reduction. Washington, DC: U.S. Environmental Protection Agency. 40 CFR 63.74.
- \*EPA. 1999d. Designation of hazardous substances. Washington, DC: U.S. Environmental Protection Agency. 40 CFR 302.4.
- \*EPA. 1999e. Discarded commercial chemical products, off-specification species, container residues, and spill residues thereof. Washington, DC: U.S. Environmental Protection Agency. 40 CFR 261.33.
- EPA. 1999f. Effective dates. Washington, DC: U.S. Environmental Protection Agency. 40 CFR 141.6.
- \*EPA. 1999g. Maximum contaminant level goals and maximum residual disinfectant level goals. Washington, DC: U.S. Environmental Protection Agency. 40 CFR 141.50 Subpart F.
- \*EPA. 1999h. Public notification. Washington, DC: U.S. Environmental Protection Agency. 40 CFR 141.32.
- EPA. 1999i. Specialized definitions. Washington, DC: U.S. Environmental Protection Agency. 40 CFR 433.11.
- \*EPA. 1999j. Toxicity characteristic. Washington, DC: U.S. Environmental Protection Agency. 40 CFR 261.24.
- \*EPA. 1999k. Universal treatment standards. Washington, DC: U.S. Environmental Protection Agency. 40 CFR 268.48.
- \*EPA. 2001a. Designation, reportable quantities, and notification. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 302.4. <http://ecfr.access.gpo.gov/otcgi/cfr/otfilter.cgi>. December 19, 2001.
- \*EPA. 2001b. Electroplating point source category. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 413.02. <http://frwebgate.access.gpo.gov/cgi-bin/>. December 20, 2001.
- \*EPA. 2001c. Metal finishing point source category. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 433.11. <http://frwebgate.access.gpo.gov/cgi-bin/>. December 20, 2001.
- \*EPA. 2001d. Nonferrous metals manufacturing point source category. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 421.274. <http://frwebgate.access.gpo.gov/cgi-bin/>. December 20, 2001.
- \*EPA. 2001e. Organic chemicals, plastics, and synthetic fibers. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 414. [http://www.access.gpo.gov/nara/cfr/cfrhtml\\_00/Title\\_40/40cfr414\\_main\\_00.html](http://www.access.gpo.gov/nara/cfr/cfrhtml_00/Title_40/40cfr414_main_00.html). December 19, 2001.
- \*EPA. 2001f. Groundwater monitoring list. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 264, Appendix IX. <http://ecfrback.access.gpo.gov/otcgi/cfr/otfilter.cgi>. December 19, 2001.
- \*EPA. 2001g. Hazardous waste management. Risk specific doses. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 266, Appendix V. <http://ecfrback.access.gpo.gov/otcgi/cfr/otfilter.cgi>. December 19, 2001.

## 9. REFERENCES

- \*EPA. 2001h. Health based limits for exclusion of waste-derived residues. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 266, Appendix VII. <http://ecfrback.access.gpo.gov/otcgi/cfr>. December 19, 2001.
- \*EPA. 2001i. Identification and listing of hazardous waste. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261.33(f). <http://ecfrback.access.gpo.gov/otcgi/cfr...8&RGN=BSECCT&SUBSET=SUBSET&FROM=1&ITEM=1> December 19, 2001.
- \*EPA. 2001j. Land disposal restrictions. Universal treatment standards. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 268.48. <http://ecfr.access.gpo.gov/otcgi/cfr>. December 19, 2001.
- \*EPA. 2001k. Maximum contaminant levels for organic contaminants. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.61(c). <http://ecfr.access.gpo.gov/otcgi/cfr/otf>. December 19, 2001.
- \*EPA. 2001l. Maximum contaminant level goals for organic contaminants. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.50(a)(22). <http://ecfr.access.gpo.gov/otcgi/cfr/otf>. December 19, 2001.
- \*EPA. 2001m. National primary drinking water regulations. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141. <http://ecfrback.access.gpo.gov/otcgi/cfr>. December 19, 2001.
- \*EPA. 2001n. Toxic chemical release reporting; Community right-to-know. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 372. <http://ecfrback.access.gpo.gov/otcgi/cfr>. December 19, 2001.
- \*EPA. 2001o. Toxic chemical release reporting; Community right-to-know. Alternate reporting thresholds and certification. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 372.27. <http://ecfrback.access.gpo.gov/otcgi/cfr>. December 19, 2001.
- \*EPA. 2001p. Toxicity characteristic. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261.24. <http://ecfrback.access.gpo.gov/otcgi/cfr>. December 19, 2001.
- Ertürk E, Grunden EE, Bryan GT. 1981. Subchronic toxicity of hexachlorobenzene (HCB) in rats, mice, and hamsters. *Fed Amer Soc Expt Bio* 40(3P1):745. (Abstract)
- \*Ertürk E, Lambrecht RW, Peters HA, et al. 1986. Oncogenicity of hexachlorobenzene. *IARC Sci Publ* 77:417-423.
- Fairey R, Taberski K, Lamerdin S, et al. 1997. Organochlorines and other environmental contaminants in muscle tissue of sportfish collected from San Francisco Bay. *Mar Pollut Bull* 34(12):1058-1071.
- Fakan F, Chlumska A, Krut J, et al. 1997. Liver cell cytoplasmic inclusions in experimental porphyrias: their demonstration with the ferric ferricyanide reduction reaction. *Exp Toxicol Pathol* 49:289-293.
- \*Falck F, Ricci A, Wolff MS, et al. 1992. Pesticides and polychlorinated biphenyl residues in human breast lipids and their relation to breast cancer. *Arch Environ Health* 47(2):143-146.
- Farm Chemicals Handbook. 1983. Willoughby, OH: Meister Publishing Co.

## 9. REFERENCES

- \*Farm Chemicals Handbook. 1993. Willoughby, OH: Meister Publishing Co.
- \*Farm Chemicals Handbook. 2000. Vol. 86. Willoughby, OH: Meister Publishing Co., C213.
- \*Farmer WT, Yank M, Letey J, et al. 1976. Land disposal of organic hazardous waste containing HCB. In: National conference of residues on land proceedings. St. Louis, MS: Environmental Protection Agency, 83-86.
- \*Fathepure BZ, Tiedje JM, Boyd SA. 1988. Reductive dechlorination of hexachlorobenzene to tri- and dichlorobenzenes in anaerobic sewage sludge. *Appl Environ Microbiol* 54:327-330.
- \*FDA. 1989. Food and Drug Administration pesticide program - residues in foods 1988. *J AOAC International* 72(5):133A-152A.
- \*FDA. 1990. Food and Drug Administration pesticide program - residues in foods 1989. *J Assoc Off Anal Chem* 73:127A-146A.
- \*FDA. 1991. Food and Drug Administration pesticide program - residues in foods 1990. *J Assoc Off Anal Chem* 74(5):121A-140A.
- \*FDA. 1992. Food and Drug Administration pesticide program - residues in foods 1991. *J Assoc Off Anal Chem* 75:135A-157A.
- \*FDA. 1994. Food and Drug Administration pesticide program - residue monitoring. Residues in food-1993. *J AOAC Int* 77(5):161A-185A.
- \*FDA. 1995. Residue monitoring, 1994 (8th annual FDA pesticide residue monitoring program report). *J AOAC Int* 78(5):119A-142A.
- FEDRIP. 1995. Federal Research in Progress. Dialog Information Service Inc. Amarillo, TX.
- \*FEDRIP. 2000. Federal Research In Progress Database. National Technical Information Service, Springfield, VA.
- \*FEDRIP. 2001. Federal Research In Progress Database. National Technical Information Service, Springfield, VA.
- \*Feldman ES, Bacon BR. 1989. Hepatic mitochondrial oxidative metabolism and lipid peroxidation in experimental hexachlorobenzene-induced porphyria with dietary carbonyl iron overload. *Hepatology* 9:686-692.
- \*Fernandez-Tome M, Billi de Catabbi SC, Aldonatti C, et al. 2000. Heme metabolism and lipid peroxidation in rat kidney hexachlorobenzene-induced porphyria: A compartmentalized study of biochemical pathogenic mechanisms. *Kidney Blood Pressure Research* 23:20-26.
- Finley B, Kirman C, Wenning RJ, et al. 1998. Does the available toxicological evidence warrant identification of hexachlorobenzene as a "dioxin-like" chemical? *Organohalogen Compounds* 38:325-329.
- Fisher J, Mahle D, Bankston L, et al. 1997. Lactational transfer of volatile chemicals in breast milk. *Am Ind Hyg Assoc J* 58:425-431.

## 9. REFERENCES

\*Fitzgerald EF, Hwang S, Deres DA, et al. 2001. The association between local fish consumption and DDE, mirex, and HCB concentrations in the breast milk of Mohawk women at Akwesasne. *J Expo Anal Environ Epidemiol* 11:381-388.

Fleischer O, Wichmann H, Lorenz W. 1999. Release of polychlorinated dibenzo-*p*-dioxins and dibenzofurans by setting off fireworks. *Chemosphere* 39(6):925-932.

\*Foley RE. 1992. Organochlorine residues in New York waterfowl harvested by hunters in 1983-1984. *Environ Monit Assess* 21:37-48.

\*Fomon SJ. 1966. Body composition of the infant: Part I: The male "reference infant". In: Falkner F, ed. *Human development*. Philadelphia, PA: WB Saunders, 239-246.

\*Fomon SJ, Haschke F, Ziegler EE, et al. 1982. Body composition of reference children from birth to age 10 years. *Am J Clin Nutr* 35:1169-1175.

Foster WG. 1998. Endocrine disruptors and development of the reproductive system in the fetus and children: Is there a cause for concern? *Can J Public Health* 89(Suppl. 1):S37-S52.

Foster W, Chan S, Platt L, et al. 2000. Detection of endocrine disrupting chemicals in samples of second trimester human amniotic fluid. *J Clin Endocrinol Metab* 85(8):2954-2957.

Foster WG, Jarrell JF, Younglai EV, et al. 1996. An overview of some reproductive toxicology studies conducted at health Canada. *Toxicol Ind Health* 12(3/4):447-459.

\*Foster WG, McMahon A, Villeneuve DC, et al. 1992a. Hexachlorobenzene (HCB) suppresses circulating progesterone concentrations during the luteal phase in the cynomolgus monkey. *J Applied Toxicol* 12:13-17.

\*Foster WG, McMahon A, Younglai EV, et al. 1995a. Alterations in circulating ovarian steroids in hexachlorobenzene-exposed monkeys. *Reprod Toxicol* 9(6):541-548.

\*Foster WG, Mertineit C, Yagminas AL, et al. 1995b. The effects of hexachlorobenzene on circulating levels of adrenal steroids in the ovariectomized rat. *J Biochem Toxicol* 10(3):129-135.

\*Foster WG, Pentick JA, McMahon A, et al. 1992b. Ovarian toxicity of hexachlorobenzene (HCB) in the superovulated female rat. *J Biochem Toxicol* 7:1-4.

\*Foster WG, Pentick JA, McMahon A, et al. 1993. Body distribution and endocrine toxicity of hexachlorobenzene (HCB) in the female rat. *J Appl Toxicol* 13:79-83.

\*Fracanzani AL, Taioli E, Sampietro M, et al. 2001. Liver cancer risk is increased in patients with porphyria cutanea tarda in comparison to matched control patients with chronic liver disease. *J Hepatol* 35:498-503.

\*Frank R, Rasper J, Smout MS, et al. 1988. Organochlorine residues in adipose tissues, blood and milk from Ontario residents, 1976-1985. *Can J Public Health* 79:150-158.

Franklin MR, Phillips JD, Kushner JP. 1997. Cytochrome P450 induction, uroporphyrinogen decarboxylase depression, porphyrin accumulation and excretion, and gender influence in a 3-week rat model of porphyria *cutanea tarda*. *Toxicol Appl Pharmacol* 147:289-299.

## 9. REFERENCES

- \*Freeman RA, Rozman KK, Wilson AG. 1989. Physiological pharmacokinetic model of hexachlorobenzene in the rat. *Health Phys* 57(Supp 1):139-145.
- FSTRAC. 1988. Summary of state and federal drinking water standards and guidelines. Washington, DC: Federal-State Toxicology and Regulatory Alliance Committee, Chemical Communication Subcommittee.
- FSTRAC. 1990. Summary of state and federal drinking water standards and guidelines. Washington, DC: Federal-State Toxicology and Regulatory Alliance Committee, Chemical Communication Subcommittee.
- \*FSTRAC. 1999. Summary of state and federal drinking water standards and guidelines. Washington, DC: Federal-State Toxicology and Regulatory Alliance Committee, Chemical Communication Subcommittee.
- Funari E. 1995. Human health implications associated with the presence of pesticides in drinking water. In: Vighi M, Funari E, eds. *Pesticide risk in groundwater*. Boca Raton, FL: CRC Press, 121-130.
- \*Garrison AW, Pellizzari ED. 1987. Application of the master analytical scheme to polar organic compounds in drinking water. In: Suffet IH, Malaiyandi M, eds. *Organic pollutants in water: Sampling, analysis, and toxicity testing*. Advances in Chemistry Series No. 214. American Chemical Society, 83-95.
- \*Gartrell MJ, Craun JC, Podrebarac DS, et al. 1986. Pesticides, selected elements, and other chemicals in infant and toddler total diet samples, October 1980 -March 1982. *J Assoc Off Anal Chem* 69:123-145.
- \*Gauthier JM, Metcalfe CD, Sears R. 1997. Chlorinated organic contaminants in blubber biopsies from northwestern Atlantic balaenopterid whales summering in the Gulf of St Lawrence. *Mar Environ Res* 44(2):201-223.
- Gauthier JM, Pelletier E, Brochu C, et al. 1998. Environmental contaminants in tissues of neonate St Lawrence Beluga whale (*Delphinapterus leucas*). *Mar Pollut Bull* 36(1):102-108.
- \*Gebauer MB, Weseloh DV. 1993. Accumulation of organic contaminants in sentinel mallards utilizing confined disposal facilities at Hamilton Harbour, Lake Ontario, Canada. *Arch Environ Contam Toxicol* 25(2):234-243.
- \*Gerhard I, Daniel V, Link S, et al. 1998. Chlorinated hydrocarbons in women with repeated miscarriages. *Environ Health Perspect* 106:675-681.
- Gerhard I, Monga B, Krahe J, et al. 1999. Chlorinated hydrocarbons in infertile women. *Environ Res* A80:299-310.
- \*Gerstenberger SL, Gallinat MP, Dellinger JA. 1997. Polychlorinated biphenyl congeners and selected organochlorines in Lake Superior fish, USA. *Environ Toxicol Chem* 16(11):2222-2228.
- Giesy JP, Bowerman WW, Mora MA, et al. 1995. Contaminants in fishes from Great Lakes-influenced sections and above dams of three Michigan rivers: III. Implications for health of bald eagles. *Arch Environ Contam Toxicol* 29:309-321.

## 9. REFERENCES

- Gillan KA, Hasspieler BM, Russell RW, et al. 1998. Ecotoxicological studies in amphibian populations of southern Ontario. *J Great Lakes Res* 24(1):45-54.
- \*Giwercman A, Carlsen E, Keiding N, et al. 1993. Evidence for increasing incidence of abnormalities of the human testis: A review. *Environ Health Perspect Suppl* 101(2):65-71.
- \*Gladen BC, Monaghan SC, Lukyanova EM, et al. 1999. Organochlorines in breast milk from two cities in Ukraine. *Environ Health Perspect* 107(6):459-462.
- \*Glynn AW, Wolk A, Aune M, et al. 2000. Serum concentrations of organochlorines in men: a search for markers of exposure. *Sci Total Environ* 263:197-208.
- \*Gocmen A, Peters HA, Cripps DJ, et al. 1989. Hexachlorobenzene episode in Turkey. *Biomed Environ Sci* 2:36-43.
- \*Goerz G, Bolsen K, Kalofoutis A, et al. 1994. Influence of oral isotretinoin on hepatic and cutaneous P-450-dependent isozyme activities. *Arch Dermatol Res* 286:104-106.
- Goerz G, Bolsen K, Seuwen P, et al. 1986. Effects of chloroquine and hydroxychloroquine on the hexachlorobenzene-induced porphyria in rats. *IARC Sci Publ* 77:513-515.
- \*Goerz G, Vizethum W, Bolsen K, et al. 1978. [Hexachlorobenzene (HCB) induced porphyria in rats. Influence of Hexachlorobenzene-metabolites on the biosynthesis of heme]. *Arch Dermatol Res* 263:189-196. (German)
- Golden RJ, Noller KL, Titus-Ernstoff L, et al. 1998. Environmental endocrine modulators and human health: an assessment of the biological evidence. *Crit Rev Toxicol* 28:109-227.
- \*Goldey ES, Taylor DH. 1992. Developmental neurotoxicity following prenatally maternal exposure to hexachlorobenzene in rats. *Neurotoxicol Teratol* 14:15-21.
- \*Goldey ES, Fisher JW, Taylor DH. 1990. Maternal transfer of hexachlorobenzene in the rat. Poster Abstract-Methods in Behavioral Toxicology and Teratology 12:562-563.
- Goldey ES, Tilson HA, Crofton KM. 1995. Implications of the use of neonatal birth weight, growth, viability, and survival data for predicting developmental neurotoxicity: A survey of the literature. *Neurotoxicol Teratol* 17(3):313-332.
- \*Goldfrank RL, et al. 1994. Goldfrank's toxicologic emergencies. 5<sup>th</sup> ed. Appleton and Lange 5<sup>th</sup> Edition.
- Goldman LR. 1997. New approaches for assessing the etiology and risks of developmental abnormalities from chemical exposure. *Reprod Toxicol* 11(2/3):443-451.
- \*Goldstein JA, Freisen M, Linder RE, et al. 1977. Effects of pentachlorophenol on hepatic drug metabolism enzymes and porphyria related to contamination with chlorinated dibenzo-*p*-dioxins and dibenzofurans. *Biochem Pharmacol* 26:1549-1557.
- \*Goldstein JA, Freisen M, Scotti TM, et al. 1978. Assessment of the contribution of chlorinated dibenzo-*p*-dioxins and dibenzofurans to hexachlorobenzene-induced toxicity, porphyria, changes in mixed function oxidases and histopathological changes. *Toxicol Appl Pharmacol* 46:633-649.

## 9. REFERENCES

- \*Goldstein JA, Linko P, Hahn ME, et al. 1986. Structure-activity relationships of chlorinated benzenes as inducers of hepatic cytochrome P-450 isozymes in the rat. *IARC Sci Publ* 77:519-526.
- \*Gopaldaswamy UV, Aiyar AS. 1986. Biotransformation and toxicity of lindane and its metabolite hexachlorobenzene in mammals. *IARC Sci Publ* 77:267-276.
- \*Gopaldaswamy UV, Nair CKK. 1992. DNA binding and mutagenicity of lindane and its metabolites. *Bull Environ Contam Toxicol* 49:300-305.
- Gorski T, Gorska E, Gorecka D, et al. 1986. Hexachlorobenzene is non-genotoxic in short-term tests. *IARC Sci Publ* 77:399-401.
- Gosselin RE, Smith RP, Hodge HC, et al, eds. 1984. *Clinical toxicology of commercial products*. 5th ed. Baltimore, MD: Williams and Wilkins, II-170.
- Gould JW, Mercurio MG, Elmetts CA. 1995. Cutaneous photosensitivity diseases induced by exogenous agents. *J Am Acad Dermatol* 33(4):551-576.
- \*Gralla EJ, Fleischman RW, Luthra YK, et al. 1977a. Toxic effects of hexachlorobenzene after daily administration to beagle dogs for one year. *Toxicol Appl Pharmacol* 40:227-239.
- \*Gralla EJ, Fleischman RW, Luthra YK, et al. 1977b. The absence of porphyria in beagle dogs administered hexachlorobenzene for twelve months. *Toxicol Appl Pharmacol* 41:202-203. (Abstract)
- \*Grant DL, Phillips WE, Hatina GV. 1977. Effect of hexachlorobenzene on reproduction in the rat. *Arch Environ Contam Toxicol* 5:207-216.
- Grant DL, Shields JB, Villeneuve DC. 1975. Chemical (HCB) Porphyria: Effect of removal of sex organs in the rat. *Bull Environ Contam Toxicol* 14(4):422-425.
- Gray LE, Monosson E, Kelce WR. 1996. Emerging issues: the effects of endocrine disrupters on reproductive development. In: Di Giulio RT, Monosson E, eds. *Interconnections between human and ecosystem health*. London: Chapman and Hall, 45-82.
- Green JA, Francis JE, Wolf CR, et al. 1989. Sexual dimorphism of cytochrome P-450 induction by hexachlorobenzene in rats. *Biochem Soc Trans* 17:1016-1017.
- \*Greizerstein HB, Stinson C, Mendola P, et al. 1999. Comparison of PCB congeners and pesticide levels between serum and milk from lactating women. *Environ Res* A80:280-286.
- \*Grimalt JO, Sunyer J, Moreno V, et al. 1994. Risk excess of soft-tissue sarcoma and thyroid cancer in a community exposed to airborne organochlorinated compound mixtures with a high hexachlorobenzene content. *Int J Cancer* 56:200-203.
- \*Grinstein M. 1977. Simplified method for the determination of porphyrins in body fluids. *Anal Biochem* 77:577-580.
- \*Guerzoni ME, Del Cupolo L, Ponti I. 1976. Mutagenic activity of pesticides. *Riv Sci Tecnol Alimenti Nutr Um* 6:161-165.

## 9. REFERENCES

- \*Gunderson EL. 1988. FDA total diet study, April 1982-April 1984. Dietary intakes of pesticides, selected elements, and other chemicals. *J Assoc Off Anal Chem* 71(6):1200-1209.
- \*Gustafson DL, Long ME, Thomas RS, et al. 2000. Comparative hepatocarcinogenicity of hexachlorobenzene, pentachlorobenzene, 1,2,4,5-Tetrachlorobenzene, and 1,4-Dichlorobenzene: application of a medium-term liver focus bioassay and molecular and cellular indices. *Toxicol Sci* 53:245-252.
- \*Guttes S, Failing K, Neumann K, et al. 1998. Chlororganic pesticides and polychlorinated biphenyls in breast tissue of women with benign and malignant breast disease. *Arch Environ Contam Toxicol* 35:140-147.
- \*Guzelian PS, Henry CJ, Olin SS, eds. 1992. Similarities and differences between children and adults: Implications for risk assessment. Washington, DC: International Life Sciences Institute Press, 1-285.
- \*Haddad LM, Winchester JF, eds. 1990. Clinical management of poisoning and drug overdose. 2nd ed. Philadelphia, PA: W.B. Saunders Co., 1084-1085.
- \*Hagmar L, Bjork J, Sjodin A, et al. 2001. Plasma levels of persistent organohalogenes and hormone levels in adult male humans. *Arch Environ Health* 56(2):138-143.
- \*Hahn ME, Gasiewicz TA, Linko P, et al. 1988. The role of the Ah locus in hexachlorobenzene-induced porphyria: Studies in congenic C57BL/6J mice. *Biochem J* 254:245-254.
- \*Hahn ME, Goldstein JA, Linko P, et al. 1989. Interaction of hexachlorobenzene with the receptor for 2,3,7,8-tetrachlorodibenzo-p-dioxin in vitro and in vivo. *Arch Biochem Biophys* 270:344-355.
- \*Hansch C, Leo A, Hoekman D. 1995. Exploring QSAR: Hydrophobic, electronic, and steric constants. Washington, DC: American Chemical Society, 15.
- \*Hansen LG, Simon J, Dorn SB, et al. 1979. Hexachlorobenzene distribution in tissues of swine. *Toxicol Appl Pharmacol* 51:1-7.
- Hanstein WG, Heitmann TD, Sandy A, et al. 1981. Effects of hexachlorobenzene and iron loading on rat liver mitochondria. *Biochim Biophys Acta* 678:293-299.
- Hardell L, Van Bavel B, Lindstrom G, et al. 1996. Higher concentrations of specific polychlorinated Biphenyl congeners in adipose tissue from non-Hodgkin's lymphoma patients compared with controls without a malignant disease. *Int J Oncol* 9:603-608.
- \*Hardell L, Van Bavel B, Lindstrom G, et al. 1997. Increased age-related concentrations of polychlorinated biphenyls in four male patients with Ewing's sarcoma. *Int J Environ Health Res* 7:307-313.
- Hawker DW, Connell DW. 1986. Bioconcentration of lipophilic compounds by some aquatic organisms. *Ecotoxicol Environ Saf* 11:184-197.
- \*Haworth S, Lawlor T, Mortelmans K, et al. 1983. Salmonella mutagenicity test results for 250 chemicals. *Environ Mutagen (suppl 1)*:3-142.

## 9. REFERENCES

- Hawthorne SB, Miller DJ. 1987. Directly coupled supercritical fluid extraction--gas chromatographic analysis of polycyclic aromatic hydrocarbons and polychlorinated biphenyls from environmental solids. *J Chromatog* 403:63-76.
- HAZDAT. 1996. Agency for Toxic Substances and Disease Registry (ATSDR), database. Atlanta, GA.
- HAZDAT. 2000. Agency for Toxic Substances and Disease Registry (ATSDR), database. Atlanta, GA.
- HAZDAT. 2001. Agency for Toxic Substances and Disease Registry (ATSDR), database. Atlanta, GA.
- \*HAZDAT. 2002. Agency for Toxic Substances and Disease Registry (ATSDR), database. Atlanta, GA.
- Headley DB, Lambrecht RW, Erturk E, et al. 1981. Neuropathology and tissue levels of hexachlorobenzene (HCB) fed to rats, mice and hamsters. *Proceedings - Fed Amer Soc Expt Bio* 40(3P1):699. (Abstract)
- \*Hebert CE, Weseloh DV, Kot L, et al. 1994. Organochlorine contaminants in a terrestrial foodweb on the Niagara Peninsula, Ontario Canada 1987-1989. *Arch Environ Contam Toxicol* 26:356-366.
- \*Herrero C, Ozalla D, Sala M, et al. 1999. Urinary porphyrin excretion in a human population highly exposed to hexachlorobenzene. *Arch Dermatol* 135:400-404.
- \*HI Dept of Health. 1999a. Hexachlorobenzene: Safe drinking water rules. Hawaii Department of Health. <http://www.hawaii.gov/health>.
- \*HI Dept of Health. 1999b. Hexachlorobenzene: clean water rules. Hawaii Department of Health. <http://www.hawaii.gov/health>.
- \*Hippelein M, Kaupp H, Doerr G, et al. 1993. Testing of a sampling system and analytical method for determination of semivolatile organic compounds in ambient air. *Chemosphere* 26(12):2255-2263.
- \*Hirsch M, Hutzinger O. 1989. Naturally occurring proteins from pond water sensitize hexachlorobenzene photolysis. *Environ Sci Technol* 23:1306-1307.
- \*Hoel DG, Davis DL, Miller AB, et al. 1992. Trends in cancer mortality in 15 industrialized countries, 1969-1986. *J Natl Cancer Inst* 84(5):313-320.
- \*Hoff RM, Muir DCG, Grift NP. 1992. Annual cycle of polychlorinated biphenyls and organohalogen pesticides in air in Ontario.2. Atmospheric Transport- and Sources. *Environ Sci Technol* 26:276-283.
- \*Hoff RM, Strachan MJ, Sweet CW, et al. 1996. Atmospheric deposition of toxic chemicals to the Great Lakes: A review of data through 1994. *Atmos Environ* 30(20):3505-3527.
- Hoffman W. 1996. Organochlorine compounds: Risk of non-Hodgkin's lymphoma and breast cancer? *Arch Environ Health* 51(3):189-192.
- Holladay SD. 1999. Prenatal immunotoxicant exposure and postnatal autoimmune disease. *Environ Health Perspect* 107(Suppl. 5):687-691.

## 9. REFERENCES

- Holladay SD, Smialowicz RJ. 2000. Development of the murine and human immune system: differential effects of immunotoxicants depend on time of exposure. *Environ Health Perspect* 108(Suppl. 3):463-473.
- Hong CS, Calambokidis J, Bush B, et al. 1996. Polychlorinated biphenyls and organochlorine pesticides in harbor seal pups from the inland waters of Washington state. *Environ Sci Technol* 30:837-844.
- Hontela A, Dumont P, Duclos D, et al. 1995. Endocrine and metabolic dysfunction in yellow perch, *Perca flavescens*, exposed to organic contaminants and heavy metals in the St. Lawrence River. *Environ Toxicol Chem* 14(4):725-731.
- \*Hooper K, Petreas MX, She J, et al. 1997. Analysis of breast milk to assess exposure to chlorinated contaminants in Kazakstan: PCBs and organochlorine pesticides in southern Kazakstan. *Environ Health Perspect* 105(11):1250-1254.
- \*Hoppin JA, Tolbert PE, Holly EA, et al. 2000. Pancreatic cancer and serum organochlorine levels. *Cancer Epidemiol Biomarkers Prev* 9:199-205.
- Horvath ME, Faux SP, Blazovics A, et al. 2001. Lipid and DNA oxidative damage in experimentally induced hepatic porphyria in C57BL/10ScSn mice. *Z Gastroenterol* 39(6):453-455,458.
- \*Hosie S, Loff S, Witt K, et al. 2000. Is there a correlation between organochlorine compounds and undescended testes? *Eur J Pediatr Surg* 10:304-309.
- Hothem RL, Zador SG. 1995. Environmental contaminants in eggs of California least terns (*Sterna antillarum browni*). *Bull Environ Contam Toxicol* 55:658-665.
- Hothem RL, Lonzarich DG, Takekawa J, et al. 1998. Contaminants in wintering canvasback and scaups for San Francisco Bay, California. *Environ Monit Assess* 50:67-84.
- \*Howard PH, ed. 1990. Handbook of environmental fate and exposure data for organic chemicals. Chelsea, MI: Lewis Publishers Vol I: 351-359.
- \*Howard PH, Boething RS, Jarvis WF, et al. eds. 1991. Handbook of environmental degradation rates. Chelsea, MI: Lewis Publishers. 452-453.
- Hoyer AP, Grandjean P, Jorgensen T, et al. 1998. Organochlorine exposure and risk of breast cancer. *Lancet* 352:1816-1820.
- HSDB. 1994. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology Information Program, Bethesda, MD. December, 1988.
- \*HSDB. 1995. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology Program (via TOXNET), Bethesda, MD. January 1995.
- \*HSDB. 1996. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology Information Program, Bethesda, MD.
- \*HSDB. 2001. Hexachlorobenzene. Hazardous Substances Data Bank. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search>. September 05, 2001.

## 9. REFERENCES

- Huang TL, Obin PO, Jaiswal R, et al. 1997. Evaluation of liver and brain esterases in the spotted gar fish (*Lepisosteus oculatus*) as biomarkers of effect in the lower Mississippi River Basin. *Bull Environ Contam Toxicol* 58:688-695.
- \*Huang X, Wang S, Fan X. 1989. The effect of hexachlorobenzene and DDT on reproductive outcomes of rural women. *Environ Mol Mutagen* 14(Suppl. 15):92.
- Hyland JL, Snoots TR, Balthis WL. 1998. Sediment quality of estuaries in the southeastern U.S. *Environ Monit Assess* 51:331-343.
- \*IARC. 1979. International Agency for Research on Cancer (IARC) monograph on the evaluation of the carcinogenic risk of chemicals to humans: some halogenated hydrocarbons. Vol. 20. International Agency for Research on Cancer, World Health Organization, Lyon, France, 155-178.
- \*IARC. 1987. IARC monograph on the evaluation of the carcinogenic risk of chemicals to humans. Supplement F to Volumes 1 to 42. International Agency for Research on cancer, World Health Organization, Lyon, France. 1979.
- \*IARC. 1998. Hexachlorobenzene (group 2B): Summary of data reported and evaluation. International Agency for Research on Cancer, World Health Organization, Lyon France. <http://193.51.164.11/htdocs/monographs/Suppl7/Hexachlorobenzene>.
- \*IARC. 2001. Hexachlorobenzene. International Agency for the Research on Cancer. <http://193.51.164.11/htdocs/Monographs/Suppl7/Hexachlorobenzene.html>. December 19, 2001.
- \*Iatropoulos MJ, Bailey J, Adams HP, et al. 1978. Response of nursing infant rhesus to clophen A-30 or hexachlorobenzene given to their lactating mothers. *Environ Res* 16:38-47.
- \*Iatropoulos MJ, Hobson W, Knauf V, et al. 1976. Morphological effects of hexachlorobenzene toxicity in female rhesus monkeys. *Toxicol Appl Pharmacol* 37:433-444.
- \*Iatropoulos MJ, Milling A, Muller WF, et al. 1975. Absorption, transport and organotropism of dichlorobiphenyl (DCB), dieldrin, and hexachlorobenzene (HCB) in rats. *Environ Res* 10:384-389.
- \*ID Dept Health Welfare. 1999. Rules for the control of air pollution in Idaho. Idaho Department of Health and Welfare. <http://www.state.id.us>.
- \*Ingebrigtsen K. 1986. Comparative studies on the distribution and excretion of <sup>14</sup>C-hexachlorobenzene by whole-body autoradiography. *IARC Sci Publ* 77:277-285.
- \*Ingebrigtsen K, Nafstad I. 1983. Distribution and elimination of <sup>14</sup>C-hexachlorobenzene after single oral exposure in the male rat. *Acta Pharmacol Toxicol* 52:254-260.
- \*Ingebrigtsen K, Skaare JU, Nafstad I, et al. 1981. Studies on the biliary excretion and metabolites of hexachlorobenzene in the rat. *Xenobiotica* 11:795-800.
- \*Ingebrigtsen K, Skaare JU, Nafstad I, et al. 1986. Metabolism of hexachlorobenzene (HCB) in the isolated perfused rat liver. *Gen Pharmacol* 17:19-24.
- IRIS. 1989. Integrated Risk Information System. U.S. Environmental Protection Agency, Washington, DC. February 1989.

## 9. REFERENCES

- IRIS. 1994. Integrated Risk Information System, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. May 1994.
- \*IRIS. 1996. Integrated Risk Information System, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. May 1996.
- \*IRIS. 2000. Integrated Risk Information System, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. May 2000.
- \*IRIS. 2001. Hexachlorobenzene. Integrated Risk Information System. <http://www.epa.gov/iris/subst/0374.htm>. September 05, 2001.
- \*IRIS. 2002. Hexachlorobenzene. Integrated Risk Information System. <http://www.epa.gov/iris/subst/0374.htm>. March 12, 2002.
- \*IRPTC. 1985. Treatment and disposal methods for waste chemicals. Geneva, Switzerland: International Registry of Potentially Toxic Chemicals, United Nations Environmental Program, 102.
- IRPTC. 1989. IRPTC data profile: Hexachlorobenzene. Geneva, Switzerland: International Register of Potentially Toxic Chemicals, United Nations Environment Programme.
- \*Isensee AR, Holden ER, Woolson EA, et al. 1976. Soil persistence and aquatic bioaccumulation potential of hexachlorobenzene (HCB). *J Agric Food Chem* 24:1210-1214.
- Ishidate M, Miura KF, Sofuni T. 1998. Chromosome aberration assays in genetic toxicology testing in vitro. *Mutat Res* 404:167-172.
- Ito N, Tsuda H, Hasegawa R, et al. 1983. Comparison of the promoting effects of various agents in induction of preneoplastic lesions in rat liver. *Environ Health Perspect* 50:131-138.
- Ivanov E, Krustev L, Adjarov D, et al. 1976. Studies on the mechanism of the changes in serum and liver gamma-glutamyl transpeptidase activity: II. Experimental hexachlorobenzene porphyria in rabbits. *Enzyme* 21 :8-20.
- Ivanov E, Savov G, Adjarov D. 1986. Changes in some intestinal enzyme activities in experimental hexachlorobenzene-induced porphyria and modifying effects of diet. *IARC Sci Publ* 77:611-618.
- \*Jackson MA, Stack HF, Waters MD. 1993. The genetic toxicology of putative nongenotoxic carcinogens. *Mut Res* 296:241-277.
- Jacobson JL, Jacobson SW. 1996. Intellectual impairment in children exposed to polychlorinated biphenyls *in utero*. *N Engl J Med* 335(11):783-789.
- Jan J, Vrecl M, Pogacnik A, et al. 2001. Bioconcentration of lipophilic organochlorines in ovine detine. *Arch Oral Biol* 46:1111-1116.
- \*Jansson B, Bergman A. 1978. Sulfur-containing derivatives of hexachlorobenzene (HCB) -metabolites in the rat. *Chemosphere* 7(3):257-268.
- \*Jantunen M, Jaakkola JJK, Kryzanowski M, eds. 1997. Pesticides. In: Assessment of exposure to indoor air pollutants. World Health Organization Regional Publications. European Series 78:96-98.

## 9. REFERENCES

- \*Jarman WM, Burns SA, Bacon CE, et al. 1996. High levels of HCB and DDE associated with reproductive failure in prairie falcons (*Falco mexicanus*) from California. *Bull Environ Contam Toxicol* 57:8-15.
- Jarrell J, Gocmen A. 2000. A review of human and sub-human primate toxicity of hexachlorobenzene. *Pure Appl Chem* 72(6):1015-1021.
- \*Jarrell J, Gocmen A, Foster W, et al. 1998. Evaluation of reproductive outcomes in women inadvertently exposed to hexachlorobenzene in Southeastern Turkey in the 1950s. *Reprod Toxicol* 12(4):469-476.
- \*Jarrell JF, McMahon A, Villeneuve D, et al. 1993. Hexachlorobenzene toxicity in the monkey primordial germ cell without induced porphyria. *Reprod Toxicol* 7:41-47.
- \*Johanson CE. 1980. Permeability and vascularity of the developing brain: Cerebellum vs cerebral cortex. *Brain Res* 190:3-16.
- John PJ, Bakore N, Bhatnagar P. 2001. Assessment of organochlorine pesticide residue levels in dairy milk and buffalo milk from Jaipur City, Rajasthan, India. *Environ Int* 26:231-236.
- Juhler RK, Lauridsen MG, Christensen MR, et al. 1999. Pesticide Residues in Selected Food Commodities: Results from the Danish National Pesticide Monitoring Program 1995-1996. *J AOAC Int* 82(2):337-358.
- \*Kan-DO Office and Pesticide Teams. 1995. Accumulated pesticide and industrial chemical findings from a ten-year study of ready to eat foods. *J AOAC Int* 78(3):614-630.
- Kannan K, Kawano M, Kashima Y, et al. 1999. Extractable organohalogen (EOX) in sediment and biota collected at an estuarine marsh near a former chloralkali facility. *Environ Sci Technol* 33:1004-1008.
- \*Karlsson H, Muir DCG, Teixeira CF, et al. 2000. Persistent chlorinated pesticides in air, water, and precipitation from the Lake Malawi Area, Southern Africa. *Environ Sci Technol* 34(6):4490-4495.
- \*Karlsson N, Fangmark I, Haggqvist I, et al. 1991. Mutagenicity testing of condensates of smoke from titanium dioxide/hexachloroethane and zinc/hexachloroethane pyrotechnic mixtures. *Mut of Res* 260:39-46.
- \*Karmaus W, DeKoning EP, Kruse H, et al. 2001. Early childhood determinants of organochlorine concentrations in school-aged children. *Pediatr Res* 50(3):331-336.
- \*Keczkes K, Barker DJ. 1976. Malignant hepatoma associated with acquired hepatic cutaneous porphyria. *Arch Dermatol* 112:125-129.
- Keith LH, Garrison SW, Allen FR, et al. 1976. Identification of organic compounds in drinking water from 13 U.S. cities. In: Keith LH, ed. *Identification and analysis of organic pollutants in water*. Ann Arbor, MI: Ann Arbor Science Publishers, Inc., 329-373.
- \*Kelly TJ, Czuczwa JM, Sticksel PR, et al. 1991. Atmospheric and tributary inputs of toxic substances to Lake Erie. *J Great Lakes Res* 17(4):504-516.

## 9. REFERENCES

- Kenaga EE. 1980. Predicted bioconcentration factors and soil sorption coefficients of pesticides and other chemicals. *Ecotoxicol Environ Saf* 4:26-38.
- \*Kenaga EE, Goring GAI. 1978. Relationship between water solubility, soil sorption, octanol-water partitioning and concentration of chemicals in biota. *Aquatic Toxicology* 79-115.
- \*Kennedy SW, Wigfield DC. 1990. Dose-response relationships in hexachlorobenzene-induced porphyria. *Biochem Pharmacol* 40:1381-1388.
- Khanna RN, Smith AG. 1986. Distribution, excretion and *in-vivo* metabolism of 14C-hexachlorobenzene and the influence of iron overload in C57BL/10 mice. *IARC Sci Publ* 77:319-321.
- \*Khera KS. 1974a. Teratogenicity and dominant lethal studies on hexachlorobenzene in rats. *Food Cosmet Toxicol* 12:471-477.
- Khera KS. 1974b. Hexachlorobenzene: Teratogenicity and dominant lethal studies in rats *Toxicol Appl Pharmacol* 29:109. (Abstract)
- Kim JJ, Lim HW. 1999. Hexachlorobenzene and porphyria *cutanea tarda*. *Arch Dermatol* 135:459-460.
- \*Kimbrough RD, Linder RE. 1974. The toxicity of technical hexachlorobenzene in the Sherman strain rat: A preliminary study. *Res Comm Chem Pathol Pharmacol* 8:653-664.
- \*Kimbrough RD, Linder RE. 1978. The effect of technical and purified pentachlorophenol on the rat liver. *Toxicol Appl Pharmacol* 46:151-162.
- \*Kishima MO, Barbisan LF, Estevao D, et al. 2000. Promotion of heptocarcinogenesis by hexachlorobenzene in energy-restricted rats. *Cancer Lett* 152:37-44.
- \*Kitchin KT, Brown JL. 1989. Biochemical studies of promoters of carcinogenesis in rat liver. *Teratogen, Carcinogen Mutagen* 9:273-285.
- \*Kitchin KT, Linder RE, Scotti TM, et al. 1982. Offspring mortality and maternal lung pathology in female rats fed hexachlorobenzene. *Toxicology* 23:33-39.
- \*Klaassen CD, Amdur MO, Doull J, eds. 1995. Casarett and Doull's Toxicology: The Basic Science of Poisons. In: Casarett and Doull's Toxicology 5th Edition, 139-163.
- Klaassen CD, Amdur MO, Doull J, eds. 1996. Casarett and Doull's Toxicology: The Basic Science of Poisons. In: Casarett and Doull's Toxicology 5th Edition. McGraw-Hill. 649-655.
- \*Kleiman de Pisarev DL, Rios de Molina MC, San Martin de Viale LC. 1990. Thyroid function and thyroxine metabolism in hexachlorobenzene-induced porphyria. *Biochem Pharmacol* 39:817-825.
- \*Kleiman de Pisarev DL, Sancovich HA, Ferramola de Sancovich AM. 1989. Enhanced thyroxine metabolism in hexachlorobenzene-intoxicated rats. *J Endocrinol Invest* 12:767-772.
- \*Kleiman de Pisarev DL, Sancovich HA, Ferramola de Sancovich AM. 1995. Hepatic indices of thyroid status in rats treated with hexachlorobenzene. *J Endocrinol Invest* 18:271-276.

## 9. REFERENCES

- \*Knauf V, Hobson W. 1979. Hexachlorobenzene ingestion by female rhesus monkeys: Tissue distribution and clinical symptomatology. *Bull Environ Contam Toxicol* 21:243-248.
- Kociba RJ. 1986. Evaluation of global literature for definition of dose-response relationship for hexachlorobenzene toxicity. *IARC Sci Publ* 77:371-378.
- \*Koizumi A. 1991. Experimental evidence for the possible exposure of workers to hexachlorobenzene by skin contamination. *Br J Ind Med* 48:622-628.
- \*Komori M, Nishio K, Kitada M, et al. 1990. Fetus-specific expression of a form of cytochrome P-450 in human livers. *Biochemistry* 29:4430-4433.
- Korrick SA, Altshul LM, Tolbert PE, et al. 2000. Measurement of PCBs, DDE, and hexachlorobenzene in cord blood from infants born in town adjacent to a PCB-contaminated waste site. *J Expo Anal Environ Epidemiol* 10:743-754.
- \*Kosatsky T, Przybysz R, Shatenstein B, et al. 1999. Fish consumption and contaminant exposure among Montreal-area sportfishers: Pilot study. *Environ Res* A80:S150-S158.
- \*Koss G, Koransky W. 1975. Studies on the toxicology of hexachlorobenzene: I. Pharmacokinetics. *Arch Toxicol* 34:203-212.
- \*Koss G, Koransky W, Steinbach K. 1976. Studies on the toxicology of hexachlorobenzene: II. Identification and determination of metabolites. *Arch Toxicol* 35:107-114.
- \*Koss G, Koransky W, Steinbach K. 1979. Studies of the toxicology of hexachlorobenzene: IV. Sulfur-containing metabolites. *Arch Toxicol* 42:19-31.
- \*Koss G, Reuter A, Koransky W. 1986. Excretion of metabolites of hexachlorobenzene in the rat and in man. *IARC Sci Publ* 77:261-266.
- \*Koss G, Seubert S, Seubert A, et al. 1978. Studies on the toxicology of hexachlorobenzene: III. Observations in a long-term experiment. *Arch Toxicol* 40:285-294.
- \*Koss G, Seubert S, Seubert A, et al. 1983. Studies on the toxicology of hexachlorobenzene: V. Different phases of porphyria during and after treatment. *Arch Toxicol* 52:13-22.
- \*Kraaij H, Connell DW. 1997. Bioconcentration and uptake kinetics of chlorobenzenes in soy-bean roots. *Chemosphere* 34(12):2607-2620.
- Krauthacker, Reiner E, Votova-Raic A, et al. 1998. Organochlorine pesticides and PCBs in human milk collected from mothers nursing hospitalized children. *Chemosphere* 37(1):27-32.
- \*Krishnan K, Andersen ME. 1994. Physiologically based pharmacokinetic modeling in toxicology. In: Hayes AW, ed. *Principles and methods of toxicology*. 3rd ed. New York, NY: Raven Press, Ltd., 149-188.
- \*Krishnan K, Andersen ME, Clewell HJ III, et al. 1994. Physiologically based pharmacokinetic modeling of chemical mixtures. In: Yang RSH, ed. *Toxicology of chemical mixtures: Case studies, mechanisms, and novel approaches*. San Diego, CA: Academic Press, 399-437.

## 9. REFERENCES

- \*Krishnan K, Brodeur J, Charbonneau M. 1991. Development of an experimental model for the study of hexachlorobenzene-induced hepatic porphyria in the rat. *Fund Appl Toxicol* 17:433-441.
- \*Krishnan K, Brodeur J, Plaa GL, et al. 1992. Modulation of hexachlorobenzene-induced hepatic porphyria by methyl isobutyl ketone in the rat. *Toxicol Lett* 61:167-174.
- \*KS Dept Health Environ. 1999. Kansas administrative regulations. Kansas Department of Health and Environment. <http://www.kdhe.state.ks.us>.
- Kuchen A, Muller F, Farine M, et al. 1999. Pesticides and other chemical residues in Swiss total diet samples. *Mitt Geb Lebensmittelunters Hyg* 90:78-107.
- \*Kucklick JR, Baker JE. 1998. Organochlorines in Lake Superior's food web. *Environ Sci Technol* 32:1192-1198.
- Kuiper-Goodman T, Grant DL. 1986. Subchronic toxicity of hexachlorobenzene in the rat: Clinical, biochemical, morphological and morphometric findings. *IARC Sci Publ* 77:343-346.
- \*Kuiper-Goodman T, Grant DL, Moodie CA, et al. 1977. Subacute toxicity of hexachlorobenzene in the rat. *Toxicol Appl Pharmacol* 40:529-549.
- \*Kutz FW, Wood PH, Bottimore DP. 1991. Organochlorine pesticides and polychlorinated biphenyls in human adipose tissue. *Rev Environ Contam Toxicol* 120:1-82.
- \*Kwok ESC, Atkinson R. 1995. Estimation of hydroxyl radical reaction rate constants for gas-phase organic compounds using a structure-reactivity relationship: An update. *Atmos Environ* 29:1685-1695.
- Lackmann G. 2001. Prenatal, transplacental uptake of polychlorinated biphenyls and hexachlorobenzene in humans. 1. Background and scientific status quo. *Umweltmed Forsch Prax* 6(2):87-96.
- \*Lackmann GM, Angerer J, Salzberger U, et al. 1999. Influence of maternal age and duration of pregnancy on serum concentrations of polychlorinated biphenyls and hexachlorobenzene in full-term neonates. *Biol Neonate* 76:214-219.
- \*Lackmann GM, Angerer J, Tollner U. 2000. Parental smoking and neonatal serum levels of polychlorinated biphenyls and hexachlorobenzene. *Pediatr Res* 47(5):598-601.
- \*Lackmann GM, Goen T, Tollner U, et al. 1996. PCBs and HCB in serum full-term German neonates. *Lancet* 348:1035.
- Lagueux J, Pereg D, Ayotte P, et al. 1999. Cytochrome P450 CYP1A1 enzyme activity and DNA adducts in placenta of women environmentally exposed to organochlorines. *Environ Res* A80:369-382.
- \*Lahaniatis ES, Bergheim W, Kettrup A. 1992. Thermal degradation of polychlorinated bornanes. In: *Proceeding International Symposium on Ecological Approaches of Environmental Chemicals*. Institut für Ökologische Chemie ed. Debrecen, Hungary, 262-267.
- Lake CA, Lake JL, Haebler R, et al. 1995. Contaminant levels in harbor seals from the Northeastern United States. *Arch Environ Contam Toxicol* 29:128-134.

## 9. REFERENCES

- \*Lamb CW, Miller FM, Dellinger RA, et al. 1994. Detailed determination of organic emissions from a preheater cement kiln co-fired with liquid hazardous wastes. *Hazard Waste Matter* 11(1):201-216.
- Lambrech RW, Darcey BA, Erturk E, et al. 1981. Tissue levels and rate of hexachlorobenzene (HCB) disappearance in fat and liver of rats, mice, and hamsters after oral administration. 72nd annual meeting of the American Association for Cancer Research, Inc. Washington DC. *Proc Am Assoc Cancer Res Am Soc Clin Oncol* 22:137.
- Lambrech RW, Erturk E, Grunden EE, et al. 1982a. Hepatotoxicity and tumorigenicity of hexachlorobenzene (HCB) in Syrian golden hamsters (H) after subchronic administration *Fed Proc* 41:329. (abstract)
- Lambrech RW, Erturk E, Grunden EE, et al. 1982b. Renal toxicity and tumorigenicity of hexachlorobenzene (HCB) in rats (R). *AACR Abstracts* 23:54. (Abstract)
- \*Lambrech RW, Erturk E, Grunden EE, et al. 1983a. Hepatocarcinogenicity of chronically administered hexachlorobenzene in rats. *Fed Proc* 42:786. (Abstract)
- Lambrech RW, Erturk E, Grunden EE, et al. 1983b. Renal tumors in rats (R) chronically exposed to hexachlorobenzene (HCB). *AACR Abstracts* 24:59. (Abstract)
- Lambrech RW, Erturk E, Peters HA, et al. 1986. Effects of ethylenediaminetetraacetic acid on hexachlorobenzene-induced changes in rats. *IARC Sci Publ* 77:505-506.
- \*Lane DA, Johnson ND, Hanely MJ, et al. 1992. Gas-and particle-phase concentrations of alpha-hexachlorocyclohexane, gamma-hexachlorocyclohexane, and hexachlorobenzene in Ontario air. *Environ Sci Technol* 26(1):126-133.
- \*Langhorst ML, Nestruck TJ. 1979. Determination of chlorobenzenes in air and biological samples by gas chromatography with photoionization detection. *Anal Chem* 51:2018-2025.
- \*Langlois C, Langis R. 1995. Presence of airborne contaminants in the wildlife of Northern Quebec. *Sci Total Environ* (160-161), 391-402.
- \*Larsen BR, Turrio-Baldassarri L, Nilsson T, et al. 1994. Toxic PCB congeners and organochlorine pesticides in Italian human milk. *Ecotoxicol Environ Saf* 28:1-13.
- \*Laseter JL, Bartell CK, Laska AL, et al. 1976. An ecological study of hexachlorobenzene (HCB). *Gov Rep Announce Index* 76:66.
- \*Laska AL, Bartell CK, Laseter JL. 1976. Distribution of hexachlorobenzene and hexachlorobutadiene in water, soil, and selected aquatic organisms along the lower Mississippi River, Louisiana. *Bull Environ Contam Toxicol* 15:535-542.
- Lavy TL, Mattice JD, Massey JH, et al. 1993. Measurements of year-long exposure to tree nursery workers using multiple pesticides. *Arch Environ Contam Toxicol* 24:123-144.
- \*Lecavalier PR, Chu I, Villeneuve D, et al. 1994. Combined effects of mercury and hexachlorobenzene in the rat. *J Environ Sci Health B29(5):951-961.*

## 9. REFERENCES

- \*Lee CL, Song HJ, Fang MD. 2000a. Concentrations of chlorobenzenes, hexachlorobutadiene and heavy metals in surficial sediments of Kaohsiung coast, Taiwan. *Chemosphere* 41:889-899.
- \*Lee RGM, Burnett V, Harner T, et al. 2000b. Short-term temperature-dependent air-surface exchange and atmospheric concentrations of polychlorinated naphthalenes and organochlorine pesticides. *Environ Sci Technol* 34:393-398.
- \*Leeder JS, Kearns GL. 1997. Pharmacogenetics in pediatrics: Implications for practice. *Pediatr Clin North Am* 44(1):55-77.
- \*Legault N, Sabik H, Cooper SF, et al. 1997. Effect of estradiol on the induction of porphyria by hexachlorobenzene in the rat. *Biochem Pharmacol* 54:19-25.
- \*Leger DA. 1992. Environmental concentrations of hexachlorobenzene in Atlantic Canada. Moncton, New Brunswick: Environment Canada, Conservation and Protection, Inland Waters Directorate, Water Quality Branch. IWD-AR-WQB-91-170.
- \*Leoni V, Fabiani L, Marinelli G, et al. 1986. Spontaneous abortion in relation to the presence of hexachlorobenzene in the Italian environment. *IARC Sci Publ* 77:143-146.
- \*Leoni V, Fabiani L, Marinelli G, et al. 1989. PCB and other organochlorine compounds in blood of women with or without miscarriage: a hypothesis of correlation. *Ecotoxicol Environ Saf* 17(1):1-11.
- \*Leung H-W. 1993. Physiologically-based pharmacokinetic modeling. In: Ballentine B, Marro T, Turner P, eds. *General and applied toxicology*. Vol. 1. New York, NY: Stockton Press, 153-164.
- \*Li SM, Deuomme MA, Leece B, et al. 1989. Hexachlorobenzene: Biochemical effects and synergistic toxic interactions with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *Toxicol Environ Chem* 22:215-227.
- Lide DR. 1994. *CRC Handbook of Chemistry and Physics*. 74th edition, Boca Raton, FL: CRC Press.
- \*Lide DR. 1998. *CRC Handbook of Chemistry and Physics*. 79th edition, Boca Raton, FL: CRC Press, 3-49.
- \*Lilienthal H, Benthe C, Heinzow B, et al. 1996. Impairment of schedule-controlled behavior by pre- and postnatal exposure to hexachlorobenzene in rats. *Arch Toxicol* 70:174-181.
- \*Liljegren G, Hardell L, Lindstrom G, et al. 1998. Case-control study on breast cancer and adipose tissue concentrations of congener specific polychlorinated biphenyls, DDE and hexachlorobenzene. *Eur J Cancer Prev* 7:135-140.
- \*Lim HW. 1989. Mechanisms of phototoxicity in porphyria cutanea tarda and erythropoietic protoporphyria. *Immunol Ser* 46:671-685.
- \*Lim HW, Cohen JL. 1999. The cutaneous porphyrias. *Semin Cutan Med Surg* 18 (4) :285-292.
- \*Linder RE, Edgerton TR, Svendsgaard DJ, et al. 1983. Long-term accumulation of hexachlorobenzene in adipose tissue of parent and filial rats. *Toxicol Lett* 15:237-243.
- \*Lindqvist R, Enfield CG. 1992. Biosorption of dichloro-diphenyltrichlorethane and hexachlorobenzene in groundwater and its implications for facilitated transport. *Appl Environ Microbiol* 58(7):2211-2218.

## 9. REFERENCES

- \*Linnet MS, Gridley G, Nyren O, et al. 1999. Primary liver cancer, other malignancies, and mortality risks following porphyria: a cohort study in Denmark and Sweden. *Am J Epidemiol* 149 (11):1010-1015.
- \*Linko P, Yeowell HN, Gasiewicz TA, et al. 1986. Induction of cytochrome P-450 isozymes by hexachlorobenzene in rats and aromatic hydrocarbon (Ah)-responsive mice. *J Biochem Toxicol* 1:95-107.
- Lino CM, Guarda LMC, Silveira MIN. 1999. Determination of organochlorine pesticide residues in medicinal plants sold in Coimbra, Portugal. *J AOAC Int* 82(5):1206-1213.
- \*Lissner R, Goerz G, Eichenauer MG, et al. 1975. Hexachlorobenzene-induced porphyria in rats--relationship between porphyrin excretion and induction of drug metabolizing liver enzymes. *Biochem Pharmacol* 24:1729-1731.
- \*Livingston, AL. 1978. Forage plant estrogens. *J Toxicol Environ Health* 4:301-324.
- Loaiza-Perez AI, Seisdedos-T, Kleiman de Pisarev DL, et al. 1999. Hexachlorobenzene, a dioxin-type compound, increases malic enzyme gene transcription through a mechanism involving the thyroid hormone response element. *Endocrinology* 140(9):4142-4151.
- Lommel A, Kruse H, Mueller E, et al. 1992. Organochlorine pesticides, octachlorostyrene, and mercury in the blood of Elb [sic] River residents, Germany. *Arch Environ Contam Toxicol* 22:14-20.
- \*Loose LD, Pittman KA, Benitz KF, et al. 1977. Polychlorinated biphenyl and hexachlorobenzene induced humoral immunosuppression. *J Reticuloendothel Soc* 22(3):253-267.
- \*Loose LD, Silkworth JB, Charbonneau T, et al. 1981. Environmental chemical-induced macrophage dysfunction. *Environ Health Perspect* 39:79-91.
- \*Loose LD, Silkworth JB, Pittman KA, et al. 1978. Impaired host resistance to endotoxin and malaria in polychlorinated biphenyl- and hexachlorobenzene-treated mice. *Infect Immun* 20:30-35.
- Lopes TJ, Furlong ET. 2001. Occurrence and potential adverse effects of semivolatile organic compounds in streambed sediment, United States, 1992-1995. *Environ Toxicol Chem* 20(4):727-737.
- \*Lordo RA, Dinh KT, Schwemberger JG. 1996. Semivolatile organic compounds in adipose tissue: estimated averages for the US population and selected subpopulations. *Am J Public Health* 86:1253-1259.
- Lovelady CA, Whitehead RA, Mabury S. 1997. Environmental contaminants in breast milk of lactating hispanic women. *FASEB J* 11(3):A240.
- \*Lovell RA, McChesney DG, Price WD. 1996. Organohalogen and organophosphorous pesticides in mixed feed rations: Findings from FDA's domestic surveillance during fiscal years 1989-1994. *J AOAC Int* 79(2):544-548.
- \*Lui H, Sweeney GD. 1975. Hepatic metabolism of hexachlorobenzene in rats. *Febs Letters* 51(1):137-138.

## 9. REFERENCES

- \*Lui H, Sampson R, Sweeney GD. 1976. Session X. Experimental chronic hepatic porphyria. Hexachlorobenzene porphyria: Purity and metabolic fate of hexachlorobenzene. In: Karger and Basel eds. *Porphyryns in Human Diseases*, 1st International Porphyrin Meeting Freiburg/Br 1975.
- \*Lunden A, Noren K. 1998. Polychlorinated naphthalenes and other organochlorine contaminants in Swedish human milk, 1972-1992. *Arch Environ Contam Toxicol* 34(4):414-423.
- Lunden EB, Lindskog A, Mowrer J. 1994. Concentrations and fluxes of organic compounds in the atmosphere of the Swedish West Coast. *Atmos Environ* 28(22):3605-3615.
- Luo J, Lim CK. 1995. Isolation and characterization of new porphyrin metabolites in human porphyria cutanea tarda and in rats treated with hexachlorobenzene by HPTLC, HPLC and Liquid secondary ion mass spectrometry. *Biomed Chromatogr* 9(3):113-122.
- Lutter C, Iyengar V, Barnes R, et al. 1998. Breast milk contamination in Kazakhstan: Implications for infant feeding. *Chemosphere* 37(9):1761-1772.
- Machala M, Vondracek J, Ulrich R, et al. 1999. Evidence for estrogenic and TCDD-like activities in extracts of blood and semen of men. *Organohalogen Compounds* 42:83-86.
- \*MacPhee IJ, Singh A, Wright GM, et al. 1993. Ultrastructure of granulosa lutein cells from rats fed hexachlorobenzene. *Histol Histopath* 8:35-40.
- \*Manes J, Font G, Pico Y. 1993. Evaluation of a solid-phase extraction system for determining pesticide residues in milk. *J Chromatogr* 642:195-204.
- \*Mann JB, Enos HF, Gonzalez J, et al. 1974. Development of sampling and analytical procedure for determining hexachlorobenzene and hexachloro-1,3-butadiene in air. *Environ Sci Technol* 8:584-585.
- Mansour M, Scheunert I, Viswanathan R, et al. 1986. Assessment of the persistence of hexachlorobenzene in the ecosphere. *IARC Sci Publ* 77:53-59.
- Marlow DA. 1986. Hexachlorobenzene exposure in the production of chlorophenols. In: Morris CR, Cabral JRP, ed. *Hexachlorobenzene: Proceedings of an International Symposium*. Lyon, France: IARC Scientific Publications, 161-170.
- \*Martens D, Balta-Brouma K, Brotsack R, et al. 1998. Chemical impact of uncontrolled solid waste combustion to the vicinity of the Kouroupitos Ravine, Crete, Greece. *Chemosphere* 36(14):2855-2866.
- \*Masini A, Trenti T, Ceccarelli, D, et al. 1988. The effect of iron overload on the mitochondrial porphyrin level in the hexachlorobenzene induced experimental porphyria. *Biochem Biophys Res Comm* 151:320-326.
- \*Masunaga S, Susarla S, Yonezawa Y. 1996. Dechlorination of chlorobenzenes in anaerobic estuarine sediment. *Water Sci Technol* 33(6):173-180.
- Matheus DR, Bononi VLR, Machado KMG. 2000. Biodegradation of hexachlorobenzene by basidiomycetes in soil contaminated with industrial residues. *World J Microbiol Biotech* 16:415-421.

## 9. REFERENCES

- Matthews HB. 1986. Factors determining hexachlorobenzene distribution and persistence in higher animals. In: Morris CR, Cabral JRP, ed. Hexachlorobenzene: Proceedings of an International Symposium. Lyon, France: IARC Scientific Publications, 253-260.
- \*Mattison DR, Wohlleb J, To T, et al. 1992. Pesticide concentrations in Arkansas breast milk. *Med Soc* 88(11):553-557.
- \*Mayr U, Butsch A, Schneider S. 1992. Validation of two *in vitro* test systems for estrogenic activities with zearalenone, phytoestrogens and cereal extracts. *Toxicology* 74:135-149.
- Mazhitova Z, Jensen S, Ritzen M, et al. 1998. Chlorinated contaminants, growth and thyroid function in schoolchildren from the Aral Sea region in Kazakhstan. *Acta Paediatr* 87:991-995.
- Meharg AA, Wright J, Osborn D. 2000. Chlorobenzenes in rivers draining industrial catchments. *Sci Total Environ* 251/252:243-253.
- \*Mehendale HM, Fields M, Matthews HB. 1975. Metabolism and effects of hexachlorobenzene on hepatic microsomal enzymes in the rat. *J Agr Food Chem* 23:261-265.
- \*Mehmood Z, Williamson MP, Kelly DE, et al. 1996. Metabolism of organochlorine pesticides: The role of human cytochrome P450 3A4. *Chemosphere* 33(4):759-769.
- Mendola P, Buck GM, Sever LE, et al. 1997. Consumption of PCB-contaminated freshwater fish and shortened menstrual cycle length. *Am J Epidemiol* 146(11):955-960.
- \*Mendonca GAS, Eluf-Neto J, Andrada-Serpa MJ, et al. 1999. Organochlorines and breast cancer: A case-control study in Brazil. *Int J Cancer* 83:596-600.
- \*Mendoza CE, Shields JB. 1976. Effects of hexachlorobenzene on malathion LD50 and on cholinesterase and carboxylesterase activities in organs of the suckling albino rat. *Toxicol and Appl Pharmacol* 35:447-453.
- Mendoza CE, Collins B, Shields JB, et al. 1977. Hexachlorobenzene residues and effects on esterase activities in pre-weanling rats after a reciprocal transfer between hexachlorobenzene-treated and control dams. *Arch Toxicol* 38:191-199.
- Mendoza CE, Collins BT, Shields JB, et al. 1978. Effects of hexachlorobenzene or hexabromobenzene on body and organ weights of preweanling rats after a reciprocal transfer between the treated and control dams. *J Agric Food Chem* 26:941-945.
- Menzie CM. 1986. Hexachlorobenzene: uses and occurrence. In: Morris CR, Cabral JRP, ed. Hexachlorobenzene: Proceedings of an International Symposium. Lyon, France: IARC Scientific Publications, 13-22.
- \*Meola T, Lim HW. 1993. The porphyrias. *Dermatol Clin* 3(11):583-596.
- Merck Index. 1989. Merck index: An encyclopedia of chemicals, drugs, and biologicals. 11th ed. Budavari S, ed. Rahway NJ: Merck & Co., Inc.
- \*Mes J. 1992. Organochlorine residues in human blood and biopsy fat and their relationship. *Bull Environ Contam Toxicol* 48:815-820.

## 9. REFERENCES

- \*Mes J, Davies DJ, Doucet J, et al. 1993. Levels of chlorinated hydrocarbon residues in Canadian human breast milk and their relationship to some characteristics of the donors. *Food Addit Contam* 10(4):429-441.
- \*Mes J, Davies DJ, Turton D. 1982. Polychlorinated biphenyl and other chlorinated hydrocarbon residues in adipose tissue of Canadians. *Bull Environ Contam Toxicol* 28:97-104.
- Mes J, Davies DJ, Turton D, et al. 1986. Levels and trends of chlorinated hydrocarbon contaminants in the breast milk of Canadian women. *Food Add Contam* 3:313-322.
- Mes J, Doyle JA, Adams BR, et al. 1984. Polychlorinated biphenyls and organochlorine pesticides in milk and blood of Canadian women during lactation. *Arch Environ Contam Toxicol* 13:217-223.
- Michael LC, Pellizari ED, Wiseman RW. 1988. Development and evaluation of a procedure for determining volatile organics in water. *Environ Sci Technol* 22:565-570.
- \*Michielsen CPPC, Bloksma N, Ultee A, et al. 1997. Hexachlorobenzene-induced immunomodulation and skin and lung lesions: A comparison between Brown Norway, Lewis, and Wistar rats. *Toxicol Appl Pharmacol* 144:12-26.
- \*Michielsen C, Boeren S, Rietjens I, et al. 2000. The mercapturic acid biotransformation pathway of hexachlorobenzene is not involved in the induction of splenomegaly, of skin and lung lesions in the Brown Norway rat. *Arch Toxicol* 74:609-617.
- \*Michielsen CPPC, Leusink-Muis A, Vos JG, et al. 2001. Hexachlorobenzene-induced eosinophilic and granulomatous lung inflammation is associated with in vivo airways hyperresponsiveness in the brown Norway rat. *Toxicol Appl Pharmacol* 172:11-20.
- \*Michielsen C, van Loveren H, Vos JG. 1999. The role of the immune system in hexachlorobenzene-induced toxicity. *Environ Health Perspect Suppl* 107(5):783-792.
- \*Mill T, Haag W. 1986. The environmental fate of hexachlorobenzene. *IARC Sci Pub* 77:61-66
- \*Miskiewicz AG, Gibbs PJ. 1994. Organochlorine pesticides and hexachlorobenzene in tissues of fish and invertebrates caught near a sewage outfall. *Environ Pollut* 84:269-277.
- \*Miura T, Torinuki W. 1977. Thin layer chromatography and fluorescent scanning analysis of porphyrins. *Tohoku J Exp Med* 121:37-61.
- \*Miyagawa M, Takasawa H, Sugiyama A, et al. 1995. The *in vivo-in vitro* replicative DNA synthesis (RDS) test with hepatocytes prepared from male B6C3F1 mice as an early prediction assay for putative nongenotoxic (Ames-negative) mouse hepatocarcinogens. *Mutat Res* 343(2-3):157-183.
- Mizell M, Hartley W, Thiyagarajah A, et al. 1995. Fish as indicators of the carcinogenic potential of chemical contaminants in a Mississippi River basin swamp utilizing medaka and zebrafish embryo (abstract). *Proc Annu Meet Am Assoc Cancer Res* 36:A698.
- \*Mollenhauer HH, Johnson JH, Younger RL, et al. 1975. Ultrastructural changes in liver of the rat fed hexachlorobenzene. *Am J Vet Res* 36:1777-1781.

## 9. REFERENCES

- \*Monheit BM, Luke BG. 1990. Pesticides in breast milk- A public health perspective. *Commun Health Stud* 14(3):269-273.
- Monosmith CL, Hermanson MH. 1996. Spatial and temporal trends of atmospheric organochlorine vapors in the central and upper Great Lakes. *Environ Sci Technol* 30:3464-3472.
- Moody RP, Chu I. 1995. Dermal exposure to environmental contaminants in the Great Lakes. *Environ Health Perspect Suppl* 103(Suppl. 9):103-114.
- Moore DRJ, Breton RL, Lloyd K. 1997. The effects of hexachlorobenzene on mink in the Canadian environment: An ecological risk assessment. *Environ Toxicol Chem* 16(5):1042-1050.
- Mora MA. 1995. Residues and trends of organochlorine pesticide and polychlorinated biphenyls in birds from Texas, 1965-88. *Fish Wild Res* 14:1-26.
- Mora MA. 1996. Organochlorines and trace elements in four colonial waterbird species nesting in the lower Laguna Madre, Texas. *Arch Environ Contam Toxicol* 31:533-537.
- Mora MA, Miller JM. 1998. Foraging flights, reproductive success and organochlorine contaminants in cattle egrets nesting in a residential area of Bryan, Texas. *Texas J Sci* 50(3):205-214.
- Mora MA, Lee MC, Jenny JP, et al. 1997. Potential effects of environmental contaminants on recovery of the Aplomado falcon in south Texas. *J Wildl Manage* 61(4):1288-1296.
- \*Morley A, Geary D, Harben F. 1973. Hexachlorobenzene pesticides and porphyria. *Med J Aust* 1:565.
- Morris CR, Cabral JR. 1986. Executive summary. Industrial chemistry and indirect exposure assessment. *IARC Sci Publ* 77:13-18.
- Morrison H, Yankovich T, Lazar R, et al. 1995. Elimination rate constants of 36 PCBs in zebra mussels (*Dreissena polymorpha*) and exposure dynamics in the Lake St. Clair - Lake Erie corridor. *Can J Fish Aquat Sci* 52:2574-2582.
- \*Morselli PL, Franco-Morselli R, Bossi L. 1980. Clinical pharmacokinetics in newborns and infants: Age-related differences and therapeutic implications. *Clin Pharmacokin* 5:485-527.
- \*Moser GA, McLachlan MS. 2001. The influence of dietary concentration on the absorption and excretion of persistent lipophilic organic pollutants in the human intestinal tract. *Chemosphere* 45:201-211.
- \*Moysich KB, Ambrosone CB, Vena JE. 1998. Environmental organochlorine exposure and postmenopausal breast cancer risk. *Cancer Epidemiol Biomark Prev* 7:181-188.
- Muir DCG, Ford CA, Rosenberg B, et al. 1996. Persistent organochlorines in beluga whales (*Delphinapterus leucas*) from the St Lawrence River Estuary-I. Concentrations and patterns of specific PCBs, chlorinated pesticides and polychlorinated dibenzo-*p*-dioxins and dibenzofurans. *Environ Pollut* 93(2):219-234.
- Muir DCG, Grift NP, Lockhart WL, et al. 1995. Spatial trends and historical profiles of organochlorine pesticides in Arctic lake sediments. *Sci Total Environ* 160/161:447-457.

## 9. REFERENCES

- \*Muir DCG, Segstro MD, Welbourn PM, et al. 1993. Patterns of accumulation of airborne organochlorine contaminants in lichens from the upper Great Lakes region of Ontario. *Environ Sci Technol* 27(6):1201-1210.
- \*Muller WF, Hobson W, Fuller GB, et al. 1978. Endocrine effects of chlorinated hydrocarbons in rhesus monkeys. *Ecotoxicol Environ Saf* 2:161-172.
- \*Munch DJ, Maxey RA, Engel TM. 1990. Methods development and implementation for the National Pesticide Survey. *Environ Sci Technol* 24(10):1446-1451.
- Munn MD, Gruber SJ. 1997. The relationship between land use and organochlorine compounds in streambed sediment and fish in the Central Columbia Plateau, Washington and Idaho, USA. *Environ Toxicol Chem* 16(9):1877-1887.
- \*Murphy R, Harvey C. 1993. Residues and metabolites of selected persistent halogenated hydrocarbons in blood specimens from a general population survey. *Environ Health Perspect* 60:113-120.
- \*Murray HE, Neff GS, Hrung Y, et al. 1980. Determination of benzo(a)pyrene, hexachlorobenzene and pentachlorophenol in oysters from Galveston Bay, Texas. *Bull Environ Contam Toxicol* 25:663-667.
- \*Murray HE, Ray LE, Giam CS. 1981. Analysis of marine sediment, water and biota for selected organic pollutants. *Chemosphere* 10:1327-1334.
- Mussalo-Rauhamaa H. 1991. Partitioning and levels of neutral organochlorine compounds in human serum, blood cells, and adipose and liver tissue. *Sci Total Environ* 103(2-3):159-175.
- \*Mussalo-Rauhamaa H, Hasanen E, Pyysalo H, et al. 1990. Occurrence of beta-hexachlorocyclohexane in breast cancer patients. *Cancer* 66(10):2124-2128.
- Mylchreest E, Charbonneau M. 1994. Ultrasound-induced epileptic form activity in rats treated with hexachlorobenzene. *NeuroToxicology* 15(2):149-155.
- \*Mylchreest E, Charbonneau M. 1997. Studies on the mechanism of uroporphyrinogen decarboxylase inhibition in hexachlorobenzene-induced porphyria in the female rat. *Toxicol Appl Pharmacol* 145:23-33.
- \*Nakashima Y, Ikegami S. 2000. Hexachlorobenzene and Pentachlorobenzene accumulated during pregnancy is transferred to pups at the accumulation ratio in dams. *Journal of Health Science* 46(2):89-97.
- \*Nakashima Y, Ohsawa S, Ikegami S. 1999. High-fat diet enhances accumulation of hexachlorobenzene in rat dams and delays its transfer from rat dams to suckling pups through milk. *J Agric Food Chem* 47:1587-1592.
- \*Nakashima Y, Ohsawa S, Umegaki K, et al. 1997. Hexachlorobenzene accumulated by dams during pregnancy is transferred to suckling rats during early lactation. *J Nutr* 127:648-654.
- Nakashima Y, Ohsawa S, Umegaki K, et al. 1998. Masking of guar gum-induced acceleration of hexachlorobenzene excretion by its rapid excretion through lactation in adult female rats. *J Agric Food Chem* 46(6):2241-2247.

## 9. REFERENCES

- \*Nakata H, Kannan K, Jing L, et al. 1998. Accumulation pattern of organochlorine pesticides and polychlorinated biphenyls in southern sea otters (*Enhydra lutris nereis*) found stranded along coastal California, USA. *Environ Pollut* 103:45-53.
- \*Nam KS, King JW. 1994. Coupled SFE/SFC/GC for the trace analysis of pesticide residues in fatty food samples. *Journal of High Resolution Chromatography* 17:577-582.
- NAS/NRC. 1980. Drinking water and health: Volume 3. Washington, DC: National Academy of Sciences, National Research Council. National Academy Press.
- \*NAS/NRC. 1989. Report of the oversight committee. In: Biologic markers in reproductive toxicology. Washington, DC: National Academy of Sciences, National Research Council, National Academy Press.
- \*Nash RG, Gish TJ. 1989. Halogenated pesticide volatilization and dissipation from soil under controlled conditions. *Chemosphere* 18(11/12):2353-2362.
- Nasir K, Bilto YY, Al-Shuraiki Y. 1998. Residues of chlorinated hydrocarbon insecticides in human milk of Jordanian women. *Environ Pollut* 99:141-148.
- NATICH. 1992. National Air Toxics Information ClearingHouse (NATICH) data base report of federal, state, and local air toxics activities. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards. EPA-453/R-92-008.
- Nerin C, Marinez M, Pons B, et al. 1996. Gas-chromatographic determination of chlorobenzenes and HCH's in an urban atmosphere. *Fresenius J Anal Chem* 354:61-65.
- \*Newsome WH, Andrews P. 1993. Organochlorine pesticides and polychlorinated biphenyl congener in commercial fish from the Great Lakes. *J AOAC Int* 76(4):707-710.
- \*Newsome WH, Ryan JJ. 1999. Toxaphene and other chlorinated compounds in human milk from northern and southern Canada: A comparison. *Chemosphere* 39(3):519-526.
- \*Newsome WH, Davies D, Doucet J. 1995. PCB and organochlorine pesticides in Canadian human milk-1992. *Chemosphere* 30(11):2143-2153.
- Newsome WH, Davies DJ, Sun WF. 1998. Residues of polychlorinated biphenyls (PCB) in fatty foods of the Canadian diet. *Food Addit Contam* 15(1):19-29.
- \*Newsome WH, Doucet J, Davies D, et al. 2000. Pesticide residues in the Canadian market basket survey-1992 to 1996. *Food Addit Contam* 17(10):847-854.
- \*NFPA. 1986. National Fire Protection Handbook. 7th edition. National Fire Protection Association Quincy, Massachusetts.
- NFPA. 1994. Hexachlorobenzene. National Fire Protection Association. One Batterymarch Park, Quincy MA.
- \*Nikolaev V, Naydenova E, Kerimova M, et al. 1986. Rat liver plasma membrane damage in hexachlorobenzene intoxication and its potential by ethanol. *Toxicol Lett* 32:269-273.

## 9. REFERENCES

- NIOSH. 1988. National occupational exposure survey. Cincinnati, OH: National Institute for Occupational Safety and Health.
- \*NIOSH. 2000. NIOSH pocket guide to chemical hazards (NPG): Hexachlorobenzene. National Institute for Occupational Safety and Health. <http://www.cdc.gov/niosh/homepage.html>.
- \*NJ Dept Env Protec. 1993. Ground water quality standards. New Jersey Department of Environmental Protection, Division of Water Quality. N.A.J.C. 7:9-6. <http://www.state.nj.us/dep/>.
- NLM. 1988. Chemline. National Library of Medicine, Bethesda, MD. December 1988.
- \*NLM. 1998. Chemline. National Library of Medicine, Bethesda, MD.
- \*NOES. 1990. National Occupational Exposure Survey 1981-83. Cincinnati OH: U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health. July 1, 1990.
- \*Noren K, Meironyte D. 2000. Certain organochlorine and organobromine contaminants in Swedish human milk in perspective of past 20-30 years. *Chemosphere* 40:1111-1123.
- \*Noren K, Weistrand C, Karpe F. 1999. Distribution of PCB congeners, DDE, hexachlorobenzene, and methylsulfonyl metabolites of PCB and DDE among various fractions of human blood plasma. *Arch Environ Contam Toxicol* 37:408-414.
- \*NRC. 1993. National Research Council. Pesticides in the diets of infants and children. Washington, DC: National Academy Press.
- NTDB. 1994. National Trade Data Bank, the export connection. U.S. Department of Commerce.
- \*NTDB. 1995. National Trade Data Bank. Washington, D.C: USDOC, Bureau of the Census.
- \*Ntow WJ. 2001. Organochlorine pesticides in water, sediment, crops, and human fluids in a farming community in Ghana. *Bull Environ Contam Toxicol* 40:557-563.
- \*NTP. 1991. Sixth annual report on carcinogens: Summary 1991. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program. NTP 85-002.
- \*NTP. 2001. Ninth report on carcinogens. National Toxicology Program. <http://ntp-server.niehs.nih.gov/>. December 20, 2001.
- \*Oberg T, Bergstrom JGT. 1985. Hexachlorobenzene as an indicator of dioxin production from combustion. *Chemosphere* 14:1081-1086.
- Ochiai T, Morishima T, Kondo M. 1997. Symptomatic porphyria secondary to hepatocellular carcinoma. *Br J Dermatol* 136:129-131.
- \*Ockner RK, Schmid R. 1961. Acquired porphyria in man and rat due to hexachlorobenzene intoxication. *Nature* (February 11):499.

## 9. REFERENCES

- \*Oehme M, Mano S, Mikalsen A. 1987. Formation and presence of polyhalogenated and polycyclic compounds in the emissions of small and large scale municipal waste incinerators. *Chemosphere* 16:143-153.
- O'Hara TM, Krahn MM, Boyd D, et al. 1999. Organochlorine contaminant levels in Eskimo harvested bowhead whales of arctic Alaska. *J Wildl Dis* 35(4):741-752.
- Ohio River Valley Water Sanitation Commission. 1979. Water treatment process modifications for trihalomethane control and organic substances in the Ohio River. Cincinnati, OH: Ohio River Valley Water Sanitation Commission.
- \*Ojala M. 1993. Simultaneous separation and determination of chlorobenzenes, PCBs, and chlorophenols using silica gel fractionation and GC-ECD analysis. *Journal of High Resolution Chromatography* 16:679-682.
- \*Oliver BG, Nicol KD. 1982a. Chlorobenzenes in sediments, water, and selected fish from Lakes Superior, Huron, Erie, and Ontario. *Environ Sci Technol* 16:532-536.
- \*Oliver BG, Nicol KD. 1982b. Gas chromatographic determination of chlorobenzenes and other chlorinated hydrocarbons in environmental samples using fused silica capillary columns. *Chromatographia* 16:336-340.
- \*Oliver BG, Niimi AJ. 1983. Bioconcentration of chlorobenzenes from water by rainbow trout: Correlations with partition coefficients and environmental residues. *Environ Sci Technol* 17:287-291.
- \*Onuska FI, Terry KA. 1993. Extraction of pesticides from sediments using a microwave technique. *Chromatographia* 36:101-104.
- \*OSHA. 1999a. Air contaminants. Occupational safety and Health Administration. 29 CFR 1910.1000.
- \*OSHA. 1999b. Air contaminants. Occupational safety and Health Administration. 29 CFR 1915.1000.
- \*OSHA. 1999c. Air contaminants. Occupational safety and Health Administration. 29 CFR 1926.55.
- \*OTA. 1990. Neurotoxicity: Identifying and controlling poisons of the nervous system. Washington, DC: Office of Technology Assessment, U.S. Congress. OTA-BA-438.
- Otero R, Santiago-Silva M, Grimalt JO. 1997. Hexachlorocyclohexanes in human blood serum. *J Chromatogr* 778:87-94.
- Ou YC, Conolly RB, Thomas RS, et al. 2001. A clonal growth model: time-course simulations of liver foci growth following penta- or hexachlorobenzene treatment in a medium-term bioassay. *Cancer Res* 61(5):1879-1889.
- \*Owen GM, Brozek J. 1966. Influence of age, sex and nutrition on body composition during childhood and adolescence. In: Falkner F, ed. *Human development*. Philadelphia, PA: WB Saunders, 222-238.
- Packe GE, Clarke CWF. 1985. Is porphyria cutanea tarda a risk factor in the development of hepatocellular carcinoma? *Oncology* 42:44-47.

## 9. REFERENCES

- Pankow, JF, Ligocki MP, Rosen ME, et al. 1988. Adsorption/thermal desorption with small cartridges for the determination of trace aqueous semivolatle organic compounds. *Anal Chem* 60:40-47.
- Pardue JH, Jackson WA, Clover CC. 1998. Natural attenuation of organics at the Petro Processors, Inc. superfund site: Potential for metal inhibition and complete anaerobic degradation. In: *Proceedings WEFTEC '98: Water Environment Federation 71st annual conference and exposition, Orlando, Florida. Alexandria, VA: Water Environment Federation, 109-123.*
- \*Park J, Wade TL, Sweet S. 2001. Atmospheric deposition of organochlorine contaminants to Galveston Bay, Texas. *Atmos Environ* 35:3315-3324.
- \*Parlar H. 1978. Organochlorine compounds and their reactions in the atmosphere. *Ecotox Environ Safety* 2:219-232.
- \*Pereira MA, Herren SL, Britt AL, et al. 1982. Sex difference in enhancement of GGTase- positive foci by hexachlorobenzene and lindane in rat liver. *Cancer Lett* 15:95-101.
- \*Pereria WE, Rostad CE, Chiou CT, et al. 1988. Contamination of estuarine water, biota and sediment by halogenated organic compounds: A field study. *Environ Sci Technol* 22:772-778.
- Perkins CR, Barclay JS. 1997. Accumulation and mobilization of organochlorine contaminants in wintering greater scaup. *J Wildl Manage* 61(2):444-449.
- \*Peters HA. 1956. Therapy of acute porphyria with bal and other agents (A report of 19 additional cases). *Diseases of the Nervous System* 17(6):351-357.
- \*Peters HA. 1993. Acute hepatic porphyria. In: RT Johnson, JW Griffin (eds.). *Current therapy in neurologic disease, 4th ed. Mosby-Year Book, Inc., 317-322.*
- \*Peters H, Cripps DJ. 1985. Chelation therapy of acute, chronic, and mixed porphyria. *Plzen Lek Sborn, suppl* 49:261-264.
- Peters HA, Cripps DJ, Gocmen A, et al. 1986a. Neurotoxicity of hexachlorobenzene-induced porphyria turcica. *IARC Sci Publ* 77:575-579.
- \*Peters H, Cripps D, Gocmen A, et al. 1987. Turkish epidemic hexachlorobenzene porphyria: A 30-year study. *Ann NY Acad Sci* 514:183-190.
- \*Peters HA, Gocmen A, Cripps DJ, et al. 1982. Epidemiology of hexachlorobenzene-induced porphyria in Turkey: Clinical and laboratory follow-up after 25 years. *Arch Neurol* 39:744-749.
- \*Peters HA, Gocmen A, Cripps DJ, et al. 1986b. Porphyria turcica: Hexachlorobenzene-induced porphyria. Neurological manifestations and therapeutic trials of ethylenediaminetetraacetic acid in the acute syndrome. *IARC Scientific Publ* 77:581-583.
- \*Peters HA, Johnson SA, Cam S, et al. 1966. Hexachlorobenzene induced porphyria: Effect of chelation on the disease, porphyrin and metal metabolism. *Am J Med Sci* 251:314-322.
- Peters HA, Levine RL, Matthews CG, et al. 1988. Extrapramidal and other neurologic manifestations associated with carbon disulfide fumigant exposure. *Arch Neurol* 45:537-540.

## 9. REFERENCES

- \*Peters HA, Woods S, Eichman PL, et al. 1957. The treatment of acute porphyria with chelating agents: A report of 21 cases. *Ann Intern Med* 47(5):889-899.
- \*Petreas M, She J, Visita P, et al. 1998. Levels of PCDD/PCDFs, PCBs and OC pesticides in breast adipose of women enrolled in a California breast cancer study. *Organohalogen Compounds* 38:37-40.
- Petty JD, Poulton BC, Charbonneau CS, et al. 1998. Determination of bioavailable contaminants in the lower Missouri River following the flood of 1993. *Environ Sci Technol* 32(7):837-842.
- \*Petzold G, Schafer M, Benthe C, et al. 1999. Dietary exposure and human body burden to organochlorine pesticides and PCBs in children and women in northern Germany. *Organohalogen Compounds* 44:119-122.
- Peven CS, Uhler AD, Hillman RE, et al. 1996. Concentration of organic contaminants in *Mytilus edulis* from the Hudson-Raritan Estuary and Long Island Sound. *Sci Total Environ* 179:135-147.
- \*Pimstone NR. 1982. Porphyria cutanea tarda. *Semin Liver Dis* 2(2):132-142.
- Pohl HR, Abadin HG. 1995. Utilizing uncertainty factors in minimal risk levels derivation. *Regul Toxicol Pharmacol* 22:180-188.
- Pohl HR, Tylanda CA. 2000. Breast-feeding exposure of infants to selected pesticides: a public health viewpoint. *Toxicol Ind Health* 16:65-77.
- Pohl HR, McClure PR, Fay M, et al. 2001. Public health assessment of hexachlorobenzene. *Chemosphere* 43:903-908.
- Pohl HR, Smith-Simon C, Hicks H. 1998. Health effects classification and its role in the derivation of minimal risk levels: developmental effects. *Regul Toxicol Pharmacol* 28:55-60.
- \*Poissant L, Koprivnjak JF, Mattieu R. 1997. Some persistent organic pollutants and heavy metals in the atmosphere over a St. Lawrence River Vally site (Villeroy) in 1992. *Chemosphere* 34(3):567-585.
- Polder A, Becher G, Savinova TN, et al. 1998. Dioxins, PCBs and some chlorinated pesticides in human milk from the Kola Peninsula, Russia. *Chemosphere* 37:1795-1806.
- \*Poli A, Biasi D, Diani F, et al. 1999. Presence of organic chlorine pesticides in the adipose tissue of the pregnant woman, in the placenta, and in the maternal milk. *Ig Mod* 112:861-871.
- \*Poole KG, Elkin BT, Bethke RW. 1998. Organochlorine and heavy metal contaminants in wild mink in western Northwest Territories, Canada. *Arch Environ Contam Toxicol* 34:406-413.
- Porta M, Jarrod M, Malats N, et al. 2000. Prevalence of K-ras mutations at diagnosis and serum levels of DDT, DDE, PCBs and other organochlorine compounds in exocrine pancreatic cancer. Amsterdam: Ios Press.
- \*Prachar V, Veningerova M, Uhnak J, et al. 1993. Levels of polychlorinated biphenyls and some other organochlorine compounds in breast milk samples in Bratislava. *Sci Total Environ (Suppl Pt 1)*:237-242.
- Pratt GC, Palmer K, Wu CY, et al. 2000. An assessment of air toxics in Minnesota. *Environ Health Perspect* 108(9):815-825.

## 9. REFERENCES

- Price PS, Keenan RE, Swartout JC, et al. 1997. An approach for modeling noncancer dose responses with an emphasis on uncertainty. *Risk Anal* 17(4):427-437.
- \*Pylypiw HM Jr., 1993. Rapid gas chromatographic method for the multiresidue screening of fruits and vegetables for organochlorine and organophosphate pesticides. *J AOAC Int* 76(6):1369-1373.
- \*Queiroz MLS, Bincoletto C, Perlingeiro RCR, et al. 1997. Defective neutrophil function in workers occupationally exposed to hexachlorobenzene. *Human Exp Toxicol* 16(6):322-326.
- \*Queiroz MLS, Bincoletto C, Perlingeiro RCR, et al. 1998a. Immunoglobulin levels in workers exposed to hexachlorobenzene. *Human Exp Toxicol* 17:172-175.
- Queiroz MLS, Perlingeiro RCR, Dantas DCM, et al. 1994. Immunoglobulin levels in workers exposed to inorganic mercury. *Pharmacol Toxicol* 74:72-75.
- \*Queiroz MLS, Quadros MR, Valadares MC, et al. 1998b. Polymorphonuclear phagocytosis and killing in workers occupationally exposed to hexachlorobenzene. *Immunopharmacol Immunotoxicol* 20(3):447-454.
- \*Quemerais B, Lemieux C, Lum KR. 1994. Concentrations and sources of PCBs and organochlorine pesticides in the St. Lawrence River (Canada) and its tributaries. *Chemosphere* 29(3):591-610.
- \*Quinsey PM, Donohue DC, Ahokas JT. 1995. Persistence of organochlorines in breast milk of women in Victoria, Australia. *Food Chem Toxicol* 33(1):49-56.
- \*Quinsey PM, Donohue DC, Cummings FJ, et al. 1996. The importance of measured intake in assessing exposure of breast-fed infants to organochlorines. *Eur J Clin Nutr* 50(7):438-442.
- \*Rahman MS, Bowadt S, Larsen B. 1993. Dual-column GC analysis of Mediterranean fish for ten organochlorine pesticides and sixty two chlorobiphenyls. *Journal of High Resolution Chromatography* 16:731-735.
- \*Rajamanickam C, Padmanaban G. 1974. Biochemical effects of hexachlorobenzene. *Indian J Biochem Biophys* 11:119-122.
- \*Rajamanickam C, Amrutavalli J, Rao MR, et al. 1972. Effect of hexachlorobenzene on haem synthesis. *Biochem J* 129:381-387.
- Randi AS, Sancovich HA, Ferramola AM, et al. 1998. Hexachlorobenzene-induced alterations of rat hepatic microsomal membrane function. *Toxicology* 125:83-94.
- Rasmussen RA. 1972. What do the hydrocarbons from trees contribute to air pollution? *J Air Pollut Control Assoc* 22(7):537-543.
- Raum E, Seidler A, Schlaud M, et al. 1998. Contamination of human breast milk with organochlorine residues: a comparison between East and West Germany through sentinel practice networks. *J Epidemiol Commun Health* 52(Suppl. 1):50S-55S.
- \*Ray LE, Murray HE, Giam CS. 1983. Organic pollutants in marine samples from Portland, Maine. *Chemosphere* 12:1031-1038.

## 9. REFERENCES

- Reeder AL, Foley GL, Nichols DK, et al. 1998. Forms and prevalence of intersexuality and effects of environmental contaminants on sexuality in cricket frogs (*Acris crepitans*). *Environ Health Perspect* 106(5):261-266.
- Renaud CB, Kaiser KLE, Comba ME. 1995. Historical versus recent levels of organochlorine contaminants in lamprey larvae of the St. Lawrence river basin, Quebec. *Can J Fish Aquat Sci* 52:268-275.
- Renner G. 1981. Biotransformation of the fungicides hexachlorobenzene and pentachloronitrobenzene. *Toxicology* 11:435-446.
- \*Renner G. 1988. Hexachlorobenzene and its metabolism. *Toxicol and Environ Chem* 18:51-78.
- \*Rhainds M, Levallois P, Ayotte P. 1999. Lead, mercury, and organochlorine compound levels in cord blood in Quebec, Canada. *Arch Environ Health* 54(1):40-47.
- \*Richter E, Schafer SG. 1981. Intestinal excretion of hexachlorobenzene. *Arch Toxicol* 47:233-239.
- \*Richter E, Renner G, Bayerl J, et al. 1981. Differences in the biotransformation of hexachlorobenzene (HCB) in male and female rats. *Chemosphere* 10:779-785.
- \*Richter J, Landa K, Reznicek J. 1994. Immune response in persons occupationally exposed to hexachlorobenzene. *Pracovni Lekarstvi* 46(4):151-154.
- Riederer M. 1995. Partitioning and transport of organic chemicals between the atmospheric environment and leaves. In: Trapp S, Mc Farlane JC, eds. *Plant Contamination: Modeling stimulation of organic chemical processes*. Boca Raton, FL: Lewis Publishers, 153-190.
- Rietjens IM, den Besten C, Hanzlik RP, et al. 1997. Cytochrome P-450-catalyzed oxidation of halobenzene derivatives. *Chem Res Toxicol* 10(6):629-635.
- Rietjens IMCM, Steensma A, Den Besten C, et al. 1995. Comparative biotransformation of hexachlorobenzene and hexaflourobenzene in relation to the induction of porphyria. *Eur J Pharmacol* 293:293-299.
- Rios de Molina MC, Billi de Catabbi S, San Martin de Viale LC. 1991. Liver ferrochelatase from normal and hexachlorobenzene porphyric rats. Mechanism of drug action. *Int J Biochem* 23:669-673.
- \*Rios de Molina MC, Wainstok e Calmanovici R, San Martin de Viale LC. 1980. Investigations on the presence of porphyrinogen carboxylase inhibitors in the liver of rats intoxicated with hexachlorobenzene. *Int J Biochem* 12:1027-1032.
- Rios De Molina R, Iglesias S, Lauria L, et al. 1996. Precancerous pathology evoked by hexachlorobenzene treatment. *Acta Physiol Pharmacol Ther Latinoam* 46(2):71-81.
- \*Ristola T, Pellinen J, Van Hoof PL, et al. 1996. Characterization of Lake Ladoga sediments. II. Toxic chemicals. *Chemosphere* 32(6):1179-1192.
- Ritchie RJ, Ambrose S. 1998. Distribution and population status of bald eagles (*Haliaeetus leucocephalus*) in interior Alaska. *Arctic* 49(2):120-128.

## 9. REFERENCES

- \*Rizzardini M, Smith AG. 1982. Sex differences in the metabolism of hexachlorobenzene by rats and the development of porphyria in females. *Biochem Pharmacol* 31:3543-3548.
- Rizzardini M, Cantoni L, Villa P, et al. 1990. Biochemical, morphological and flow-cytometric evaluation of the effects of hexachlorobenzene on rat liver. *Cell Biol Toxicol* 6:185-203.
- \*Robinson PE, Mack GA, Remmers J, et al. 1990. Trends of PCB, hexachlorobenzene, and beta-benzene hexachloride levels in the adipose tissue of the U.S. population. *Environ Res* 53:175-192.
- \*Roche P, Prados M. 1995. Removal of pesticides by use of ozone or hydrogen peroxide/ozone. *Ozone Sci Eng* 17:657-672.
- Rodolico S, Aleandri V, Parrocchia S, et al. 1999. [Chlorinated compounds in human breast milk: levels of conatmination and infant intake]. *L'Igiene Moderna* 111:119-131.
- \*Rodrigues MA, Sanchez-Negrette M, Mantovani MS, et al. 1991. Liver response to low-hexachlorobenzene exposure in protein- or energy-restricted rats. *Food Chem Toxic* 29: 757-764.
- Roe SL, MacIsaac HJ. 1998. Temporal variation of organochlorine contaminants in the zebra mussel *Dreissena polymorpha* in Lake Erie. *Aquat Toxicol* 41:125-140.
- Rogers HR. 1996. Sources, behaviour and fate of organic contaminants during sewage treatment and in sewage sludges. *Sci Total Environ* 185:3-26.
- Rohrig L, Meisch H. 2000. Application of solid phase micro extraction for the rapid analysis of chlorinated organics in breast milk. *Fresenius J Anal Chem* 366:106-111.
- \*Romanic SH, Krauthacker B. 2000. Organochlorine Pesticides and Polychlorinated Biphenyls in Ambient Air Collected in Zagreb, Croatia. *Bull Environ Contam Toxicol* 64:811-816.
- Roots O. 1996. Polychlorinated biphenyls and chlororganic pesticides, assessment of health risk associated with the consumption of seafood. *Proc Estonian Acad Sci Ecol* 6:124-135.
- Rosenkranz HS, Zhang YP, Klopman G. 1998. Studies on the potential for genotoxic carcinogenicity of fragrances and other chemicals. *Food Chem Toxicol* 36:687-696.
- \*Rostad CE, Pereira WE, Leiker TJ. 1988. Distribution and transport of selected anthropogenic organic compounds in Mississippi River suspended sediment USA May-June 1988. *J Contam Hydrol* 16(2):175-199.
- \*Rostad CE, Pereira WE, Leiker TJ. 1999. Distribution and transport of selected anthropogenic lipophilic organic compounds associated with Mississippi River suspended sediment, 1989-1990. *Arch Environ Contam Toxicol* 36:248-255.
- \*Rostad CE, Pereira WF, Leiker TJ. 1993. Distribution and transport of selected anthropogenic organic compounds on Mississippi River suspended sediment (U.S.A.), May/June 1988. *J Contam Hydrol* 16:175-199.
- Rothman N, Cantor KP, Blair A, et al. 1997. A nested case-control study of non-Hodgkin lymphoma and serum organochlorine residues. *Lancet* 350:240-244.

## 9. REFERENCES

\*Roy RR, Wilson P, Laski RR, et al. 1997. Monitoring of domestic and imported apples and rice by the U.S. Food and Drug Administration Pesticide Program. *J AOAC Int* 80(4):883-894.

Rozman K, Gorski JR, Rozman P, et al. 1986. Reduced serum thyroid hormone levels in hexachlorobenzene-induced porphyria. *Toxicol Lett* 30:71-78.

\*Rozman K, Mueller W, Coulston F, et al. 1977a. Long-term feeding study of hexachlorobenzene in rhesus monkeys. *Chemosphere* 2/3:81-84.

Rozman K, Mueller W, Coulston F, et al. 1977b. Long-term feeding study of hexachlorobenzene in rhesus monkeys. *Toxicol Appl Pharmacol* 41:217.

\*Rozman K, Mueller WF, Coulston F, et al. 1978. Chronic low dose exposure of rhesus monkeys to hexachlorobenzene (HCB). *Chemosphere* 2:177-184.

Rozman K, Mueller W, Coulston F, et al. 1979. The involvement of the lymphatic system in the absorption, transport, and excretion of hexachlorobenzene in rats and rhesus monkeys. *Toxicol Appl Pharmacol* 48:A93.

\*Rozman K, Rozman T, Greim H. 1981. Enhanced fecal elimination of stored hexachlorobenzene from rats and rhesus monkeys by hexadecane or mineral oil. *Toxicology* 22:33-44.

RTI. 1993. National listing of state fish and shellfish consumption advisories and bans. Research Triangle Park, NC: Research Triangle Institute Center for Environmental Analysis for U.S. EPA Office of Water, Office of Science and Technology, Fish Contamination Section.

Rugo HS, Damon, LE. 1990. Occupational Hematology. In: Ladou JL, ed. Occupational medicine. Norwalk, CT: Appelton and Lange, 161-162.

\*Rumack BH, Lovejoy FH Jr. 1991. Clinical toxicology. In: Amdur MO, Doull J, Klaasen CD, eds. Casarett and Doull's toxicology: The basic science of poisons, 4th ed. New York, NY: Pergamon Press, 924-946.

\*Rumsby PC, Evans JG, Phillimore HE, et al. 1992. Search for Ha-ras codon 61 mutations in liver tumours caused by hexachlorobenzene and aroclor 1254 in C57BL/10ScSn mice with iron overload. *Carcinogenesis* 13:1917-1920.

Russell RW, Gillan KA, Haffner GD. 1997. Polychlorinated biphenyls and chlorinated pesticides in southern Ontario, Canada, green frogs. *Environ Toxicol Chem* 16(11):2258-2263.

\*Russell RW, Lazar R, Haffner GD. 1995. Biomagnification of Organochlorines in Lake Erie White Bass. *Environ Toxicol Chem* 14(4):719-724.

\*Rutten GA, Schoots AC, Vanholder R, et al. 1988. Hexachlorobenzene and 1,1-di(4-chlorophenyl)-2,2-dichloroethene in serum of uremic patients and healthy persons: Determination by capillary gas chromatography and electron capture detection. *Nephron* 48:217-221.

Ryckman DP, Weseloh DV, Hamr P, et al. 1998. Spatial and temporal trends in organochlorine contamination and bill deformities in double-crested cormorants (*Phalacrocorax auritus*) from the Canadian Great Lakes. *Environ Monit Assess* 53:169-195.

## 9. REFERENCES

- Saboori AM, Newcombe DS. 1992. Environmental chemicals with immunotoxic properties. In: DS Newcombe, NR Rose, JC Bloom eds. *Clinical Immunotoxicology*. New York, NY: Raven Press Ltd., 365-400.
- \*Sala M, Ribas-Fito N, Cardo E, et al. 2001a. Levels of hexachlorobenzene and other organochlorine compounds in cord blood: exposure across placenta. *Chemosphere* 43:895-901.
- \*Sala M, Ribas-Fito N, de Muga ME, et al. 1999a. Hexachlorobenzene and other organochlorine compounds incorporation to the new-borns and its effects on neonatal neurological development at 6-8 weeks of life. *Organohalogen Compounds* 44:241-242.
- \*Sala M, Sunyer J, Herrero C, et al. 2001b. Association between serum concentrations of hexachlorobenzene and polychlorobiphenyls with thyroid hormone and liver enzymes in a sample of the general population. *Occup Environ Med* 58:172-177.
- \*Sala M, Sunyer J, Otero R, et al. 1999b. Health effects of chronic high exposure to hexachlorobenzene in a general population sample. *Arch Environ Health* 54(2):102-109.
- \*Salata H, Cortes JM, Enriquez de Salamanca R, et al. 1985. Porphyria *cutanea tarda* and hepatocellular carcinoma: Frequency of occurrence and related factors. *J Hepatol* 1:477-487.
- \*Sandberg S, Romslo I, Hovding G, et al. 1982. Porphyrin-induced photodamage as related to the subcellular localization of the porphyrins. *Acta Derm Venereol (Stockh)* 100:75-80.
- San Martin de Viale LC, Tomio JM, Ferramola AM, et al. 1975. Experimental porphyria induced in rats by hexachlorobenzene. *Proceedings - 1st International Porphyrin Meeting, Porphyrins in Human Disease*, 453-458.
- \*Sasaki YF, Izumiyama F, Nishidate E, et al. 1997. Detection of rodent liver carcinogen genotoxicity by the alkaline single-cell gel electrophoresis (Comet) assay in multiple mouse organs (liver, lung, spleen, kidney, and bone marrow). *Mutat Res* 391:201-214.
- \*Savitskii IV. 1964. The basis for determining safe permissible concentrations of hexachlorobenzene and pentachloronitrobenzene in the air. *Vopr Prom i Sel'skokhoz Toksikol* :158-173.
- \*Savitskii IV. 1965. The basis for determining safe permissible concentrations of hexachlorobenzene and pentachloronitrobenzene in the air. *Chemical Abstracts* 63:8952.
- \*Sax N. 1984. *Dangerous properties of industrial materials*. 6<sup>th</sup> ed. New York, NY: Van Nostrand Reinhold Company, 1505-1506.
- Sax NI, Lewis RJ Sr. 1987. *Hawley's condensed chemical dictionary - 11th ed*. New York, NY: Van Nostrand Reinhold Company, 263, 596.
- Schantz SL, Sweeney AM, Gardiner JC, et al. 1996. Neuropsychological assessment of an aging population of Great Lakes fish eaters. *Toxicol Ind Health* 12(3-4):403-417.
- \*Schauerte W, Lay JP, Klein W, et al. 1982. Long-term fate of organochlorine xenobiotics in aquatic ecosystems. Distribution, residual behavior, and metabolism of hexachlorobenzene, pentachloronitrobenzene, and 4-chloroaniline in small experimental ponds. *Ecotox Environ Saf* 6:560-569.

## 9. REFERENCES

- \*Schechter A, Ryan JJ, Papke O. 1998. Decrease in levels and body burden of dioxins, dibenzofurans, PCBs, DDE, and HCB in blood and milk in a mother nursing twins over a thirty-eight month period. *Chemosphere* 37(9-12):1807-1816.
- \*Scheele J, Teufel M, Niessen KH. 1995. A comparison of the concentrations of certain chlorinated hydrocarbons and polychlorinated biphenyls in bone marrow and fat tissue of children and their concentrations in breast milk. *J Environ Pathol Toxicol Oncol* 14:11-14.
- \*Scheele J, Teufel M, Niessen K-H. 1996. Chlorinated hydrocarbons in human bone marrow of healthy individuals and leukemia patients. *Arch Env Health* 51(1):22-25.
- \*Scheufler E, Rozman K. 1984a. Comparative decontamination of hexachlorobenzene exposed rats and rabbits by hexadecane. *J Toxicol Environ Health* 14:353-362.
- \*Scheufler E, Rozman K. 1984b. Effect of hexadecane on the pharmacokinetics of hexachlorobenzene. *Toxicol Appl Pharmacol* 75:190-197.
- \*Scheunert I, Marra C, Viswanathan R, et al. 1983. Fate of hexachlorobenzene - 14C in wheat plants and soils under outdoor conditions. *Chemosphere* 12:843-858.
- \*Schielen P, Den Besten C, Vos JG, et al. 1995a. Immune effects of hexachlorobenzene in the rat: Role of metabolism in a 13-week feeding study. *Toxicol Appl Pharmacol* 131:37-43.
- \*Schielen P, Schoo W, Tekstra J, et al. 1993. Autoimmune effects of hexachlorobenzene in the rat. *Toxicol Appl Pharmacol* 122:233-243.
- Schielen P, Van der Pijl A, Bleumink R, et al. 1996. Local popliteal lymph node reactions to hexachlorobenzene and pentachlorobenzene: Comparison with systemic effects. *Immunopharmacology* 31:171-181.
- \*Schielen P, Van Rodijnen W, Pieters RHH, et al. 1995b. Hexachlorobenzene treatment increases the number of splenic B-1 like cells and serum autoantibody levels in the rat. *Immunology* 86:568-574.
- Schiff K, Allen MJ. 2000. Chlorinated hydrocarbons in flatfishes from the Southern California, USA, bight. *Environ Toxicol Chem* 19(6):1559-1565.
- \*Schlummer M, Moser GA, McLachlan MS. 1998. Digestive tract absorption of PCDD/Fs, PCBs, and HCB in humans: Mass balances and mechanistic considerations. *Toxicol Appl Pharmacol* 152:128-137.
- \*Schmitt CJ, Zajicek JL, Peterman PH. 1990. National contaminant biomonitoring program: Residues of organochlorine chemicals in U.S. freshwater fish, 1976-1984. *Arch Environ Contam Toxicol* 19:748-781.
- Schmitt CJ, Zajicek JL, Ribick MA. 1985. National pesticide monitoring program: Residues of organochlorine chemicals in fresh water fish 1980-1981. *Arch Environ Contam Toxicol* 14:225-260.
- \*Schoula R, Hajslova J, Bencko V, et al. 1996. Occurrence of persistent organochlorine contaminants in human milk collected in several regions of Czech republic. *Chemosphere* 33(8):1485-1494.

## 9. REFERENCES

- \*Schrang CS, Cormier SM, Blazer VS. 1997. Contaminant exposure, biochemical, and histopathological biomarkers in white suckers from contaminated and reference sites in the Sheboygan River, Wisconsin. *J Great Lakes Res* 23(2):119-130.
- \*Schroll R, Bierling B, Cao B, et al. 1994. Uptake pathways of organic chemicals from soil by agricultural plants. *Chemosphere* 28(2):297-303.
- Schwab BW. 1999. The TEF approach for hexachlorobenzene. *Environ Health Perspect* 107(4):A183-A184.
- Schwetz BA, Norris JM, Kociba RJ, et al. 1974. Reproduction study in Japanese quail fed hexachlorobutadiene for 90 days. *Toxicol Appl Pharmacol* 30:255-265.
- \*SD Dept Environ Natural Resources. 1998. Drinking water standards. South Dakota Department of Environmental and Natural Resources. <http://www.state/sd.us/state/executive/denr/denr.html>.
- \*Seidel V, Linder W. 1993. Universal sample enrichment technique for organochlorine pesticides in environmental and biological samples using a redesigned simultaneous steam distillation- solvent extraction apparatus. *Anal Chem* 65:3677-3683.
- Selden A, Floderus Y, Bodin L, et al. 1998. Porphyrins in aluminum foundry workers exposed to hexachlorobenzene and octachlorostyrene. *Organohalogen Compounds* 38:263-265.
- \*Selden AI, Floderus Y, Bodin LS, et al. 1999. Porphyrin status in aluminum foundry workers exposed to hexachlorobenzene and octachlorostyrene. *Arch Environ Health* 54(4):248-253.
- \*Selden A, Jacobson G, Berg P, et al. 1989. Hepatocellular carcinoma and exposure to hexachlorobenzene: A case report. *Br J Ind Med* 46:138-140.
- \*Selden AS, Westberg HB, Hanberg A, et al. 1997. Congener-specific monitoring of PCB and hexachlorobenzene in hazardous waste incineration workers. *Organohalogen Compounds* 33:398-401.
- \*Setchell BP, Waites GMH. 1975. The blood-testis barrier. In: Creep RO, Astwood EB, Geiger SR, eds. *Handbook of physiology: Endocrinology V*. Washington, DC: American Physiological Society.
- \*Shan TH, Hopple JA, Foster GD. 1994. Alternative tissue analysis method developed for organochlorine contaminants in aquatic organisms. *Bull Environ Contam Toxicol* 53:382-389.
- Sharipova GA, Gulyaeva LF, Lyakhovich VV. 1998. Cytochrome P-4501A activity and mRNA level in liver and lungs of rats induced with various xenobiotics. *Mol Biol* 32(3):471-474.
- Sheppard SC. 1998. Geophagy: who eats soil and where do possible contaminants go? *Environ Geol* 33:109-114.
- \*Sherwood RL, Thomas PT, O'Shea WJ, et al. 1989. Effects of inhaled hexachlorobenzene aerosols on rat pulmonary host defenses. *Toxicol Ind Health* 5:451-461.
- Shirai T. 1997. A medium-term rat liver bioassay as a rapid in vivo test for carcinogenic potential: A historical review of model development and summary of results from 291 tests. *Toxicol Pathol* 25(5):453-460.

## 9. REFERENCES

- \*Shirai T, Miyata Y, Nakanishi K, et al. 1978. Hepatocarcinogenicity of polychlorinated terphenyl (PCT) in ICR mice and its enhancement by hexachlorobenzene (HCB). *Cancer Lett* 4:271-275.
- \*Siegel-Scott C, Johnson AE. 1986. A risk analysis of hexachlorobenzene-related reproductive outcomes. *IARC Sci Publ* 77:629-634.
- \*Siekel P, Chalupa I, Beno J, et al. 1991. A genotoxicological study of hexachlorobenzene and pentachloroanisole. *Teratogen, Carcinogen Mutagen* 11:55-60.
- Siersema PD, Cleton-Soeteman MI, Bruijn WC, et al. 1993. Ferritin accumulation and uroporphyrin crystal formation in hepatocytes of C57Bl/10 mice: A time-course study. *Cell Tissue Res* 274:405-412.
- \*Siersema PD, ten Kate FJW, Mulder PGH, et al. 1992. Hepatocellular carcinoma in porphyria cutanea tarda: Frequency and factors related to its occurrence. *Liver* 12:56-61.
- \*Siersema PD, Van Helvoirt RP, Ketelaars DAM, et al. 1991. Iron and uroporphyrin in hepatocytes of inbred mice in experimental porphyria: A biochemical and morphological study. *Hepatology* 14:1179-1188.
- Siljeholm J. 1997. A hazard ranking of organic contaminants in refinery effluents. *Toxicol Ind Health* 13(4):527-551.
- \*Silkworth JB, Loose LD. 1981. Assessment of environmental contaminant-induced lymphocyte dysfunction. *Environ Health Perspect* 39:105-128.
- \*Simon GS, Tardiff RG, Borzelleca JF. 1979. Failure of hexachlorobenzene to induce dominant lethal mutations in the rat. *Toxicol Appl Pharmacol* 47:415-419.
- \*Simonich SL, Hites RA. 1995. Organic pollutant accumulation in vegetation. *Environ Sci Technol* 29(12):2905-2914.
- \*Sims DE, Singh A, Donald A, et al. 1991. Alteration of primate ovary surface epithelium by exposure to hexachlorobenzene: A quantitative study. *Histol Histopath* 6:525-529.
- \*Sinclair PR, Gorman N, Sinclair JF, et al. 1995. Ascorbic acid inhibits chemically induced uroporphyrin in ascorbate requiring rats. *Hepatology*, August 22(2):565-572.
- Sinclair PR, Gorman N, Walton HS, et al. 2000. CYP1A2 is essential in murine uroporphyrin caused by hexachlorobenzene and iron. *Toxicol Appl Pharmacol* 162:60-67.
- Sinclair PR, Walton HS, Gorman N, et al. 1997. Multiple roles of polyhalogenated biphenyls in causing increases in cytochrome P450 and uroporphyrin accumulation in cultured hepatocytes. *Toxicol Appl Pharmacol* 147:171-179.
- Sinkkonen S, Raitio H, Paasivirta J, et al. 1995a. Concentrations of persistent organochlorine compounds in spruce needles from western Finland. *Chemosphere* 30(4):1415-1422.
- \*Sinkkonen S, Rantio T, Vattulainen A, et al. 1995b. Chlorohydrocarbons, PCB congeners, polychlorodioxins, furans and dibenzothiophenes in pine needles in the vicinity of a metal reclamation plant. *Chemosphere* 30(12):2227-2239.

## 9. REFERENCES

- \*Sinkkonen S, Welling L, Vattulainen A, et al. 1996. Short chain aliphatic halocarbons and polychlorinated biphenyls in pine needles: Effects of metal scrap plant emissions. *Chemosphere* 32(10):1971-1982.
- \*Sitarska E, Klucinski W, Faundez R, et al. 1995. Concentration of PCBs, HCB, DDT, and HCH isomers in the ovaries, mammary gland, and liver of cows. *Bull Environ Contam Toxicol* 55:865-869.
- Sittig M, ed. 1980. *Pesticide manufacturing and toxic materials control encyclopedia*. Park Ridge, NJ: Noyes Data Corporation, 448-450.
- Sittig M, ed. 1994. *World-wide limits for toxic and hazardous chemicals in air, water, and soil*. Park Ridge, NJ: Noyes Publications, 408-409.
- \*Siyali DS. 1972. Hexachlorobenzene and other organochloride pesticides in human blood. *Med J Aust* 2:1063-1066.
- \*Skaare JU, Bernhoft A, Wiig O, et al. 2001. Relationships between plasma levels of organochlorines, retinol and thyroid hormones from polar bears (*Ursus maritimus*) at Svalbard. *J Toxicol Environ Health* 62(part A):227-241.
- \*Smelt JH, Leistra M. 1974. Hexachlorobenzene in soils and crops after soil treatment with pentachloronitrobenzene. *Agric Environ* 1:65-71.
- \*Smith AG. 1989. Iron-mediated mechanisms of liver injury by polyhalogenated aromatic chemicals *Human Tox* 8:149-150. (Abstract)
- \*Smith AG. 1991. Chlorinated hydrocarbon insecticides. In: Hayes Jr WJ, Laws Jr ER, eds. *Handbook of pesticide toxicology*. vol. 2: Classes of pesticides. San Diego, CA: Academic Press, 731-915.
- \*Smith AG, Cabral JR. 1980. Liver-cell tumors in rats fed hexachlorobenzene. *Cancer Lett* 11:169-172.
- \*Smith AG, De Matteis F. 1990. Oxidative injury mediated by the hepatic cytochrome P-450 system in conjunction with cellular iron: Effects on the pathway of haem biosynthesis. *Xenobiotica* 20:865-877.
- \*Smith AG, Francis JE. 1983. Synergism of iron and hexachlorobenzene inhibits hepatic uroporphyrinogen decarboxylase in inbred mice. *Biochem J* 214:909-913.
- \*Smith AG, Francis JE. 1987. Chemically-induced formation of an inhibitor of hepatic uroporphyrinogen decarboxylase in inbred mice with iron overload. *Biochem J* 246:221-226.
- \*Smith AG, Cabral JR, Carthew P, et al. 1989. Carcinogenicity of iron in conjunction with a chlorinated environmental chemical, hexachlorobenzene, in C57BL/10ScSn mice. *Int J Cancer* 43:492-496.
- \*Smith AG, Cabral JRP, De Matteis F. 1979. A difference between two strains of rats in their liver non-haem iron content and in their response to the porphyrogenic effect of hexachlorobenzene. *Chem Biol Interact* 27:353-363.
- \*Smith AG, Carthew P, Francis JE, et al. 1993. Enhancement by iron of hepatic neoplasia in rats caused by hexachlorobenzene. *Carcinogenesis* 14(7):1381-1387.

## 9. REFERENCES

- \*Smith AG, Dinsdale D, Cabral JR, et al. 1987. Goitre and wasting induced in hamsters by hexachlorobenzene. *Arch Toxicol* 60:343-349.
- \*Smith AG, Francis JE, Bird I. 1986d. Distinction between octachlorostyrene and hexachlorobenzene in their potential to induce ethoxyphenoxazone deethylase and cause porphyria in rats and mice. *J Biochem Toxicol* 1:105-117.
- Smith AG, Francis JE, De Matteis F. 1980. Lobes of rat liver respond at different rates to challenge by dietary hexachlorobenzene. *Biochem Pharmacol* 29(23):3127-3131.
- \*Smith AG, Francis JE, Dinsdale D, et al. 1985. Hepatocarcinogenicity of hexachlorobenzene in rats and the sex difference in hepatic iron status and development of porphyria. *Carcinogenesis* 6(4):631-636.
- \*Smith AG, Francis JE, Green JA, et al. 1990. Sex-linked hepatic uroporphyrin and the induction of cytochromes P450IA in rats caused by hexachlorobenzene and polyhalogenated biphenyls. *Biochem Pharmacol* 40:2059-2068.
- \*Smith AG, Francis JE, Kay SJE, et al. 1986a. Mechanistic studies of the inhibition of hepatic uroporphyrinogen decarboxylase in C57BL/10 mice by iron-hexachlorobenzene synergism. *Biochem J* 238:871-878.
- Smith AG, Stewart FP, Francis JE. 1986c. Genetic, iron status and sex factors of porphyria induced by hexachlorobenzene. *IARC Sci Publ* 77:433-439.
- \*Smith AG, Wright AL, Cabral JRP. 1986b. Influence of hexachlorobenzene on thyroids of male hamsters. *IARC Sci Publ* 77:357-359.
- Smith DW. 1995. Synchronous response of hydrophobic chemicals in herring gull eggs from the Great Lakes. *Environ Sci Technol* 29:740-750.
- Soliman AS, Smith MA, Cooper SP, et al. 1997. Serum organochlorine pesticide levels in patients with colorectal cancer in Egypt. *Arch Env Health* 52(6):409-415.
- \*Somers JD, Goski BC, Barbeau JM, et al. 1993. Accumulation of organochlorine contaminants in double-crested cormorants. *Environ Pollut* 80(1):17-23.
- \*Sopena de Kracoff YE, Ferramola de Sancovich AM, Sancovich HA, et al. 1994. Effect of thyroidectomy and thyroxine on hexachlorobenzene induced porphyria. *J Endocrinol Invest* 17:301-305.
- \*SRI. 1993. Stanford Research Institute International. 1993. Directory of chemical producers: United States of America. Menlo Park, CA.
- \*SRI. 1999. Stanford Research Institute International. 1993. Directory of chemical producers: United States of America. Menlo Park, CA.
- \*SRI. 2001. Stanford Research Institute International. 1993. Directory of chemical producers: United States of America. Menlo Park, CA.
- \*Stachel B, Dougherty RC, Lahl U, et al. 1989. Toxic environmental chemicals in human semen: Analytical method and case studies. *Andrologia* 21:282-291.

## 9. REFERENCES

- Stangroom SJ, Collins CD, Lester JN. 1998. Sources of organic micropollutants to lowland rivers. *Environ Technol* 19:643-666.
- Staples CA, Werner AF, Hoogheem TJ. 1985. Assessment of priority pollutant concentrations in the United States using STORET database. *Environ Toxicol Chem* 4:131-142.
- Stein JE, Hom T, Collier TK, et al. 1995. Contaminant exposure and biochemical effects in outmigrant juvenile chinook salmon from urban and nonurban estuaries of Puget Sound, Washington. *Environ Toxicol Chem* 14(6):1019-1029.
- Stellman SD, Djordjevic MV, Muscat JE, et al. 1998. Relative abundance of organochlorine pesticides and polychlorinated biphenyls in adipose tissue and serum of women in Long Island, New York. *Cancer Epidemiol Biomarkers Prev* 7:489-4986.
- \*Stewart FP, Smith AG. 1986. Metabolism of hexachlorobenzene by rat-liver microsomes. *IARC Sci Publ* 77:325-327.
- Stewart FP, Manson MM, Cabral JR, et al. 1989. Hexachlorobenzene as a promoter of diethylnitrosamine-initiated hepatocarcinogenesis in rats and comparison with induction of porphyria. *Carcinogenesis* 10:1225-1230.
- Stonard MD, Poli G, De Matteis F. 1998. Stimulation of liver heme oxygenase in hexachlorobenzene-induced hepatic porphyria. *Arch Toxicol* 72(6):355-361.
- \*Strand LJ, Manning J, Marver HS. 1971. Acute intermittent porphyria: Studies on the enzymatic basis of disordered haem biosynthesis. *S Afr J Lab Clin Med* 17:108.
- Strandberg B, Hites RA. 2001. Concentration of organochlorine pesticides in wine corks. *Chemosphere* 44:729-735.
- \*Strandberg B, Bandh C, van Bavel R, et al. 2000. Organochlorine compounds in the Gulf of Bothnia: sediment and benthic species. *Chemosphere* 40:1205-1211.
- Strik JJ. 1986. Subacute toxicity of hexachlorobenzene. *IARC Sci Publ* 77:335-342.
- Stringer RL, Jacobs MN, Johnston PA, et al. 1996. Organochlorine residues in fish oil dietary supplements. *Organohalogen Compounds* 28:551-556.
- \*Stuetz W, Prapamontol T, Erhardt JG, et al. 2001. Organochlorine pesticide residues in human milk of a hmong hill tribe living in Northern Thailand. *Sci Total Environ* 273:53-60.
- Stutz W, Scherbaum V. 2000. Declining contamination of breast milk by organochlorine compounds-Germany in a worldwide comparison. *Ernaehr-Umsch* 47(10):375-381.
- \*Sufit RL, Hodach R, Arends R, et al. 1986. Decreased conduction velocity and pseudomyotonia in hexachlorobenzene-fed rats. *IARC Sci Publ* 77:361-362.
- \*Sundlof SF, Hansen LG, Koritz GD, et al. 1982. The pharmacokinetics of hexachlorobenzene in male beagles: Distribution, excretion, and pharmacokinetics model. *Drug Metab Dispos* 10:371-381.

## 9. REFERENCES

- \*Sundlof SM, Parker AJ, Simon J, et al. 1981. Sub-acute toxicity of hexachlorobenzene in female beagles, including electroencephalographic changes. *Vet Hum Toxicol* 23:92-96.
- \*Susarla S, Yonezawa Y, Masunaga S. 1997. Transformation kinetics and pathways of chlorophenols and hexachlorobenzene in fresh water lake sediment under anaerobic conditions. *Environ Technol* 18:903-911.
- Suwalsky M, Rodriguez C, Villena F, et al. 1999. The pesticide hexachlorobenzene induces alterations in the human erythrocyte membrane. *Pestic Biochem Physiol* 65:205-214.
- Swain WR. 1978. Chlorinated organic residues in fish, water, and precipitation from the vicinity of Isle Royale, Lake Superior. *J Great Lakes Res* 4:398-407.
- \*Swann RL, Laskowski DA, McCall PJ, et al. 1983. A rapid method for the estimation of the environmental parameters octanol/water partition coefficient, soil sorption constant, water to air ratio, and water solubility. *Residue Rev* 85:17-28.
- \*Sweeney GD, Basford D, Drestynski F. 1986. The role of contaminants in hexachlorobenzene toxicity. *IARC Sci Publ* 77:363-370.
- \*Swift BL, Foley RE, Batcheller GR. 1993. Organochlorines in common Goldeneyes wintering in New York. *Wildl Soc Bull* 21(1):52-56.
- \*Szymczynski GA, Waliszewski SM. 1981. Comparison of the content of chlorinated pesticide residues in human semen, testicles and fat tissues. *Andrologia* 13:250-252.
- \*Tabak HH, Quave SA, Mashni CI, et al. 1981. Biodegradability studies with organic priority pollutant compounds. *J Water Pollut Control Fed* 53:1503-1518.
- \*Takei GH, Kauahikaua SM, Leong GH. 1983. Analyses of human milk samples collected in Hawaii for residues of organochlorine pesticides and polychlorobiphenyls. *Bull Environ Contam Toxicol* 30:606-613.
- \*Tate CM, Heiny JS. 1996. Organochlorine compounds in bed sediment and fish tissue in the South Platte River Basin, USA, 1992-1993. *Arch Environ Contam Toxicol* 30:62-78.
- \*Taylor DH, Goldey E. 1990. Assessment of the behavioral and neurotoxic effects of hexachlorobenzene (HCB) in the developing rat. AAMRL-TR-90-076.
- \*Tchounwou PB, Abdelghani AA, Pramam YV, et al. 1998. Health risk assessment of hexachlorobenzene and hexachlorobutadiene residues in fish collected from a hazardous waste contaminated wetland in Louisiana, USA. In: Little EE, Greenberg BM, DeLonay AJ, eds. *Environmental toxicology and risk assessment*. 7<sup>th</sup> Vol., 368-382.
- \*Ten Hulscher TEM, Van Der Velde LE, Bruggeman WA. 1992. Temperature dependence of Henry's law constants for selected chlorobenzenes, polychlorinated biphenyls and polycyclic aromatic hydrocarbons. *Env Toxicol Chem* 11:1595-1603.
- \*Teufel M, Niessen KH, Sartoris J, et al. 1990. Chlorinated hydrocarbons in fat tissue: Analyses of residues in healthy children, tumor patients, and malformed children. *Arch Environ Contam Toxicol* 19(5):646-652.

## 9. REFERENCES

- \*Thier H-P, Zeumer H. 1987a. Organochlorine, organophosphorus nitrogen-containing and other pesticides. Deutsche Forschungsgemeinschaft: Manual of pesticide residue analysis. Vol. 1. Weinheim, Germany: VCH, 383-400.
- \*Thier H-P, Zeumer H. 1987b. Organochlorine and organophosphorus pesticides. Deutsche Forschungsgemeinschaft: Manual of pesticide residue analysis. Vol. 1. Weinheim, Germany. VCH, 298-307.
- \*Thomas RG. 1990. Volatization from water. In: Lyman WJ, Reehl WF, Roseblatt DH, eds., Handbook of chemical property estimation methods. Environmental Behavior of Organic Compounds. Washington DC: American Chemical Society, 15-15-15-17.
- Thomas RS, Gustafson DL, Ramsdell HS, et al. 1998. Enhanced regional expression of glutathione S-transferase P1-1 with colocalized AP-1 and CYP 1A2 induction in chlorobenzene-induced porphyria. *Toxicol Appl Pharmacol* 150:22-31.
- Thompson RPH, Nicholson DC, Farnan T, et al. 1970. Cutaneous porphyria due to a malignant primary hepatoma. *Gastroenterology* 59:779-783.
- \*Tiernan TO, Solch JG, Garrett JG, et al. 1990. A concerted analytical method for determination of various halogenated and related bioaccumulating compounds in fish and sediments. Brominated Compound, Short-Chain Aliphatics 2:225-228.
- \*Tiernan TO, Taylor ML, Garrett JH, et al. 1985. Sources and fate of polychlorinated dibenzodioxins, dibenzofurans and related compounds in human environments. *Environ Health Persp* 59:145-158.
- Tilbury KL, Adams NG, Krone CA, et al. 1999. Organochlorines in stranded pilot whales (*Globicephala melana*) from the coast of Massachusetts. *Arch Environ Contam Toxicol* 37:125-134.
- \*Tintinalli JE, Ruiz E, and Krone RL, eds. 1996. Emergency medicine. A comprehensive study. American College of Emergency Physicians. 4<sup>th</sup> ed. The McGraw-Hill Companies, Inc.
- \*Tobin P. 1985. Known and potential sources of hexachlorobenzene. In: Morris CR, Cabral JRP, ed. Hexachlorobenzene: Proceedings of an International Symposium. Lyon, France: IARC Scientific Publications, 3-11.
- To-Figueras J, Barrot C, Rodamilans M, et al. 1995. Accumulation of hexachlorobenzene in humans: a long standing risk. *Human Exp Toxicol* 14:20-23.
- \*To-Figueras J, Barrot C, Sala M, et al. 2000. Excretion of hexachlorobenzene and metabolites in feces in a highly exposed human population. *Environ Health Perspect* 108(7):595-598.
- \*To-Figueras J, Gomez-Catalan J, Rodamilans M, et al. 1991. Studies on sex differences in excretion of sulphur derivatives of hexachlorobenzene and pentachloronitrobenzene by rats. *Toxicol Lett* 56:87-94.
- \*To-Figueras J, Gomez-Catalan J, Rodamilans M, et al. 1992. Sulphur derivative of hexachlorobenzene in human urine. *Human Exp Toxicol* 11:271-273.
- \*To-Figueras J, Sala M, Otero R, et al. 1997. Metabolism of hexachlorobenzene in humans: Association between serum levels and urinary metabolites in a highly exposed population. *Environ Health Perspect* 105(1):78-83.

## 9. REFERENCES

TOMES. 1993. Toxicology, Occupational Medicine and Environment Series electronic database. Creosote: Phenol and related agents. Micromedex, Inc. Vol 78.

\*Tomlin CDS. 1997. The pesticide manual. 11<sup>th</sup> ed. British Crop Protection Council, 977-979, 1084-1086.

\*Topi GC, D'Alessandro Gandolfo L, Griso D, et al. 1980. Porphyrin cutanea tarda and hepatocellular carcinoma. *Int J Biochem* 12:883-885.

\*Torinuki W, Kumai N, Miura T. 1981. Histopathological studies on sun-exposed hexachlorobenzene-induced porphyric rat skin. *Tohoku J Exp Med* 134:425-430.

Townsend BA, Carlson GP. 1981. Effect of halogenated benzenes on the toxicity and metabolism of malathion, malaoxon, parathion, and paraoxon in mice. *Toxicol Appl Pharmacol* 60:52-61.

Trenti T, Ventura E, Ceccarelli D, et al. 1986. Functional derangement of liver mitochondria from hexachlorobenzene-treated rats. *IARC Sci Publ* 77:329-331.

TRI91. 1993. National Toxicology Information Program, Toxic Chemical Release Inventory. National Library of Medicine Bethesda, MD.

TRI93. 1995. National Toxicology Information Program, Toxic Chemical Release Inventory. National Library of Medicine Bethesda, MD.

\*TRI98. 2000. National Toxicology Information Program, Toxic Chemical Release Inventory. National Library of Medicine Bethesda, MD. <http://www.epa.gov/enviro/ad>. 6/13/00

\*TRI99. 2001. TRI explorer: Providing access to EPA's toxics release inventory data. Washington, DC: Office of Information Analysis and Access, Offices of Environmental Information, U.S. Environmental Protection Agency. Toxic Release Inventory. <http://www.epa.gov/triexplorer/>. 11/26/01.

\*Trotter WJ, Dickerson R. 1993. Pesticide residues in composited milk collected through the U.S. Pasteurized Milk Network. *J AOAC Int* 76(6):1220-1225.

Tryphonas H. 1998. The impact of PCBs and dioxins on children's health: Immunological considerations. *Can J Public Health* 89(Suppl. 1):S49-S52.

Tsambaos D, Bolsen K, Georgiou S, et al. 1994. Effects of oral thalidomide on rat liver and skin microsomal P450 isozyme activities and on urinary porphyrin excretion: Interaction with oral hexachlorobenzene. *Arch Dermatol Res* 286:347-349.

\*Tsuda H, Matsumoto K, Ogino H, et al. 1993. Demonstration of initiation potential of carcinogens by induction of preneoplastic glutathione S transferase P-form-positive liver cell foci: Possible *in vivo* assay system for environmental carcinogens. *Jpn J Cancer Res* 84:230-236.

Umegaki K, Ikegami S. 1998. Feeding fish oil to rats accelerates the metabolism of hexachlorobenzene. *J Nutr Sci Vitaminol* 44:301-311.

\*UNEP. 1996. UNEP survey on sources of POPs: A report prepared for an IFCS expert meeting on persistent organic pollutants: Manila, the Philippines, 17-19 June 1996. United Nations Environment Programme. <http://www.chem.unep.ch/pops/indxhtmls/manexp3.html>.

## 9. REFERENCES

- \*USC. 1998. Hazardous air pollutants. U.S. Code: Title 42, section 7412. <http://www4.law.cornell.edu/uscode/42/7412.text.html>.
- \*USC. 2001. Hazardous air pollutants. United States Code. 42 USC 7412. <http://www4.law.cornell.edu/uscode/42/7412.text.html>. November 29, 2001.
- U.S. Congress. 1990. Clean Air Act Amendments of 1990. Title III. Hazardous air pollutants, section 112-hazardous air pollutants as amended, October 26, 1990. 101st congress, 2nd session report, 101-952.
- USDA. 2000a. Accreditation of chemistry laboratories. United States Department of Agriculture, Food Safety and Inspection Service. 9 CFR 318.21.
- USDA. 2000b. Accreditation of chemistry laboratories. United States Department of Agriculture, Food Safety and Inspection Service. 9 CFR 381.153.
- \*USDA. 2000c. Germination standards for vegetable seeds in interstate commerce. United States Department of Agriculture, Agricultural Marketing Service. 7 CFR 201.31.
- \*USDA. 2001. Labeling treated seed. United States Department of Agriculture. Code of Federal Regulations. 7 CFR 201.31a(b). <http://frwebgate.access.gpo.gov/cgi-bin/>. December 19, 2001.
- U.S. International Trade Commission. 1991. (USITC). Harmonized tariff schedule of the United States (1991). Washington, DC.
- U.S. International Trade Commission. 1992. (USITC). Preliminary report on U.S. production of selected synthetic organic chemicals (including synthetic plastics and resin materials) first quarter, second quarter, and cumulative totals, Washington DC.
- van Birgelen APMJ. 1998. Hexachlorobenzene as a possible major contributor to the dioxin activity of human milk. *Environ Health Perspect* 106(11):683-688.
- van Birgelen APJM. 1999. Uncertainties in the toxic equivalency factor concept: Future directions. *Organohalogen Compounds* 44:505-508.
- \*Van Den Berg KJ. 1990. Interaction of chlorinated phenols with thyroxine binding sites of human transthyretin, albumin and thyroid binding globulin. *Chem Biol Interact* 76:63-75.
- \*Van Loveren H, Kranjnc EI, Rombout PJA, et al. 1990. Effects of ozone, hexachlorobenzene, and bis(tri-*n*-butyltin)oxide on natural killer activity in the rat lung. *Toxicol Appl Pharmacol* 102:21-33.
- Van Loveren H, Steerenberg PA, Vos JG. 1995. Early detection of immunotoxicity: from animal studies to human biomonitoring. *Toxicol Lett* 77:73-80.
- \*van Ommen B, Hendriks W, Bessems JGM, et al. 1989. The relation between the oxidative biotransformation of hexachlorobenzene and its porphyrinogenic activity. *Toxicol Appl Pharmacol* 100:517-528.
- \*van Ommen B, Van Bladeren PJ, Temmink JHM, et al. 1985. Formation of pentachlorophenol as the major product of microsomal oxidation of hexachlorobenzene. *Biochem Biophys Res Comm* 126:25-32.

## 9. REFERENCES

- \*van Raaij JAGM, Frijters CMG, van den Berg KJ. 1993a. Hexachlorobenzene-induced hypothyroidism: Involvement of different mechanism by parent compound and metabolite. *Biochem Pharmacol* 46(8):1385-1391.
- \*van Raaij JAGM, Frijters CMG, Wong Yen kong L, et al. 1994. Reduction of thyroxine uptake into cerebrospinal fluid and rat brain by hexachlorobenzene and pentachlorophenol. *Toxicology* 94:197-208.
- \*van Raaij JAGM, Kaptein E, Visser TJ, et al. 1993b. Increased glucuronidation of thyroid hormone in hexachlorobenzene-treated rat. *Biochem Pharmacol* 45(3):627-631.
- \*van Raaij JA, van den Berg KJ, Engel R, et al. 1991a. Effects of hexachlorobenzene and its metabolites pentachlorophenol and tetrachlorohydroquinone on serum thyroid hormone levels in rats. *Toxicology* 67:107-116.
- van Raaij JA, van den Berg KJ, Notten WR. 1991b. Hexachlorobenzene and its metabolites pentachlorophenol and tetrachlorohydroquinone: Interaction with thyroxine binding sites of rat thyroid hormone carriers ex vivo and in vitro. *Toxicol Lett* 59:101-107.
- \*Veith GD, DeFoe DL, Bergstedt BV, et al. 1979. Measuring and estimating the bioconcentration factor of chemicals in fish. *J Fish Res Bd Can* 36:1040-1048.
- Vena JE, Buck GM, Kostyniak P, et al. 1996. The New York angler cohort study: Exposure characterization and reproductive and developmental health. *Toxicol Ind Health* 12:327-334.
- \*Verschueren K. 1983. Handbook of environmental data on organic chemicals. 2nd ed. New York, NY: Van Nostrand Reinhold Company, 712-717.
- \*Verschueren K. 1996. Handbook of environmental data on organic chemicals. 3rd ed. New York, NY: Van Nostrand Reinhold Company, 1064-1069.
- Vetter W, Scholz E, Gaus C, et al. 2001. Anthropogenic and natural organohalogen compounds in blubber of dolphins and dugongs (Dugong dugon) from Northeastern Australia. *Arch Environ Contam Toxicol* 41:221-231.
- \*Vieira I, Sonnier M, Cresteil T. 1996. Developmental expression of *CYP2E1* in the human liver: Hypermethylation control of gene expression during the neonatal period. *Eur J Biochem* 238:476-483.
- \*Vilanova R, Fernandez P, Martinez C, et al. 2001. Organochlorine pollutants in remote mountain lake waters. *J Environ Qual* 30:1286-1295.
- Vilas GL, Aldonatti C, San Martin de Viale LC, et al. 1999. Effect of  $\alpha$ lipoic acid amide on hexachlorobenzene porphyria. *Biochem Mol Biol Int* 47(5):815-823.
- \*Villeneuve DC, Hierlihy SL. 1975. Placental transfer of hexachlorobenzene in the rat. *Bull Environ Contam Toxicol* 13:489-491.
- Villeneuve DC, Newsome WH. 1975. Toxicity and tissue levels in the rat and guinea pig following acute hexachlorobenzene administration. *Bull Environ Contam Toxicol* 14:297-300.
- \*Villeneuve DC, Panopio LG, Grant DL. 1974a. Placental transfer of hexachlorobenzene in the rabbit. *Environ Physiol Biochem* 4:112-115.

## 9. REFERENCES

- Villeneuve DC, Phillips WEJ, Panopio LG, et al. 1974b. The effects of phenobarbital and carbon tetrachloride on the rate of decline of body burdens of hexachlorobenzene in the rat. *Arch Environ Contam Toxicol* 2:243-252.
- \*Villeneuve DC, Van Logten MJ, Den Tonkelaar EM, et al. 1977. Effect of food deprivation on low level hexachlorobenzene exposure in rats. *Sci Total Environ* 8:179-186.
- \*Vincent SH, Smith AG, Muller-Eberhard U. 1989. Modulation of hepatic heme-binding Z protein in mice by the porphyrogenic carcinogens griseofulvin and hexachlorobenzene. *Cancer Lett* 45:109-114.
- \*Visser O, Van den Berg JW, Edixhoven-Bosdisk A, et al. 1989. Development of hexachlorobenzene porphyrin in rats: Time sequence and relationship with lipid peroxidation. *Food Chem Toxicol* 27:317-321.
- Vos JG. 1986. Immunotoxicity of hexachlorobenzene. *IARC Sci Publ* 77:347-356.
- Vos J, Van Loveren H. 1995. Markers for immunotoxic effects in rodents and man. *Toxicol Lett* 82/83:385-394.
- \*Vos JG, Brouwer GMJ, van Leeuwen FXR, et al. 1983. Toxicity of hexachlorobenzene in the rat following combined pre- and post-natal exposure: Comparison of effects on immune system, liver and lung. In: Gibson GG, Hubbard R, Parke DV, eds. *Immunotoxicology*. London, England: Academic Press, 219-235.
- Vos JG, van der Maas HL, Musch A, et al. 1971. Toxicity of hexachlorobenzene in Japanese quail with special reference to porphyria, liver damage, reproduction, and tissue residues. *Toxicol Appl Pharmacol* 18:944-957.
- \*Vos JG, van Logten MJ, Kreeftenberg JG, et al. 1979a. Effect of hexachlorobenzene on the immune system of rats following combined pre- and postnatal exposure. *Drug Chem Toxicol* 2:61-76.
- \*Vos JG, van Logten MJ, Kreeftenberg JG, et al. 1979b. Hexachlorobenzene-induced stimulation of the humoral immune response in rats. *Ann NY Acad Sci* 320:535-550.
- \*Vos RME, Snoek MC, Van Berkel WJH, et al. 1988. Differential induction of rat hepatic glutathione S-transferase isoenzymes by hexachlorobenzene and benzyl isothiocyanate: Comparison with induction by phenobarbital and 3-methylcholanthrene. *Bio Chem Pharmacol* 37:1077-1082.
- Vreel M, Jan J, Pogacnik A, et al. 1996. Transfer of planar and non-planar chlorobiphenyls, 4,4'-DDE and hexachlorobenzene from blood to milk and to suckling infants. *Chemosphere* 33(11):2341-2346.
- \*VT Air Control Division. 1998. Air toxics report. Vermont Agency of Natural Resources. <http://www.anr.state.vt.us/>.
- \*WA Dept of Ecology. 1998. Controls for new sources of toxic air pollutants. Chapter 173-460 WAC. Washington State Department of Ecology, Air Quality Program. <http://www.wa.gov/ecology/air/airhome.html>.
- \*Wada O, Yano Y, Urata G, et al. 1968. Behavior of hepatic microsomal cytochromes after treatment of mice with drugs known to disturb porphyrin metabolism in liver. *Biochem Pharmacol* 17:595-603.

## 9. REFERENCES

- \*Waddington RT. 1972. Short notes of rare or obscure cases. A case of primary liver tumour associated with porphyria. *Brit J Surg* 59:653-654.
- Wagman N, Strandberg B, Van Bavel B, et al. 1999. Organochlorine pesticides and polychlorinated biphenyls in household composts and earthworms (*Eisenia foetida*). *Environ Toxicol Chem* 18(6):1157-1163.
- Wagner U, Schlebusch H, Van der Ven H, et al. 1990. Accumulation of pollutants in the genital tract of sterility patients. *J Clin Chem Clin Biochem* 28:683-688.
- \*Wainstok de Calmanovici R, San Martin de Viale LC. 1980. Effect of chlorophenols on porphyrin metabolism in rats and chicken embryo. *Int J Biochem* 12:1039-1044.
- Wainstok de Calmanovici R, Billi de Catabbi SC, Aldonatti CA. 1989. Influence of the strain of rats on the induction of hexachlorobenzene induced porphyria. *Int J Biochem* 21:377-381.
- Wainstok de Calmanovici R, Cochon AC, Aldonatti C, et al. 1990. Synergistic effect of mammary tumors on hexachlorobenzene-induced porphyria in rats. *Cancer Letters* 55:67-73.
- \*Wainstok de Calmanovici R, Cochon AC, Aldonatti C, et al. 1991. Sex comparison of heme pathway in rats bearing hepatic tumors. *Tumori* 77:379-384.
- Wainstok de Calmanovici R, Rios de Molina MDC, Taira de Yamasato MC, et al. 1984. Mechanism of hexachlorobenzene-induced porphyria in rats: Effect of phenobarbitone pretreatment. *Biochem J* 218:753-763.
- \*Waliszewski SM, Szymczynski GA. 1985. Inexpensive, precise method for the determination of chlorinated pesticide residues in soil. *J Chromatogr* 321:480-483.
- \*Waliszewski SM, Aguirre AA, Benitez A, et al. 1999a. Organochlorine pesticide residues in human blood serum of inhabitants of Veracruz, Mexico. *Bull Environ Contam Toxicol* 62(4):397-402.
- Waliszewski SM, Aguirre AA, Infanzon RM, et al. 1998. Time trend of organochlorine pesticide residues in human adipose tissue in Veracruz, Mexico: 1988-1997 survey. *Sci Total Environ* 221:201-204.
- \*Waliszewski SM, Aguirre AA, Infanzon RM, et al. 1999b. Comparison of organochlorine pesticide levels in adipose tissue and human milk of mothers living in Veracruz, Mexico. *Bull Environ Contam Toxicol* 62(6):685-690.
- \*Waliszewski SM, Aguirre AA, Infanzon RM. 1999c. Levels of organochlorine pesticides in blood serum and umbilical blood serum of mothers living in Veracruz, Mexico. *Fresenius Environ Bull* 8:171-178.
- \*Waliszewski SM, Aguirre AA, Infanzon RM, et al. 2000a. Comparison of organochlorine pesticide levels in adipose tissue and blood serum from mothers living in Veracruz, Mexico. *Bull Environ Contam Toxicol* 64:8-15.
- Waliszewski SM, Aguirre AA, Infanzon RM, et al. 2000b. Partitioning coefficients of organochlorine pesticides between mother blood serum and umbilical blood serum. *Bull Environ Contam Toxicol* 65:293-299.

## 9. REFERENCES

- \*Waliszewski SM, Aguirre AA, Infanzon RM, et al. 2001. Organochlorine pesticide levels in maternal adipose tissue, maternal blood serum, umbilical blood serum, and milk from inhabitants of Veracruz, Mexico. *Arch Environ Contam Toxicol* 40:432-438.
- \*Waliszewski SM, Pardo Seda VT, Chantiri JN, et al. 1996. Organochlorine pesticide residues in human breast milk from tropical areas in Mexico. *Bull Environ Contam Toxicol* 57:22-28.
- Walters SM. 1986. Cleanup of samples. In: Zweig G, Sherma J, eds. *Analytical methods for pesticides and plant growth regulators*. Vol 15. New York, NY: Academic Press, 67-110.
- \*Wania F, Mackay D. 1993. Global fractionation and cold condensation of low volatility organochlorine compounds in polar regions. *Ambio* 22(1):10-18.
- \*Wania F, Mackay D. 1995. A global distribution model for persistent organic chemicals. *Sci Total Environ* 160/161:211-232.
- Waters MD, Stack HF, Jackson MA. 1999. Genetic toxicology data in the evaluation of potential human environmental carcinogens. *Mutat Res* 437:21-49.
- Weast RC, ed. 1985. *CRC handbook of chemistry and physics*. Boca Raton, FL: CRC Press, Inc., C-109, C-114.
- \*Weiderpass E, Adami HO, Baron JA, et al. 2000. Organochlorines and endometrial cancer risk. *Cancer Epidemiol Biomarkers Prev* 9:487-493.
- Weis IM, Muir DCG. 1997. Geographical variation of persistent organochlorine concentrations in blubber of ringed seal (*Phoca hispida*) from the Canadian Arctic: Univariate and multivariate approaches. *Environ Pollut* 96(3):321-333.
- \*Weisenberg E. 1986. Hexachlorobenzene in human milk: A polyhalogenated risk. *IARC Sci Publ* 77:193-200.
- \*Weisenberg E, Arad I, Grauer F, et al. 1985. Polychlorinated biphenyls and organochlorine insecticides in human milk in Israel. *Arch Environ Contam Toxicol* 14:517-521.
- \*Westrand C, Noren K. 1998. Polychlorinated naphthalenes and other organochlorine contaminants in human adipose and liver tissue. *J Toxicol Environ Health* 53:293-311.
- Weseloh DV, Hamr P, Bishop CA, et al. 1995. Organochlorine contaminant levels in waterbird species from Hamilton Harbour, Lake Ontario: an IJC area of concern. *J Great Lakes Res* 21(1):121-137.
- Weseloh DVC, Rodrigue J, Blonkpoel H, et al. 1997. Contamination concentrations in eggs of black terns (*Chlidonias niger*) from southern Ontario and southern Quebec, 1989-1996. *Colonial Waterbirds* 20(3):604-616.
- \*West JR, Smith HW, Chasis H. 1948. Glomerular filtration rate, effective renal blood flow, and maximal tubular excretory capacity in infancy. *J Pediatr* 32:10-18.

## 9. REFERENCES

- Westgate AJ, Muir DCG, Gaskin DE, et al. 1997. Concentrations and accumulation patterns of organochlorine contaminants in the blubber of harbour porpoises, *phocoena phocoena*, from the coast of Newfoundland, the gulf of St. Lawrence and the Bay of Fundy/Gulf of Maine. *Environ Pollut* 95(1):105-119.
- \*Whitmore RW, Immerman FW, Camann DE, et al. 1994. Non occupational exposures to pesticides for residents of two U.S. cities. *Arch Environ Contam Toxicol* 26(1):47-59.
- WHO. 1984a. Guidelines for drinking-water quality: Volume I: Recommendations. Geneva, Switzerland: World Health Organization, 203-228.
- WHO. 1984b. Guidelines for drinking-water quality: Volume II: Health criteria and other supporting information. Geneva, Switzerland: World Health Organization, 203-228.
- WHO. 1984c. Environmental Health Criteria 41, Quintozene. Geneva: United Nations Environment Programme, the International Labour Organisation, and the World Health Organization.
- \*WHO. 1996. Pesticides. Guidelines for drinking water quality. World Health Organization. Lyon, France. [http://www.who.int/water\\_sanitation\\_health/GDWQ/Summary\\_tables/Tab2c.htm](http://www.who.int/water_sanitation_health/GDWQ/Summary_tables/Tab2c.htm). May 15, 2002.
- \*WHO. 1997. Hexachlorobenzene. Environmental Health Criteria, No. 195. World Health Organization. Lyon, France. [Http://www.who.int/pcs/ehc/summaries/ehc\\_195.htm](http://www.who.int/pcs/ehc/summaries/ehc_195.htm). May 15, 2002.
- \*WI Dept Natural Resources. 1997. Air management program, Control of hazardous pollutants. Wisconsin Department of Natural Resources. <http://www.dnr.state.wi.us/org/aw/air>.
- \*Wickstrom K, Pyysalo H, Siimes MA. 1983. Levels of chlordane, hexachlorobenzene, PCB and DDT compounds in Finnish human milk in 1982. *Bull Environ Contam Toxicol* 31:251-256.
- \*Widdowson EM, Dickerson JWT. 1964. Chemical composition of the body. In: Comar CL, Bronner F, eds. Mineral metabolism: An advanced treatise. Volume II: The elements Part A. New York: Academic Press.
- \*Williams PL, Burson JL. 1985. Biotransformation: A basic liver action upon exogenous chemicals. In: Industrial Toxicology Safety and Health Applications in the Workplace. 83-88, Van Nostrand Reinhold Company, NY.
- Wilson R, Allen-Gil S, Griffin D, et al. 1995. Organochlorine contaminants in fish from an arctic lake in Alaska, USA. *Sci Total Environ* 160/161:511-519.
- Woods SM, Peters HA, Johnson SAM. 1958. Cutaneous porphyria with porphobilinogenuria. *AMA Arch Dermatol* 77:559-567.
- Worthing CR, Walker SB. 1983. Hexachlorobenzene. The pesticide manual. 7th edition. British Crop Protection Council.
- \*Yalkowsky SH. 1992. Aquasol database of aqueous solubility. 5<sup>th</sup> edition. Tucson, AR: University of Arizona, College of Pharmacy.

## 9. REFERENCES

- \*Yamashita N, Tanabe S, Ludwig JP et al. 1992. Embryonic abnormalities and organochlorine contamination in double crested Cormorants (*Phalacrocorax auritus*) and Caspian terns (*Hydroprogne caspia*) from the upper Great Lakes in 1988. *Environ Pollut* 79(2):163-173.
- \*Yang RSH, Pittman KA, Rourke DR, et al. 1978. Pharmacokinetics and metabolism of hexachlorobenzene in the rat and the Rhesus monkey. *J Agric Food Chem* 26:1076-1083.
- \*Yasuhara A, Shiraishi H, Nishikawa M, et al. 1999. Organic components in leachates from hazardous waste disposal sites. *Waste Manage Res* 17:186-197.
- \*Yesair DW, Feder PI, Chin AE, et al. 1986. Development, evaluation and use of a pharmacokinetic model for hexachlorobenzene. *IARC Sci Publ* 77:297-318.
- \*Yess NJ, Gunderson EL, Roy RR. 1993. U.S. Food and Drug Administration monitoring of pesticide residues in infant foods and adult foods eaten by infants/children. *J AOAC Int* 76:492-507.
- \*Yuan SY, Su CJ, Chang BV. 1999. Microbial dechlorination of hexachlorobenzene in anaerobic sewage sludge. *Chemosphere* 38(5):1015-1023.
- \*Zabik ME, Schemmel R. 1980. Influence of diet on hexachlorobenzene accumulation in Osborne Mendel rats. *J Environ Pathol Toxicol* 4:97-103.
- Zabik ME, Booren A, Zabik MJ, et al. 1996. Pesticide residues, PCBs and PAHs in baked, charbroiled, salt boiled and smoked Great Lakes lake trout. *Food Chem* 55(3):231-239.
- \*Zabik ME, Zabik MJ, Booren AM, et al. 1995. Pesticides and total polychlorinated biphenyls in chinook salmon and carp harvested from the Great Lakes effects of skin on and skin off processing and selected cooking methods. *J Agric Food Chem* 43(4):993-1001.
- Zahm SH, Ward MH. 1998. Pesticides and childhood cancer. *Environ Health Perspect Suppl* 106(Suppl. 3):893-908.
- Zail SS, Joubert SM. 1968. Hepatic delta aminolevulinic acid synthetase activity in symptomatic porphyria. *Br J Haematol* 15:123.
- Zhang C, Valsaraj KT, Constant WD, et al. 1998. Nutrient and surfactant enhancement for the biodegradation of chlorinated hydrocarbons in the wastewater from a Louisiana superfund site. *J Hazard Mater* 62:41-58.
- \*Zheng T, Holford TR, Mayne ST, et al. 1999. Environmental exposure to hexachlorobenzene (HCB) and risk of female breast cancer in Connecticut. *Cancer Epidemiol Biomarkers Prev* 8:407-411.
- \*Ziegler EE, Edwards BB, Jensen RL, et al. 1978. Absorption and retention of lead by infants. *Pediatr Res* 12:29-34.
- Zitko V, Hutzinger O. 1976. Uptake of chloro- and bromobiphenyls, hexachloro- and hexabromobenzene by fish. *Bull Environ Contam Toxicol* 16:665-673.
- Zlatkis A, Kim K. 1976. Column elution and concentration of volatile compounds in biological fluids. *J Chromatogr* 126:475-485.

## 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 ( $K_d$ )**—The amount of a chemical adsorbed by a 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 which 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.

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**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 which 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.

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**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.

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

**Immunological Effects**—Functional changes in the immune response.

**In Vitro**—Isolated from the living organism and artificially maintained, as in a test tube.

**In Vivo**—Occurring within the living organism.

**Lethal Concentration<sub>(LO)</sub> (LC<sub>LO</sub>)**—The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

**Lethal Concentration<sub>(50)</sub> (LC<sub>50</sub>)**—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<sub>(LO)</sub> (LD<sub>LO</sub>)**—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<sub>(50)</sub> (LD<sub>50</sub>)**—The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

**Lethal Time<sub>(50)</sub> (LT<sub>50</sub>)**—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.

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**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) which represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed.

**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 science of quantitatively predicting 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 whereby 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 which quantitatively describes the relationship between target tissue dose and toxic end

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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  $\mu\text{g/L}$  for water,  $\text{mg/kg/day}$  for food, and  $\mu\text{g/m}^3$  for air).

**Recommended Exposure Limit (REL)**—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentrations 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  $\text{mg/m}^3$  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.

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**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.

**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 min continually. No more than four excursions are allowed per day, and there must be at least 60 min 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<sub>(50)</sub> (TD<sub>50</sub>)**—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 study of 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.

## 10. GLOSSARY

A default for each individual UF is 10; if complete certainty in data exists, a value of one can be used; however a reduced UF of three may be used on a case-by-case basis, three being the approximate logarithmic average of 10 and 1.

**Xenobiotic**—Any chemical that is foreign to the biological system.



## APPENDIX A

### ATSDR MINIMAL RISK LEVEL 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.

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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 a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

## APPENDIX A

**MINIMAL RISK LEVEL (MRL) WORKSHEET**

Chemical name: Hexachlorobenzene  
CAS number: 118-74-1  
Date: May 2002  
Profile status: Draft 3 Post-Public Comment  
Route:  Inhalation  Oral  
Duration:  Acute  Intermediate  Chronic  
Key to figure: 23  
Species: Rat

MRL: 0.008  mg/kg/day  ppm  mg/m<sup>3</sup>  
(LOAEL = 2.5 mg/kg/day; total uncertainty factors = 300)

Reference: Goldey ES and Taylor DH. 1992. Developmental neurotoxicity following prenatally maternal exposure to hexachlorobenzene in rats. *Neurotoxicol and Teratol*, 14: 15–21.

Experimental design (human study details or strain, number of animals per exposure/control group, sex, dose administration details): Groups of 30 virgin female Sprague-Dawley rats were dosed by gastric intubation for 4 days with 0, 2.5, or 25 mg/kg/day hexachlorobenzene to achieve a total dose of 0, 10, or 100 mg/kg for the 4-day period. Dosing was completed 2 weeks before breeding. The developmental neurotoxicity of hexachlorobenzene was assessed using a battery of behavioral tests. Negative geotaxis response was assessed in two male and two female pups from each litter on postnatal day (PND) 6, 8, and 10. Olfactory discrimination/homing was assessed in two male and two female pups from each litter on PND 9, 10, and 11. This test simultaneously measures sensory discrimination, motivation, and locomotor ability. The development of exploration and locomotion was assessed in whole litters between PND 15 and 20. Acoustic startle response (ASR) was assessed on PND 23 and 90. Visual discrimination learning, as measured in the water-filled T-maze, was assessed in offspring on PND 40. Motor activity in mature offspring (PND 60) was measured in an open area. These adult animals were again tested for exploratory activity on PND 100.

Effects noted in study and corresponding doses: Hexachlorobenzene affected multiple pathways throughout the developing nervous system, manifested as slight hyperactivity, at a LOAEL of 2.5 mg/kg/day. The offspring rats showed faster response times in negative geotaxis and olfactory discrimination/homing tests at the 2.5 or 25 mg/kg/day maternal dose level. Offspring exposed to maternal doses of 2.5 or 25 mg/kg/day showed either significantly increased exploratory behavior, slight hyperactivity, or both during the early life (19–20 days of age). Hexachlorobenzene-exposed offspring at the 25 mg/kg/day dose level exhibited significantly decreased ASR (23-day-old pups). When rats were tested later as adults (90 days old), response amplitude was significantly elevated in males in both groups exposed *in utero* to 2.5 and 25 mg/kg/day, compared to controls. Maternal exposure of rats to hexachlorobenzene did not result in any significant changes in learning ability, locomotor activity (60-day-old offspring), or exploratory activity (100-day-old offspring).

Dose end point used for MRL derivation:

NOAEL  LOAEL

2.5 mg/kg/day; hyperactivity in offspring.

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Uncertainty factors used in MRL derivation:

1  3  10 (for use of a minimal LOAEL)  
 1  3  10 (for extrapolation from rats to humans)  
 1  3  10 (for human variability)  
Total uncertainty factors: 3 x 10 x 10 = 300

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: Review of the located human and animal oral acute toxicity data for hexachlorobenzene indicate that the 4-day developmental study by Goldey and Taylor (1992) provides the most appropriate data for use deriving oral acute MRL for hexachlorobenzene. The LOAEL of 2.5 mg/kg/day is the most refined LOAEL for the acute toxicity of hexachlorobenzene.

Adverse neurological signs and symptoms have also been observed in human offspring of maternally exposed to hexachlorobenzene. Children of mothers who had eaten hexachlorobenzene-contaminated bread (estimated hexachlorobenzene intake of 0.05–0.2 g/day) in Turkey exhibited muscle weakness, pinched facies, cogwheel rigidity, and sensory shading. Hexachlorobenzene was detected in the breast milk of the mothers, indicating lactational transfer (Cam and Nigogosyan 1963; Peters et al. 1982, 1987). Since hexachlorobenzene crosses the placenta and accumulates in fetal tissues in several animal species including the rat (Cripps 1990; Villeneuve and Hierlihy 1975), rabbit (Villeneuve et al. 1974a), and mouse (Courtney and Andrews 1985; Courtney et al. 1979), it is likely that the human offspring were also exposed to hexachlorobenzene during gestation. Development of neurotoxic signs has also been reported in other neonatal animals. These signs included convulsions, tremors, and progressive weakness in rats (Cripps 1990). Oral hexachlorobenzene has also been shown to interfere with the function of the nervous system in adult animals, inducing tremors, ataxia, and paralysis in unspecified strain of rats (Ockner and Schmid 1961); clonic convulsions, tremors, hyper-excitability, reversible muscle fasciculations, and lethargy in adult Wistar rats (Kennedy and Wigfield 1990; Koss et al. 1978; Nikolaev et al. 1986); mild reduction in conduction velocity of sciatic nerve, denervation, fibrillations, and chronic repetitive discharges in adult Sprague-Dawley rats (Sufit et al. 1986); tremor and hyperexcitability in adult Sherman rats (Kimbrough and Linder 1974); dysrhythmic electroencephalogram in adult Beagle dogs (Sundlof et al. 1981); tremor in adult C57B1/6J mice (Hahn et al. 1988); severe tremors and muscular weakness in adult Rhesus monkeys (Knauf and Hobson 1979); and tremors, panting, and unsteady gait in adult SPF pigs (Den Tonkelaar et al. 1978).

Agency Contact (Chemical Manager): Dr. Jessilynn Taylor

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**MINIMAL RISK LEVEL WORKSHEET**

Chemical name: Hexachlorobenzene  
CAS number: 118-74-1  
Date: May 2002  
Profile status: Draft 3 Post-Public Comment  
Route:  Inhalation  Oral  
Duration:  Acute  Intermediate  Chronic  
Key to figure: 129  
Species: Monkey

MRL: 0.0001  mg/kg/day  ppm  mg/m<sup>3</sup>  
(LOAEL = 0.01 mg/kg/day; total uncertainty factors = 90)

References: Bourque AC, Singh A, Lakhanpal N, et al. 1995. Ultrastructural changes in ovarian follicles of monkeys administered hexachlorobenzene. *Am J Vet Res* 56: 1673–1677.

Jarrell JF, MacMahon A, Villeneuve D, et al. 1993. Hexachlorobenzene toxicity in the monkey primordial germ cell without induced porphyria. *Reproductive Toxicology* 7:41–47.

Experimental design (human study details or strain, number of animals per exposure/control group, sex, dose administration details): In the Jarrell et al. (1993) study, groups of four female *Cynomolgus* monkeys were administered 0, 0.1, 1, or 10 mg/kg/day hexachlorobenzene in gelatin capsules for 90 days. No systemic toxicity was noted in any of the animals. After treatment, the animals were sacrificed and one ovary was removed from each animal from each dose group (including controls) and examined by transmission electron microscopy for alterations to surface epithelium. A cycle of *in vitro* fertilization with oocytes removed from exposed females during the menstrual cycle was performed to evaluate fertility. Induction of ovarian hyperstimulation (performed with human menopausal gonadotropin) was conducted to evaluate oocyte function. In the follow-up Bourque et al. (1995) study, groups of four female *Cynomolgus* monkeys were administered 0, 0.01, 0.1, 1, or 10 mg/kg/day hexachlorobenzene in gelatin capsules for 90 days. Monkeys were then given a preparation containing follicle-stimulating and luteinizing hormones on days 2–7 of the next menstrual cycle to stimulate follicle development, and human chorionic gonadotropin was administered on day 8 of the cycle. Oophorectomy was performed on day 10 of the cycle via laparotomy. The ovary was examined by transmission electron microscopy.

Effects noted in study and corresponding doses: In the Jarrell et al. (1993) study, *in vitro* fertilization and ovarian hyperstimulation in terms of percent fertilization, estradiol response to gonadotropin, follicular development, oocyte recovery rates and maturation, and early embryo development were not significantly different from control animals. Hexachlorobenzene treatment caused a decrease in the total number of oocytes and primordial follicles. Ultrastructural changes in ovarian epithelium included a decrease in nuclear membrane distinction, an increase in density and granularity of oocyte nuclei, an increase in vacuoles, aggregated lysosomes in ooplasm of follicular cells, and pyknotic granulosa cells. The ooplasm of some follicles was necrotic, and some follicles had mild to moderate degenerative changes. These changes were observed in all exposed animals; the severity of symptoms increased in a dose-dependent manner. The follow-up study by Bourque et al. (1995) extended the observation of ultrastructural effects in the ovary to 0.01 mg/kg/day. At this dose, mitochondria in developing follicles were condensed and deformed. At higher doses, the mitochondria were progressively more damaged and additional changes, such as indentation of nuclear membranes and abnormal accumulation of lipid in the cytoplasm of follicular cells, were noted.

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Dose end point used for MRL derivation:

NOAEL  LOAEL

0.01 mg/kg/day; degenerative lesions in ovarian follicles

Uncertainty factors used in MRL derivation:

1  3  10 (for use of a minimal LOAEL)

1  3  10 (for extrapolation from monkeys to humans)

1  3  10 (for human variability)

Total uncertainty factors:  $3 \times 3 \times 10 = 90$

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: Review of the located human and animal oral intermediate toxicity data for hexachlorobenzene indicate that the 90-day studies by Bourque et al. (1995) and Jarrell et al. (1993) provide the most appropriate data for use in deriving an oral intermediate MRL for hexachlorobenzene.

In humans, 15 fetal deaths (comprising 13 miscarriages and 2 stillbirths) and 173 live births occurred in 42 females in a 4-year period (1977–1981) several years after the widespread accidental ingestion of hexachlorobenzene-treated seed grain in Turkey (Peters et al. 1982, 1987). These mothers also had 0.51 ppm hexachlorobenzene in their breast milk as compared to 0.07 ppm in unexposed controls (Gocmen et al. 1989). It has also been demonstrated that hexachlorobenzene in human milk can readily cross to the child during lactation and accumulate in the offspring (Ando et al. 1985; Weisenberg 1986; Weisenberg et al. 1985).

Animal studies provide additional evidence that hexachlorobenzene is toxic to the mammalian ovary and may interfere with mechanisms regulating ovarian steroidogenesis. Female Cynomolgus monkeys exhibited a dose-dependent decrease in serum progesterone levels during the luteal phase of the menstrual cycle when administered hexachlorobenzene doses of \$0.1 (0.1, 1, 10) mg/kg/day as capsules for 90 days; the decrease in levels of progesterone was not observed during the follicular and periovulatory phases. Lengthening of the menstrual cycle was also observed, as well as dose-dependent ultrastructural changes in surface epithelium of the ovary (indicative of cellular degeneration) and changes in ovary surface epithelial cell shape (length to width ratio), in all treatment groups, the severity of which was increased in a dose-dependent manner (Foster et al. 1992a; Sims et al. 1991). Increased serum progesterone levels and elevated ovarian weights were observed in superovulated female Sprague-Dawley rats orally administered \$1 mg/kg/day hexachlorobenzene by gavage (in corn oil) for 21 days (Foster et al. 1992b). Serum levels of estradiol and progesterone of female Sprague-Dawley rats receiving daily doses of 50 mg/kg/day hexachlorobenzene by gavage in corn oil for 5 days were not significantly affected, although super-ovulated rats (dosed with pregnant mare serum gonadotropin and human chorionic gonadotropin) exposed to hexachlorobenzene in this study exhibited significant elevation of serum levels of progesterone (Foster et al. 1993). In a subsequent study with ovariectomized female Sprague-Dawley rats administered daily oral

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doses of 1, 10, or 100 mg/kg/day hexachlorobenzene in corn oil by gavage for 30 days, circulating levels of corticosterone levels were reduced by 25 and 51% at the 1 and 10 mg/kg/day hexachlorobenzene dose levels, respectively. Circulating cortisol levels were also significantly reduced ( $p < 0.05$ ). Hexachlorobenzene treatment had no effect on the levels of circulating aldosterone and progesterone levels, or on absolute and relative weights of the adrenal glands. The investigators concluded that hexachlorobenzene exposure induces alterations in steroidogenesis of cells of the adrenal cortex inner zone (Foster et al. 1995b).

A study conducted with female Rhesus monkeys given gavage doses of 8, 32, 64, or 128 mg/kg/day hexachlorobenzene in methylcellulose for 60 days found degenerative changes of the ovarian follicle, stroma, and germinal epithelium at dose levels of 64 mg/kg/day (Iatropoulos et al. 1976). In another monkey study, adult female Rhesus monkeys given oral doses of 8, 16, 32, 64, or 128 mg/kg/day hexachlorobenzene for 60 days showed significantly depressed (29%,  $p < 0.01$ ) whole serum cholesterol levels in weeks 3, 5, and 8. On day 60, depressed serum potassium and elevated SGOT were seen at the 128 mg/kg/day dose level. The authors suggested that the changes in potassium and cholesterol levels may be due to liver histopathology. The authors suggested that the changes in potassium levels may be due to unusual steroidogenic activity associated with changes in ovarian morphology (Knauf and Hobson 1979).

Agency Contact (Chemical Manager): Dr. Jessilynn Taylor

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**MINIMAL RISK LEVEL WORKSHEET**

Chemical name: Hexachlorobenzene  
CAS number: 118-74-1  
Date: May 2002  
Profile status: Draft 3 Post-Public Comment  
Route:  Inhalation  Oral  
Duration:  Acute  Intermediate  Chronic  
Key to figure: 162  
Species: Rat

MRL: 0.00005  mg/kg/day  ppm  mg/m<sup>3</sup>  
(LOAEL = 0.016 mg/kg/day; total uncertainty factors = 300)

Reference: Arnold DL, Moodie CA, Charbonneau SM, Grice HC, et al. 1985. Long-term toxicity of hexachlorobenzene in the rat and the effect of dietary vitamin A. *Food Chem Toxicol*, 23(9): 779–793.

Experimental design (human study details or strain, number of animals per exposure/control group, sex, dose administration details): Groups of Sprague-Dawley rats (40 per sex) of the F<sub>1</sub> generation were exposed to dietary hexachlorobenzene at 0, 0.32, 1.6, 8, or 40 ppm (approximate doses of 0, 0.016, 0.08, 0.4, or 2 mg/kg/day) from weaning for life (130 weeks). The groups of rats were also exposed *in utero* to hexachlorobenzene since variable numbers (40–66 per sex) of the F<sub>0</sub> generation rats, from which the F<sub>1</sub> generation rats used in this study were randomly selected, were exposed to corresponding doses 3 months prior to mating and weaning of the F<sub>1</sub> rats. The F<sub>0</sub> rats were killed and examined at weaning of the F<sub>1</sub> rats. The F<sub>1</sub> rats in this study were sacrificed after the animals had been on test for 130 weeks. A total of 35 tissues and organs (including brain, heart, liver, extrahepatic bile duct, lungs, spleen, pancreas, small intestine, adrenals, kidneys, bladder, ovaries, uterus, skin, pituitary, thyroid, parathyroid, thymus, prostate, testes, and bone) were histopathologically examined.

Effects noted in study and corresponding doses: Significant dose-response trends were observed in both sexes for hepatic basophilic chromogenesis at 0.4 mg/kg/day, and in males for peribiliary lymphocytosis and fibrosis at or greater than the lowest dose tested (0.016 mg/kg/day). Chronic nephrosis, severe in males, and reduced pup viability were observed at 2 mg/kg/day. Tumors were also increased at 2 mg/kg/day, including neoplastic liver nodules in females, parathyroid adenoma in males, and adrenal pheochromocytoma in both males and females. No treatment related effects in the rat offspring were observed with respect to feed consumption or body weight.

For derivation of the MRL, the increased incidences of peribiliary lymphocytosis and fibrosis in treated males were considered to represent a minimal effect. These are common spontaneous lesions in aging rats and occurred in approximately 30% of controls in this study. For peribiliary fibrosis, incidence was increased in all treated groups (statistically significant in the 0.016 and 2 mg/kg/day groups), but there was no clear evidence of a dose-response (13/48, 23/48, 21/48, 21/49, and 23/49 in the control, 0.016, 0.08, 0.4, and 2 mg/kg/day groups, respectively). For peribiliary lymphocytosis, the incidence was increased in all treated groups (statistically significant in the 0.016, 0.08, and 2 mg/kg/day groups), and while the trend with dose was not very impressive, it was statistically significant (16/48, 27/48, 26/48, 21/49, and 32/49, respectively). Incidences of these lesions in the control and treated females were similar to the control males (ranging from 6/49 to 14/49), suggesting that the incidence levels in control males were not unusually low. Overall, these findings suggest that hexachlorobenzene produced a

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minimal hepatic effect in male rats at the lowest doses administered by increasing the incidence of age-related hepatic lesions.

Dose end point used for MRL derivation:

NOAEL  LOAEL

0.016 mg/kg/day; peribiliary lymphocytosis and fibrosis of the liver.

Uncertainty factors used in MRL derivation:

1  3  10 (for use of a minimal LOAEL)

1  3  10 (for extrapolation from rats to humans)

1  3  10 (for human variability)

Total uncertainty factors:  $3 \times 10 \times 10 = 300$

Was a conversion factor used from ppm in food or water to a mg/body weight dose?

Yes. Dose = 0.32 ppm or 0.32 mg hexachlorobenzene/kg feed. The average rat consumes 0.05 kg of feed per kg body weight per day (EPA 1986 reference food factor for rats). Thus, the average daily dose of hexachlorobenzene is estimated to be  $0.32 \text{ mg/kg} \times 0.05 \text{ kg feed/kg body weight/day} = 0.016 \text{ mg/kg/day}$ .

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 liver appears to be a target organ of hexachlorobenzene; therefore, using hepatic effects (peribiliary lymphocytosis and fibrosis) to calculate the MRL is appropriate. Also, review of the located human and animal oral chronic toxicity data for hexachlorobenzene indicate that the 130-week rat study by Arnold et al. (1985) provide the most appropriate data to derive a chronic MRL because the study provides the most refined LOAEL for the characteristic chronic toxicity (hepatic effects) of hexachlorobenzene.

Other studies in several animal species have demonstrated that the liver is the major target organ of hexachlorobenzene exposure. Typical signs included microscopic lesions, increased porphyrin levels, and interference with hepatic enzymes involved in the heme biosynthesis pathway.

Oral exposure to hexachlorobenzene induced liver histopathology and altered liver histochemistry in the rats. The relative liver weights of male rats were increased by 46% while those of females were increased by 23% in a study in which both sexes of Sprague-Dawley rats were given oral hexachlorobenzene doses of 27.5 mg/kg/day for 4 weeks (Richter et al. 1981). Cytoplasmic vacuolation, anisokaryosis, and pyknotic hepatocytes were seen in the liver of female Sprague-Dawley rats administered single gavage doses of 400 or 600 mg/kg hexachlorobenzene in corn oil and observed for 14 days. Relative liver weights were increased by 16–18 and 13–18% in the 400 and 600 mg/kg dose group animals, respectively. Serum cholesterol levels were increased by 13–30 and 7–31% in the 400 and 600 mg/kg dose group animals, respectively. No changes in serum sodium, potassium, inorganic phosphorus, total bilirubin, alkaline phosphatase, aspartate aminotransferase, total protein, calcium, glucose, and lactate dehydrogenase content were found. Liver microsomal aminopyrine demethylase, aniline hydroxylase, and ethoxyresorufin deethylase (EROD) activities were unchanged by hexachlorobenzene exposure (Lecavalier et al. 1994). Liver weight was significantly increased by nearly 45% in animals treated with

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1,000 mg/kg/day for 7 days. Liver porphyrin carboxylase activity was significantly decreased in animals receiving 1,000 mg/kg/day (Kleiman de Pisarev et al. 1990). In rats given 100 mg/kg/day of hexachlorobenzene for 60 days, the liver became enlarged, and liver degeneration and increased hepatic porphyrins were observed (Ockner and Schmid 1961). A 67% hepatomegaly was observed in male Wistar (WAG/MBL) rats given oral doses of 120 mg/kg/day hexachlorobenzene, 3 times a week for 4 weeks (van Raaij et al. 1993b). Similarly, an 81% liver enlargement was reported at a hexachlorobenzene dose of 10 mg/kg/day for a group of Fischer 344 rats in a 15-week study. Liver-to-body weight ratios also increased at dose levels of 10 and 25 mg/kg/day (Andrews et al. 1989). Similarly, significantly increased liver weights were observed in rats fed 100 mg/kg/day hexachlorobenzene in the diet for 5 days (Rajamanickam and Padmanaban 1974).

Porphyria, as an index of hepatopathology, was also seen in several animal studies following oral exposure to hexachlorobenzene. Uroporphyrin and hepatic porphyrin accumulation were reported in a 13-week study in female Wistar rats administered 7.5 or 15 mg/kg/day hexachlorobenzene in the feed. Rats in the 7.5 and 15 mg/kg/day dose group exhibited elevated d-ALA synthase levels (94 and 483%, respectively). At the low dose (7.5 mg/kg/day), relative liver weight increased by 31%, and at the highest dose tested (15 mg/kg/day), relative liver weight increased by 103%. Hypertrophic hepatocytes with eosinophilic cytoplasm with thready basophilic structures, as well as inflammatory cell infiltrates, were observed in the livers of animals dosed with 15 mg/kg/day hexachlorobenzene. By the end of the study, uroporphyrin in the 15 mg/kg/day dose group was 1,400% that of control animals. Liver accumulations of porphyrins were 1,054 and 15,104%, respectively, for the 7.5 and 15 mg/kg/day dose group animals compared to undosed controls. Liver retinoid and plasma retinol were decreased by 70 and 53%, respectively, at the 15 mg/kg/day dose level (den Besten et al. 1993).

Female Sprague-Dawley rats exhibited elevated urinary and hepatic porphyrins following administration of 50 mg/kg/day hexachlorobenzene for 12 consecutive days (cumulative dose of 600 mg/kg), and 10 days (2 weeks, 5 days/week, cumulative dose of 500 mg/kg), or 100 mg/kg/day for 5 consecutive days (cumulative dose of 500 mg/kg). The porphyria seen was reported to be similar in severity to that observed in female rats receiving a cumulative dose of 1,500 mg/kg over a 6-week period. Porphyria induced by a cumulative dose of 500 mg/kg (either protocol) persisted for more than 500–600 days after exposure (Krishnan et al. 1991). Similarly, female Wistar rats given hexachlorobenzene in the diet at a dose of 150 mg/kg/day for 107 days exhibited a 91% decrease in uroporphyrinogen decarboxylase activity and 2,888-fold increase in hepatic porphyrin concentration (Elder and Urquhart 1986).

Oral exposure to hexachlorobenzene resulted in altered liver function and histology in: adult female Rhesus monkeys given oral doses of 8, 16, 32, 64, or 128 mg/kg/day hexachlorobenzene for 60 days (Knauf and Hobson 1979); female Wistar rats exposed to 50 mg/kg/day hexachlorobenzene by gavage for 15 weeks (Koss et al. 1978, 1983); female Agus Wistar rats fed diets containing 5 mg/kg/day hexachlorobenzene (with 2% arachis oil) for 75–90 weeks (Smith and Cabral 1980); female Wistar rats exposed to 5 or 50 mg/kg hexachlorobenzene for 56 days (Kennedy and Wigfield 1990); both sexes of Charles River rats fed hexachlorobenzene doses of 0.5, 2, 8, or 32 mg/kg/day (Kuiper-Goodman et al. 1977); monkeys given doses of 8 mg/kg/day for 60 days (Iatropoulos et al. 1976); and adult female Beagle dogs administered 25 mg/kg/day hexachlorobenzene in gelatin capsules for 21 days (Sundlof et al. 1981). Induction of liver microsomal enzymes, increased liver weight, and microscopic lesions were demonstrated at a hexachlorobenzene dose of 5 mg/kg/day, while centrilobular hypertrophy, elevated urinary coproporphyrinogen, and depressed glucose-6-phosphatase activity were observed at a lower dose level (0.5 mg/kg/day) in pigs treated for 90 days (Den Tonkelaar et al. 1978).

Several animal studies also found increased induction of P-450 isozymes and other hepatic enzymes, usually accompanied by hepatic or uroporphyrin, as an index of adverse effects in the liver (Adjarov et al. 1982; Hahn et al. 1988, 1989; Kitchin and Brown 1989; Kleiman de Pisarev et al. 1995; Li et al. 1989; Linko et al. 1986; Lissner et al. 1975; Mehendale et al. 1975; Rajamanickam and Padmanaban 1974; Smith et al. 1985; Wada et al. 1968).

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Agency Contact (Chemical Manager): Dr. Jessilynn Taylor



## 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 they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, 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. If data are located in the scientific literature, a table of genotoxicity information is included.

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.

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**Interpretation of Minimal Risk Levels**

Where sufficient toxicologic information is available, we have derived minimal risk levels (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. They 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 the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

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 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 LSE Tables.

**Chapter 3****Health Effects****Tables and Figures for Levels of Significant Exposure (LSE)**

Tables (3-1, 3-2, and 3-3) and figures (3-1 and 3-2) 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, minimal risk levels (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 No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

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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 LSE Table 3-1**

- (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. When sufficient data exists, 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 Table 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 2 "18r" data points in 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 regimen 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 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 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, 1 systemic effect (respiratory) was investigated.

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- (8) NOAEL A No-Observed-Adverse-Effect Level (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 Lowest-Observed-Adverse-Effect Level (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 Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.
- (12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

**LEGEND****See Figure 3-1**

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 intermediate and chronic 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<sup>3</sup> or ppm and oral exposure is reported in mg/kg/day.
- (16) NOAEL In this example, 18r NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. 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 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

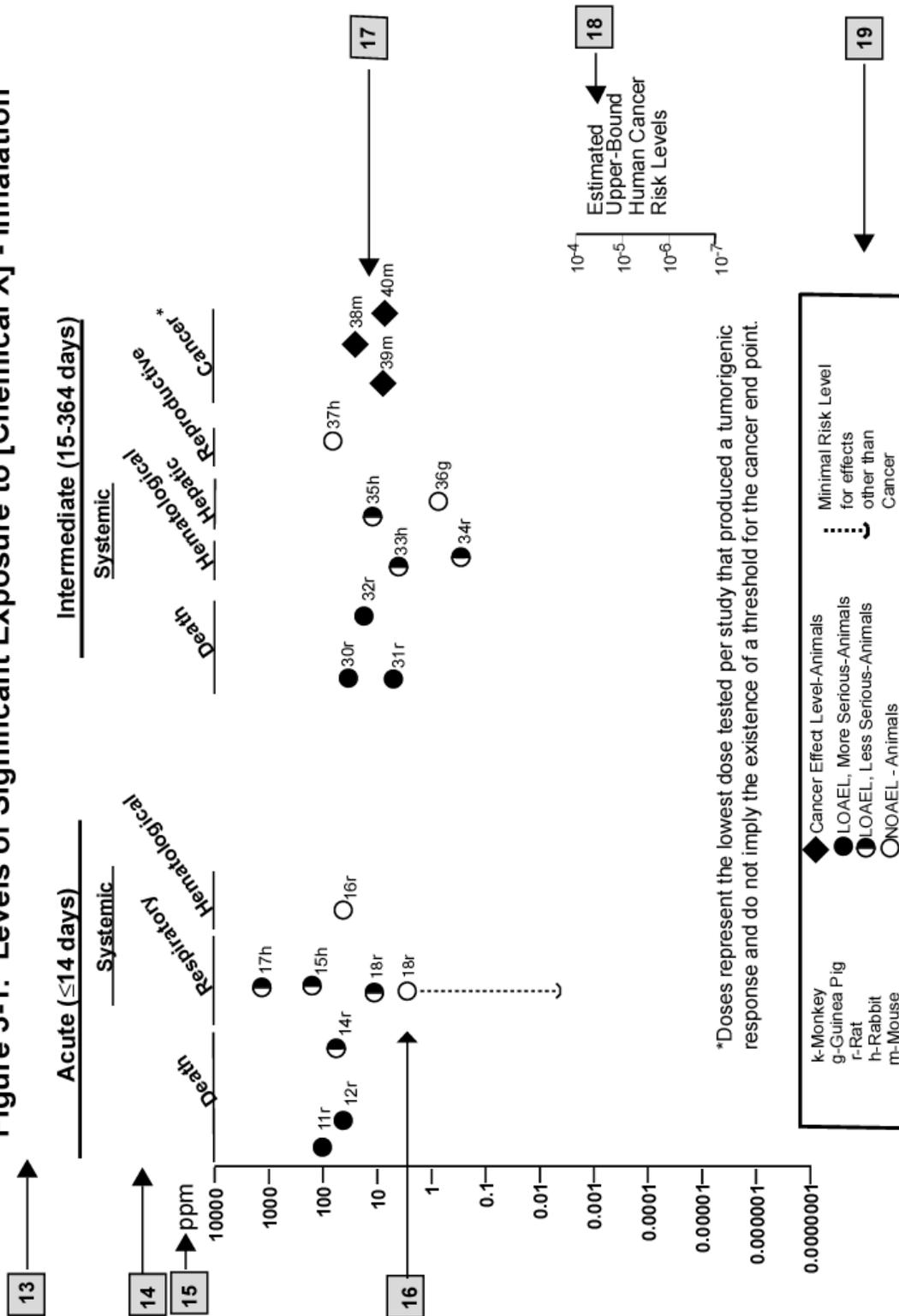
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- (18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound 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

**Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation**





## APPENDIX C

### ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACOEM	American College of Occupational and Environmental Medicine
ACGIH	American Conference of Governmental Industrial Hygienists
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AOEC	Association of Occupational and Environmental Clinics
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
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
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

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DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F <sub>1</sub>	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	<i>Federal Register</i>
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
K <sub>d</sub>	adsorption ratio
kg	kilogram
K <sub>oc</sub>	organic carbon partition coefficient
K <sub>ow</sub>	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC <sub>Lo</sub>	lethal concentration, low
LC <sub>50</sub>	lethal concentration, 50% kill
LD <sub>Lo</sub>	lethal dose, low
LD <sub>50</sub>	lethal dose, 50% kill
LDH	lactic dehydrogenase
LH	lutinizing hormone
LT <sub>50</sub>	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	<i>trans,trans</i> -muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal

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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
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
NHANES	National Health and Nutrition Examination Survey
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
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic

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PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PID	photo ionization detector
pg	picogram
pmol	picomole
PHS	Public Health Service
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
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	reportable quantity
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 <sub>50</sub>	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

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%	percent
$\alpha$	alpha
$\beta$	beta
$\gamma$	gamma
$\delta$	delta
$\mu\text{m}$	micrometer
$\mu\text{g}$	microgram
$q_1^*$	cancer slope factor
-	negative
+	positive
(+)	weakly positive result
(-)	weakly negative result



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